19th – 22nd SEP

International Symposium

NEWroscience 2023

Epilepsy & Neuropsychiatric Comorbidities
From Semiology, to Neuroplasticity of
Vulnerable/Resilient Networks, to Personalized Therapies

FINAL PROGRAM AND ANNALS

International Symposium

NEW roscience 2023

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FINAL PROGRAM

International Symposium
NEW*roscience* 2023

"Epilepsy and Neuropsychiatric Comorbidities: From Semiology to Neuroplasticity of Vulnerable/Resilient Networks, to Personalized Therapies"

19th September

7:15 PM to 8:00 PM

OPENING CEREMONY AND KEYNOTE SPEECH

Norberto Garcia-Cairasco - Physiology Department. Ribeirão Preto Medical School. University of São Paulo. *''Promoting Paradigm Shifts in Epileptology over four decades. The Neurophysiology and Experimental Neuroethology Laboratory (LNNE) Historical Contributions in Brazil, Latin America, and the World".* <ngcairas@usp.br>

8:00PM to 10:00PM

WELCOME COCKTAIL

20th September

First Round Table: Morning Session

8:15AM to 12:15AM

What can we learn from the Combination of Orthodox Scientific and Ancestral Epistemologies, Multiple Knowledges, as applied to Epilepsy and Neuropsychiatric Comorbidities?

Chair: Norberto Garcia-Cairasco; Co-Chair: Sandra Orozco

8:15AM to 8:45AM

1. Dinesh Upadhya. - Department of Anatomy, Kasturba Medical College, Manipal, India. *Joining Ayurvedic Medicine and Contemporary Neuroscience in Epileptology Research <dineshupadhya@gmail.com>*

8h45AM to 9:15AM

2. Symon Kariuki. *Integrating Traditional and Complementary Medicine in the Treatment of Epilepsies and Comorbidities. African Challenges and Reflections.* KEMRI/Wellcome Trust Research Programme: Kilifi, Kenia, Africa. <*skariuki@kemri-wellcome.org*>

9:15AM to 9:45AM

3. Elizabeth Dogbey. School of Pharmacy, Department of Pharmacology and Toxicology, University of Ghana, Accra, Ghana, Africa. *Integrating Traditional Healers Knowledge and Ethnopharmacology with Contemporary Neurology in the Epilepsies*. *<knoxemaliz2002@yahoo.com>*

9:45AM to 10:15AM
COFFEE-BREAK

10:15AM to 10:45AM
4. Bruno Benitez. Harvard Medical School - Beth Israel Deaconess Medical Center Broad Institute - MIT & Harvard. Boston, USA. *A Multi-omic Approach Applied to Alzheimer's Disease and Epilepsy*. *<bbenitez@bidmc.harvard.edu>*
10:45AM to 11:15M
5. Sergio Nojiri. Ribeirão Preto Law School. University of São Paulo, Ribeirão Preto, Brasil. *Neuroscience, Law and the Epilepsies. <nojiri@usp.br>*

11:15AM to 12:15AM
GENERAL DISCUSSION

12:15AM to 2:00PM
LUNCH-BREAK

20th September
Second Round Table: Afternoon Session
2:00PM to 6:00PM
From Bench to Bedside: New Techniques for Analyzing Behavior and Correlated Brain Activity.
Chair: Maria Elisa Calcagnotto; Co-Chair: Patrick Forcelli

2:00 PM to 2:30PM
1. **Maria Emília Rodrigues de Oliveira Thais.** Departamento de Neurologia. Universidade Federal de Santa Catarina. Florianópolis, Brasil. *Theory of Mind in the Epilepsies* *<mariaemiliathais@me.com>*
2:30 PM to 3:00PM
2. Claudia Mauer Morelli. *From Zebra fish to Epileptic seizures in Patients: The Power of Translation*. Universidade Estadual de Campinas, Campinas, Brasil. *<cmorelli@unicamp.br>*
3:00 PM to 3:30PM
3. **Aline Pansani.** Department of Physiological Sciences - Biological Sciences Institute, Universidade Federal de Goiás. Goiás, Brasil. *From Breath to Beat: The Cardiorespiratory Factors in SUDEP <alineppansani@gmail.com>*

3:30 PM to 4:00PM
COFFEE-BREAK

4:00 PM to 4:30PM
4. **Hana Kubová.** Department of Developmental Epileptology, Institute of Physiology, Czech Academy of Sciences, Prague, Czech Republic. *Status Epilepticus: Lessons from Laboratory Animals. <kubova@biomed.cas.cz).*
4:30 PM to 5:00PM

5. **Maria Elisa Calcagnotto.** Universidade Federal do Rio Grande do Sul. Porto Alegre, Brasil. *Synaptic and Brain Oscillation Patterns in Misshapen Neuronal Networks* *<elisa.calcagnotto@ufrgs.br>*

5:00 PM to 6:00PM
GENERAL DISCUSSION

21st September
8:15AM to 12:15AM
Third Round Table: Morning Session
Channels, Neurons, Glia and Vascular Protagonists of Complex Epileptogenic Networks.
Chair: Prof. Victor R. Santos; Co-Chair: Vera Cristina Terra

8:15AM to 8:45AM
1. **Olagide Wagner de Castro.** *Crack Cocaine and Epilepsy: What We Do Not Know Yet?* Universidade Federal de Alagoas. Maceió, Brasil. *<olagidewww@gmail.com>*
8:45AM to 9:15AM
2. **Patrick Forcelli.** Georgetown University, Washington DC, USA. *Basal Ganglia-Brainstem Networks in Epilepsy. <paf22@georgetown.edu>*
9:15AM to 9:45AM
3. **Jenny Hsieh.** *Stem Cell Approaches to Understanding Acquired and Genetic Epilepsies.* Univ Texas San Antonio, San Antonio, USA. <*jenny.hsieh@utsa.edu*>

9:45AM to 10:15AM
COFFEE-BREAK

10:15AM to 10:45AM
4. **Cristina Ruedell Reschke**. RCI University of Medicine and Health Sciences, School of Pharmacy and Biomolecular Sciences, Dublin, Ireland. *The Molecular Rhythms of Epileptogenesis. <cristinarreschke@rcsi.com>*
10:45AM to 11:15AM
5. Alberto Lazarowski. Faculty of Pharmacy and Biochemistry, University of Buenos Aires. Buenos Aires, Argentina. *Ferroptosis in the Epileptic Context and Risk of SUDEP*.
11:15AM to 12:15AM
GENERAL DISCUSSION

12:15AM to 2:00PM
LUNCH-BREAK

21st September
2:00PM to 6:00PM
Fourth Round Table: Afternoon Session
Epilepsy and Neuropsychiatric Comorbidities. Challenges for Diagnosis, Treatment and the Concept of Pharmacoresistance.
Chair: Prof. Luisa Rocha; Co-Chair: Prof. Alan Talevi

2:00PM to 2:30PM

1. Vera Cristina Terra. Comprehensive Care Center for Epilepsy –EPICENTRO, Nossa Senhora das Graças Hospital, Curitiba, Brasil. *Pseudoseizures, Seizures and Epilepsies: How Can we Objectively Differentiate them <v.c.terra@gmail.com>*

2:30PM to 3:00AM

2. **Luisa Rocha** - Universidad Autónoma de Mexico. Ciudad de Mexico, Mexico. *Pharmacoresistance in the Epilepsies: Clues from Animal Models and Resected Human Tissue*. *<lrocha@cinvestav.mx>*

3:00PM to 3:30PM

3. Alan Talevi. Laboratorio de Investigación y Desarrollo de Bioactivos
Universidad de La Plata. La Plata, Argentina. *"The Underestimated Association Between Drug Resistant Epilepsies and Neuropsychiatric Comorbidities" <atalevi@biol.unlp.edu.ar>*

3:30PM to 4:00PM

COFFEE-BREAK

4:00PM to 4:30PM

4. Idrish Ali. - Monash University. Melbourne, Australia. "*Neuroinflammation as Biomarker and Preventive Option for Epilepsy and Neurobehavioural Consequences". <idrish.ali@monash.edu*

4:30PM to 5:00PM

3. Peter A. Tass. Department of Neurosurgery, Stanford University School of Medicine, Stanford, USA. *Vibrotactile Fingertip Stimulation for the Treatment of Parkinson's Disease and Possible Applications to Epilepsy. <ptass@stanford.edu*

5:00PM to 6:00PM

GENERAL DISCUSSSION

22st September

8:15AM to 12h15AM

Fifth Round Table: Morning Session

Neuropathology, Inflammation, Connectomes, Negative and Positive Neuroplasticity

Chair: Cristina Ruedell Reschke; Co-Chair: Olagide Wagner de Castro

8:15AM to 8:45AM

1. **Rossella Di Sapia.** Laboratory of Experimental Neurology - Mario Negri Institute for Pharmacological Research. Milano. Italy. *Neuroactive Peptides and Inflammatory Mediators in the Etiopathogenesis of Seizures and their Impact in the Mechanisms of Pharmacoresistance. <rossella.disapia@marionegri.it>*

8:45AM to 9:15AM

2. **Sandra Orozco.** Medical Research Unit in Neurological Diseases, Specialty Hospital, National Medical Center, Ciudad de Mexico, Mexico. *Assessment of Neuroinflammation in Drug - Resistant Epilepsy: The Role of Autoimmunity. <sorozco5@hotmail.com>*

9:15AM to 9:45AM

3. Victor Rodrigues Santos. Universidade Federal de Minas Gerais. Belo Horizonte, Brasil. *The Treatment of Immature Brain Seizures and Epileptogenesis from the Viewpoint of Cannabinoids <victorrsantos@gmail.com>*

9:45AM to 10:15AM
COFFEE-BREAK

10:15AM to 10:45AM
4. **Maira Licia Foresti** - Universidade Federal de São Paulo. São Paulo, Brazil. *Modeling of Post-Traumatic Epilepsy and Experimental Research aimed at its Prevention <mairalicia@yahoo.com.br>*

10:45AM to 11:15AM
5. **Efrain Buriticá.** Universidad del Valle. Cali, Colombia. *On Post-Traumatic Epilepsies and other Drug-Resistant Epilepsies: In the Search for Biomarkers in Surgical Human Brain Tissue <efrain.buritica@correounivalle.edu.co>*

11:15AM to 12:15AM
GENERAL DISCUSSION

12:15AM to 2PM
LUNCH-BREAK

22st September
2:00PM to 6:00PM
Sixth Round Table: Afternoon Session
Paradigm Shifts towards Integrative Views in the Research of the Epilepsies and Neuropsychiatric Comorbidities
Chair: Prof. Marcio Flávio Dutra Moraes; Co-Chair: Hana Kubová

2:00PM to 2:30PM
1. **Candi LaSarge.** Department of Anesthesia. Cincinnati Children's Hospital. University of Cincinnati. Cincinnati, USA. *mTOR Hyperactivity Initiates an Epileptogenic Cascade. <candi.lasarge@cchmc.org>*

2:30PM to 3:00PM
2. Ana Carolina Coan. Department of Neurology Universidade de Campinas - UNICAMP. Campinas. Brasil. *Mapping the Maze: Navigating the Complex Relationship of Epilepsy, White Matter Integrity, and Neurodevelopmental Impairment. <acoan@unicamp.br>*

3:00PM to 3:30PM
3. David-Ahmedt Aristizabal. Imaging and Computer Vision Group CSIRO Data61. Canberra, Australia. *Computer Vision for Understanding Patients' Behavior: A Focus on Epilepsy and other Motor Disorders. <david.ahmedtaristizabal@data61.csiro.au>*

3:30PM to 4:00PM
COFFEE-BREAK

4:00PM to 4:30PM
4. **Marcio F.D. Moraes.** University of Minas Gerais. Belo Horizonte, Brasil. *Changing a Localizationist Brain Architecture View for One of Temporally Organized Packages. The*

Concept of Coincidence Detectors instead of Integration-Response and its Impact in the Treatment of the Epilepsies. <marcionnc@gmail.com>

4:30PM to 5:00PM

5. Norberto Garcia-Cairasco. Ribeirão Preto School of Medicine. University of São Paulo. Ribeirão Preto, Brasil. *Challenges to Decipher the Main Intertwined Protagonists of Epileptogenesis and Comorbidities in a Complex Landscape of Semiology, Neuroanatomical Networks and their Neuroplastic Abnormal Activity. <ngcairas@usp.br>*

5:00PM-6:00PM
GENERAL DISCUSSION

22st September
5:45PM to 6:00PM
GENERAL REFLEXIONS/FINAL COMMENTARIES

6:00PM to 6:30PM
FINAL COMMENTARIES

6:30PM to 7:00PM
CLOSING REMARKS

7:00PM to 10:00PM
FAREWELL PARTY

Acknowledgements: To all the past and present members of the Neurophysiology and Experimental Neuroethology Laboratory (LNNE) at the Physiology Department at the Ribeirão Preto Medical School at the University of São Paulo, Brasil, to whom the current International Symposium **NEW***roscience* 2023 is dedicated, because of the 35th celebration of the foundation of LNNE. As in other opportunities, in addition to the small group of Faculty members involved in the organization of this event, LNNE members, both students and technical staff, are those who compose the various committees responsible for this enormous endeavor.

To all the members of the Departments of Physiology, Psychobiology and Neuroscience and Behavioral Science and their corresponding Graduate Programs, respectively, in Physiology, Psychobiology and Neurology/Neuroscience, for their continuous support to the LNNE Academic, Scientific and Outreach (*Neuro-Art*) activities, over almost four decades. To the Brazilian Research Foundations FAPESP, CNPq, CAPES, FAEPA for their financial support with grants and fellowships. Thanks always to the Liga Brasileira de Epilepsia (LBE), Sociedade Brasileira de Fisiologia (SBFis), Sociedade Brasileira de Neurociências e Comportamento (SBNeC), Federação Brasileira de Sociedades de Biologia Experimental (FESBE), Colegio Colombiano de Neurociencias (COLNE), International Brain Research Organization (IBRO), Dana Foundation for Brain Initiatives - Brain Awareness Week.

To **Professor Steve C. Schachter**, from University of Harvard, Founder and former *Editor-in-Chief* of *Epilepsy & Behavior* (E&B) - Elsevier. Thanks to his vision and generosity, we developed the **NEW***roscience* series of Special Issues of E&B, since 2008, followed every five years by the successful volumes **NEW***roscience* 2013, 2018.

The current International Symposium **NEW***roscience* 2023 and the associated *Special Issue* of *Epilepsy & Behavior* with 30 articles/reviews written by the invited speakers (15 female scientists and 15 male scientists from the 5 continents; details in the program) of the Conference are also supported by **Professor Marco Mula** from University of London as the current *Editor-in-Chief* of *Epilepsy & Behavior* and obviously by Elsevier.

This event is a realization of the ***Science, Arts, Education and Society - ScienArtES - Network*** from the Institute for Advanced Studies (IEA) at the Campus of Ribeirão Preto at the University of São Paulo. A final thanks to the whole team of the IEA who made this event possible and available throughout its site, digital and social media channels.

Observation: For guidance for those who will be coming for the first time to our event, please, take a look at the previous *Special Issue of E&B* associated with the International Symposium **NEW***roscience* 2018 at the following link:

https://www.sciencedirect.com/journal/epilepsy-and-behavior/vol/121/part/PB

CELEBRATING WOMEN IN SCIENCE & ART

1. Best Scientific Poster in Epilepsy. ***Cassidy Megan, the Founder of the Purple Day, Award.***
2. Best Scientific Poster in Neuroscience. ***Rosalind Franklin, the Mother of the DNA, Award.***
3. Best Poster in Neuroscience & Arts. ***Nise da Silveira, the Rebel Psychiatrist, Award.***

THE DIPLOMA LEONARDO DA VINCI AWARD

- Given to LNNE PhD Students Graduated from 2013 to 2018.

6:30PM – 7:00PM | Closing Remarks

SCIENTIFIC COMMITTEE

- ***Norberto Garcia-Cairasco***
- ***Marcio F.D. Moraes***

7:00PM| ***Farewell Party***

International Symposium

NEW*roscience* 2023

"Epilepsy and Neuropsychiatric Comorbidities: From Semiology to Neuroplasticity of Vulnerable/Resilient Networks, to Personalized Therapies"

INVITED SPEAKERS

NORBERTO GARCIA-CAIRASCO

UNIVERSITY OF SÃO PAULO – RIBEIRÃO PRETO, BRAZIL.
Physiology/Neuroscience & Behavioral Sciences Departments. Ribeirão Preto School of Medicine.

KEYNOTE SPEECH

LECTURE: ***PROMOTING PARADIGM SHIFTS IN EPILEPTOLOGY OVER FOUR DECADES. THE NEUROPHYSIOLOGY AND EXPERIMENTAL NEUROETHOLOGY LABORATORY (LNNE) HISTORICAL CONTRIBUTIONS IN BRAZIL, LATIN AMERICA, AND THE WORLD***

DINESH UPADHYA.

DEPARTMENT OF ANATOMY, KASTURBA MEDICAL COLLEGE, MANIPAL INDIA.
Associate Professor and Coordinator
Centre for Molecular Neurosciences

Round Table 1 - ***What can we learn from the Combination of Orthodox Scientific and Ancestral Epistemologies, Multiple Knowledges, as applied to Epilepsy and Neuropsychiatric Comorbidities?***

LECTURE: *JOINING AYURVEDIC MEDICINE AND CONTEMPORARY NEUROSCIENCE IN EPILEPTOLOGY RESEARCH.*

Dr Dinesh Upadhya (M.SC, PhD); Dr Shripathi Adiga (MD in Ayurveda)

Epilepsy, a chronic non-communicable disease of the brain, is one of the most common neurological diseases globally, that affects people of all ages. The existence of medical, neurological, psychiatric, and cognitive comorbidities has always undermined the available advanced treatment strategies for epilepsy. New-generation antiepileptic drugs being less successful in completely controlling the seizures and observance of complex diseases, including drug-resistant cases, have provided scope for integrating and incorporating the therapeutic modalities of Ayurveda, the ancient Indian art of holistic medicine, in the effective management of epilepsy. Epilepsy can be correlated to Apasmara, described in the classics of Ayurveda as the transient appearance of unconsciousness with loathsome expression due to derangement of memory, intelligence, and mind. The multifaceted therapeutic approach of Ayurveda, which involves pharmacologic and nonpharmacologic measures, purificatory and pacifying procedures, herbal and herbo-mineral formulations, disease, and host-specific approaches, have enhanced the potential of not only relieving symptoms but also modifying the pathophysiology of the disease. Newer paradigms of research in Ayurveda, along with holistic and integrative approaches with contemporary medicine, can benefit the existing healthcare system and impact future healthcare management of epilepsy.

SYMON KARIUKI.
KEMRI/WELLCOME TRUST RESEARCH PROGRAMME: KILIFI, KE.

