KONAČNI PROGRAM I SAŽECI

Međunarodnog znanstvenog simpozija

„Noviji napredak u neuroznanosti - mozak prije i poslije rođenja“

8. 12. 2023.

Hotel DoubleTree by Hilton Zagreb

Ulica grada Vukovara 269 a, Zagreb

ACADEMIA SCIENTIARUM ET ARTIUM EUROPAEA
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INTERNACIONALNA AKADEMIJA NAUKA I UMJETNOSTI U BOSNI I HERCEGOVINI
INTERNATIONAL ACADEMY OF SCIENCE AND ARTS IN BOSNIA AND HERZEGOVINA

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akademik Ivica Kostović
akademkinja Vida Demarin

Predsjednici:
akademkinja Aida Salihagić Kadić
akademik Srećko Gajović
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Službeni jezici: hrvatski i engleski

PROGRAM

- 08:30-09:00 Registracija učesnika
- 09:00-09:15 Otvaranje Simpozija - pozdravne riječi
  Akademik Asim Kurjak – predsjednik Internacionalne akademije nauka i umjetnosti u Bosni i Hercegovini i predsjednik Međunarodne akademije perinatalne medicine
  Akademik Dušan Šuput – dekan razreda Medicina Europske akademije znanosti i umjetnosti
- 09:15-11:30 Predsjedavajući: Asim Kurjak, Srećko Gajović
- 09:15-09:35 Ivica Kostović: Kritična razdoblja sinaptogeneze u fetusa čovjeka
- 09:35-09:55 Asim Kurjak: Doprinos 4D ultrazvuka u procjeni strukture i funkcije mozga fetusa
- 09:55-10:15 Osman Sinanović: Mogućnosti i značaj prenatalne dijagnostike neuromišićnih bolesti
- 10:15-10:35 Aida Salihagić Kadić: Fetalni mozak i stres te njegove posljedice na zdravlje
- 10:35-10:55 Helena Dukić: Prenatalno podrijetlo muzičke emocije: teorija i prijedlog istraživanja
- 10:55-11:15 Milan Stanojević: Kontinuitet ponašanja od fetusa do novorođenčeta: zbog čega je važan?
- 11:15-11:30 Pitanja i odgovori
- 11:30-11:45 Pauza – kava
- 11:45-14:00 Predsjedavajući: Ivica Kostović, Aida Salihagić Kadić
- 11:45-12:05 Dušan Šuput: Magnetic resonance spectroscopy and imaging in developing brain
- 12:05-12:25 Goran Krakar: SENDD - Umjetna inteligencija kao alat za rano otkrivanje potencijalnih neurorazvojnih odstupanja u dojenačkoj dobi
- 12:25-12:45 Damjan Osredkar: Personalised gene therapies for neurodevelopmental disorders — tools at our hands and challenges we face
- 12:45-13:05 Oliver Vasilj: Prvi pokušaj postnatalne motoričke procjene desetogodišnjaka nakon antenatalnog testiranja KANET-om

PROGRAM

- 13:05-13:25 Almir Badnjević: Koliko umjetna inteligencija može pomoći ultrazvučnoj dijagnostici u otkrivanju bolesti mozga u djece i odraslih
- 13:25-13:45 Dinko Mitrečić: Primjena naprednih *in vitro* modela u istraživanju normalnih i patoloških zbivanja u živčanom tkivu prije i poslije rođenja
- 13:45-14:00 Pitanja i odgovori
- 14:00-15:00 Domjenak
- 15:00-16:55 Predsjedavajući: Vida Demarin, Vanja Bašić Kes
- 15:00-15:20 Vida Demarin: Neuroplastičnost u zdravlju i bolesti
- 15:20-15:40 Fran Borovečki: Uloga genomike u personaliziranoj neurologiji
- 15:40-16:00 Vanja Bašić Kes: Neuroimunologija danas
- 16:00-16:20 Srećko Gajović: Izazovi oporavka mozga nakon moždanog udara - od kortikogeneze fetusa do kortikoprotekcije odraslih
- 16:20-16:40 Miro Jakovljević: Mozak i duša prije i poslije rođenja
- 16:40-16:55 Pitanja i odgovori
- 16:55-17:20 Zatvaranje Simpozija - akademkinja Aida Salihagić Kadić, predsjednica Organizacijskog i Znanstvenog odbora

Prijave i upiti:
Obavezno je prijaviti se za sudjelovanje na Simpoziju. To možete učiniti na jedan od sljedećih načina:
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Croatian Institute for Brain Research, Honorary Director
Scientific Centre of Excellence for Basic, Clinical and Translational Neuroscience, Group Leader
Croatian Academy of Sciences and Arts, Full Member
Zagreb, Croatia

Akademik Asim Kurjak
Profesor u trajnom zvanju, Sveučilište u Zagrebu, Medicinski fakultet
Profesor emeritus, Sveučilište Sarajevo School of Science and Technology
Predsjednik Internacionalne akademije nauka i umjetnosti u Bosni i Hercegovini
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Direktor Ian Donald School of Ultrasound in Medicine
Zagreb, Hrvatska

Akademik Osman Sinanović
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University Sarajevo School of Science and Technology, Sarajevo Medical School
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Tuzla, Bosna i Hercegovina

Akademkinja Aida Salihagić Kadić
Sveučilište u Zagrebu, Medicinski fakultet, Zavod za fiziologiju
V.d. pročelnice Katedre za fiziologiju i imunologiju i predstojnice Zavoda za fiziologiju
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Redovita članica Internacionalne akademije nauka i umjetnosti u Bosni i Hercegovini
Redovita članica Međunarodne akademije perinatalne medicine
Zagreb, Hrvatska