ROUND TABLE 1 - ***WHAT CAN WE LEARN FROM THE COMBINATION OF ORTHODOX SCIENTIFIC AND ANCESTRAL EPISTEMOLOGIES, MULTIPLE KNOWLEDGES, AS APPLIED TO EPILEPSY AND NEUROPSYCHIATRIC COMORBIDITIES?***

LECTURE: INTEGRATING TRADITIONAL AND COMPLEMENTARY MEDICINE IN THE TREATMENT OF EPILEPSIES AND COMORBIDITIES. AFRICAN CHALLENGES AND REFLECTIONS

Traditional and complementary medicine (T&CM) encompasses products, practices and practitioners that do not form part of conventional treatment and are not an integral part of the main health care systems. They are very common in the management of epilepsy and its associated complications, particularly in low- and middle-income countries (LMIC). For instance, in population survey in Africa, over 70% of people with epilepsy had visited a traditional health practitioner before the survey. Accessibility, cultural appropriateness, and pragmatic explanations and practices were some of the reasons the communities preferred T&CM over biomedical medicine. There is growing interest in T&CM worldwide because of its economic potential, concerns and safety and quality and potential for integration into the health care systems. There is urgent need to develop and implement national TM&CM policies and programmes aimed at expanding the knowledge base and providing guidance on regulatory and quality assurance standards. However, LMIC continues to lag in implementation of these policies and guidelines, especially the areas of research and development and regulation of T&CM practice. Working with stakeholders, countries are advised to assess their own national situations in relation to T&CM, and then come up with practical solutions to these realities. For instance, surveying benefits and risks of T&CM in the management of epilepsy in the local context and using this to promote appreciation of a role for T&CM, which will ease integration into the main health systems.

ELIZABETH DOGBEY

School of Pharmacy, Department of Pharmacology and Toxicology, University of Ghana.

ROUND TABLE 1 - ***WHAT CAN WE LEARN FROM THE COMBINATION OF ORTHODOX SCIENTIFIC AND ANCESTRAL EPISTEMOLOGIES, MULTIPLE KNOWLEDGES, AS APPLIED TO EPILEPSY AND NEUROPSYCHIATRIC COMORBIDITIES?***

LECTURE: INTEGRATING TRADITIONAL HEALERS KNOWLEDGE AND ETHNOPHARMACOLOGY WITH CONTEMPORARY NEUROLOGY IN THE EPILEPSIES

Traditional medicine is a comprehensive healthcare system that comprises specialties such as spiritualism, divination, and herbalism. It is believed that epilepsy and neuropsychiatric comorbidities have both natural and supernatural causes.

Plants have been used for decades for the treatment of epilepsy and neuropsychiatric comorbidities. Unlike contemporary medicine which comprises pure compounds, and applies a systematic way of diagnosis and treatment, plant medicine is administered as a whole concoction that may contain cytotoxic substances and neurotoxins that are harmful to the body; which is the main drawback in traditional medicine practice. But contemporary medicine also comes with downsides including, cost and side effects, making the preference for herbal medicine by low-income individuals high.

In recent times traditional medicine is being integrated into contemporary treatment where the compound responsible for the activity is isolated, screened, and taken through several stages of clinical trials. With cutting-edge research, this integration can be tailored toward personalized treatment. Where different lead can be identified for the treatment of the different types of epilepsy and neuropsychiatric comorbidities based on individual symptoms, considering the variety of plants used traditionally for treatment.

Future prospects are quite bright if traditional medicine is formally acknowledged and integrated into Western medicine.

Bruno A. Benitez

HARVARD MEDICAL SCHOOL - BETH ISRAEL DEACONESS MEDICAL CENTER. BROAD INSTITUTE - MIT & HARVARD

ROUND TABLE 1 - ***WHAT CAN WE LEARN FROM THE COMBINATION OF ORTHODOX SCIENTIFIC AND ANCESTRAL EPISTEMOLOGIES, MULTIPLE KNOWLEDGES, AS APPLIED TO EPILEPSY AND NEUROPSYCHIATRIC COMORBIDITIES?***

A Multi-omic Approach Applied to Alzheimer's Disease and Epilepsy

The "omics" technologies are generating highly detailed molecular atlases for neurological diseases, including Alzheimer's disease (AD) and Epilepsy. However, a single omic technology analysis captures changes in only one component of the biological cascade. Integrating multiple omic modalities is a powerful tool for identifying complex diseases' molecular subtypes.

Methods: We integrated transcriptomic (~60,000 transcripts), proteomic (1,092 proteins), metabolomic, and lipidomic (627 metabolites) profiles of AD cases (n=462) and controls (n=139) from multiple cortical regions and three different cohorts. We use machine learning techniques, digital deconvolution, and traditional statistical analysis to integrate and analyze multiple omics (survival analysis, differential expression, cell type-specific effect, and cell proportions inference analysis).

Results: We identified a molecular profile associated significant cognitive impairment at the time of death, shorter survival, higher markers of neurodegeneration and astrogliosis, and reduced levels of metabolomic profiles. This profile shows a significant dysregulation of synaptic genes (p=1.0×10-15) in multiple cortical regions. Subsequent AD staging, pathways, co-expression, and CSF survival analyses identified synaptic genes dysregulated at different stages of AD and associated with dementia progression.

Conclusions: Our results demonstrate that molecular profiles of AD with clinical and biological relevance can be found by integrating multiple omic data.

SERGIO NOJIRI

RIBEIRÃO PRETO LAW SCHOOL. UNIVERSITY OF SÃO PAULO, BRASIL. ***PROFESSOR DE GRADUAÇÃO E PÓS-GRADUAÇÃO DA FDRP-USP***

ROUND TABLE 1 - *What can we learn from the Combination of Orthodox Scientific and Ancestral Epistemologies, Multiple Knowledges, as applied to Epilepsy and Neuropsychiatric Comorbidities?*

LECTURE: NEUROSCIENCE, LAW AND THE EPILEPSIES

The theme of epilepsy is little studied by scholars of Brazilian law. A quick internet search demonstrates an absolute lack of interest on the part of our jurists in the subject. This article intends, albeit in a small proportion, to narrow this gap. It is interesting to note that in the 19th and early 20th centuries, epilepsy was one of the most investigated disorders in forensic psychiatry and psychology. There was the figure of the "epileptic criminal", considered extremely violent and capable of committing brutal acts. The theory of this criminality was duly refuted in the 20th century. This article intends to explore this and other theories of epileptic criminality from a renewed vision of neurosciences.

MARIA EMÍLIA RODRIGUES DE OLIVEIRA THAIS

DEPARTAMENTO DE NEUROLOGIA. UNIVERSIDADE FEDERAL DE SANTA CATARINA - BRASIL.

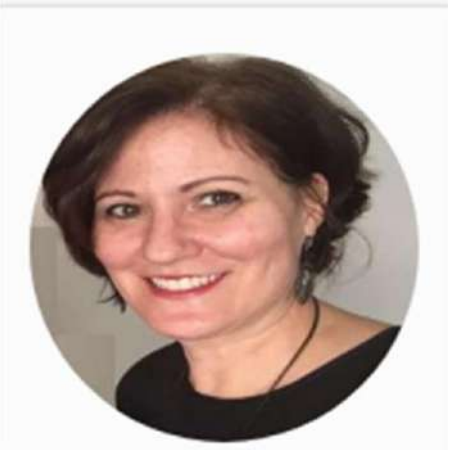
ROUND TABLE 2 - FROM BENCH TO BEDSIDE: NEW TECHNIQUES FOR ANALYZING BEHAVIOR AND CORRELATED BRAIN ACTIVITY.

LECTURE: THEORY OF MIND IN THE EPILEPSIES

Epilepsy is characterized by recurrent, chronic and unprovoked seizures. Epilepsy has a significant negative impact on quality of life of patients even if seizures are well controlled. In addition to the distress caused by seizures, patients with epilepsy may suffer from cognitive impairment with serious social consequences such as poor interpersonal relationships, loss of employment, and reduced social networks.

Pathological changes and functional connectivity abnormalities observed in patients with epilepsy can disrupt the neural network responsible for theory of mind. Theory of mind is the ability to attribute mental states to other people (intentions, beliefs, and emotions). It is a complex aspect of social cognition and includes cognitive and affective constructs.

In recent years, numerous studies, including meta-analysis assessed the relationship between social cognition, including theory of mind, in patients with epilepsy and suggests impairment in this domain. Interventions targeting theory of mind can be potentially helpful to improve the quality of life of patients with epilepsy.



Claudia Mauer Morelli

Universidade Estadual de Campinas, SP, Brasil. Professora Associada do Departamento de Medicina Translacional, Faculdade de Ciências Médicas, UNICAMP e Assessora de Gabinete da Pró-Reitoria de Pós-graduação da UNICAMP.

ROUND TABLE 2 - FROM BENCH TO BEDSIDE: NEW TECHNIQUES FOR ANALYZING BEHAVIOR AND CORRELATED BRAIN ACTIVITY.

LECTURE: From Zebrafish to Epileptic Seizures in Patients: The Power of Translation

This presentation aims to highlight the attributes of zebrafish for epilepsy and seizure studies. Zebrafish (Danio rerio) is a valuable and widely accepted model in research due to its conserved molecular and genetic pathways with humans, cost-effectiveness, and translational potential. High-throughput drug screening using zebrafish larvae is a powerful approach for identifying compounds with anti-seizure properties. Zebrafish larvae exhibit behaviors indicative of seizure activity, making them an effective tool for screening potential therapeutic compounds. Furthermore, by generating zebrafish models with specific genetic mutations associated with epilepsy, it is possible to study the effects of these mutations on seizure development and response to different treatments leading to more effective and tailored treatments for patients. Additionally, zebrafish models allow for the evaluation of drug safety and potential side effects, addressing critical concerns in the development of new treatments. In summary, zebrafish models offer a powerful and versatile platform for epilepsy and seizure studies, encompassing mechanistic investigations, drug screening, and personalized medicine approaches.

ALINE PANSANI

DEPARTMENT OF PHYSIOLOGICAL SCIENCES - BIOLOGICAL SCIENCES INSTITUTE, UNIVERSIDADE FEDERAL DE GOIÁS.
Professora Adjunta.

ROUND TABLE 2 - FROM BENCH TO BEDSIDE: NEW TECHNIQUES FOR ANALYZING BEHAVIOR AND CORRELATED BRAIN ACTIVITY.

LECTURE: FROM BREATH TO BEAT: THE CARDIORESPIRATORY FACTORS IN SUDEP

Sudden Unexpected Death in Epilepsy (SUDEP) represents one of the primary causes of death directly associated with epilepsy. Approximately 1 in 1,000 people with epilepsy die from SUDEP each year. As a complex phenomenon, the underlying mechanisms of SUDEP remain unknown. However, there is increasing evidence suggesting an important role for cardiac and respiratory alterations in this context. These include cardiac arrhythmias, cardiac and autonomic changes, central and obstructive apnea, and disruptions in both arousal mechanisms and the chemoreflex.
Therefore, this lecture will address the scientific evidence, both clinical and experimental, that links cardiac and respiratory dysfunctions to higher risk and even as a cause of SUDEP. The aim is to deepen understanding of this complex topic, which profoundly impacts those living with epilepsy.

HANA KUBOVÁ

**Department of Developmental Epileptology,
Institute of Physiology, Czech Academy of Sciences,
Prague, Czech Republic.**

ROUND TABLE 2 - FROM BENCH TO BEDSIDE: NEW TECHNIQUES FOR ANALYZING BEHAVIOR AND CORRELATED BRAIN ACTIVITY.

LECTURE: THE BEHAVIOURAL OUTCOME OF STATUS EPILEPTICUS –LESSONS FROM LABORATORY ANIMALS

Status epilepticus (SE) is the brain insult most frequently used to induce epilepsy in all age groups of laboratory rodents. It triggers epileptogenesis in majority of animals, causes brain damage and permanent behavioral abnormalities. The consequences of SE are dependent upon age, the model used, and SE duration. The outcome of experiments with this model is however highly affected by experimental conditions and methods used to assess selected parameters. Of particular importance is experimental design in a case of behavioral testing. Rodent behavioral testing has proven difficult and very labor intensive as well as sensitive to environmental factors and test results may vary depending on many variables that are frequently reported insufficiently by experimenters. This makes comparison of results across laboratories complicated or even impossible. Although electrophysiology, neuropathology and molecular genetics represent key tools for understanding mechanisms underlying development of epilepsy and its comorbidities, behavior represents the final output of the CNS.
Therefore standardization of laboratory approaches, harmonization of scientific methodology, and improvement in data collection and reporting can improve the comparability of data among laboratories as well as the translation of preclinical data to clinical studies.

MARIA ELISA CALCAGNOTTO

UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL - UFRGS. BRASIL.

ROUND TABLE 2 - FROM BENCH TO BEDSIDE: NEW TECHNIQUES FOR ANALYZING BEHAVIOR AND CORRELATED BRAIN ACTIVITY.

LECTURE: SYNAPTIC AND BRAIN OSCILLATION PATTERNS IN MISSHAPEN NEURONAL NETWORKS

Brain structural and functional abnormalities are a continuum in epilepsy. Neuronal diversity and functional spatiotemporal dynamics in the network are key points in establishing the normal connectivity in the brain that develops through a sequence of coordinated events and electrical activity. Pyramidal neurons have considerable connectional and processing complexity in brain circuits. These highly specialized neurons in the network also show vulnerabilities and can contribute to epileptogenesis. Pyramidal cells are crucial but not the only cells participating in hyperexcitability; glial cells are also important for synaptic plasticity during epileptogenesis. In addition, GABAergic interneurons are implicated in different aspects of ictogenesis and epileptogenesis. GABAergic synapses at different pyramidal cell domains and vice-versa, coordinated by synapse-driven activity patterns, contribute to spontaneous network oscillations in the brain. A large diversity of cells operates in intricate circuits formed by synapses at distinct cellular domains and at different times to encode, process, store, and send information, contributing to marked synaptic remodeling. Aberrant morphology, synaptic organization, and plasticity of the neuronal network, can recruit distinct microcircuits at different locations at specific times, which could alter synchronicity, inducing abnormal oscillations and consequent behavior, resulting in epilepsy and neuropsychiatric disorders.

OLAGIDE WAGNER DE CASTRO

UNIVERSIDADE FEDERAL DE ALAGOAS - UFAL.

ROUND TABLE 3 - CHANNELS, NEURONS, GLIA AND VASCULAR PROTAGONISTS OF COMPLEX EPILEPTOGENIC NETWORKS

LECTURE: CRACK COCAINE AND EPILEPSY: WHAT WE DO NOT KNOW YET?

Crack cocaine is a highly addictive and dangerous substance that can trigger or worsen epileptic seizures. However, the molecular mechanisms underlying crack cocaine's effects on epilepsy are not fully elucidated. Recent evidence involves the inhibition of acetylcholinesterase (AChE) by crack cocaine, increasing the levels of acetylcholine in the brain, leading to overstimulation of cholinergic receptors and neuronal excitability. Another alarming factor is the exposure of fetuses to crack cocaine during the gestational period. Studies indicate that crack cocaine and its metabolites cross through the placenta, causing premature delivery, fever, irritability, sweating, and seizures in the first months of life. In children, the effects of crack cocaine have been associated with cognitive impairments, verbal difficulties, aggression, and depression, as well as an increased risk of epileptic seizures, including Status Epilepticus (SE) in adulthood. In animal models crack cocaine exposure during the gestational period leads to an increased propensity to anxiety and depression, long-term memory deficit and reduction of the threshold of epileptic seizures associated with neuronal death, which predispose crack cocaine babies to develop epilepsy and other neuropsychological disorders. In the International Symposium NEWroscience, we will address the latest research on the impact of crack cocaine on animal models and their offspring. Additionally, will be discussed the mechanisms and consequences of direct and prenatal exposure to crack, and how they relate to the development of epilepsy and other neurological disorders. The aim of the discussion is to provide a comprehensive overview of the current state of knowledge and future directions in this research field.

PATRICK FORCELLI

GEORGETOWN UNIVERSITY, USA.

ROUND TABLE 3 - CHANNELS, NEURONS, GLIA AND VASCULAR PROTAGONISTS OF COMPLEX EPILEPTOGENIC NETWORKS

LECTURE: OPTOGENETIC AND CHEMOGENETIC JOINT APPROACHES CAN SOLVE EPILEPSY AND NEUROPSYCHIATRIC COMORBIDITIES?

The basal ganglia have, for over 40 years, been recognized as a choke point in seizure networks. Focal manipulations within basal ganglia targets suppress seizures in a wide range of experimental models. Here I present an overview of our recent and ongoing studies examining focal modulation and monitoring of activity within the striatum, substantia nigra, superior colliculus and pedunculopontine nucleus in the control of experimental seizures in rodent models. I also present data extending this to a non-human primate model. Together, these studies aim to elaborate the circuit mechanisms by which basal ganglia manipulations control seizures.

JENNY HSIEH
UNIV TEXAS SAN ANTONIO, US.

ROUND TABLE 3 - CHANNELS, NEURONS, GLIA AND VASCULAR PROTAGONISTS OF COMPLEX EPILEPTOGENIC NETWORKS

LECTURE: STEM CELL APPROACHES TO UNDERSTANDING ACQUIRED AND GENETIC EPILEPSIES

The Hsieh lab focuses on the mechanisms that promote neural stem cell self-renewal and differentiation in embryonic and adult brain. Using mouse models, video-EEG monitoring, viral techniques, and imaging/electrophysiological approaches, we elucidated many of the key transcriptional/epigenetic regulators of adult neurogenesis and showed aberrant new neuron integration in adult rodent hippocampus contribute to circuit disruption and seizure development. Building on this work, I will present our recent studies describing how Ca2+ activity mediated genes regulates the production of aberrant adult-born granule cells.
Furthermore, we are using human induced pluripotent stem cells and brain organoid models as approaches to understand brain development and disease. Mutations in one gene, Aristaless-related homeobox (ARX), are of considerable interest since they are known to cause a common spectrum of neurodevelopmental disorders including epilepsy, autism, and intellectual disability. We have generated cortical and subpallial organoids from patients with poly-alanine expansion mutations in ARX. To understand the nature of ARX mutations in the organoid system, we are currently performing cellular, molecular, and physiological analyses. I will present these data to gain a comprehensive picture of the pathogenesis of ARX mutations, which has the potential to impact the diagnosis and care of patients with ARX-related epilepsies.

CRISTINA RUEDELL RESCHKE
RCSI UNIVERSITY OF MEDICINE AND HEALTH SCIENCES, SCHOOL OF PHARMACY ANDBIOMOLECULAR SCIENCES, DUBLIN, IRELAND.

ROUND TABLE 3 - CHANNELS, NEURONS, GLIA AND VASCULAR PROTAGONISTS OF COMPLEX EPILEPTOGENIC NETWORKS

LECTURE: THE MOLECULAR RHYTHMS OF EPILEPTOGENESIS?

Although features of epilepsy display strong circadian variation and >80% of protein coding genes display circadian rhythmicity, the chronobiology of epilepsy remains poorly understood at molecular level.
Circadian rhythms are present in all mammalian cells and endogenously control behavioural/physiological processes over 24-hours period. They are regulated by both external factors (light/dark) and internal cues (molecular clocks). Clock genes are rhythmically expressed throughout the brain and are critical to regulate brain homeostasis and in disease.
The epileptogenesis process is associated with large-scale changes in gene expression, which contribute to the remodeling of brain networks permanently altering excitability. These impactful changes are largely regulated and under strong circadian variation. Here, I will systematically address the dysregulation in diurnal rhythms during epileptogenesis providing insights into potential mechanisms that underlie changes in gene expression and rationale for pursuing the study of the molecular clock in epilepsy.

ALBERTO LAZAROWSKI

FACULTY OF PHARMACY AND BIOCHEMISTRY, UNIVERSITY OF BUENOS AIRES, ARGENTINA.

ROUND TABLE 4 - EPILEPSY AND NEUROPSYCHIATRIC COMORBIDITIES. CHALLENGES FOR DIAGNOSIS AND PHARMACORESISTANCE.

LECTURE: FERROPTOSIS IN THE EPILEPTIC CONTEXT AND RISK OF SUDEP

Iron (Fe) is a vital element for almost all organisms due to its ability to donate and accept electrons with relative ease. It serves as a cofactor for many proteins and enzymes necessary for the proper use of oxygen and energy generation, as well as its deregulation is related to the processes of oxidative stress and iron-mediated cell death called FERROPTOSIS. It is a new type of cell death that was discovered in recent years and is usually accompanied by a large amount of iron accumulation and lipid peroxidation during the cell death process. Refractory Epilepsy (RE) occurs in approximately 30-40% of patients with epilepsy and has a higher risk of sudden unexpected death in epilepsy (SUDEP). According with seizures are considered hypoxic-ischemic episodes that trigger intracellular oxidative stress, recent studies showed that repetitive spontaneous seizures can be related to an increase in oxidative stress and reactive oxygen derivatives (ROS) production in a hypoxia inducible factor 1 alpha (HIF-1) dependent manner. This process causes lipid peroxidation, protein oxidation, and destruction of nuclear genetic material, enzyme inhibition, and cell death with an increase of intracellular free iron (Fe2+) concentration. Repetitive tonic-clonic seizures (GTCS) are the main risk factor of SUDEP. The hypoxic stress induced by seizure results in neurodegeneration with iron accumulation as well as cardiogenic dysfunctions related to Iron Overload and Cardiomyopathy (IOC). ROS production, severe lipid peroxidation can be an effective inducer of the named "epileptic heart" (EH), which is characterized by altered autonomic function and a high risk of malignant or fatal bradycardia. Our studies demonstrated that recurrent experimental seizures induce in cardiomyocytes: HIF-1 activation, P-glycoprotein overexpression, low expression of Inwardly Rectifying Potassium (Kir) Channesl (Kir), hemosiderin precipitation, and functionally the developing of long Q-T interval, severe bradycardia associated with high spontaneous death ratio. We postulate that severe seizures induce systemic hypoxia and heart FERROPTOSIS associated with SUDEP. We propose that inhibition of FERROPTOSIS with ROS scavenger's, iron chelators, antioxidants, could provide reduce epileptic dependent neurodegeneration as well as Iron Overload and Cardiomyopathy (IOC) associated with SUDEP risk, by heart Ferroptosis protection.

VERA CRISTINA TERRA

EPICENTRO, NOSSA SENHORA DAS GRAÇAS HOSPITAL, CURITIBA, BRAZIL.

ROUND TABLE 4- EPILEPSY AND NEUROPSYCHIATRIC COMORBIDITIES. CHALLENGES FOR DIAGNOSIS, TREATMENT AND THE CONCEPT OF PHARMACORESISTANCE.

LECTURE: PSEUDOSEIZURES, SEIZURES AND EPILEPSIES: HOW CAN WE OBJECTIVELY DIFFERENTIATE THEM?

In this presentation it will be discussed that since ancient times, several mythical, non-natural explanations, either of demons or blessings were used to explain paroxysmal events with the generic names of fits, convulsions, or seizures. Those entities were afterwards explained phenomenologically, either through mechanistic proposals and with the advent of the arsenal and knowledge of science and technology, with objective semiological definitions and electrophysiological or imaging correlates. Consequently, their classification as non-epileptic seizures (pseudo-seizures; psychogenic seizures), actual epileptic seizures, and epilepsies and their differential diagnosis was made possible. however, even in current times, there is a great deal of variations of presentations of these neurological and neuropsychiatric manifestations (other paroxysmal events, rather than seizures), that it is necessary to clarify what are the differences between them and how to proceed from the first diagnostic moment to the recognition that several of them can be expressed simultaneously as comorbidities and how much they influence or modify each other. It will be therefore highlighted here that ignoring those issues will deeply affect differential diagnosis, treatment and prognosis, with dangerous impacts such as lack of, or erroneous diagnosis and treatment, risks of sudden death, among others.

LUISA LILIA ROCHA ARRIETA

UNIVERSIDAD AUTÓNOMA DE MEXICO - MEXICO.

ROUND TABLE 4 - EPILEPSY AND NEUROPSYCHIATRIC COMORBIDITIES. CHALLENGES FOR DIAGNOSIS, TREATMENT AND THE CONCEPT OF PHARMACORESISTANCE

LECTURE: PHARMACORESISTANCE IN THE EPILEPSIES: CLUES FROM ANIMAL MODELS AND RESECTED HUMAN TISSUE

Drug-resistant epilepsy (DRE) is a condition in which there is persistence of seizures after "adequate trials of two tolerated and appropriately chosen and used ASM schedules" according to the International League Against Epilepsy (ILAE). This condition presents a high prevalence (about 30%) in patients with epilepsy in spite of the different anti-seizure medications used. At present, several hypotheses try to explain the drug-resistance condition in epilepsy. However, no single hypothesis can explain all cases of DRE. In addition, these hypotheses do not consider clinical conditions such as the age and gender of the patients and the high prevalence of comorbid psychiatric disorders associated with DRE.

This presentation will focus to discuss the relevance to consider different clinical factors in experimental models of DRE, including epigenetic and side effects induced by antiseizure medications that may facilitate the drug-resistant condition. Other important issue is the relevance to evaluate new therapeutic strategies in the brain tissue obtained from patients with DRE and submitted to epilepsy surgery. These actions will facilitate the identification of new antiseizure medications to control DRE.

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ALAN TALEVI

LABORATORIO DE INVESTIGACIÓN Y DESARROLLO DE BIOACTIVOS
UNIVERSIDAD DE LA PLATA, LA PLATA, ARGENTINA.

ROUND TABLE 4 - EPILEPSY AND NEUROPSYCHIATRIC COMORBIDITIES. CHALLENGES FOR DIAGNOSIS, TREATMENT AND THE CONCEPT OF PHARMACORESISTANCE.

LECTURE: THE UNDERESTIMATED ASSOCIATION BETWEEN DRUG RESISTANT EPILEPSIES AND NEUROPSYCHIATRIC COMORBIDITIES

The association between epilepsies and a wide array of comorbid disorders, including both CNS and non-CNS conditions has long been known. This may be related to neurobiological factors (e.g., common underlying pathophysiology), to the way that the experience of living and dealing with epilepsy affects a person's view of the world and the person's locus of control or, most likely, to the interplay between neurobiology and social setting. Several anticonvulsant drugs have proven positive effects on mood disorders, and several drugs used to treat mood disorders have positive effects on seizure control in severe drug resistant epilepsies (e.g., Dravet syndrome). The occurrence of comorbid disorders in patients with epilepsy is associated with a negative prognosis regarding the chances of achieving and sustaining a seizure-free status and, most interesting, some common comorbid disorders such as depression and anxiety are, like epilepsy, associated with abnormal neural networks and poor response to pharmacotherapy. The influence of the psychosocial context on mood disorders has been extensively recognized. Is it possible that its role in epilepsies has been underestimated?

IDRISH ALI

MONASH UNIVERSITY - MELBOURNE – AUSTRALIA

ROUND TABLE 4 - EPILEPSY AND NEUROPSYCHIATRIC COMORBIDITIES. CHALLENGES FOR DIAGNOSIS, TREATMENT AND THE CONCEPT OF PHARMACORESISTANCE.

LECTURE: STATU NEUROINFLAMMATION AS BIOMARKER AND PREVENTIVE OPTION FOR EPILEPSY AND NEUROBEHAVIORAL CONSEQUENCES.

There is a long and strong history of the involvement of inflammatory processes in epilepsy, both as a cause and consequence. Idrish will present some recent data relating to microglia depletion in newly validated model of self-sustained electrical SE in mice and its impact on the development of temporal lobe epilepsy and related behavioral impairments. He will then discuss the clinically translatable post-traumatic epilepsy model, he is using in his current DoD and R01 funded projects, where around 25-30% rats develop epilepsy following a fluid percussion injury. The animals also display chronic behavioral impairments, and these are related to the early neuroinflammatory cascade induced by the brain trauma.

Peter A. Tass

DEPARTMENT OF NEUROSURGERY, STANFORD UNIVERSITY SCHOOL OF MEDICINE, STANFORD, CA, USA.

ROUND TABLE 4 - EPILEPSY AND NEUROPSYCHIATRIC COMORBIDITIES. CHALLENGES FOR DIAGNOSIS, TREATMENT AND THE CONCEPT OF PHARMACORESISTANCE

LECTURE: VIBROTACTILE FINGERTIP STIMULATION FOR THE TREATMENT OF PARKINSON'S DISEASE AND POSSIBLE APPLICATIONS TO EPILEPSY.

Abnormally strong neuronal synchronization is a hallmark of parkinson's disease (pd), epilepsy and other brain disorders. For instance, in medically refractory pd patients, standard deep brain stimulation (dbs) reduces specific symptoms during stimulus delivery. Coordinated reset (cr)-dbs is a computationally developed technique which uses dedicated patterns of electrical stimuli to specifically counteract abnormal neuronal synchronization by desynchronization. The very goal of cr stimulation is to make neuronal populations unlearn abnormal synaptic connectivity patterns, in this way inducing long-lasting relief. Long-lasting therapeutic and desynchronizing cr-dbs effects were demonstrated in parkinsonian (mptp) monkeys and externalized pd patients. To provide a non-invasive alternative to dbs, we developed vibrotactile coordinated reset (vcr) fingertip stimulation. To this end, instead of administering electrical bursts through depth electrodes, we non-invasively deliver weak vibratory bursts in a cr mode to patients' fingertips. In pilot studies in pd patients, vcr fingertip stimulation turned out to cause a statistically and clinically significant reduction of mds-updrs iii scores together with a significant reduction of high beta (21-30 hz) power in the sensorimotor cortex, both observed after medication withdrawal. In addition, cr was successfully tested in vitro and in vivo in pre-clinical epilepsy models and will soon be tested in patients with epilepsy.

ROSSELLA DI SAPIA

LABORATORY OF EXPERIMENTAL NEUROLOGY - MARIO NEGRI INSTITUTE FOR PHARMACOLOGICAL RESEARCH. MILANO. ITALY.

ROUND TABLE 5 - NEUROPATHOLOGY, INFLAMMATION, CONNECTOMES, NEGATIVE AND POSITIVE NEUROPLASTICITY.

LECTURE: NEUROACTIVE PEPTIDES AND INFLAMMATORY MEDIATORS IN THE ETIOPATHOGENESIS OF SEIZURES AND THEIR IMPACT IN THE MECHANISMS OF PHARMACORESISTANCE.

The presentation will give an overview of the contribution of neuroinflammation to epilepsy showing evidence from epileptogenic human brain regions and animal models of acquired epilepsy. The talk will summarize cellular and molecular inflammatory targets identified for developing new antiepileptogenic therapies. The talk will focus on the IL-1 receptor-Toll-like receptor 4 axis, the arachidonic acid-prostaglandin cascade, oxidative stress and transforming growth factor-β signalling associated with blood-brain barrier dysfunction, all of which are pathways that are activated in drug-resistant human epilepsy. These pathways can be modulated in animal models at various disease stages to mediate therapeutic effects on seizures, neuronal cell loss and neurological comorbidities. Moreover, the diagnostic, prognostic and predictive value of inflammatory molecules in blood or CSF and neuroimaging of brain inflammation will be shown together with evidence of clinical translation of preclinical findings.

SANDRA OROZCO

MEDICAL RESEARCH UNIT IN NEUROLOGICAL DISEASES, SPECIALTY HOSPITAL, NATIONAL MEDICAL CENTER, MEXICO.

ROUND TABLE 5 - NEUROPATHOLOGY, INFLAMMATION, CONNECTOMES, NEGATIVE AND POSITIVE NEUROPLASTICITY.

LECTURE: ASSESSMENT OF NEUROINFLAMMATION IN DRUG -RESISTANT EPILEPSY: THE ROLE OF AUTOIMMUNITY.

The mechanisms of refractory epilepsy (RE) are multifactorial and involve environmental, genetic and disease and treatment related factors, another factor to consider in this complex system is neuroinflammation. Recently, neuroinflammation and BBB dysfunction have been proposed as possible mechanisms. The inflammatory process has been shown to trigger hyperexcitability due to different cellular and molecular events. However, information regarding inflammation and DRE is limited. In recent decades, autoantibodies have emerged as underlying causes of unexplained epilepsy, and a link between autoimmunity and epilepsy has been suggested. In addition to the increased susceptibility to seizures caused by inflammation, a direct epileptogenic role of many specific autoantibodies against a large diversity of neuronal and glial proteins has been recognized, making diagnosis more difficult. The International League Against Epilepsy (ILAE) introduced the concept of "epilepsy of immunologic etiology" (AEAE) to refer to patients whose epilepsy "is the direct result of an immunologic disorder in which seizures are a central symptom. The pathophysiology of AEAE is clearly distinct from that of autoimmune encephalitis epileptic seizures (AIE).
On the other hand, histopathological studies have shown that intracellular antibody conditions are caused by a cytotoxic T-cell attack against neurons in a complex immunological network, leading to structural brain damage. All these highlight the need for further research on the role of inflammation and the immune response in the central nervous system, particularly in RE, to understand the mechanisms in this clinical entity and to identify new immunomodulatory treatments, particularly for those cases in which surgery is not a therapeutic alternative. This review summarizes the current knowledge on the role of specific neuronal antibodies in epilepsy-related syndromes, the incidence in our population and the main clinical presentations that will help the clinician to improve diagnosis and treatment.

VICTOR RODRIGUES SANTOS

UNIVERSIDADE FEDERAL DE MINAS GERAIS – BELO HORIZONTE, BRASIL.
Universidade Federal de Minas Gerais.

ROUND TABLE 5 - NEUROPATHOLOGY, INFLAMMATION, CONNECTOMES, NEGATIVE AND POSITIVE NEUROPLASTICITY.

LECTURE: THE TREATMENT OF IMMATURE BRAIN SEIZURES AND EPILEPTOGENESIS FROM THE VIEWPOINT OF CANNABINOIDS.

Convulsive seizures are more prevalent in children. Specifically in neonates, seizures can lead to the development of epilepsy and cognitive and psychiatric comorbidities in adulthood. As pharmacological control is ineffective in up to 20% of cases, childhood crises, for the most part, impair brain development.
Notably, research in the field of epilepsy has relentlessly sought treatments that have fewer side effects and are more effective in controlling childhood seizures. Given this scenario, cannabinoids with no psychotropic effect found in Cannabis sativa, has shown promise for its effects on rodents. However, in order for it to be truly approved as a therapeutic agent, studies are needed that answer important questions such as: what are the CBG's mechanisms of action in the control of childhood crises? Does the CBG efficient in control of seizure at Dravet Syndrome? Predicting the combination of different drugs in the treatment of childhood attacks, how does CBG interact with antiepileptic drugs (AEDs)? In the case of a developing brain, what would be the chronic effects of treating CBG alone and in combination with other AEDs in an immature brain?
This project aims to answer these questions. We will conduct an extensive investigation of the effects of acute and chronic treatment with cannabinoids alone or in combination with AEDs in the brain of newborn rodents, under physiological conditions and in models of epileptic seizures. Our experimental strategy has involved behavioral and histopathological analysis. We focus on the morphological analysis of pathophysiological events known to impact brain development such as neuronal death, hippocampal neurogenesis, gliosis and inflammation.

MAIRA LÍCIA FORESTI

UNIVERSIDADE FEDERAL DE SÃO PAULO (UNIFESP). BRAZIL.

ROUND TABLE 5 - NEUROPATHOLOGY, INFLAMMATION, CONNECTOMES, NEGATIVE AND POSITIVE NEUROPLASTICITY.

LECTURE: MODELING OF POST-TRAUMATIC EPILEPSY AND EXPERIMENTAL RESEARCH AIMED AT ITS PREVENTION.

Research on the prevention of post-traumatic epilepsy has made important advances in recent years. Based on the search for biomarkers that may indicate individual susceptibility and unveil pathophysiological mechanisms, the development of new animal models focusing on different factors related to brain injury and the investigation of new drugs and treatment techniques, the general understanding of the epileptogenic process has prospered. Together, the different approaches favor the understanding of this relevant, but not yet preventable, medical condition.

EFRAIN BURITICÁ

UNIVERSIDAD DEL VALLE. COLOMBIA.

ROUND TABLE 5 - NEUROPATHOLOGY, INFLAMMATION, CONNECTOMES, NEGATIVE AND POSITIVE NEUROPLASTICITY.

LECTURE: ON POST-TRAUMATIC EPILEPSIES AND OTHER DRUG-RESISTANT EPILEPSIES: IN THE SEARCH FOR BIOMARKERS IN SURGICAL HUMAN BRAIN TISSUE.

Most of the studies in the literature on post-traumatic epilepsy are clinical and epidemiological. Among those who study its pathophysiology or neurobiology, most do so in animal models. Almost all the studies that identify biomarkers of post-traumatic epilepsy and other refractory epilepsies do so in plasma and cerebrospinal fluid. Therefore, very little is known about the cellular mechanisms of post-traumatic epilepsy and drug-resistant epilepsy in human brain tissue. In this conference I will show the previous evidence of these biomarkers, as well as recent evidence that we have obtained in the process of identifying the cell types that express some markers of refractory epilepsy in cortical tissue of post-surgical epilepsy. We have advanced the study with markers of cytoarchitecture, neurodevelopment and neuroinflammation in cortical tissue samples from patients with refractory epilepsy, including post-traumatic epilepsy, in which we have found alterations in the subtypes of GABAergic interneurons, an increase in cell proliferation and death markers, and we identified the cell populations that most express neuroinflammation markers. Some of these markers are being used for the first time in brain tissue from humans with refractory epilepsy, so our histological findings would reinforce those found by others in blood, CSF, or animal models.

CANDI LASARGE

DEPARTMENT OF ANESTHESIA. CINCINNATI CHILDREN'S HOSPITAL. UNIVERSITY OF CINCINNATI. CINCINNATI, OH, USA..

ROUND TABLE 6 - PARADIGM SHIFTS TOWARDS INTEGRATIVE VIEWS IN THE RESEARCH OF THE EPILEPSIES AND NEUROPSYCHIATRIC COMORBIDITIES

LECTURE: *MTOR* HYPERACTIVITY INITIATES AN EPILEPTOGENIC CASCADE

The phosphatidylinositol-3-kinase (PI3K) - mammalian target of rapamycin (mTOR) pathway controls cell proliferation, growth, development, and survival. To date, numerous mutations in genes that regulate this pathway have been identified in connection with epilepsy, including loss of function mutations in the negative pathway regulators phosphatase and tensin homologue (PTEN) and tuberous sclerosis complex 1 and 2 (TSC). These mTOR pathway mutations are often present as mosaic variants in focal epilepsy and can produce lesions that range from focal cortical dysplasia to hemimegalencephaly. Unfortunately, the mechanisms underlying seizure development have yet to be fully understood. Our lab developed animal models with either a PTEN deletion from a small population of dentate granule cells or a focal cortical loss of the TSC2 gene to investigate how neurons with mTOR hyperactivation contribute to an epileptic network. Both genetic manipulations recapitulate an epilepsy phenotype that is associated with abnormal neuron development. In our model, PTEN knockout cells drive a hyperexcitable dentate, and when the knockout cell population reaches a threshold around 15%, additional secondary changes in the circuit support a shift from focal hippocampal epilepsy to a generalized seizure phenotype. Focal deletion of TSC2 from neonatal cortical excitatory neurons reliably produces a robust seizure phenotype, while initiating cortical changes that include a localized increase in vessel density. Together, data suggest an epileptogenic cascade follows gene deletion from selected populations of neurons that supports the development of spontaneous seizures. Disease severity may reflect combinatorial effects of the affected cell population size and the secondary changes initiated by the abnormal neurons.