Dr.sc. Helena Dukić
Muzička Akademija Zagreb
Zagreb, Hrvatska

Akademik Milan Stanojević
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Zagreb, Hrvatska

Academician Dušan Šuput
Full professor (tenure) Faculty of Medicine, Ljubljana
Dean of Class Medicine, European Academy of Sciences and Arts
Vice-president of the Slovenian Medical Academy
Ljubljana, Slovenia

Dr.sc. Goran Krakar, dr.med., neuropedijatar
Poliklinika za dječje bolesti dr Sabol
Ravnatelj
Zagreb, Hrvatska

Damjan Osredkar, MD, PhD
Associate Professor of Pediatrics
Head of the Department for Pediatric Neurology
University Children's Hospital, University Medical Centre Ljubljana
Ljubljana, Slovenia

Doc.dr.sc. Oliver Vasilj, dr. med.
Specijalist ginekologije i porodništva
Subspecijalist fetalne medicine
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Sarajevo, Bosna i Hercegovina

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Hrvatski institut za istraživanje mozga
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Član Upravnog odbora Europskog programa za neurodegenerativne bolesti
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Zagreb, Hrvatska

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Predsjednica Međunarodnog instituta za zdravlje mozga
Redovita članica Internacionalne akademije nauka i umjetnosti u Bosni i Hercegovini
Zagreb, Hrvatska

Prof. dr. sc. Fran Borovečki, dr. med.
Voditelj, Odjel za neurodegenerativne bolesti i neurogenomiku, Klinika za neurologiju KBC Zagreb
Sveučilište u Zagrebu, Medicinski fakultet, Centar za translacijska i klinička istraživanja, pročelnik
Zagreb, Hrvatska

Akademkinja Vanja Bašić Kes
Redovita profesorica Stomatološkog fakulteta, Sveučilišta u Zagrebu
specijalist neurolog, subspecijalist neuroimunologije i subspecijalist intenzivne medicine, Klinika za neurologiju, Klinički bolnički centar Sestre milosrdnice
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Redovita članica Hrvatske akademije medicinskih znanosti
Zagreb, Hrvatska

Akademik Srećko Gajović
BIMIS - Biomedicinsko istraživačko središte Šalata, v.d. ravnatelja
Hrvatski institut za istraživanje mozga
Katedra za histologiju i embriologiju
Sveučilište u Zagrebu, Medicinski fakultet
Redoviti član Europske akademije znanosti i umjetnosti
Redoviti član Internacionalne akademije nauka i umjetnosti u Bosni i Hercegovini
Zagreb, Hrvatska

Akademik Miro Jakovljević
Profesor emeritus, Sveučilište u Zagrebu, Medicinski fakultet
Hrvatski institut za istraživanja i edukaciju o mentalnom zdravlju
Redoviti član Europske akademije znanosti i umjetnosti
Redoviti član Internacionalne akademije nauka i umjetnosti u Bosni i Hercegovini
Zagreb, Hrvatska

SPONZORI:

SAŽECI

CRITICAL PERIODS IN THE SYNAPTOGENESIS OF THE HUMAN FETAL CORTEX

Akademician Ivica Kostovic
Professor Emeritus
Croatian Institute for Brain Research, Honorary Director
School of Medicine, University of Zagreb, Dean's Adviser for Science
Scientific Centre of Excellence for Basic, Clinical and Translational Neuroscience, Group Leader
Croatian Academy of Sciences and Arts, Full Member
Academia Europea, Member
Zagreb, Croatia

Previous studies of development of the human fetal neocortex and alocortex indicate that formation of cortical synaptic networks begins during early fetal life. The aim of the present review is to discuss laminar distribution of synapses during two critical periods (subplate and cortical plate phase) of synaptogenesis and relate these data to the histological, immunocytochemical and in vivo MR landmarks and correlate this data with in vivo MR images, in order to bridge different scales of resolution in analysis of connectivity of the human cortex. The basis of the review is the concept of transient arrangement of neuronal circuitry elements within distinct transient cellular compartments described by us as "compartmental" approach. First critical period of synaptogenesis begins around 13 postconceptional weeks (PCW) by increased synaptogenesis during formation of deep synapse-rich compartment. We present novel finding showing that synapses are formed within expanding "upper" subplate which contains growing thalamocortical and basal forebrain afferents. This first critical period last from 13 to 22 PCW and synapses formed participate in first spontaneous functional oscillations and endogenously evoked activity during fetal movements (no typical electrical gap junctions were found!). During second critical period which begins around 23-24 PCW, a significant contingent of thalamocortical axons relocate in the cortical plate while some axons remain in the subplate compartment enabling thalamocortical system to serve as the most powerful integrator of functional cortical connectivity underlying first domain specific functions (pain, auditory stimuli).

The parallel analysis of synapse distribution in cingular cortex, which integrates social, emotional and cognitive functional hubs, and synaptogenesis in the hippocampus (memory functions) show early onset of synapse formation and accelerated tempo of synaptogenesis. In conclusion, typical chemical synapses are present in both neocortical and alocortical functional networks during spontaneous neuronal oscillations and movement-related functions. Coexistence of transient and permanent functional circuitry and their accelerated changes after 22 PCW explain changing pattern of EEG and behavioural states in early preterm period. The beginning of synaptogenesis during first trimester is important for study of neurodevelopmental, mental and neurological disorders emerging during potentially vulnerable periods of synaptogenesis upon various genetic and environmental triggers.