ANA CAROLINA COAN

DEPARTMENT OF NEUROLOGY UNIVERSIDADE DE CAMPINAS - UNICAMP. CAMPINAS. BRASIL.

ROUND TABLE 6 - PARADIGM SHIFTS TOWARDS INTEGRATIVE VIEWS IN THE RESEARCH OF THE EPILEPSIES AND NEUROPSYCHIATRIC COMORBIDITIES

LECTURE: MAPPING THE MAZE: NAVIGATING THE COMPLEX RELATIONSHIP OF EPILEPSY, WHITE MATTER INTEGRITY, AND NEURODEVELOPMENTAL IMPAIRMENT

Children who experience the onset of epilepsy during the first years of life are at a high risk of neurodevelopmental delay, learning disorders, or intellectual disability. Epilepsy has negative impact on the maturation of cognitive functions in children. Starting from the first months of life, there is a progressive increase in the appearance and maturation of synapses. These synapses gradually organize into diffusely distributed neural networks. The formation of synapses and the organization of neural networks are strongly influenced by genetic factors, although extrinsic factors also play a significant role. Paradoxically, prolonged seizures occurring in the first years of life are less likely to result in neuronal loss and hippocampal injury compared to what is observed in adults. However, the occurrence of recurrent seizures can reduce neurogenesis, leading to abnormal patterns of white matter networks. Neuroimaging studies in children with epilepsy have shown evidence of microstructural white matter damage, which is significantly influenced by early seizure onset. Evidence of the impact of white matter and its impact on the phenotype of childhood epilepsies will be discussed.

DAVID-AHMEDT ARISTIZABAL

IMAGING AND COMPUTER VISION GROUP
CSIRO DATA61. CANBERRA – AUSTRALIA.

ROUND TABLE 6 - PARADIGM SHIFTS TOWARDS INTEGRATIVE VIEWS IN THE RESEARCH OF THE EPILEPSIES AND NEUROPSYCHIATRIC COMORBIDITIES

LECTURE: *COMPUTER VISION FOR UNDERSTANDING PATIENTS' BEHAVIOR: A FOCUS ON EPILEPSY AND OTHER MOTOR DISORDERS*.

Medical applications have greatly benefited from the rapid progress in the field of computer vision. While previous studies primarily focused on analyzing diagnostic procedure data to predict the presence of diseases, there has been less attention given to areas such as patient behavior monitoring, and motor and mental disorder assessment. From a clinical perspective, behavior monitoring tools offer several key benefits: (i) they provide complementary, objective, and quantitative information to clinicians; (ii) they enable the detection and quantification of events that are challenging to observe, such as nocturnal falls; (iii) they reduce the time and effort required for documenting relevant diagnostic information; and (iv) they allow assessment in locations and clinics where human expertise may be limited. Vision-based systems have gained significant attention due to their non-invasive nature, demonstrating promising results in analyzing patient-specific poses and behaviors (including facial and body motions) across various clinical contexts, such as Epilepsy, Parkinson's disease, autism spectrum disorders, breathing disorders, infant motions, and pain management. Although these developments will never replace the expertise of individual clinicians, they can enhance medical decisions and ultimately improve the standard of care provided to patients by offering more quantitative evidence and appropriate decision support.

MARCIO FLAVIO DUTRA MORAES

UNIVERSIDADE FEDERAL DE MINAS GERAIS – BELO HORIZONTE, BRASIL.
Professor Titular da Universidade Federal de Minas Gerais.

ROUND TABLE 6 - PARADIGM SHIFTS TOWARDS INTEGRATIVE VIEWS IN THE RESEARCH OF THE EPILEPSIES AND NEUROPSYCHIATRIC COMORBIDITIES

LECTURE: CHANGING A LOCALIZATIONIST BRAIN ARCHITECTURE VIEW FOR ONE OF TEMPORALLY ORGANIZED PACKAGES. THE CONCEPT OF COINCIDENCE DETECTORS INSTEAD OF INTEGRATION-RESPONSE AND ITS IMPACT IN THE TREATMENT OF THE EPILEPSIES.

There is a trend in Neuroscience, that started a couple of decades ago, into adopting a new conceptual framework for brain architecture, in which time and thus temporal patterns of activity plays a central role in the neuronal representation – and processing - of sampled data from the world. The relevance of brain rhythms in the overall functional architecture of the nervous system (especially regarding large scale brain communication) has reached a point in which this "new found" conceptual framework is influencing therapeutic approaches towards several brain disfunctions. This lecture discusses our contribution to the topic using temporally complex deep-brain electrical stimulation schemes and how they may impact neuromodulation strategies in the treatment of epilepsy. The focus on desynchronizing neuronal networks, even at the cost of increasing excitation, has provided strong evidence against the long-held assumption that excitation drives synchronization as the cause of ictogenesis. Using temporally unstructured stimulation we dynamically drove the brain's functional connectogram, through neuromodulation, in a manner that would not favor any specific neuronal assembly and/or circuit, thus re-stabilizing a system that otherwise would transition to fall under the control of a single attractor. We also worked with physiological applications of temporally-structured stimulation showing that specific areas of the brain are capable of differentiating temporal patterns and redirecting circuitry output pathways accordingly.

NORBERTO GARCIA CAIRASCO
RIBEIRÃO PRETO SCHOOL OF MEDICINE. UNIVERSITY OF SÃO PAULO. BRAZIL.

ROUND TABLE 6 - PARADIGM SHIFTS TOWARDS INTEGRATIVE VIEWS IN THE RESEARCH OF THE EPILEPSIES AND NEUROPSYCHIATRIC COMORBIDITIES

LECTURE: CHALLENGES TO DECIPHER THE MAIN INTERTWINED PROTAGONISTS OF EPILEPTOGENESIS AND COMORBIDITIES IN A COMPLEX LANDSCAPE OF SEMIOLOGY, NEUROANATOMICAL NETWORKS AND THEIR NEUROPLASTIC ABNORMAL ACTIVITY

Seizures, Epilepsies, and Neuropsychiatric Comorbidities are broad and general names for a group of complex entities with a profound impact on the behavior of sensory, motor, emotional, memory and/or cognitive networks. In the scenario of homeostasis, during real-life activities, brain networks can express their enormous diversity, and complexity through sensory communication and plasticity, motor imagining or execution, and marvelous cognition, among dozens of other functions which, integrated, give emergence to even more complex processes such as behavior and consciousness. In these cases, however, we still know very little about their precise underlying causation in terms of development, control, learning, and plasticity processes along the dynamics of the lifetime. Furthermore, with additional complexity, when deleterious, pathological, aberrant/chaotic/abnormal activity, such as those presented in the Epilepsies and their associated Neuropsychiatric Comorbidities, we also do not really know about the relationships in time and space of the myriad of factors and events that produce different semiology after trauma, lesions, or dysfunctions, all of them translated into neuroplastic abnormal entities. We would like to know, in fact, how much different integrated methods such as video capture, structural and functional imaging, surface or deep electrophysiology, microscopy, cell and molecular biology (omics) are used to reveal specific signatures of those alterations, and what is their potential for disease modifications or treatment (pharmacological, surgical, neuromodulation). In addition, we are dealing with a huge amount of data coming from freely-moving animals, organoids, mini-brains, brain slices, cell cultures and in silico modeling.

Finally, our main goal is to discuss the Epilepsies and Neuropsychiatric Comorbidities, using methods of complex systems with associated emergence properties, computational modeling, and deep and machine learning. We will present how scientists worldwide are dealing with such an amount of data in such different scenarios, ideally dealing with big data coming from multinational collaborative efforts (e.g., Blue Brain Project, Allen Brain Institute, Epilepsy without Walls, Epilepsy Global Project, Distributed Archives for Neurophysiology Data Integration, Neuroscience Multi-Omic Archive, among other platforms). We will also discuss critically how much they are, or should be, open to sharing and collaborative endeavors.

NEUROSCIENCE AND EPILEPSY ABSTRACTS

International Symposium

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"Epilepsy & Neuropsychiatric Comorbidities from Semiology, to Neuroplasticity of Vulnerable/Resilient Networks, to Personalized Therapies"

NEUROSCIENCE ABSTRACTS

01 - Assessment of Neuropsychomotor Development in Children Aged 12 to 72 Months After School Reopening During the COVID-19 Pandemic.

Authors: Guillermo Andrey Ariza Traslaviña[1], Tainá Souza e Silva[1], Amanda Dourado Souza Akahosi Fernandes[2].

[1] Department of Medicine of the Federal University of São Carlos, São Carlos, Brazil, [2] Department of Occupational Therapy of the Federal University of São Carlos.

Rationale. The COVID-19 pandemic has raised concerns about child development, particularly regarding potential neuropsychomotor delays and increased symptoms related to autism spectrum disorder (ASD). It is essential to understand these potential effects in the Brazilian context. This study aims to contribute to this understanding, focusing on identifying possible developmental delays and early ASD symptoms. This research sought to evaluate the neuropsychomotor development (NPMD) milestones and autism symptoms in children aged 12 to 72 months residing in the municipality of São Carlos.

Methods: A cross-sectional study was conducted in the first semester of 2022. An electronic questionnaire was distributed to parents and caregivers of children in São Carlos. It included sociodemographic queries, NPMD milestones from the booklet of child health, and the M-CHAT questionnaire for autism symptom screening. The study received approval from the research ethics committee of the Federal University of São Carlos (CAAE 50168121.4.0000.5504).

Results: A total of 49 questionnaires were received. The sample was predominantly composed of white males (59%) between 12 to 24 months, full-term births (89.8%), and attended school (81%). Caregivers reported no suspicions of neurological diseases in 67.3% of the cases. However, language and behavior delays were observed in 36.7% and 16.3% of the sample, respectively. Most children played for more than 5 hours daily (67%) and had a screen time of ≤3 hours per day (73.5%). According to the NPMD milestones, 42.9% displayed appropriate development, while 57.1% showed delays in the following milestones: personal-social (53.5%), fine-adaptive motor skills (50%), language (42.8%), and gross motor skills (21%). Among children aged 16 to 30 months, 40% exhibited failures in the Modified Checklist for Autism in Toddlers (M-CHAT) questionnaire.

Conclusions. The study found an increase in NPMD milestone failures in children aged 12 to 72 months following the reopening of schools during the pandemic, compared to pre-pandemic data from Brazil (Pilz EML, Schermann LBL. Ciência Saúde Coletiva, 12, 181, 2007). These results are multifactorial and could be attributed to a complex interaction between limited social interaction due to initial pandemic restrictions and changes in the daily routine in the family environment.

The authors declare no conflicts of interest or financial support.

02 - Pharmacological Evidence For Opioid Disinhibitory And Gabaergic Inhibitory Links Between The Inferior Colliculus And The Dorsal Periaqueductal Grey Matter: The Role Of κ-Opioid Receptor In The Modulation Of Defensive Behaviour.

Authors: DE PAIVA, Y.B. [a,b] , COIMBRA, N.C. [a,b,c] .

[a]Laboratory of Neuroanatomy and Neuropsychobiology, Department of Pharmacology, School of Medicine of Ribeirão Preto of the University of São Paulo (FMRP-USP), Ribeirão Preto, Brazil, [b] Institute of Neuroscience and Behaviour (INeC), Ribeirão Preto, Brazil, [c]NAP-USP-Neurobiology of Emotions Research Centre (NuPNE), School of Medicine of Ribeirão Preto of the University of São Paulo (FMRP-USP), Ribeirão Preto, Brazil.

Rationale: Some convergent studies have demonstrated the existence of a complex interaction between connections mediated by endogenous opioid peptides and neural pathways mediated by GABA. Our group showed the presence of a disinhibitory opioid connective link between inferior colliculus and dorsal periaqueductal grey matter neurons. It has been proposed that opioid neurons exert a modulatory influence on GABAergic interneurons, which, in turn, exert a tonic inhibitory control over mesencephalic structures that organizes fear-induced behaviours. Thus, at the mesencephalic level, opioid peptides can exert disinhibitory actions on GABAergic inhibitory projections to mesencephalic tectum, thus contributing to the expression of defensive behaviours.

Methods: We used a selective GABA-A receptor antagonist (bicuculline) microinjected either in the dorsal column of the periaqueductal grey matter (dPAG) or in the inferior colliculus (IC), respectively, to elicit innate fear-related behavioural responses. Our hypothesis considers that opioid neurotransmission depresses the activity of GABAergic pathways that project both to the IC and to the dPAG, facilitating the elaboration of the defensive responses induced by intratectal blockade of GABAergic receptors in each of the

structures addressed in this study (CEUA-FMRP-USP;process 092/2016). Male Wistar-Hannover rats underwent stereotaxis for cannula implantation (IC and dPAG). After the 5th day of recovery, different groups received microinjection of bicuculline (40 ng/kg) or vehicle in the IC, and Nor-binaltorphimine, a κ-OR antagonist (nor-BNI;0.05, 0.5 or 5 µg/ 0.2 µl) or vehicle in the dPAG, and placed in an open-field, and recorded their behavior for 15 minutes. Behaviors were quantified (X-Plo-Rat software) and data submitted to one-way ANOVA and multiple comparisons, followed by the Newman-Keuls post hoc test ($p<0.05$).

Results: Pre-treatment with intracollicular nor-BNI promoted an important attenuation of the defensive behaviors evoked by the administration of bicuculline in dPAG. A panicolytic effect was observed by the significant reduction, duration and frequency, respectively, of alert behaviors, ($F_{4.48}=14.02$; $F_{4.48}=11.52$; $p<0.0001$), freezing (frequency: $F_{4.52}=3.891$; $p<0.0001$), escape ($F_{4.50}=18.02$; $F_{4.51}=45.3$; $p<0.0001$), jump ($F_{4.38}=8.322$; $F_{4.51}=13.96$; $p<0.0001$) and rotation ($F_{4.37}=8.484$; $F_{4.51}=19.31$; $p<0.0001$), compared to the control. Furthermore, nor-BNI microinjection intra-dPAG significantly attenuated freezing time, $p<0,01$ ($F_{4.40}=5.618$). Frequency and duration, respectively: escape ($F_{4.38}=4.622$; $F_{4.38}=11.83$; $p<0.0001$), jump ($F_{4.31}=5.198$; $F_{4.31}=4.129$) and rotation (duration: $F_{4.51}=4.518$), compared to the control.

Conclusions: The blockade of kappa opioid receptors in both IC or in the dPAG caused a significant panicolytic-like effect, reducing the intensity of defensive alert, defensive immobility and escape responses. These data suggest a reciprocal opioid modulation between the structures of the tectum involved in the elaboration of fear and panic.

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03 - Molecular and Cellular Responses to Neurotoxic Stimuli by Human Brain Slice Cultures.

Authors: Giovanna Orlovski Nogueira[1]; Almeida, G.M.[1]; Niele D. Mendes[3]; Podolsky-Gondim, G.[2]; Neder, L.[3]; Adriano Silva Sebollela[1]

[1]Departament of Biochemistry and Immunology – Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, SP, Brazil; [2]Dept. of Surgery and Anatomy, Ribeirão Preto Clinics Hospital, Ribeirão Preto Medical School, University of São Paulo, SP, Brazil; [3]Dept. of Pathology and Forensic Medicine, Ribeirão Preto Medical School, University of São Paulo, SP, Brazil;

Rationale: Three-dimensional (3D) models, such as organoids and histocultures, are key for advancing translational neuroscience. These 3D models present advantages compared to widely used 2D platforms, namely cell cultures, provided mainly by the preservation of cell diversity and connections originally found *in vivo*. Slice cultures prepared from either animal or human brains may be considered preferable models as these allow modeling the central nervous system at different stages (development, mature) under tissue-relevant cell connectivity, extracellular matrix composition, and cell diversity. Consequently, studies on neurotoxic events triggered by eg. infections and proteinopathies using brain slice cultures are more likely to reflect biologically relevant phenomena. Our group has been working to establish and optimize slice cultures from human brains as a preferred model to investigate neurotoxic events. Altogether, our data accumulated so far place the human brain slice model as a powerful model for studies on neurotoxic events associated with human brain diseases.

Methods: Brain tissue is obtained from either adult donor subjected to temporal lobectomy for refractory epilepsy treatment (Ethics Committee approval HCRP17578/15) or Sprague Dawley rat (CEUA #141/2020). Briefly, slices (200µm thick) are cultured free-floating up to day *in vitro* 5 and challenged with toxic stimuli at day *in vitro* 1-3. Challenged slices were used for MTT viability assay, confocal imaging, western blot analysis, and ELISA for quantification of cytokines levels in conditioned media. Data is represented as mean ± S.E.M. (n= 2-3 slices, from at least 2 different donors or n=4-6 slices, from at least 3 different rats).

Results and Discussion: We have seen that human brain-derived slice cultures are sensitive to Alzheimer's associated Aβ oligomers (AβOs), can be pharmacologically modulated with NMDA receptor inhibitors, and are susceptible to experimental infection by neurotropic viruses such as Oropouche virus and SARS-Cov2. Moreover, using an oligomer-selective ELISA, we detected AβO binding to brain slices in concentrations as low as 125 nM without decrease in cell viability, suggesting a high-affinity interaction prior to neuronal death. Improvements in the protocol aimed to increase slice culture viability are also being developed in rat brain slice cultures. We have seen that gentle agitation during incubation increased viability throughout the days in culture, an effect thought to be correlated to improved oxygenation.

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04 - Cannabidiol treatment in young adult rats with comorbidities caused by gestational exposure to crack.

Authors: SILVA, F.S[1], PACHECO, A.L.D[1], SIQUEIRA, E.S[1], SOUZA, F.M.A[1], SILVA, B.R.M[1], OLIVEIRA, K.L.S[1], OLIVEIRA, K.B[1], PEIXOTO, B.O.M[1], SÁ, L.B.M[1], COUTINHO, A.B[1], OLIOSI, E.B[1], TORRES, R.G.D[1], HOMERO, M.T.A[1], VIEIRA, M.P.S, LINS, M.P[1], MELO, I.S[1], CASTRO, O.W[1]

[1]Institute of Biological Sciences and Health, Federal University of Alagoas (UFAL), Maceio, AL, Brazil.

Rationale: The use of crack cocaine during the gestational period causes short- and long-term effects for the offspring, such as withdrawal syndromes, seizures, mood disorders and depression. Alternative treatments with cannabidiol (CBD) have shown beneficial therapeutic effects in neurodegenerative diseases such as epilepsy, Alzheimer's, and Parkinson's, as well as for comorbidities such as anxiety, depression, and cognitive deficits in several animal models. Our aim was to examine the potential therapeutic effects of CBD in reducing anxiety- and depressive-like behaviors, such as cognitive deficits observed in the offspring.

Methods: Wistar rats [female (n=20) and male (n=15)] were obtained from the central animal facility of the Federal University of Alagoas (BIOCEN/UFAL; protocol number #28/2021). The animals were mated in a 2:1 ratio, and to confirm the pregnancy, day 0 of gestational day (GD 0) was considered. After that, pregnant rats were randomized into control (CTRL) and CRACK groups and exposed to air or crack cocaine during the prenatal period (PN) from the 5th to the 21st of GD. The offspring (females and males, n = 72) were treated with oral CBD oil (30 mg/kg) or 0.9% saline solution (VEH) for 14 days, once a day between P21 (weaning) and P35, with the following experimental groups: CTRL+VEH (n=9); CTRL+CBD (n=9); CRACK+VEH (n=9) and CRACK+CBD (n=9). Posteriorly, the animals were submitted to the elevated plus-maze (EPM), forced swim (FST), open field (OF) and step-down (SD) tests to assess anxiety/depressive-like behavior, locomotion activity, and cognitive deficit, respectively. For statistical analysis, a two-way ANOVA followed by Tukey's post-hoc test was applied. All result values are presented as mean ± SEM with a significance of $p < 0.05$.