THE CONTRIBUTION OF 4D ULTRASOUND IN THE ASSESSMENT OF STRUCTURE AND FUNCTION OF THE FETAL BRAIN

Academician Asim Kurjak
Professor of Obstetrics and Gynecology, Medical School University of Zagreb, Croatia
Professor Emeritus, University Sarajevo School of Science and Technology, Sarajevo, Bosnia and Herzegovina

One of the greatest challenges of obstetrical ultrasonography is the better understanding of fetal neurological function. Neurological problems such as cerebral palsy are poorly understood and often falsely attributed to intrapartum events, while for the majority of cerebral palsy cases it has been proven that the causative pathway starts long before delivery. Several attempts have been made in order to define normal and abnormal fetal neurological function and to develop a method of assessment of the integrity of the fetal nervous system, but still without satisfactory sensitivity.

Fetal behavioral patterns are directly reflecting developmental and maturational processes of fetal central nervous system. It has been suggested that the assessment of fetal behavior during different periods of gestation may provide valuable information about normal and abnormal brain development, and contribute to the early diagnosis of various structural or functional neurological abnormalities.
The introduction of three and four dimensional ultrasound (3D & 4D) allowed real time assessment of fetal behavior. Details of the fetal face, and especially movements of mouth, eyes (facial expressions) and fingers have been made possible with the introduction of 4D ultrasound.

KANET is the first method that attempted to use 4D ultrasound in order to assess and combine parameters of fetal behavior and form a scoring system that would assess the fetus in a comprehensive and systematic approach, in the same way that neonatologists perform a neurological assessment in newborns during the first days of their life, in order to determine their neurological status. KANET appears to be able to identify functional characteristics of the fetus that predict normal and abnormal neurological development and hopefully future results of the prospective multicentric studies that are taking place at the moment in the next few years it will provide more information on fetal neurology. Such information will be of great value in counseling mothers of high risk pregnancies, like for example in cases with previous child with cerebral palsy and also provide valuable evidence for cases of litigation.

POSSIBILITIES AND IMPORTANCE OF PRENATAL DIAGNOSIS OF NEUROMUSCULAR DISORDERS

Academician Osman Sinanović
Medical Faculty, University of Tuzla, 75000 Tuzla; Medical School, Sarajevo School of Science and Technology; International Academy of Sciences and Arts in Bosnia and Herzegovina, 7100 Sarajevo, Bosnia and Herzegovina

Many neuromuscular diseases (NMD) are genetic disorders. A genetic disorder is caused by changes in one or more genes. In recent decades, scientists have discovered more than 500 genes that can cause neuromuscular diseases, and the number is still growing. These advances make it possible for more individuals living with neuromuscular disease to get a specific diagnosis through genetic testing and gain access to high-quality care.

Conventional medications for neuromuscular diseases are mainly used to help manage symptoms or try to slow down their progression, but these medicines will not eliminate symptoms or stop them from progressing. Gene targeted therapies hold great promise because they seek to fix the underlying cause of a genetic disorder. There are different types of genetargeted therapies being studied and developed. Currently, targeted therapies that replace or alter the expression of genes or enzymes are available for several neuromuscular conditions: Pompe disease, spinal muscular atrophy (SMA), Duchenne muscular dystrophy (DMD), and TTR amyloidosis. Clinical trials are ongoing for therapies to treat certain genetic types of many different neuromuscular conditions, including muscular dystrophies, congenital myopathies, hereditary neuropathies, and amyotrophic lateral sclerosis (ALS).

New approved gene therapies are, on the one hand, very expensive and not easily available, and on the other hand, we do not yet have enough experience about their effectiveness for the NMDs, prenatal genetic counseling and prenatal diagnosis are very imprtant. Chorionic villus sampling (CVS) and amniocentesis (AC) are commonly used invasive prenatal testing (IPTs) for the prenatal diagnosis of DMD and SMA. Testing performed during a pregnancy can be done between the 10th and 14th weeks via CVS and later via amniocentesis between the 16th and 20th weeks. For both CVS and AC, ultrasound imaging is used throughout the procedure to help ensure that it's done safely and accurately. So, these tests can detect a genetic condition early in the pregnancy. The decision about whether to get prenatal testing for SMA is personal, and for some it may be difficult. Some people decide to continue the pregnancy and explore treatment options, while others may decide to end the pregnancy.

Key words: Neuromuscular diseases – Chorionic villus sampling – Amniocentesis – Prenatal diagnosis

FETAL BRAIN AND STRESS AND ITS CONSEQUENCES ON HEALTH

Academician Aida Salihagić Kadić
Full Professor of Physiology and Neuroscience (tenure), University of Zagreb, Medical School, Department of Physiology

The fetus needs physiological, stress-free environment for normal growth and development. A large number of factors can alter the intrauterine environment and lead to fetal stress. Maternal undernutrition or placental insufficiency, maternal emotional stress or stressful life events, as well as fetal pain may trigger the fetal stress response. A high serum level of fetal stress hormones has been found in pregnancies complicated with intrauterine growth restriction as well as preeclampsia.The stress has primarily protective role inducing different adaptations of the organism and allowing survival. However, prenatal stress can interfere with the fetal neurodevelopment and leave the long-term and profound consequences on the brain structure and function. It also affects the development of many other organs and organ systems, and has lifelong consequences. Adaptation of the fetus to stress includes the activation of the neuroendocrine stress axis from midgestation and the secretion of the corticotropin releasing hormone (CRH), adrenocorticotropic hormone (ACTH) and cortisol.

Fetal cortisol, on one hand, accelerates maturation of the brain and the lungs, enabling survival of premature infants, but also, it may have negative effects on the lung and brain development as well as on growth of the fetal organism in a whole. It has been known that low birth weight is a marker of the harmful intrauterine environment and fetal stress.

Accelerated maturation of the brain is associated with the structural as well as behavioral changes. Stress induces structural changes of the hippocampus that are associated with memory impairment and learning disabilities later in life. Hyperalertness and impaired fetal responsiveness to novel stimuli are behavioral changes associated with accelerated brain development.

A cause of irritability and diminished attention may be fetal ACTH as well.

Additionally, ACTH impairs movement coordination and muscle tonus. Fetal CRH influences the timing of the birth, which means that the fetus has an active role in the initiation of the delivery.

Furthermore, fetal stress increases the risk of preterm delivery. It is important to point out that attention deficit hyperactivity disorder, sleep disorders, unsociable and inconsiderate behavior, psychiatric disorders, including schizophrenia, depressive and neurotic symptoms, drug abuse, and anxiety as well as emotional and cognitive disorders are considered as potential neurodevelopmental consequences of prenatal stress exposure.

The adaptive changes made by the fetus in response to an adverse intrauterine environment and prenatal stress result in permanent changes in physiology, structures of organs and metabolism. It has been shown that the underlying etiology of some of the most common diseases of the modern society, such as hypertension, obesity, diabetes and coronary heart disease, has been traced in intrauterine environment. Further, there is experimental evidence that increased maternal care and environmental enrichment can compensate for prenatal stress-induced effects.

Recent data have also indicated gender differences in vulnerability to fetal stress. Finally, stress-free intrauterine environment is crucial not only for normal prenatal and postnatal growth and development, but also for good health in childhood and adulthood. Prevention of certain diseases in childhood as well as some chronic diseases in adulthood should start even before birth.

PRENATAL ORIGIN OF MUSICAL EMOTION: THEORY AND RESEARCH METHODOLOGY

Dr.sc. Helena Dukić
Academy of Music, University of Zagreb, Croatia

Studies suggest that the origin of musicality may be traced back to prenatal development (Parncutt & Chuckrow, Teie, 2016), where the fetus may passively acquire information about the associations between patterns of sound, movement, and emotion that characterize music through repeated exposure to their mother's internal patterns of sound and movement that depend on her physical and emotional state (Parncutt & Chuckrow, 2018).

Fetus is unable to reflect on emotions as adults do, but nowadays, we have the possibility of observing fetal movements and facial expressions in 4D sonography, which can provide insights into fetal emotional states (Kurjak et al., 2017).

Fetal movements and facial expressions reflect fetal emotional states (Delafield-Butt et al., 2013). Facial recognition neurons in the amygdala reflect the emotional significance of facial expressions (Hata et al., 2012). The development of the amygdala begins in early embryonic life and matures in the first postnatal year (Humphrey, 1968). Thus, facial emotion-like expressions may be indicators of fetal emotional state (Hata et al., 2012).

We propose a methodology for studying the role of sound in the emotional attachment between a mother and her fetus. How might induced maternal emotions influence fetal facial expressions and movements?

Mothers will hear music or pink noise through headphones, while foetuses will hear the same sounds from a loudspeaker on the mother's abdomen. The design will be within-subject with five conditions: (1) Mothers hear self-selected music that induces positive valence and high arousal. Foetuses hear noise. (2) Mothers hear self-selected music that induces negative valence and low arousal. Foetuses hear noise. (3) Foetuses hear the music that the mother heard in (1). Mothers hear noise. (4) Foetuses hear the music the mother heard in (2). Mothers hear noise. (5) Control condition: both mothers and foetuses hear noise.

Psychological and biological parameters will be monitored in mothers and foetuses. The study predicts more laughing-gestalt faces and more/larger limb movements in Condition 1, and more crying-gestalt faces and fewer/smaller limb movements in Condition 2. For Conditions 3 and 4, the study predicts no effect. However, the findings of the study could contradict these predictions.

CONTINUITY OF BEHAVIOR FROM FETUS TO NEWBORN: WHY IS IT IMPORTANT?

Academician Milan Stanojević
Department of Obstetrics and Gynecology Medical School University of Zagreb, Clinical Hospital Sveti Duh, Zagreb, Croatia
Center for the Mother and Child Gineko, Zagreb, Croatia

Behavior that reflects the development of the central nervous system (CNS), and especially the brain, is a very complex process that develops during pregnancy and continues after birth. It is important to understand how the CNS produces different types of movements which may indicate pathological CNS development. Due to complexity, voluntary control, and stereotypies, there are different groups of movements such as reflex movements, movements with fixed patterns, movements with rhythmic motor patterns, and directed movements. Prechtl stated that spontaneous neural activity is a marker of normal and disturbed brain function. Observing the spontaneous movements of the unstimulated fetus is one of the best methods for assessing the CNS function. Endogenously generated patterns of spontaneous movements that arise without CNS stimulation can be observed as early as 7 to 8 weeks postmenstrual age with the development of a rich repertoire of movements during the next two to three weeks through five to six months postnatally. This continuous endogenously generated activity from the prenatal to the postnatal period represents a significant opportunity to detect high-risk fetuses and infants of developing a neurodevelopmental disorder. The most important among these movements are general movements (GMs). The goal is to show that there is a continuity of GMs from the prenatal to the postnatal period, the monitoring of which could contribute to the easier detection of human individuals at risk for the development of more severe neurodevelopmental conditions.

There is very compelling evidence to suggest that impaired GMs are a more sensitive indicator of brain damage than reactivity to sensory stimuli during reflex testing. In newborns with various brain damage, the number of spontaneous movements (quantity) does not change, but their elegance, fluency, and complexity (quality) are lost. As brain development is a unique and continuous process that takes place throughout pregnancy and after birth, it is expected that there is a continuity of movements from the prenatal to the postnatal period, and these movements are a functional indicator of brain development.

In our study of fetal behavior using four-dimensional ultrasound (4D US), we were able to observe various movements and expressions of the fetal face, which resulted in the introduction of a standardized test for neurological assessment of the fetus: the Kurjak Antenatal Neurodevelopmental Test (KANET).