Results: Our preliminary results demonstrate that treatment with CBD increased the percentage of time (%OAT; $p < 0.05$) and entries in open arms (%EOA; $p < 0.05$) of male rats F1 in the EPM. For FST, animals exposed to crack prenatally show a decrease in the latency for immobility (males and females; $p < 0.05$) and an increase in total mobility (females; $p < 0.05$), demonstrating a depressive-like behavior. CBD treatment attenuated these behaviors, demonstrating an antidepressant-like effect. Additionally, treatment with

CBD improved the exploratory capacity of male rats exposed to OF ($p < 0.05$). None of the treatments showed changes in memory in SD.

Discussion/Conclusions: Our results demonstrated that CBD attenuated the effects on the offspring caused by prenatal exposure to crack-cocaine. Therefore, it has future therapeutic potential for comorbidities caused by psychoactive substances.

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Conflicts of Interest Disclosure: The authors declare that they have no conflict of interest.

Acknowledgements: We would like to acknowledge FAPEAL, CNPq, CAPES and the Laboratory of Neuropharmacology and Integrative Physiology for their support during the work.

05 - The impact of crack cocaine exposure during gestation: behavioral and cellular changes

Authors: TORRES, R.G.D[1], SANTOS, Y.M.O[1], PACHECO, A.L.D[1], REITER, M.M.J.H[1], COSTA, M.A[1], PIRES, K.S.N[1], SOUZA, F.M.A[1], SANTOS, J.F[1], BARBOSA, M.R[1], LINS, M.P[1], COUTINHO, A.B[1], OLIOSI, E.B[1], SILVA, B.R.M[1], OLIVEIRA, K.L.S[1], SILVA, F.S[1], DUZZIONI, M[1], BORBELY, A.U[1], MELO, I.S[1], CASTRO, O.W[1].

[1]Institute of Biological Sciences and Health, Federal University of Alagoas (UFAL), Maceio, AL, Brazil.

Rationale: Drugs of abuse represent a public health problem. The use of crack cocaine by pregnant women has been associated with Central Nervous System (CNS) malformations and cellular and placental damage. Therefore, we examined implantation site cell viability, ectoplacental cone growth, reflexology, maternal, nonmaternal, and anxiety-like behaviors, and hippocampal and extra-hippocampal regions in pregnant rats under the influence of prenatal exposure to crack cocaine.

Methods: Pregnant Wistar rats (*Rattus norvegicus* [n= 29, 200-300g, 2-3 months old]) were exposed to air or crack cocaine (200 mg, for 10 min) during gestation or until the end of gestation, according to a protocol approved by the UFAL Ethics Committee (Protocol nº.

28/2021). The MTT cell viability assay was used to assess ectoplacental cone cell toxicity isolated after exposure to crack cocaine, while the cell death assay with annexin V/propidium iodide by flow cytometry was used to evaluate with greater sensitivity the effects of crack cocaine on trophoblast cells. The anxiety-like phenotype and spontaneous locomotor behavior (Control, n = 12; Crack, n = 13) were examined using the elevated plus-maze and the open field test, respectively. After the pups were born, we analyzed maternal care daily over the 18 days of lactation, and the development of sensorimotor reflexes in the offspring was assessed. Finally, the neurodegeneration process was evaluated by FluoroJade (FJ) histochemistry in the hippocampus and amygdala of lactating rats. All data were expressed as mean ± standard error of the mean, assuming a significance level of 5% ($P < 0.05$) for all statistical tests.

Results: We observed that gestational exposure to crack cocaine did not affect the number of gestational implantation sites or the viability of ectoplacental cone cells compared to the control group ($P > 0.05$), as well as an increase in trophoblastic cell death associated with reduced ectoplacental cone outgrowth in vitro (*t test,* t_{13}= 2.257, P = 0.023) and a reduction of viable cells (*t test,* t_{16}=4.63, P = 0.0003). Closed-arm entries and ethological parameters increased in lactating rats, suggesting anxiogenic-like behavior, GRO (*t test*, t_{17} = 2.76, P = 0.01) and pSAP (*t test*, t_{17} = 2.54, P = 0.02), but locomotor activity remained unchanged in the center (*Mann Whitney test*, U = 57, P = 0.85) and in the corners (*Mann Whitney test*, U = 63, P = 0.91), as well as the number of entries in the center (*Mann Whitney test*, U = 62.50, P = 0.61) and in the corners (*Mann Whitney test*, U = 42, P = 0.08). In addition, after gestational exposure to crack cocaine, we observed that lactating rats exhibited reduced performance in the maternal care of their offspring, (*two-way* ANOVA, F (4, 14) = 10.21, P = 0.006). Furthermore, the development of sensorimotor reflexes in the offspring has not changed (*Mann Whitney test*, U = 120.5, P = 0.79). Finally, gestational exposure to crack cocaine did not promote neuronal death in the subareas of the hippocampus, but FJ+ cells were observed in the amygdaloid nucleus [lateral, dorsolateral part (LaDL)].

Discussion/Conclusion: Our findings offer novel insights into gestational shifts induced by crack cocaine exposure. Consequently, comprehending these ramifications during pregnancy assumes vital importance for maternal-fetal care. In essence, our discoveries delineated *in vitro* alterations in ectoplacental cone cells, alongside psychiatric and behavioral issues, and amygdala changes after pregnant rats were exposed to crack cocaine. Taken together, studying the deleterious effects of crack cocaine should be the target of research and therapies that

support future clinical interventions and treatments to recover the health of drug users in treatment.

Financial Support: This project was supported by FAPEAL (nº E:60030.0000000161/2022 e nº E:60030.0000000328/2023), CNPq (406727/2021-0), and CAPES.

Conflicts of Interest Disclosure: The authors declare that they have no conflict of interest.

Acknowledgments: We would like to acknowledge FAPEAL, CNPq, CAPES and the Laboratory of Neuropharmacology and Integrative Physiology for their support during the work.

06 - Evaluation of the neuroprotective potential of dimethyltryptamine and harmine, components of ayahuasca, isolated and in combination, against cocaine-induced neurotoxicity in sh-sy5y cells

Authors: GABRIELA SALLES DOS SANTOS[1], ISABELLA DE CARVALHO ALVES[1], CAROLINA APARECIDA DE FARIA ALMEIDA[2], DANIELA APARECIDA CHAGAS DE PAULA[3], ALBERT KATCHBORIAN NETO[3], KARINA CAMARGO TEIXEIRA[3], TANIA MARCOURAKIS[4], LARISSA HELENA LOBO TORRES[2], RAPHAEL CAIO TAMBORELLI GARCIA[1].

[1]Institute of Environmental, Chemical and Pharmaceutical Sciences, Universidade Federal de São Paulo (UNIFESP), [2]School of Pharmaceutical Sciences, Universidade Federal de Alfenas (UNIFAL), [3]Institute of Chemistry, Federal University of Alfenas (UNIFAL), [4]School of Pharmaceutical Sciences, University of São Paulo (USP).

Rationale: Ayahuasca is a psychoactive tea used by the indigenous population of the Amazon in shamanic rituals and by religious groups such as the União do Vegetal and Santo Daime. The tea is prepared by the infusion Psychotria viridis – which contains dimethyltryptamine (DMT) – and Banisteriopsis caapi – which contains harmine. DMT is the substance responsible for the psychoactive effects of the tea. Harmine inhibits DMT's biotransformation and allows it to interact with serotonin receptors 5-HT2A and 5-HT1A in the central nervous system, acting as an agonist. There are several studies that investigate the pharmacological potential of ayahuasca in different scenarios, including substance use disorders (SUD), such as cocaine, alcohol, etc. However, the literature lacks information about its neurotoxicity, as

well as its neuroprotective potential, which is very relevant when considering ayahuasca's possible application against SUD. Thus, this study aims to evaluate the in vitro: 1) neurotoxicity of the tea, DMT and harmine, isolated and in combination; 2) cocaine lethal concentration 50% (LC50); and 3) neuroprotective potential of DMT and harmine, isolated and in combination, against cocaine-induced toxicity.

Materials and methods: The study was performed using SH-SY5Y human neuroblastoma cell culture. The concentration-response curves (CRC) for all substances were determined after 48 hours of exposure. DMT and harmine concentrations tested were 0.1–1000 µM, and the DMT:harmine concentrations were 10:10–10:100 µM, based on the tea proportions. Cocaine concentrations tested were 0.5–5 mM. The LC50 of cocaine was used to verify the neuroprotective potential of the DMT and harmine. The MTT cell viability assay was used for all CRCs. Results were analyzed by one-way analysis of variance (ANOVA) followed by Bonferroni's multiple comparisons post hoc test. A p-value less than 0.05 was considered statistically significant.

Results and Conclusion: DMT at concentrations ranging from 0.1 to 100 µM did not show significant toxicity, but at 1000 µM the cell viability was 66.7%. Harmine showed a 55.5% reduction in cell viability at 100 µM, but not significant toxicity at other concentrations. The DMT-harmine combination did not exhibit significant toxicity at concentrations from 10:10 to 10:50 µM, but showed 19.8% of viable cells at the 10:100 µM ratio. Cocaine at concentrations of 2.5 and 5 mM showed reduction in cell viability, with 2.5 mM being the closest to its LC50. Subsequently, non-toxic concentrations of DMT, harmine and their combination, which was 10 µM for each and 10:20 and 10:50 µM for the combination, was used to assess their neuroprotective potential against cocaine induced toxicity. The DMT-cocaine and harmine-cocaine groups showed an increase in cell viability (69.7% and 74.0%, respectively) compared to the cocaine group (49.4%). Despite this neuroprotective effect, more experiments are necessary to confirm this preliminary result, such as flow cytometry to determine if DMT and harmine are able to prevent cocaine-induced apoptosis, demonstrating the importance of these substances as new pharmacological approaches for the treatment of SUD.

Keywords: dimethyltryptamine, harmine, ayahuasca, neurotoxicity, SH-SY5Y.

Conflict of Interests Disclosure: The authors whose names are listed certify that they have NO affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest in the subject matter or materials discussed in this manuscript.

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07 - Implementation and Analysis of Convolutional Neural Networks (CNNs) for Alzheimer's Disease Diagnosis Using an Open Source Dataset

Authors: Furigo, P.M.[a], Ramalho, B.A.C.[b], Spadaro, A.P.[c], Wichert-Ana L.[d], da Silva, M.A.A[c], Padovan-Neto, F.E.[e], de Lacerda, K.J.C.C.[d,e]

[a]Institute of Exact and Technological Sciences - ICET, Computer Science, Paulista University, Ribeirão Preto, Brazil, [b]Department of Physics, Faculty of Philosophy, Sciences and Letters of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil, [c]Department of Biomolecular Sciences, Faculty of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil, [d]Nuclear Medicine & Molecular Imaging Section, Image Science and Medical Physics Center, Internal Medicine Department and Postgraduate Program, Ribeirão Preto School of Medicine, University of São Paulo, Ribeirão Preto, Brazil, [e]Department of Psychology, Faculty of Philosophy, Sciences and Letters of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil.

Rationale: Alzheimer's disease (AD) stands as the foremost cause of dementia worldwide. Current diagnostic methods for Alzheimer's disease are multifaceted, relying on patient history, neuropsychological test outcomes, and imaging assessments. Nevertheless, the interpretation of results and the diagnosis of the disease, particularly in its early stages, exhibit substantial variability, deviating from a linear paradigm of sensitivity and specificity. In light of the progress in artificial intelligence (AI), the domains of machine learning and deep learning can be harnessed within the realm of healthcare, with the potential to enhance the diagnosis of AD by discerning intricate patterns within medical images and clinical data. Artificial neural networks, encompassing convolutional and multi-layer perceptrons, can be amalgamated to scrutinize an extensive array of clinical data, thereby affording more precise insights into a patient's disease stage. These networks necessitate training to acquire disease-related patterns and proficiency in patient classification, a process that may be facilitated through the utilization of open-access image repositories such as Kaggle.

Methods: The Sequential Keras API, a Python library for constructing neural network models, simplifies the layer-by-layer construction process, abstracting the complexities of underlying matrix computations. It is noteworthy that multiple neural network architectures are encompassed within Keras, including fully connected, convolutional, and recurrent

networks. The library is built on top of TensorFlow and can be seamlessly integrated with other popular machine learning libraries, such as PyTorch and Scikit-Learn. An illustrative example for constructing a Convolutional Neural Network (CNN) using the Sequential Keras API involves a sequential implementation of steps: 1) importing necessary libraries; 2) creating a sequential model object; 3) adding convolutional and Max Pooling layers; 4) adding flattening; 5) adding dense (fully connected) layers; 6) compiling the model; 7) training the model with fitting and evaluating it with scoring. The efficacy of this approach is evidenced through the construction of a CNN model employing T1-weighted magnetic resonance imaging data obtained from Kaggle for Alzheimer's disease diagnosis, wherein a dataset split of 70/15/15 for training, validation, and testing is employed, encompassing 3200 healthy individuals and 2240 individuals with advanced Alzheimer's.

Results: The parameters of precision, recall, f1-score, and support showcase how well the neural network model classifies each patient class and its overall performance. Accordingly, a precision of 99% was achieved for true negative cases and 97% for true positive cases. The network accurately identified 471 patients as healthy and produced 9 false-positive results among the 480 individuals who were actually healthy. Moreover, it precisely identified 332 patients with Alzheimer's disease as having the condition, with only 4 instances of false negatives among the 336 patients diagnosed with Alzheimer's.

Discussion/Conclusions: The developed neural network model (whose code will be made available in future publications) exhibited remarkable performance, achieving an efficacy exceeding 97% across all performance parameters. This suggests the feasibility of implementing CNNs to assist in Alzheimer's disease diagnosis, thereby enhancing diagnostic sensitivity and specificity, leading to expedited disease detection, and subsequently improving the patients' quality of life.

Keywords: Alzheimer's disease diagnosis; Convolutional Neural Network; Deep learning

Final observations: The authors are appreciative to CNPq (National Council for Scientific and Technological Development), FAPESP (São Paulo Research Foundation), UNIP (Paulista University) and USP (University of São Paulo), and we declare no conflicts of interest.

08 - Development of an Open-Source Python Automation for Reliable Behavioral Analysis in Neuroscience Research

Authors: Ramalho, B.A.C.[a], Cerveira, A.J.D.O.[b], de Souza, C.C.B.[b], Spadaro, A.P.[c], Ramos, B.A.[b], Wichert-Ana, L.[d], Padovan-Neto, F.E.[b], de Lacerda, K.J.C.C.[b,d]

[a]Department of Physics, Faculty of Philosophy, Sciences and Letters of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil, [b]Department of Psychology, Faculty of Philosophy, Sciences and Letters of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil, [c]Department of Biomolecular Sciences, Faculty of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil, [d]Nuclear Medicine & Molecular Imaging Section, Image Science and Medical Physics Center, Internal Medicine Department and Postgraduate Program, Ribeirão Preto School of Medicine, University of São Paulo, Ribeirão Preto, Brazil.

Rationale: The application of automated analysis in behavioral tests has been shown to be advantageous for reducing errors inherent to human analysis as well as providing accurate and fast data analysis. Furthermore, the availability of software that performs this type of analysis is limited due to its high cost, lack of customization options, and dependence on specific test apparatus configurations. In order to address this issue, we developed an open-source protocol and software (using the OpenCV library in Python) for the automated analysis of the Morris Water Maze (MWM) and Open Field (OF) tests.

Methods: The Morris Water Maze (MWM) and Open Field (OF) tests are commonly used to evaluate behavior and cognition in preclinical models. The MWM is used to assess spatial learning, and the OF test assesses animal locomotor activity. In our protocol, male B6129SF2/J mice (8 months old, n=8) were used in the MWM test, and male C57BL/6 mice (7 months old, n=10) were used in the OF test. All animal procedures were approved by the Ethics Committee for Animal Experimentation (CEUA) from the Faculty of Philosophy, Sciences and Letters of Ribeirão Preto at the University of São Paulo (protocol number 22.1.195.59.0). The open-source software developed for automated analysis used the Python programming language, the OpenCV 4.7.0 library, responsible for image processing and computer vision, the Tkinter library, responsible for creating graphical interface elements, and the Matplotlib library for plotting 2D graphs and data visualization. In the MWM test, our program was used to track the animal in each of the predetermined quadrants, calculate the time the animal remained in each of these quadrants, and measure the escape latency when

necessary. In the OF test, the algorithm proportionally delineates the central and edge areas, calculates the time the animal spent in each area, and calculates the number of crossings between them. The results of the parameters obtained with the software were compared, using the Student's t-test, with the results obtained in individual manual analyses conducted by five researchers in a blind manner.

Results: In the MWM, both automated and manual analysis revealed similar results regarding the time the mice stayed in the target quadrant ($p = 0.109$). In the OF test, both automated and manual analysis revealed similar results regarding the time the mice stayed in the center ($p = 0.520$) and border ($p = 0.503$) of the field.

Discussion/Conclusions: The automated analysis protocol has several advantages over manual analysis. It saves time, reduces human errors, can be customized, and provides more consistent information about animal behavior during tests. We conclude that the automated protocol described here is reliable and provides consistent behavioral analysis in mice. This automated protocol can lead to a deeper view of behavioral neuroscience by visualizing deeper insights into behavior.

Keywords: Automated analysis using python, Morris water maze test, Open Field test, openCV image processing

Final observations: The authors are appreciative to CNPq (National Council for Scientific and Technological Development), FAPESP (São Paulo Research Foundation #2017/00003-0 (F.E.P.-N.)), and USP (University of São Paulo - #312009/2022-4 (F.E.P.-N.)), and we declare no conflicts of interest.

09 - Neural decoding of fear or safety and approach or avoidance by brain-wide network dynamics

Authors: Danilo Benette Marques; Matheus Teixeira Rossignoli; Bruno de Avó Mesquita; Tamiris Prizon; Leonardo Rakauskas Zacharias; Rafael Naime Ruggiero; João Pereira Leite.

Department of Neuroscience and Behavioral Sciences, Ribeirão Preto Medical School, University of São Paulo.

Rationale: The ability to differentiate between safety and threat and to discern positive and negative outcomes of adversity are fundamental for mental health. Conversely, imbalances of these appraisals are hallmarks of prevalent psychiatric disorders such as major depression, generalized anxiety disorder, and posttraumatic stress disorder. While various brain structures have been implicated in adaptive and maladaptive stress coping, how multiple regions

function together as a coordinated network in processing such information remains poorly understood.

Methods: In this study, we recorded local field potentials across seven key regions of the mesolimbic-hippocampal-prefrontal cortical network (MLHFC) in male Sprague Dawley rats (N = 6) throughout 3-5 daily sessions of conditioning of a 20- s light stimulus (CS) to the absence (CS-; safety) and, days later, to the anticipation (CS+; fear) of footshocks in an adapted shuttle box. We assessed CS associations every day in an adapted approach-avoidance task, wherein we quantified crossings towards a reward device (approach) or a shock-free platform (avoidance) located apart (CEUA: 0004/2020). Spectral estimates were obtained using multitaper decomposition across 1-s epochs. To investigate the relevance of specific features of network oscillatory activity (regions, circuits, frequencies, power, coherence, and directionality) in the decoding of fear (CS+) versus safety (CS-) and approach versus avoidance, we developed a machine learning pipeline established as a regularized interpretable deterministic generalized linear model of principal components dimensionality-reduced normalized multi-spectra data. For comparisons, we estimated classification performances by the area under the receiver operating characteristics curve (AUC).