The test made it possible to distinguish fetuses at risk for neurodevelopmental disorders from those without risk. In our research, we have shown the existence of continuity of behavior from the fetal to the newborn period, especially the GMS, which is not affected by gravity-like voluntary movements. It is possible to establish the prenatal onset of brain damage by the detection of morphological and functional signs using 4D US. The diagnosis might at least be a retrospective marker of prenatal injury. However, it is still not entirely clear whether we are approaching the time when we will be able to assess the function of the CNS using this prenatal neurological test. Even postnatally, there are several neurological methods for assessment of the neurological condition of the newborn, and the evaluation of the fetus in utero is even more complex because the fetus has an immature brain and is in a different microgravity environment. At the same time, it is not clear whether any additional functional methods will be needed that would postnatally confirm the prenatal finding of neurological damage. Although the development of the CNS is very complex, it takes place continuously from the prenatal to the postnatal period. A reflection of the function of the CNS is movements controlled by different parts of the brain. Environmental conditions significantly affect the occurrence of movement both prenatally and postnatally. The intrauterine environment with prevailing microgravity conditions is probably friendly and comfortable for the fetus, while extrauterine conditions require adaptation and development of antigravity muscle control after birth. In some cases, maldevelopment of the fetal brain can adversely affect the behavior of the fetus and its cognitive development and other neurodevelopmental functions. After birth, the fetus is the same person in a different environment, continuing all life-important processes. Investigation of continuity of behavior might contribute to a better understanding of the development and function of the CNS.

MAGNETIC RESONANCE SPECTROSCOPY AND IMAGING IN DEVELOPING BRAIN

Academician Dušan Šuput
Full professor (tenure), Faculty of Medicine, Ljubljana, Slovenia

Brain development and brain plasticity have been extensively studied using many techniques. This presentation will deal with Magnetic resonance imaging (MRI) and

spectroscopy (MRS) as noninvasive tools to study human brain development from early intra-uterine life to the end of life.

In young children, the capacity to absorb and process data is overwhelming. With time, this broad capacity is replaced by a more narrow but more efficient brain function serving everyday needs. This process involves a tremendous decrease in interneuronal connections/synapses, but the rate of brain maturation in children varies. Nevertheless, clinical guidelines for assessing prenatal brain development (1,2) have been well defined. Magnetic resonance spectroscopy can detect abnormalities in the absence of morphological findings (3,4) and functional MRI is a powerful tool to study brain function and functional connectivity throughout the lifespan. Resting-state functional MRI has been used to assess brain function before birth and early childhood. In the presence of gross brain anomalies group analysis of MRI data using standard analytical software tools becomes quite challenging. Using segmentation priors from local image properties is computationally demanding but a robust tool for reliable semi-automatic image segmentation (5). Metabolic changes affect brain function during childhood, adolescence (6) and in adults. Brain function slowly declines in adulthood, but several data indicate that brain plasticity can modulate or ameliorate brain function after acute events such as stroke (7). MRI and MRS are popular tools to investigate neurodegenerative disorders, such as Alzheimer's disease (8) or other forms of dementia. MRI and MRS remain the only tools to detect brain structure, chemical composition, and function noninvasively with high spatial and temporal resolution. Combined with other research approaches, it provides a solid basis for further improving our understanding of brain function and structure.

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SENDD – ARTIFICIAL INTELLIGENCE AS A TOOL FOR EARLY DETECTION OF POTENTIAL NEURODEVELOPMENTAL DEVIATIONS IN INFANCY

Goran Krakar (1), Tomislav Strgar (2), Goran Kuzmac (1), Alessandro Ninković (1), Zlatko Sabol (1).

1. Outpatient pediatric clinic Sabol, IV Cvjetno naselje 21, Zagreb, Croatia

2. TIS GRUPA d.o.o. Heinzelova 33, Zagreb, Croatia

General movements (GMs) assessment is a reliable method of gestalt evaluation of movement complexity and variation with high predictive value to identify neurological issues that may lead to cerebral palsy or minor neuromotor dysfunction. The quality of GMs in the fidgety period has been found to have the highest predictive value.

We developed a System for Early Neurological Deviation Detection (SENDD) using artificial intelligence to annotate and assist in the conclusion of the quality of the general movements.

We included more than 1500 videos (still increasing) of infants in fidgety age collected institutionally or by smartphone camera/app assisted in home-setting. All videos were checked for inclusion and exclusion criteria depending on technical and child requirements. All collected videos were evaluated by trained professionals using the Hadders-Algra system. For GMs annotations and assessments 25 different machine learning (ML) models and algorithams (AI systems) were consecutively tested.

At the moment there is a fully developed and reliable 15-keypoint annotation tool. Home video can replace institutional recording and be a reliable source of videos. For this purpose WEB and MOBILE APPS were developed. The most reliable and trainable neural networks were selected. Accuracy of AI conclusions compared with trained human assessments for Hadders-Algra 4-category system and screening toll using only 2-category system (normal, abnormal). Most reliable ML models with the best precision and accuracy results are DensNet169 (pose estimation & computer vision) and CNN. Higher accuracy is directly related to the number and diversity of videos used for training, as annotation time was reduced.

SENDD is of great relevance for users and families. It saves medical resources and represents a time-effective screening tool both for professionals and families.

PERSONALISED GENE THERAPIES FOR NEURODEVELOPMENTAL DISORDERS – TOOLS AT OUR HANDS AND CHALLENGES WE FACE

Assoc. Prof. Damjan Osredkar, MD, PhD
Department of Pediatric Neurology, University Children's Hospital, University Medical Centre Ljubljana, Bohoričeva 20, 1525 Ljubljana, Slovenia, ORCID 0000-0002-2188-420X, damjan.osredkar@kclj.si

Rare diseases, often caused by a single gene defect, pose significant challenges owing to their low prevalence and high morbidity and mortality. Until recently, symptomatic treatment was not available for most of these diseases, but technological advancements and a better understanding of the biochemical processes caused by genetic mutations have enabled the emergence of novel disease-modifying treatments (DMT).

Innovative treatment strategies for genetic disorders have dramatically increased over the last decade. The first examples of novel DMT were the treatment of spinal muscular atrophy (SMA) with an antisense nucleotide (nusinersen) (1) and later gene replacement therapy (onasemnogene abeparvovec) (2) and a small molecule (risdiplam). (3) All of which have been proven to be efficient in slowing the progression of the disease, or even halting it, thus changing the natural course of the disease in a beneficial way. Clinical studies and real-world data (4) suggest that early diagnosis and treatment of SMA with any of the therapies, preferably in the presymptomatic phase, can dramatically improve the outcome of these patients, as in some cases, children treated in the presymptomatic phase can demonstrate a completely normal development.

Duchenne muscular dystrophy (DMD) is another rare disease with a novel DMT available. In Europe, a small molecule ataluren has been conditionally approved for treatment of nonsense mutations of the DMD gene, (5) and exon-skipping therapies are avaliablle for particular mutations on the DMD gene. (6,7) Gene replacement therapy for DMD has been recently approved for DMD in the US. (8)

Furthermore, several attempts have been made to design and produce therapies for rare diseases outside of big pharmaceutical companies, financed by several innovative sources. An example of such therapy is gene replacement therapy developed and given to a patient with hereditary spastic paraplegia with a mutation in the SPG50 gene. (9) Although novel disease-modifying treatments and gene therapies hold great promise for treating rare diseases, they also present significant challenges in many domains. Continued research and innovative solutions are needed to ensure that these potentially life-changing treatments can reach those who need them the most.

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THE FIRST ATTEMPT AT POSTNATAL MOTOR ASSESSMENT OF TEN-YEAR-OLDS AFTER ANTENATAL TESTING WITH KANET

Assistant professor Oliver Vasilj, MD, PhD; associate professor Tatjana Trošt Bobić, PhD; Dora Marinić, PhD student
University North; Polyclinic Medifem doo, Zagreb, Croatia

Fetal behavior can be defined as spontaneous fetal activity or activity that occurred as a reaction to external stimuli. It is a direct reflection of complex developmental and maturational processes within the fetal central nervous system. Several studies have shown that there could be deviations in fetal behavior in various forms of high-risk pregnancies. The initial point of this study was to find a change in fetal behavior between pregnancies with gestational diabetes and normal pregnancies and to find a correlation between altered fetal behavior and HbA1c value. Statistically significant differences were shown for four studied forms of fetal behavior. Also, the results showed that there is a positive correlation between the value of HbA1c and altered fetal behavior. Numerous studies have shown possible influence of gestational diabetes on future development of the children. Considering that the second measurement of this longitudinal study was carried out ten years later. The aim of this study was to determine the potential long-term impact of gestational diabetes on the sensorimotor development of children. A total of 100 children from the initial study participated in this measurement point (50 experimental and 50 control groups). We used standardized measuring instruments to assess the development of gross and fine motor skills, sensory integration, visual-motor coordination and graphomotor skills. Also, the level of daily physical activity of the children was objectively measured. Statistical analysis of the data showed certain differences in the sensorimotor development of the experimental and control groups, as well as the influence of fetal behavior patterns on the development of different sensorimotor skills. This is the first longitudinal study that shows the long-term impact of gestational diabetes on sensorimotor development of children, which determined the possibility of predicting certain sensorimotor skills using the KANET test and with the evaluation of fetal behavior by 4D ultrasound.

HOW ARTIFICIAL INTELLIGENCE CAN HELP ULTRASOUND DIAGNOSTICS IN DETECTING BRAIN DISEASES IN CHILDREN AND ADULTS

Academician Almir Badnjević
Director of Agency for Identification Documents, Registers and Data Exchange of Bosnia and Herzegovina

This paper explores the intersection of artificial intelligence (AI) and ultrasonic diagnostics in the realm of brain disease detection.
Current challenges in traditional ultrasound imaging for neurological disorders necessitate more advanced diagnostic tools. We investigate the potential of AI, specifically machine learning algorithms, to enhance the accuracy and efficiency of ultrasound diagnostics for brain diseases in both children and adults. Our presentation outlines the limitations of conventional ultrasound techniques and emphasizes the need for sophisticated solutions. We showcase the capabilities of AI in analyzing intricate ultrasound data, identifying nuanced patterns indicative of various neurological conditions. Specific applications of AI in early detection, such as tumors, vascular abnormalities, and developmental disorders, are discussed, supported by case studies illustrating improved diagnostic outcomes. Additionally, ethical considerations and potential limitations in AI integration into medical diagnostics are addressed. The paper aims to provide a comprehensive understanding of the benefits and challenges associated with leveraging AI in ultrasonic diagnostics. In conclusion, this work sheds light on the promising collaboration between artificial intelligence and ultrasonic diagnostics, presenting a forward-looking perspective on how this synergy can elevate brain disease detection across diverse age groups.

APPLICATION OF ADVANCED IN VITRO MODELS IN RESEARCH OF NORMAL AND PATHOLOGICAL EVENTS IN THE NERVOUS TISSUE BEFORE AND AFTER BIRTH

Prof. Dinko Mitrecic, MD, PhD
Department of Histology & Embryology, Laboratory for Stem Cells, Croatian Institute for Brain Research, School of Medicine University of Zagreb

Faced with a burden of diseases of the nervous system, affecting both adults, but as well children and fetuses, modern medicine still searches for approaches which might result in development of new therapeutic strategies. Here we present research direction arising from technology of stem cells upgraded to the advanced models comprising 3D cultures of human brain tissue in the form of brain organoids.