Results: First, we validated the behavioral significance of the CS as it promoted greater probabilities of approach after conditioning to safety ($t(4) = 4.69$, $p = 0.0047$) while greater probabilities of avoidance after conditioning to fear ($t(4) = 2.35$, $p = 0.039$). We found in all rats that decoding performance improved as a function of the number of brain regions (number of regions × mean AUC linear regression range: $r(5)2 = 0.67$-0.96, $p = 7.9×10$-5 - 0.02), reaching the optimal classification if all regions were considered collectively. Furthermore, our analysis pointed to the theta frequency range (4-10 Hz) as the most informative for successful decoding (theta vs. non-theta average AUC t-test: $t(5) = 4.32$, $p = 0.007$). Notably, decoder models showed good performances for new data from different days within individuals (AUC median and interquartile range = 0.76 ± 0.24) but a poor classification between subjects (AUC = 0.48 ± 0.06). Nevertheless, we were also able to identify patterns of MLHFC activity that successfully decoded stress-coping states from all rats (average decoder scores AUC = 1). These patterns were characterized by enhanced brain-wide theta synchrony during periods of fear anticipation and preceding approach.

Discussion/Conclusions: Our results evidence that stress-coping information is encoded at the brain-wide network level, highlighting individual variability in this neural processing. Our findings also suggest that MLHFC network theta activity underlies active stress coping with

both aversive and, especially, positive motivational valences. We suggest that theta rhythm large-scale network activity patterns may be valuable biomarkers to guide the development of individualized neurophysiologically-informed psychiatric treatments for stress-related, anxiety, and mood disorders.

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10 - Harmine but not dimethyltryptamine prevents ethanol neurotoxicity in sh-sy5y cells

Authors: Almeida, C.A.F.[1], Alves, I.C.[2], Santos, G.S.[2], Castelhano, F.V.D.[2], Ribeiro, J.M.[2], Silva, A.O.[1], Katchborian Neto. A.[3], Teixeira, K.C.[3], Paula, D.A.C[3], Ceron, C.S.[1], Marcourakis, T[4], Garcia, R.C.T.[2], Torres, L.H.L[1].

[1]Faculdade de Ciências Farmacêuticas, Universidade Federal de Alfenas (UNIFAL), Minas Gerais – MG, [2]Instituto de Ciências Ambientais, Químicas e Farmacêuticas, Universidade Federal de São Paulo (UNIFESP), São Paulo- SP, [3]Instituto de Química, Universidade Federal de Alfenas (UNIFAL), Minas Gerais-MG, [4]Faculdade de Ciências Farmacêuticas, Universidade de São Paulo (USP), São Paulo- SP.

Rationale: Abusive ethanol consumption may lead to alcohol use disorder (AUD). Its neurotoxic effects are still not clear, although oxidative stress is involved in neuronal apoptosis induced by ethanol. Ayahuasca is a traditional tea with psychoactive effects used in spiritual rituals. Some studies have demonstrated that tea extracts block the expression of ethanol sensitization, showing its possible neuroprotective capacity against ethanol, and may be considered as a possible therapeutic intervention in the treatment of AUD. However, studies with *in vitro* models are scarce.

Objective: To evaluate the neurotoxicity and neuroprotective potential of main compounds found in ayahuasca tea – dimethyltryptamine (DMT) and harmine (HRM) – against ethanol-induced neurotoxicity in SH-SY5Y neuroblastoma cells.

Methodology: A concentration-response curve (CRC) was obtained for both DMT and HRM (0,1, 1, 10, 100 and 1000 µM of each), and also for the fraction of both together (1:1, 1:2, 1:5

and 1:10, DMT and HRM). The highest concentration without neurotoxic effect (NOAEL) was determined for both drugs. Incubations were performed for 48h in SH-SY5Y human neuroblastoma cells. Subsequently, the NOAEL of DMT and HRM were incubated for 48 hours in the presence of the lethal concentration 50 of ethanol (250 mM). Cell viability tests were performed using MTT assay which consists of reducing MTT to formazan (violet-colored precipitate) by the mitochondrial enzyme succinate dehydrogenase, whose activation occurs in cells with intact respiratory metabolism. The cells were incubated in 24-well plates - $1x10^5$ cells per well - in different concentrations of compounds for 48h, a 250 mM KCL solution was used as a positive cell death control and the absorption of the precipitate is read at 595 nm. The Data were compared using analysis of variance (ANOVA) to compare two or more groups, followed by the *Bonferroni* post-test. Differences were considered significant at a value of $p<0.05$.

Results: While NOAEL for DMT was 100 µM, NOAEL for HRM was 10 µM. Thus, the concentration chosen for both substances to continue the experiment was 10 µM. The NOAEL for the substances fraction was 1:2. DMT–ethanol association did not show statistical significance compared to ethanol alone. However, HRM–ethanol association and DMT/HRM fraction-ethanol association were able to prevent ethanol neurotoxicity.

Conclusion: These data suggest that HRM and DMT/HRM fraction, but not DMT, have demonstrated neuroprotective potential. We already know about the mechanism of action of DMT - a serotonergic inhibitor - and HRM - a monoamine oxidase inhibitor - and these results can help in the new research for new AUD treatment However, further studies are needed to understand these interactions.

Keywords: harmine, ethanol, ayahuasca, toxicity, SH-SY5Y.

11 - Analysis of Cannabidiol Treatment in an Animal Model of Autism Caused by Prenatal Exposure to Valproic Acid

Authors: Fernandes, R.A.[1], Oliveira, M.S.[1], Santos. V.R.[1]

[1]Departamento de morfologia, UFMG, Belo Horizonte/MG

Rationale: Autism Spectrum Disorder (ASD) is a neurodevelopmental condition characterized by challenges in social interaction and communication, along with restricted and repetitive behavioral patterns. The ASD has a prevalence of approximately 1% worldwide, but there is currently no effective cure or treatment for the disorder. Valproate (VPA) when

administered during the embryonic period, can induce autism-like behaviors in rodents, making it a suitable animal model for ASD research. The mechanisms underlying VPA-induced autism-like behaviors are associated with dysregulation in the endocannabinoid system (ES) and neuroinflammation. Cannabidiol (CBD) is a non-psychotropic phytocannabinoid found in *Cannabis sativa*. It acts on the central nervous system by modulating the ES and exhibits neuroprotective and anti-inflammatory properties in certain conditions. Therefore, CBD holds promise as a potential therapeutic option for the treatment of ASD.

Methods: The study utilized female Wistar rats and their pups for the experiments. All procedures and animal care adhered to the guidelines set by the Ethics Committee on the Use of Animals (CEUA), following protocol 226/2022. To establish the animal model, pregnant female rats received either VPA at a dosage of 500 mg/kg or saline via intraperitoneal (IP) route on embryonic day 12.5. CBD treatment at a dosage of 30 mg/kg was administered to the pregnant rats on gestational day 12.5, also through IP administration. The assessment of neurodevelopmental abnormalities various behavioral tests were conducted on postnatal days (PND) 9 to 19, including weight analysis, eye opening assessment from PND 13 to 17, posture reflex, and olfactory discrimination on PND 9. To evaluate social interaction and preference, the three-chamber test was performed on PND 30. Short-term memory was assessed using the Novel Object Recognition test on PND 31. Lastly, on PND 32, the Activity Cage test was conducted to observe compulsive self-grooming behaviors. All the tests were analyzed using the Anymaze program.

Results: The neurodevelopmental behavioral tests revealed differences between the VPA-exposed group and the vehicle group, indicating adverse effects of VPA on behavior. However, the group treated with CBD in combination with VPA showed a reversal of the altered behaviors caused by VPA exposure. Controlled tests from PND 30 onwards also exhibited notable distinctions between the VPA-exposed group and the CBD+VPA group, the latter showing a greater preference for social novelty in the three-chamber test (VPA 29.8±16.2, CBD+VPA 60.44±18.37, $p < 0.05$). It is worth mentioning that the offspring of the CBD+VPA group exhibited a curled tail, which is a common characteristic observed in animals exposed to VPA during the embryonic period. These findings suggest that CBD has the potential to alleviate some behavioral impairments of VPA on neurodevelopmental behaviors associated with ASD; it may not completely reverse all physical manifestations associated with VPA exposure.

Discussion/Conclusions: In conclusion, these results suggest that CBD holds promise as a therapeutic intervention for autism-like behaviors induced by VPA. However, further studies are needed to delve into the mechanisms underlying the beneficial effects of CBD and its ability to reverse the detrimental effects of VPA exposure.

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12 - Reduced melatonin during intra-uterine and early post-natal development affects sociability and motor behavior in rats.

Authors: Faria, E.S., Magalhães, L.C.; Carvalho, J.V., Ferraz, J.B.S., Vasconcelos, L.S., Pradela, B.S., Barbosa, L.A.O.; Tilelli, C.Q.

Federal University of São João del-Rei (UFSJ), Divinópolis, MG, Brazil.

Rationale: Autism spectrum disorders (ASD) are associated with sleep deprivation and low levels of melatonin hormone, genetically or environmentally induced. They are characterized by reduced sociability, repetitive behaviors and restricted interests, and can present with comorbidities. Among those, attention deficit and hyperactivity disorder (ADHD) is commonly observed. In this work, we aimed to investigate if the reduction of maternal melatonin interferes with the litter neurodevelopment, as seen by behavioral tests, focusing on sociability, exploratory behavior, anxiety and fear.

Methods: Dams (6- 7 weeks old) were divided into three groups: pinealectomized rats with (MEL, n=3) and without (PTX, n=3) melatonin supplementation (approx. 0.5 mg/kg in the drinking water, 18h00-06h00), and rats subjected to a surgical procedure without pineal removal (SHAM, n=3). After complete recovery from surgery, they were mated with same age male rats. Litter was pruned to 8 pups at the 3rd postnatal day and remained with their mothers until 22 days old. Only part of the litter was used for the experiments described here (SHAM, n=12; PTX, n=8; MEL, n=8). Behavior tests were performed during the 4th week of age, from 18h00 to 23h00, with 24 hours interval between them, in the following order: sociability (3-chamber test), open field, elevated plus maze, and elevated t maze. Data was parametric, thus we used the ANOVA test followed by Tukey´s post-hoc (JASP 0.17.3, University of Amsterdam). Results are presented as mean +/- SEM. Statistical significance

was set for p value equal to or lower than 0.05. UFSJ ethics committee approval: protocol 011/2018.

Results: A group effect was detected for time of interaction with unknown rat, time spent in the empty chamber and sociability coefficient (time spent with unknown rat / total time ratio) ($F(2, 53)=16.03$, 14.12, and 16.08, respectively; $p<0.001$). PTX induced reduced time spent with unknown rat (SHAM: 157.1+/-7.4s; PTX: 100.7+/-17.7s; MEL: 194.6+/-7.4s; $t(2)=-5.61$, PTX vs MEL, $p<0.001$; $t(2)=-3.69$, PTX vs SHAM, $p=0.001$), increased time spent in the center chamber (SHAM: 105.5+/-6.9s; PTX: 165.7+/-19.6s; MEL: 76.7+/-5.4s; $t(2)=5.18$, PTX vs MEL, $p<0.001$; $t(2)=3.84$, PTX vs SHAM, $p<0.001$), and reduced the sociability coefficient (SHAM: 0.54+/-0.03; PTX: 0.34+/-0.06; MEL: 0.65+/-0.02; $t(2)=-5.62$, PTX vs MEL, $p<0.001$; $t(2)=-3.70$, PTX vs SHAM, $p=0.001$). PTX also increased ambulatory behavior, detected in the open field test, as seen with total number of quadrants visited ($F(2, 33)=3.77$; $p=0.033$; SHAM: 60.3+/-5.0; PTX: 98.3+/-7.7; MEL: 61.4+/-6.8; $t(2)=2.51$, PTX vs MEL, $p=0.044$; $t(2)=2.71$, PTX vs SHAM, $p=0.028$). There was no evidence of altered anxiety or fear, from the open field, elevated plus maze, and elevated t maze tests ($p>0.05$).

Discussion/Conclusion: Reduced maternal melatonin can induce altered behavior in the litter, similar to some seen in ASD (reduced sociability) and ADHD (increased motor activity). Our group is currently investigating other aspects of these effects, such as brain oxidative stress and seizures susceptibility, which will enrich the understanding of this model.

Keywords: Autism, Melatonin, Pinealectomy, Behavior, Sociability, Neurodevelopment.

Financial Support: Students received scholarships from UFSJ, FAPEMIG and CNPq. UFSJ provided animals, laboratory structure, and most materials and equipment. LAOB and CQT purchased some materials and equipment.

13 - Characterisation of the behavioural alterations in an animal model of nonmotor symptoms of parkinson's disease

Authors: Schweizer, B.L.A.*[1,2], Prates-Rodrigues, M.[1,2], Gomes, C.P.[1,2], Beraldo, I.J.S.[1,2], Hubner, I.B.[1,2], Mourao, F.A.G.[1], [3], Padovan-Neto, F.E.[4,5], Lopes-Aguiar, C.[1,2].

[1]Departamento de Fisiologia e Biofísica, UFMG, Belo Horizonte/MG., [2]Laboratório de Neurociências Molecular e Comportamental (LANEC), Faculdade de Filosofia e Ciências Humanas (FAFICH), UFMG, [3]Núcleo de Neurociências (NNC), UFMG, [4]Departamento de

Psicologia, USP, Ribeirão Preto/SP, [5]Laboratório de Neuropsicofarmacologia das Doenças Neurodegenerativas, USP.

Rationale: Parkinson's disease (PD) is a neurodegenerative disorder classically defined by progressive degeneration of the nigrostriatal dopaminergic pathway and the presence of motor symptoms (i.e., bradykinesia, resting tremor and/or rigidity). However, a wide range of non-motor symptoms are also common and their mechanisms are still not well understood. These include cognitive impairments, dysfunction of the sleep-wake cycle, depression and anxiety. Such symptoms represent a significant burden for both patients and caregivers as well as a challenge for therapeutic interventions. In particular, sleep abnormalities may precede other symptoms by several years and are likely to worsen the disease prognosis. To investigate the underlying mechanism of sleep disturbances in PD patients and its association with other non-motor symptoms, we first sought to characterise an animal model of early PD.

Methods: The protocol used to generate the PD model was selected after a comprehensive and systematic review of the literature. Adult male Wistar rats were used, and all experiments were carried out in accordance with the guidelines of the Research Ethics Committee of UFMG (CEUA PP0154/2022). To generate the PD model, the rats were submitted to bilateral 6- hydroxydopamine (6-OHDA) infusion into the dorsal striatum to produce a partial loss of dopaminergic neurotransmission (Vehicle: N=8 and 6-OHDA: N=11) and subsequently tested for behavioural alterations resembling those observed in PD patients. Statistical analyses were performed using GraphPad Prism version 9.00 (GraphPad Software, Inc). The homogeneity of variance of all variables was assessed using Shapiro-Wilk and Kolmogorov–Smirnov tests. Student's t-test was used to analyse variables between groups in all tests and two-way repeated measures (RM) analysis of variance (ANOVA) was also performed in the open field test. The accepted level of significance was $p \leq 0.05$ and the values are indicated as mean ± standard deviation.

Results: The footprint test was used to assess possible changes in gait during the 3rd week following infusion. No significant difference was observed between the mean hindlimb ($t(14)=0.234$, $p=0.4$) and forelimb ($t(14)=0.427$, $p=0.34$) stride lengths when comparing the 6-OHDA group and the control. Both groups were also then tested for 15 min in the open field test. Two-way RM ANOVA analysis revealed no statistically significant interaction between the effects of time and treatment ($F(14, 238)=1,124$, $p=0.34$). Distance travelled decreased over time in both groups ($F(14, 238)=13.08$, $p=0.0001$), but no treatment effect was observed ($p=0.1143$). However, the 6-OHDA group crossed the central zones fewer times than the

control group (t(14)=3.979, p=0.007), suggesting possible anxiety-like phenotypes that deserve further investigation. A difference in sucrose preference (as an indicator of anhedonia) between the control and 6-OHDA groups was only apparent at week 1 (t(14)=2.507, p=0.01), not at week 3 (t(14)=1.579, p=0.07). At 3 weeks post-infusion, we also found reduced social interaction in the 6-OHDA group compared to the control group (t(14)=2.394, p=0.02).

Conclusion: The PD model successfully reproduced some of the non-motor alterations observed in the PD patients. The next steps will involve combining electrophysiological recordings with behavioural tests to investigate possible associations between sleep and the observed behavioural alterations.

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14 - Contributions of neuroscience to innovation in neurophysiology teaching

Authors: Érica Maria Granjeiro

Biological Departament of State University of Feira de Santana (UEFS)

Rationale: This work presents the description and analysis of a didactic experience developed in a public University in northeastern Brazil, involving the use of a learning stations enabling innovation in the neurophysiology teaching. This is an experience report about the use of active and participatory methodologies, based on neurocience concepts, the purspose of building an innovative environment in the classroom. Therefore teaching learning stations were introduced as a tool that could help the student to contemplate the complexity of the concepts and mechanisms involved in neuronal activity.

Methods: In the second semester of 2022 and the first semester of 2023, the learning stations were implemented during the courses of biological bases of psychology provided to 45 students of the Department of Health at the State University of Feira de Santana. To this end, a learning trail was created and implemented, contemplating different learning styles, including visual, auditory and kinesthetic. For these purposes, didactic activities, in the hybrid format were implemented, which involved a systematic set of different face-to-face and online didactic activities including: dialogued lectures, construction three-dimensional models of neurons, reading of scientific articles, group debates, teaching by through research, vídeos, podcasts, Information and Communication Technologies (TICS), virtual reality, as well as the

elaboration of Portfolios and presentation of Seminars.

Results: The pedagogical activities in the classroom were applied by the teacher considering neuroscience concepts, especially those involved in the basic processes for the formation of short and long-term memory, through the elicitation of prior knowledge, the creation of cognitive conflict, as well as involving the students in matters of interest and related to their day-to-day activities. During the entire teaching-learning process, the students had the help of the teacher for the application and appropriation of knowledge and carried out a reflection on learning, at the end of the course.

Discussion: In the present work, students developed an investigative attitude and were able to create opportunities for acquiring knowledge in a conceptually consistent way, in addition to developing important skills for problem solving and teamwork. It is importante to note, some aspects that supported the application of such methodologies for the teaching-learning process of human neurophysiology content in classes of undergraduate health courses, and supported their planning by the professor, such as: (1) difficulties of students in understanding the classic physiological mechanisms of synapses and neuronal plasticity, as well as the theoretical and practical bases for understanding the pathophysiology of neurological diseases (2) to integrate such mechanisms with the contents studied in the disciplines of anatomy, biochemistry and biophysics (3) to establish the relationship between teaching and research in the classroom, introducing undergraduate health students to investigative processes in their specific area; (4) to encourage autonomous learning and teamwork.

Conclusion: It is hoped that this work can contribute to the reflection on the importance of Neuroscience innovation in undergraduate teaching, especially for the contents of Neurophysiology, providing students with active, interactive, contextualized and meaningful learning situations, based on neuroscience concepts related to how the brain learns.