By applying protocols invented or significantly upgraded by our own group we developed several in vitro models which include cells of the nervous tissue (neurons, astrocytes) in various stages of their development. Moreover, by long term growing (up to 150 days) of brain organoids during which cytoarchitectonic of all 6 layers of neocortex develops, our activities are based on detection of events present both in normal, but as well in disturbed brain cortical structures. Here we present a brief overview of application of advanced models of the nervous tissue with the goal to detect phenomena present after hypoxic/ischemic incident. One of the elements we focused on was how lack of oxygen in immature cells of the brain cortex influences integrity of mitochondria, leading to mitophagy and various types of cell death. Moreover, we used brain organoid models to decipher cellular and molecular phenomena present in the Down`s Syndrome and in the Alzheimer`s disease. This allowed us to detect genes involved in both detrimental processes in the cortical tissue (e.g. DYRK1A, involved in cellular aging) or genes which bring cell-protective effects (e.g. BACE2, anti-amyloidogenic action).

NEUROPLASTICITY IN HEALTH AND DISEASE

Academician Vida Demarin
Full member of Croatian Academy of Sciences and Arts

Human brain, the key of individual and social human behaviour is certainly the most complicated system on the earth and enormous investigations tried, and are still trying to resolve the secret of its functioning. Results of numerous investigations during Decade of the Brain, by sofisticated diagnostic methods, point out the importance of brain's neuroplasticity, the mechanism that was described already at the end of 19th century, but at that time, still without scientific proof. This mechanism shows that brain is not a static organ, but on the contrary, by development of a new connections between cells and new pathways, its functions could be restored as well as preserved even in the older age.Spanish neuroscientist, Nobel prize winner Santiago Ramon y Cayal set the roots of neuroplasticity in his book Textura de Sistema Nervioso, published 1904. Bruce McEven published his important work on changing structure of the brain during stress in Nature 1968. Further research followed by Paul Bach y Rita with his sensory supstitution, Pascal Leone with imagining and mental practice, Beatriz Calvo Merino with neurocognitive mechanisms involved in action observation, expertise and dance.

Another Nobel prize winner Eric Kandel investigated the molecular biology of memory storage as dialog between genes and synapses. Michael Merzenich's research is devoted to the role of neuroplasticity in preserving our brain's health. And Norman Doidge in his groundbreaking book „The Brain that Changes Itself" explains the brain's ability to change its own structure based on neuroplasticity, together with the same approach in his second book „The Brain's Way of Healing."

Neuroplasticity, capacity of neurons and neural networks in the brain to change their connections and behavior in response to new information, sensory stimulation, development, damage, or dysfunction is considered generally to be a complex, multifaceted, fundamental property of the brain.

As with many medical and health-related fields, during life-span, in health and disease, interventions targeting mechanisms of plasticity should follow an individualized approach by harnessing individual differences to best utilize the brain's innate capacity to change.

THE IMPORTANCE OF GENOMICS IN PERSONALIZED NEUROLOGY

Prof. Fran Borovečki, MD, PhD

Department for neurodegenerative diseases and neurogenomics, Neurology Clinic, University Clinical Hospital Zagreb

Center for translational and clinical research, University of Zagreb School of Medicine and University Clinical Hospital Zagreb

Neurological diseases represent one of the most important causes of disability and mortality in modern society. Considering the prevalence, clinical characteristics and associated costs of treatment, neurological diseases represent an increasing public health problem, and due to the aging of the population, their impact on society as a whole is increasingly significant. Despite extensive clinical research and dynamic development in the field of neurology, especially regarding the development of new drugs and therapeutic procedures that modify the disease, there is still no effective drug that could stop or even slow down the deterioration of neurons. An increasing number of studies indicate a clear role of genetic mechanisms in the development and progression of neurological diseases. Although numerous genes are responsible for the occurrence of monogenic forms of neurological diseases, in most cases the inheritance is genetically complex and occurs through the interaction of several genes and the environment.

Genomic approaches, such as gene chips or next-generation sequencing, provide better insight into the genetic risk factors responsible for neurological diseases. Next-generation sequencing approaches such as whole-genome, exome, and panel sequencing have greatly improved our ability to uncover the genetic causes of neurological diseases. In the future, new genomic approaches will allow not only the discovery of new risky genetic variants, but will also contribute to increasing the effectiveness of treatment and reducing the frequency of side effects to existing and future therapies. In this way, a personalized approach to the diagnosis and treatment of patients with neurological diseases will be enabled.

NEUROIMMUNOLOGY TODAY

Academician Vanja Bašić Kes
Neurology Clinic, Clinical Hospital Center "Sisters of Mercy", Zagreb, Croatia

Neuroimmunology today is an interdisciplinary field that brings together knowledge from neurology and immunology. Neuroimmunologists seek to better understand the interactions of these two complex systems during development, homeostasis, and response to injuries.

Technological advances have greatly aided our knowledge of how the immune system influences the nervous system during development and ageing, and how such responses contribute to disease as well as regeneration and repair.

Despite this evidence, it is surprising that the term 'neuroimmunology' was only first used on PubMed in 1982, coinciding with the first Neuroimmunology Congress in Stresa, Italy and following the launch of the Journal of Neuroimmunology in 1981.

One of the greatest misconceptions that impeded progress in neuroimmunology was the idea that the blood–brain barrier (BBB) and the perceived immunological privilege of the brain prevent cross-talk between the CNS and immune systems.