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No Conflicts of Interest Disclosure.

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15 - Standardization of an in vivo Experimental Model of Dementia to Evaluate Donepezil Treatment

Authors: Anauana Karolyna de Souza[1], Gislaine Ribeiro Pereira[2], Isabelly Fernanda Ferraz de souza[2], Letícia Arvalho Rocha[2], Maria Júlia Plácido[2], Marília Gabriella Alves Goulart Pereira[1], Rodrigo Vicentino Plácido[3], Thainá Cristina Marques[1]

[1]Federal University of Alfenas (UNIFAL-MG), Alfenas, Minas Gerais, Brazil/Department of Biochemistry of the Institute of Biomedical Sciences; [2]Department of Food and Medicines (UNIFAL-MG); [3]Department of Clinical and Toxicological Analysis (UNIFAL-MG).

Rationale: Dementia is a chronic and progressive neuropathological condition, responsible for causing profound cognitive changes, such as behavioral changes and memory loss. Alzheimer's disease is the cause of dementia most often associated with aging. The standardization of experimental designs developed with the aim of reproducing the pathophysiological aspects of dementia, including Alzheimer's disease, is of paramount importance for the evaluation of promising pharmacological therapies.

Methodology: Three experimental groups of twelve animals each were used, receiving aluminum chloride (AlCl3) (100 mg/kg) by gavage for 42 consecutive days (approved by CEUA, protocol No. 0014/2020). The tests were carried out with male Wistar rats aged between 6-7 weeks, weighing between 200-250 grams. The induction positive control group received aluminum chloride (100 mg/kg) and no treatment. The Negative Induction Control group received water orally and no treatment. The third and last group received aluminum chloride (100 mg/Kg) and was treated with a solution of donepezil (3 mg/kg), via oral administration. In order to evaluate the effectiveness of the model of Alzheimer's dementia tested, the animals that had the disease induced were submitted to the test of spontaneous recognition of objects. Thus, statistical calculations were performed based on the time spent by each animal, in their respective experimental groups, to recognize the objects. Calculations were developed based on the main cognition values: relative discrimination index and cognition index. The sample mean and standard deviation were obtained using the GraphPad Prism© program. As well as the comparison of the data that was performed by one-way ANOVA, followed by the Tukey test, with a confidence level of $p \leq 0.05$.

Results: The Alzheimer's disease induction groups (AlCl3) presented significantly lower values of relative discrimination and discrimination index (51.00 ± 7.09 and 0.02 ± 0.14) when compared to the control group (water) (70.40 ± 9.11 and 0.41 ± 0.18). The group induced by AlCl3 and treated with oral donepezil showed significantly higher values of relative discrimination and discrimination index (0.32 ± 0.10 and 66.04 ± 5.08%), respectively, compared to the AlCl3 group (51.00 ± 7.09 and 0.02 ± 0.14).

Discussion/Conclusion: The experimental delineation of induction of Alzheimer's disease dementia in rats presented, proved to be suitable for the standardization of the induction model. Likewise, its efficiency in evaluating new treatments for Alzheimer's disease with donepezil has been proven. These results were expected, since numerous studies have shown that aluminum chloride affects the central nervous system, causing pathological changes characteristic of Alzheimer's disease, such as dementia and other cognitive changes. Therefore, the induction model used in this study is proven to be effective, less invasive than other models described in the literature, in addition to enabling future replications.

Keywords: Alzheimer's disease; induction; aluminum; treatment; donepezil.

Funding/Support: FAPEMIG, CNPq, Capes (funding code 001), UNIFAL-MG.

Declaration of conflicts of interest: The authors of this research declare that there is no conflict of interest.

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16 - Participation of asic1a cation channels in locus coeruleus in co2-induced behavioral alterations in mice

Authors: Pinheiro, L.R.*, Frias, A.T., Bícego, K.C, Gargaglioni, L.H.

Dept of Animal Morphology and Physiology, São Paulo State University, FCAV, Brazil.

Introduction: Panic disorder (PD) is characterized by panic attacks, in which the patient can quickly develop behavioral changes and respiratory symptoms. Although the pathophysiology of this disorder remains unclear, some studies suggest a putative connection between alterations in CO2 /pH chemosensitivity and PD, since episodes of hypoxia or hypercapnia can trigger panic attacks. ASIC1a channels are responsive to decrease in pH, which have been identified as relevant to CO2-induced panicogenic responses. The locus coeruleus (LC) is a chemosensitive region capable of generating emotional and physical responses during episodes of stress, in addition to having an important role in the ventilatory response to CO2.

Objective: To evaluate the participation of LC ASIC1a channels in the behavioral responses to an exposure of 20% CO2 in male mice after intra-LC microinjection of Psalmotoxin-1 (Pstx-1; selective blocker for ASIC1a channel).

Methodology: The experiments were carried out in C57BL/6 male mice (8 weeks old; Protocol CEUA/FCAV-UNESP: 3451/22), which underwent stereotaxic surgery for the implantation of guide cannulas directed to the LC. Seven days later, 50 ng/0.1 uL of Pstx-1 or saline solution were administered intra-LC. Behaviors related to panic attack were recorded by a camera, positioned so that the observer could clearly see the animal's movements. The escape response was analyzed following the parameters: number of jumps, freezing, running and rearing.

Results: The results found in the control group (n=6) and Pstx-1 (n=5) indicate that the ASIC1a channels participate in those behavioral responses, since a decrease in the number of jumps and freezing in the animals that received intra-LC administration of Pstx-1 was observed (Saline: 9.33 ± 5.85 vs Pstx-1: 3.40 ± 3.85). No difference in running and rearing behavior was observed.

Conclusion: Our data suggest that ASIC1a channels in the LC are involved in CO2-induced-panic behavior.

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17 – Maternal melatonin absence and sodium valproate exposure impact oxidative stress parameters in central nervous system of wistar rat´s neonates

Authors: Granato, J.L., Ramos, S.; Ribeiro, E.H.P.; Faria, A.C.F.; Maia, G.A.S.; Barbosa, L.A.; Tilelli, C.Q.

Federal University of São João del-Rei (UFSJ), Campus Centro-Oeste D. Lindu, Divinópolis, MG, Brazil.

Rationale: Melatonin, a hormone provided by the mother to the fetus during development, acts as an antioxidant in important cellular processes of the nervous system. The exposure to valproic acid (VPA) during intrauterine development serves as a model for studying Autism Spectrum Disorder (ASD). The mechanism behind the VPA-induced effects is not yet clear but involves the promotion of reactive oxygen species formation and oxidative stress in the nervous system, resulting in associated neurological conditions. Our study aimed to assess whether the absence of maternal melatonin during intrauterine development results in impairments similar to those observed in the VPA model of ASD in the offspring.

Methods: The research project was approved by UFSJ ethics committee, protocol 011/2018. Dams Wistar rats were divided into five groups: pinealectomized rats with (MEL) and without (PTX) melatonin supplementation (0.5 mg/kg in drinking water, 18h00-06h00), rats subjected to a surgical procedure without pineal removal (SHAM), rats injected intraperitoneally with sodium valproate (500 mg/kg) on the 13th day of gestation (VPA), and rats injected with saline (SAL) on the 13th day of gestation. Female rats became pregnant after complete post-surgical recovery (MEL, PTX, and SHAM groups). The pups were euthanized 48 hours after birth, and their brains were extracted and analyzed for GSH content (nmol GSH/mg protein), hydrogen peroxide (H2O2) production (nmol H2O2 /mg protein), and lipid peroxidation (nmol MDA/mg protein). We used ANOVA, after testing for normality distribution (GraphPad Prism 8.0.1) for all comparisons: SAL (n=9), VPA (n=11), SHAM (n=12), PTX (n=11), and MEL (n=12). Results are shown as mean +/- SEM.

Results: There was a group effect detected by ANOVA ($F(4, 50)=4.056$, $p=0.0063$). VPA treatment increased oxidative stress as shown by lipid peroxidation ($t(50)=3.201$; $p=0.0024$; VPA=783.4+/-131.8; SAL=274.7+/-43.27), as well as the SHAM procedure ($t(50)=2.049$, SHAM vs PTX, $p=0.0457$; $t(50)=2.148$, SHAM vs MEL, $p=0.0366$; PTX=429.9+/-60.27; SHAM=732.4+/-156.3; MEL=422.3+/-66.37). Preliminary data comparing male vs female neonates suggests increased oxidative stress in males in H2O2 content, lipid peroxidation, and

GSH activity (F(1,5)=84.72; p=0.0003; F(1,11)=9.643; p=0.01; F(1,12)=30.37; p=0.0001; respectively).

Discussion/Conclusion: Our data suggests that the lack of melatonin during embryogenesis and early development could be an important factor in pathological processes underlying neurodevelopmental disorders similar to those seen in ASD. Additionally, possible differential modulation of oxidative stress in male and female pups could contribute to the variation of effects of VPA treatment in the induction of ASD depending on their sex, as reported by others.

Keywords: Autism, Melatonin, Pinealectomy, Oxidative Stress, VPA, Na+/K+-ATPase Activity, Neurodevelopment.

Financial Support: Students received scholarships from UFSJ, FAPEMIG and CNPq. UFSJ provided animals, laboratory structure, and most materials and equipment. LAOB and CQT purchased some materials and equipment.

18 - Performance of 3xTg-AD Alzheimer's Disease Mice in Memory Tests in Aversive and Non-aversive Contexts

Authors: Cerveira, A.J.D.O.[a], de Souza, C.C.B.[a], Ramalho, B.A.C.[b], Costa, H.B.[b], de Lacerda, K.J.C.C.[a,c], Padovan-Neto, F.E.[a]

[a]Department of Psychology, Faculty of Philosophy, Sciences and Letters of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil, [b]Department of Physics, Faculty of Philosophy, Sciences and Letters of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil, [c]Nuclear Medicine & Molecular Imaging Section, Image Science and Medical Physics Center, Internal Medicine Department and Postgraduate Program, Ribeirão Preto School of Medicine, University of São Paulo, Ribeirão Preto, Brazil.

Rationale: Alzheimer's disease (AD) is a progressive neurocognitive disorder that affects memory and cognition. AD's neurophysiology can be mimicked in transgenic animal models, like the 3xTg-AD mouse strain. Memory tests are commonly used to assess memory deficits in these mice. To better understand AD with this model, it's important to characterize the mice's deficit progression and differentiate between different types of tasks.

Methods: Male 3xTg-AD mice (n=16) were compared to B6 129 SF2/J control mice (n=20). The object recognition test and the active avoidance test were administered at three life stages

of the animals: T1 (4 to 6 months), T2 (8 to 10 months), and T3 (12 to 14 months). The object recognition test relies on mice's natural tendency to explore novel objects over familiar ones, assessing declarative memory by recognizing a new object in a non-aversive context. The animals were exposed for 5 minutes to two similar objects in different quadrants of the apparatus. After a 15-minute interval, they were exposed for another 5 minutes to one of the familiar objects (FO) alongside a new object (NO). The ability to recognize the NO was measured by a recognition index based on the time the animals spent in the NO quadrant relative to the FO quadrant. The active avoidance test was conducted to evaluate memory in an aversive learning context. Each mouse underwent three consecutive days of learning, each with 40 cycles, where a sound was triggered for 10 seconds after 30 to 90 seconds. Crossing to the opposite side of the box during the sound prevented a 0.3 mA shock lasting 3 seconds right after the sound ended. This avoidance behavior contrasted with escape (crossing the box during the shock) and failure (not crossing the box, resulting in a 3-second shock). Results were analyzed by the Student's t-test (significance level of 0.05) to compare both groups at each time point. The Holm-Sidak correction was applied.

Results: Both groups performed similarly in object recognition in T1 and T2 but the 3xTg-AD group showed a lower recognition index in T3 ($p=0.02$). Both groups had comparable avoidance, escape, and failure rates. Compared to the control group, the 3xTg-AD group had shorter avoidance latency in T2 ($p=0.04$) and reduced escape latency in T3 ($p=0.03$).

Discussion/Conclusions: The lower recognition index observed in the 3xTg-AD animals in T3 suggests the development of declarative memory deficits. However, our findings regarding avoidance, escape, and failure rates indicate a higher preservation of evoked memory in an aversive context. Additionally, the shorter avoidance latency (T2) and escape latency (T3) in the 3xTg-AD group appear to indicate increased sensitivity to anxiety in these animals, which corresponds with findings in the literature. It is likely that the animals' anxiety sensitivity contributes to the maintenance of evoked memory in the active avoidance test. In conclusion, the indicators of cognitive alterations may be related to the level of aversiveness in the context used in the tasks. This study enhances understanding of 3xTg-AD memory performance in distinct contexts, aiding future Alzheimer's research in animals in humans.

Keywords: Alzheimer’s disease; 3xTg-AD; memory tests; aversive context

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Declaration of Interests: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this abstract.

19 - Development of nanoparticles of biosurfactants/protease inhibitors and study of the effects on in vitro inflammation model by lps in glial cells

Authors: Camila dos Santos Oliveira[1]; João Augusto Ferreira Gonzaga[1], José Maurício Schneedorf Ferreira da Silva[1], Kris Simone Tranches Dias[1], Marina Quádrio Raposo Branco Rodrigues[2], Diego Fernandes Livio[2], Paulo Afonso Granjeiro[2], José Antônio da Silva[2], George Augusto Veloso de Oliveira[1]; Marilia Gabriella Alves Goulart Pereira[1].

[1]Federal University of Alfenas, Brazil, [2]Federal University of São João Del-Rei, Brazil.

Introduction: The Acute Respiratory Syndrome caused by SARS-CoV-2 and its neurological consequences generate a serious public health problem. Three years after the beginning of the biggest pandemic of the last century, there are still few therapeutic agents with multiple actions to treat neurological symptoms.

Rationale: Previous results obtained by our research group show that biosurfactants associated with protease inhibitors may have an important antiviral role against SARS-CoV-2 (patent pending). Therefore, it is believed that the development of nanoparticles (NPs) from these substances, as well as pharmacodynamic analysis and in vitro tests in glial cells against the inflammatory process, will bring perspectives on their potential use for the treatment of neurological symptoms, caused by SARS-CoV-2 and other viruses.

Methods: The present study developed biosurfactant NPs associated with protease inhibitors (AcTI and Nafamostat), produced by the A/O/A double microemulsion method. Samples from the purification of NPs in dialysis bags were submitted to encapsulation efficiency analysis by colorimetric method to determine the total concentration of inhibitor in the NPs and concentration of free protease inhibitor in the dialysis water. The release study of protease inhibitors incorporated into NPs was performed as described by ZU and coworkers (ZU, Yuangang et al, Drug delivery, Volume 23, Initial page 971-981 and Year 2016).The evaluation of the cytotoxicity of the compounds was carried out in a primary culture of astrocytes and microglia using the methyl thiazolyl tetrazolium (MTT) assay.

Results: The characterization of the nanoparticles demonstrated that the control NPs exhibited a size range with an average diameter between 477.4 and 408.04 nm, with a

polydispersion index (PDI) of 0.391-0.395. On the other hand, the NPs with AcTI inhibitor showed larger mean diameters, ranging from 895.06 and 802.2 nm, demonstrating PDIs of 0.386- 0.619. In relation to the NPs with Nafamostat inhibitor, they present results with smaller average diameter, between 194.3 and 202.9 nm, with PDIs of 0.246-0.216. The release assay carried out with Biosurfactant NPs and nafamostat inhibitor, demonstrated a controlled release over 72 hours. The cell viability test demonstrating that the biosurfactant control NPs did not affect the metabolic activity of the cells, showing cell viability in different mg/ml dilutions.

Discussion/Conclusions: The size of NPs influences their systemic behavior, making NPs-nafamostat a promising option due to their smaller size and reduced polydispersion. The biosurfactant in the NPs may possess anti-inflammatory properties, modulating the immune response and reducing pro-inflammatory cytokines. The encapsulation of protease inhibitors in NPs-biosurfactant resulted in controlled release over 72 hours, extending their therapeutic potential. Cell viability tests demonstrated that glial cells remained metabolically active when exposed to NPs-control biosurfactant, indicating their safety. In summary, our findings suggest that NPs-nafamostat have the potential to cross the blood-brain barrier, reduce inflammatory processes, and offer prolonged therapy for central nervous system disorders.

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20 - Effects of changes in extracellular osmolality on calcium intracellular concentrations and lactate release by hypothalamic cultured astrocytes

Authors: Silvia Graciela Ruginsk[1], Leticia Cruz de Almeida[1], Milton Kennedy Aquino Junior[2], Marilia Gabriela Alves Goulart Pereira[2]

[1]Department of Physiological Sciences, Biomedical Sciences Institute, Federal University of Alfenas, [2]Department of Biochemistry, Biomedical Sciences Institute, Federal University of Alfenas.

Rationale: The central nervous system is comprised of neurons and glial cells (or neuroglia), which together participate in important homeostatic function, such as osmoregulation. In neurons, osmotic signal transduction is mediated by the opening or closing of ion channels, some of which are also expressed by astrocytes, such as the transient receptor potential vanilloid type 1 (TRPV1 channel). Therefore, the present study aimed to evaluate the

participation astrocytic TRPV1 channels in Ca^{2+} and lactate balances in response to changes in extracellular fluid (ECF) osmolality.

Methods: Astrocytes were isolated from murine neonate hypothalami and cultured for 7-15 days. On the day of the experiment, cells were pre-incubated for 30 minutes with conventional culture medium containing or not Capsazepine (CAPS, 30 µM, TRPV1 channel antagonist). After this period, cells were incubated for 2h with Hank solutions (230, 290 or 350 mOsm/Kg H_2O), containing or not CAPS. Lactate concentrations in the medium were estimated after 1 and 2h of incubation with Hank solutions using a colorimetric assay. Calcium intracellular concentrations were measured using a colorimetric reaction, performed with cell lysates obtained after 2h of stimulation. Cell viability and total protein content were also estimated. All the results were analyzed by Two-Way Analysis of Variance, followed by Sidak's multiple comparison posttest.

Results: Lactate release was not altered following exposure to changes in ECF osmolality. However, incubation with CAPS significantly increased lactate concentrations in the medium after 2h of stimulation ($p<0.001$), regardless of the ECF osmolality (290 mOsm/Kg H_2O = 27.04±1.55 *versus* 41.16±1.79 µg/mg of protein; 230 mOsm/Kg H_2O = 24.81±1.62 *versus* 48.12±1.62 µg/mg of protein; 350 mOsm/Kg H_2O = 25.36±1.72 *versus* 38.71±1.12 79 µg/mg of protein). Under hypotonic conditions (230 mOsm/Kg H_2O), CAPS also increased lactate release after 1h of stimulation (27.56±1.37 *versus* 34.70±0.94 µg/mg of protein, $p<0.05$). The increase in lactate release induced by CAPS treatment was greater under hypotonic conditions, when compared to isotonic and hypertonic stimulations. No relevant changes were found in total Ca^{2+} intracellular concentrations in astrocytes incubated for 2h under different ECF osmolalities. Treatment with CAPS, in turn, reduced this parameter only under isotonic conditions (14.70±0.25 *versus* 12.76±0.60 µg/mg protein, $p<0.01$). No significant changes in cell viability were found among different experimental groups.

Conclusions: The results obtained so far indicate that alterations in Ca^{2+} balance are not likely to be detected after a 2h exposure to osmolality imbalances or TRPV1 antagonism. Lactate release, however, is highly affected by TRPV1 blockade, particularly under hypotonic conditions.