This long-standing dogma has been challenged by recent studies and the discovery of glymphatics and meningeal lymphatic vessels. Although this paradigm shift is a recent advancement in thinking of nervous-immune system cross-talk, such changes in the field, beginning over 150 years earlier, have been generally linked to technological advances Although neuroimmunology research has focused on multiple sclerosis, immune responses are also observed in Guillain–Barré syndrome (GBS), white matter diseases, psychiatric disorders, infections, trauma and neurodegenerative diseases. Multiple sclerosis is a condition that can affect the brain and spinal cord, causing a wide range of potential symptoms, including problems with vision, arm or leg movement, sensation or balance. It's a lifelong condition that can sometimes cause serious disability, although it can occasionally be mild.

Neuroimmunology today presents an opportunity to deliver new therapeutic approaches for a broad range of conditions, including many neurological and psychiatric conditions.

THE CHALLENGES OF BRAIN REPAIR AFTER STROKE – FROM FETAL CORTICOGENESIS TO ADULT CORTICOPROTECTION

Academician Srećko Gajović
BIMIS – Biomedical Research Center Šalata, University of Zagreb School of Medicine, Zagreb, Croatia

The stroke is the second cause of death and the first cause of disabilities in the developing countries. Although recanalization therapies establishing reperfusion are available, still there is no therapeutic approach addressing neuroprotection or neurorestoration. In our research group, we focus on neurorestoration strategies leading to the brain repair and functional recovery. Subsequently, we hypothesized that the cellular and molecular mechanisms active during fetal brain development could as well contribute to the brain repair after ischemic brain injury. As candidate genes having the hypothetic potential for the brain repair, we have chosen two corticogenesis-related transcription factors, BCL11B and SATB2. BCL11B (B-cell lymphoma/leukemia 11B, aka CTIP2—chicken ovalbumin upstream promoter transcription factor interacting protein 2) and SATB2 (special AT-rich sequence binding protein 2) are key developmental determinants of two major neuronal subclasses: cortico-subcortical (BCL11B) and cortico-cortical (SATB2).

As a model for the human ischemic stroke, transient middle cerebral artery occlusion for 30 minutes was done in mice. Three and 7 days after ischemic brain injury the animals were analyzed by in vivo magnetic resonance imaging, they were assessed functionally by neurological deficit score and the isolated brains analyzed by immunohistochemistry.

BCL11B and SATB2 were indeed reactivated after ischemic brain injury and their expression higher in the lesioned animals than in the control, sham operated animals. BCL11B co-localized with another transcription factor, ATF3, known to be beneficial after ischemic stroke. Moreover, the expression of corticogenesis-related transcription factors correlated positively with the recovery rates measured by both, structural parameters (lesion reduction visualized by magnetic resonance imaging), and functional parameters (functional recovery measured by a decrease of neurological deficit score).

The performed study supported the initial hypothesis of reactivation of the genes active in the fetal brain development after brain injury. It can be used as an example of the power of combined analysis of the living animals by in vivo imaging, their functional status, and the cellular and molecular analysis possible only on the isolated post-mortem brains.

The functional importance of the corticogenesis-related transcription factors in the brain repair was claimed by the fact that they indeed were associated with the parameters of structural and functional recovery. This opens an exciting perspective of the potential therapeutical interventions oriented to enhance the reactivation of developmentally relevant genes. The importance of developmental mechanisms in relation to the therapeutic potentials for the adult brain can be a basis for neurorestoration strategies contributing to the regenerative medicine applications in neurology.

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BRAIN AND MIND BEFORE AND AFTER THE BIRTH

Academician Miro Jakovljević
Professor Emeritus, University of Zagreb, Medical School
Croatian Institute for Research and Education on Mental Health

Human development is based on the complex interactions between nature and nurture in our ANTROPOCENE cyber-age. There are for hierarchically related paradigms explaining brain and mind relationship before and after the birth. According to the body paradigm the mind and mental functions are results of maturation of the brain and neural networks responding to ongoing experience so that mind is a by-product of brain activity. It is a framework in which orthodox biological psychiatry and clinical psychopharmacology operate.

The mind-body paradigm is framework in which psychosomatic or mind body medicine operate. According to this paradigm mind and brain are separated but interconnected entities which influence on each other. The body-energy paradigm explains health and illness as results of the flow and balances of life energies.

Energy psychology and quantum psychiatry operates within this paradigm. According to the body-spirit paradigms humans are spiritual beings in a physical body. This paradigm is a framework for transpersonal psychology and spiritual psychiatry. According to transdisciplinary integrative concept Body-Mind-Spirit-Energy are for mutually interconnected domains of human beings in health and illness.

We live in five different realities 1. material reality or the world of things; 2. psychic reality, the world of ideas, feelings and stories; 3. social reality, the world of interpersonal communications and social relations; 4. spiritual reality, the world of invisible forces and entities, and connections into wholeness, and 5. virtual cyber-reality which may significantly influence on our brain and mind during the whole our life. Our brain is involved in everything what we do, and what we do, feel and think change our brain. Our brain is the hardware of our mind and our very essence as human being, our selfhood, identity, personality and life styles. The interplay between genome, epigenome, and environment shapes a phenotype of human health or illness even before birth. The three-hit hypothesis: hit-1 genetic predisposition; hit-2 early life environment stress, and hit-3: later life environment stress is fundamental for understanding the role of the brain and mind in health (eustress, resilience and antifragility) and illness (distress, disorder, disease). The quality of life in the womb, our temporary home before we were born, programs our susceptibility for many somatic diseases and mental disorders. It is well known that babies enter the world with different temperaments; some are easy and calm, others are more sensitive to environment, more reactive and difficult to soothe. Prenatal or fetal programming of risk for adult mental disorders has become an important and intriguing topic.

Key words:
brain-mind relations, body paradigm, mind-body paradigm, body-energy paradigm, body-spirit paradigm, three-hit hypothesis in health and illness