Financial Support: Leticia Cruz de Almeida hold an individual institutional scholarship from Fundação Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES).

Conflicts of Interest Disclosure: Nothing to declare.

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21 - Sex-difference in respiratory function in adult mice exposed to a neonatal model of stress

Authors: Camila Migliano de Oliveira[1]; Angela Cristina Nicola[1]; Luciane H. Gargaglioni[1], Luana Tenorio-Lopes[1]

[1]Department of Animal Morphology and Physiology, Sao Paulo State University, Jaboticabal, SP Brazil.

Background: There is a scientific consensus that stress has persistent and sex-specific effects on health. The brain is considered a major target of the effects of stress, and exposure to early life adversities significantly increases the risk of developing psychiatric conditions, such as panic disorder (PD) and anxiety in adulthood. The neural system regulating breathing is of great interest in the study of those disorders since some of the symptoms observed in patients include hyperventilation and increased chemosensitivity to CO_2. Although anxiety affects more than 7% of the world's population and has a sex-specific prevalence affecting double of women compared to men, its physiological mechanisms are not completely understood. Neonatal maternal separation (NMS) is a well-established and clinically relevant form of stress commonly used in basic research. NMS disrupts the function of the hypothalamus-pituitary-adrenal (HPA) axis resulting in a prolonged elevation of the stress hormone, corticosterone. It was previously demonstrated that female adult rats previously exposed to NMS present an increased hypercapnic ventilatory response (HcVR) observed through an increase in respiratory frequency (Tenorio-Lopes et al., 2020). However, that response was not observed in male rats exposed to the same conditions. These results suggest that NMS causes a sex-specific increase in the chemosensitivity response to CO_2, the same features observed in patients suffering from anxiety disorders.

Aim: Our question here was to investigate if the NMS protocol can trigger the same sex-specific HcVR in mice, allowing us to extend our investigation of anxiety disorders using mice as animal models.

Methods: To address our question, we used male and female C57BL6 mice that were subjected to the NMS protocol. From post-natal day 3 to 12, pups were separated from their mother. They were placed in an incubator for 3 h/day separated from each other. Control pups remained undisturbed. Mice were reared until adulthood and when reached 8-10 weeks the experiments were performed. The ventilatory response to hypercapnia was measured by whole-body plethysmography (7%CO_2 for 15 min).

Results: Our results showed that both male and female mice increased the HcVR compared with their respective controls during normocapnia. Additionally, there was a sex-specific difference between NMS male and female mice. Female NMS mice present a lower tidal volume in response to hypercapnia compared to male NMS mice.

Conclusion: These results show that mice seem to respond differently to the effects of NMS and hypercapnia compared to rats. Additionally, C57BL6 female mice seem to be a reliable model for investigating the physiopathology mechanisms regarding respiratory control in anxiety disorders.

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22 – Gene mutation in neurocutaneous melanosis and ruptured arterial aneurysm

Authors: João Thiago Aragão Fermiano[1] ; Lívia Ferreira Silva Verzola[2] ; Maitê Lôbo Kolarik[3] ; Marlei Josiele Augusto[1] ; Deisy Mara da Silva Longo[1] ; Fernando Silva Ramalho[1].

[1] Department of Pathology and Legal Medicine, Ribeirão Preto School of Medicine - University of São Paulo (FMRP-USP); [2] Franca Municipal University Center (UNI-FACEF); [3] Genomic Medicine Center of the Clinical Hospital of Ribeirão Preto School of Medicine - University of São Paulo (CMG HCFMRP-USP).

Rationale: A 6 months and 15 days old girl clinically diagnosed with Neurocutaneous Melanosis was treated in 2014 at the Clinical Hospital of Ribeirão Preto School of Medicine – University of São Paulo (HCFMRP-USP) as a victim of convulsive seizures and aspiration of breast milk, going to death shortly after entry. During the necropsy examination, a ruptured

left subclavian artery aneurysm with hemothorax was identified, with hypovolemic shock being the cause of death, in addition to the identification of several nevi in the brain and skin (neurocutaneous), and the genetic cause was raised as the inductor of this joint condition. The research aims to identify a possible mutation in BRAF V600E and NRAS Q61R in the tissue of the neurocutaneous nevus and the ruptured left subclavian artery aneurysm with the formation of the aneurysm and its rupture, correlating with the cause of death, clinical record and histopathological changes.

Methods: Samples of aneurysm and neurocutaneous nevus were collected from the Pathology Service (SERPAT) of HCFMRP-USP and fixed in buffered formaldehyde and embedded in paraffin, for the production of histological sections, followed by section preparation and hematoxylin and eosin (HE) staining. Histopathological alterations were evaluated using two specific stains: for elastic fibers, staining with Verhoeff's hematoxylin was used, while for collagen deposition, staining with Masson's trichrome in paraffin-embedded arterial tissue was used. Immunohistochemistry was performed to identify: epithelioid cells by anti-HMB-45 antibody and melanocytes by anti-Melan-A antibody. Genetic sequencing of the neurocutaneous nevus was also carried out, through the extraction of DNA from the paraffin-embedded sample, its quantification and sequencing by the Sanger method in the V600E codon of BRAF and NRAS Q61R by the 3500 Genetic Analyzer sequencer by the Genomic Medicine Center (CMG) of HCFMRP-USP and Hemocentro Foundation of Ribeirão Preto. This research was submitted to analysis by the Research Ethics Committee (CEP) of HCFMRP-USP and obtained its approval (number: 6017254/2023).

Results: The V600E mutation in BRAF was identified in the neurocutaneous nevus tissue and several melanocytic populations positive for Melan-A and HMB-45 were identified in the same tissue, confirming the neurocutaneous melanosis caused by this mutation. In the aneurysm tissue, collagen deposition was identified to the detriment of elastic fibers, but the mutation in NRAS Q61R and V600E BRAF was not identified.

Discussion/Conclusions: The fatal rupture of the aneurysm was due to altered collagen deposition to the detriment of elastic fibers, being the cause of this fatal hemodynamic disorder. Mutant BRAF caused the formation of nevi and the general picture of neurocutaneous melanosis and clinical record of epilepsy and seizures. Among the contributions to health science, the shared picture of neurocutaneous melanosis and ruptured aneurysm is considered extremely rare and its fatal rupture may be related to other gene mutation.

Financial Support: This research was financed by our laboratory (Hepatic Pathology Laboratory of the Department of Pathology and Legal Medicine at FMRP-USP) and CMG HCFMRP-USP, with no funding through project submission to public research funding agencies or private financing external to FMRP-USP

Conflicts of Interest Disclosure: The authors declare that there is no conflict of interest.

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23 - Investigation of the role of parafovea and fovea in the inspection of facial expressions

Urtado, M. B.[1], Rodrigues, R. D.[2], Fukusima, S. S.[1]

[1]Perception and Psychophysics Laboratory, Department of Psychology, Faculty of Philosophy, Sciences, and Letters of Ribeirão Preto, University of São Paulo (USP), [2]Institute of Mathematical and Computational Sciences (ICMC), University of São Paulo (USP).

Rationale: The investigation into visual patterns and attentional processes in recognizing fundamental emotional facial expressions remains inconclusive. This uncertainty might stem from the eye tracking method, which solely registers the foveal region of the visual field, despite simultaneous peripheral and parafoveal information. Identifying the location of visual input within the visual field is crucial in isolating critical facial areas for expression recognition. Such exploration contributes to an enhanced comprehension of the visual processing of emotional faces, whether it hinges on holistic or feature-based processing. This study aims to investigate the visual pattern in the recognition of basic facial expressions under conditions of visual unrestricted viewing (NRV), visual restriction at the parafoveal (PFV) and foveal (FV) levels.

Methods: The study involved 174 healthy volunteers across three groups (NVR, PFV, FV). Procedures included surveys, acuity tests, eye tracker calibration, and exposure to facial stimuli. Controlled visual field restriction was accomplished through eye tracking and gaze-contingency methods, enabling the analysis of approaches to assess 30 facial expressions divided into five categories (happy, sad, neutral, fearful, and angry). This method allowed the

differentiation of the fixated elements from processed elements. Eye tracking data was submitted to Eye Movement Metrics and Visualization (Eye MMV) for fixation transformation. The statistical analysis incorporated mean fixation count, duration, visual inspection time, and recognition accuracy as dependent variables, while NVR, PFV, and FV served as independent variables. The analysis employed Kruskal-Wallis and Dunn's tests.

Results: Preliminary results showed significant variations in recognition accuracy among groups (FV: 85%, PFV: 93%, NRV: 93%, $\rho < .05$). Post hoc Dunn's tests highlighted notable differences, with FV differing from both PFV ($\rho = .00$) and NRV ($\rho = .00$). Inspection times also varied significantly among groups ($\rho < .05$). Fixation counts differed significantly between FV/PFV and NRV ($\rho = .00$). Additionally, fixation durations showed significant differences across all groups ($\rho < .05$), increasing with more restriction ($\rho = .00$). FV group had significantly lower accuracy in recognizing sadness and anger expressions compared to PFV and NRV groups ($\rho = .00$). The average inspection time for all facial expressions exhibited statistically significant differences among groups ($\rho = .00$). Regarding sadness and anger expressions, the average fixation count differed significantly between groups ($\rho = .00$). Fixation count for happiness, neutrality, and fear expression varied between FV/PFV and NRV groups ($\rho = .00$). Average fixation duration displayed statistical significance across all experimental groups for all facial expressions ($\rho = .00$).

Discussion/Conclusions: The findings highlight the role of specific visual areas in expression recognition. Parafoveal vision shows comparable accuracy to unrestricted viewing, underscoring its importance. In the FV group, lower accuracy is observed in recognizing sadness and anger expressions. Exclusive central focus doesn't enhance performance, unlike parafoveal vision, which is similar in accuracy to the NVR group. These results emphasize parafoveal and peripheral vision's importance, advancing our understanding of cognitive processes. In subsequent research, we will explore visual restriction's impact on observed patterns by AOIs (Area of Interest).

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24 - Neural Pathways to Success in Higher Education: Linking Neuroscience and Academic Self-Efficacy

Ana Julia Ribeiro[1] ; Janine Albuquerque Nogueira[2] ; Miguel Garcia Rufino[1] ; Victoria Marcella Macedo Martins[1] ; Vitória Ferrari Shiroma[1] ; Fernando Eduardo Padovan Neto[1]

[1] Universidade de São Paulo, Faculdade de Filosofia Ciências e Letras de Ribeirão Preto, Ribeirão Preto, SP, Brasil. [2] Universidade de Fortaleza, Fortaleza, CE, Brasil.

Rationale: Academic self-efficacy refers to undergraduates' belief in their abilities to execute the necessary actions to meet academic goals. Higher academic self-efficacy is linked to improved academic performance and positive emotions associated with learning. Furthermore, academic self-efficacy can influence goal-setting and student motivation. Studies suggest that academic self-efficacy plays a pivotal role in an undergraduate's development, affecting their integration, retention, and academic success. Research also indicates that understanding general neuroscience concepts can shape perceptions of efficacy and the motivation to overcome challenges and achieve success in the educational setting. Given this background, this study hypothesizes that exposure to neuroscience correlates with elevated levels of academic self-efficacy among undergraduates.

Methods: Data from 412 undergraduate students, ranging in age from 18 to 68, were collected through electronic form responses. Of this group, 67% are female, 32% are male, and 1% identify with other genders. Participants completed a sociodemographic survey and another questionnaire concerning their prior exposure to neuroscience, evaluating the significance and frequency of their interactions with neuroscientific topics. The Higher Education Self-Efficacy Scale (AEFS) was used to measure perceptions of academic self-efficacy within the context of higher education. Additionally, a survey on neuroscience knowledge was carried out to ascertain students' familiarity with this subject. Quantitative data were processed using the Just Another Statistics Program (JASP 0.17.1.0) software, adopting a 5% alpha significance level for statistical analyses.

Results: The majority of students agree that understanding neuroscience is essential for their careers, with 85% in agreement. They also emphasize the importance of dialogue between students and neuroscientists, with 89% highlighting its significance. However, a notable portion reported that they had not taken neuroscience courses during their undergraduate studies (51%), did not attend any courses related to the field (79%), or did not receive neuroscientific information from their academic institutions (33%). Those with more

comprehensive exposure to neuroscience, including participation in extracurricular courses and specialized disciplines, scored significantly higher on the AEFS ($t(410)=2.54$, $p=0.01$) and on the general neuroscience knowledge questionnaire ($t(410)=4.74$, $p<0.001$) compared to those unfamiliar with the neuroscience field.

Conclusions: Undergraduates clearly recognize the importance of both knowledge in and interaction with the field of neuroscience for their future careers. The results of this study indicate a positive relationship between familiarity with neuroscience and perceptions of academic self-efficacy. Given the crucial role of self-efficacy in academic success, strategies that introduce students to neuroscience could further enhance this perception, potentially boosting academic performance among undergraduates.

25 - Personality traits in organizational leaders of private companies in brazil

Authors: Clarice Santana[(1);] Carmen Flores-Mendoza[(2)]

[1]Master's Degree in Neurosciences of the Institute of Biological Sciences of the Federal University of Minas Gerais – ICB/UFMG; [2]Department of Psychology, Faculty of Philosophy and Human Sciences, Federal University of Minas Gerais – FAFICH/UFMG.

Introduction: Fundamental personality traits are characterized by stable patterns of cognition, emotion, and behavior, which receive biological and environmental influences. Traits significantly influence behavioral variation, including those related to the ability to lead, which impacts the effectiveness of organizational performance. Several studies have brought important insights into the relationships between the five personality traits and leadership, revealing that some of them may be stronger in leaders.

Objective: To investigate the possible differences in the indices of personality factors in leaders and non-leaders and to verify how the gender variable is related to the differences found.

Method: the sample was composed of employees of 19 private companies from different segments and regions of Brazil, of both sexes, with a mean age of 38 years, totaling 584 respondents (270 leaders and 314 non-leaders). Participants were asked to answer, *online*, the NEO PI R Personality Inventory that assesses the five dimensions of personality: Neuroticism, Extraversion, Openness, Agreeableness and Conscientiousness. The analyses

were performed using *the Statistical Product and Service Solutions - SPSS* software and, for comparison of the groups, the Mann-Whitney U test was performed, due to the variables presenting non-parametric distribution.

Results: there was a statistically significant difference between the groups for the factors Neuroticism (U = 32209,500; $p < 0.001$), Extraversion (U = 33034.500; $p < 0.001$), Agreeableness (U = 37432.000; $p < 0.05$) and conscientiousness (U=34553.000; $p < 0.001$). When considering the gender variable, there was a statistically significant difference in the indices of Neuroticism (U = 7068,500; $p < 0.05$) and Extraversion (U = 6506.500; $p < 0.05$) between the groups when the participants were female. For males, there was a statistically significant difference between leaders and non-leaders in the Neuroticism indices (U = 9051,500; $p < 0.05$), Extraversion (U = 9135.500; $p < 0.05$) and Conscientiousness (U = 9123,000; $p < 0.05$).

Conclusion: In the comparisons that showed a statistically significant difference, the leaders had lower scores in Neuroticism and Agreeableness, and higher scores in Extraversion and Conscientiousness. When considering female leaders and non-leaders, there was a statistically significant difference in the indices of Neuroticism (U = 7068.500; $p < 0.05$) and Extraversion (U = 6506.500; $p < 0.05$). When considering male leaders and non-leaders, a statistically significant difference was observed in the indices of Neuroticism (U = 9051.500; $p < 0.05$), Extroversion (U = 9135.500; $p < 0.05$) and Conscientiousness (U = 9123.000; $p < 0.05$). The results indicate that leaders have higher scores in Emotional Stability (reverse of Neuroticism). Overall, these results are consistent with the literature that indicate specificity in the personality traits of organizational leaders, highlighting low Neuroticism and high Conscientiousness and Extroversion.

Keywords: Leadership traits, personality traits, organizational leadership, personality.

26 - Short-term social stress induces anhedonia, memory impairment and autonomic alteration in rats. A model of depression or posttraumatic stress disorder

Authors: Ivaldo Jesus Almeida Belém-Filho[1], Antonio Furtado de Silva-Júnior[1], Luana Omena Giati[2], Cristiane Busnardo[2], Letícia Barros dos Santos[1]. Matheus Zaparolli Bonazone Bonazoni[1], Leonardo Resstel Barbosa Moraes[1], Fernando Morgan de Aguiar Corrêa[1]

[1]Department of Pharmacology. Medical School of Ribeirão Preto. University of São Paulo, [2]Department of Pharmaceuticals and Medicines. Faculty of Pharmaceutical Sciences of Araraquara. State university of São Paulo.

Rationale: Social interactions are important to animals, especially mammals. Social conflicts such as aggression, social defeat, abuse, violence, or bullying can be harmful to the development of various species. Animal models such as resident-intruder protocol (RI-protocol) can be used to study changes induced by social conflicts, and using defeated animals can be studies disorders (normally for depression model), however, there is a lack of data on autonomic alterations induced by these conflicts. Literature findings demonstrate that there may be symptoms in common between the depressive phenotype and PTSD-like disorders in animals subjected to social stress induced by social defeat.

Methods: we used the resident-intruder protocol (RI-protocol) adapted. In this model, we use Sprague Dawley rats as resident/aggressors and Wistar rats as intruders/defeated presented for 20 min at first day and 7 days 10 minutes per day followed by social isolation of intruders. The control group was placed in groups of 5 animals per cage and not disturbed during the protocol. After, animals were tested in splash test, novelty object recognition (NOR), contextual fear conditioning (CFC) and cardiovascular recording through femoral arterial catheter in two situations (home cage and resident cage).

Results: During all RI-protocol, animals were weighting, and stressed group showed a decrease in body weight and weight gain ($P<0.05$) compared to control group at day 7 of stress. Indeed, stressed animals showed an increase on latency time and reduction of grooming time in splash test compared to control animals ($P<0.01$). NOR showed a memory impairment on stressed group in short- ($P<0.05$) and long-term memory ($P<0.05$), tested 1.5 hour and 24 hours after training with object. CFC protocol was made in 3 days and all animals showed same levels of freezing during conditioning (day 1) and extinction (day 2, $P>0.05$), however at test day stressed animals showed high levels of freezing compared to control ($P<0.05$) showing memory deficit at CFC. For the autonomic assays, stressed animals showed an increase of basal heart rate at home cage compared to control ($P<0.05$) but did not change mean arterial pressure. Both groups showed an increase of MAP and HR ($P>0.05$) during exposition to aggressor at resident cage.

Discussion/Conclusions: Models of depression and post-traumatic stress disorder show similar symptoms regarding HPA axis activation and memory actions. This model, which uses exposure for 7 days, caused behavioral and autonomic changes related to depression and

PTSD. This model can be used for the study of both disorders. Furthermore, what is most interesting is that this short-term exposure was able to promote changes in cardiac control, such as an increase in baseline heart rate. This may demonstrate the relationship between autonomic changes and psychiatric disorders such as depression and PTSD.

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27 - Micromap: low-cost multichannel electrophysiological acquisition system

Authors: Montalvão, T.M.M.[1,3] , Moreira, J.P.C.[1,2] , Passos, M.C.[1,2] , Mourão, F.A.G.[1,3] , Guarnieri, L.O.[1,2] , Mendes, E.M.A.M.[1,2] , Moraes, M.F.D.[1,2,3]

[1]Núcleo de Neurociências (NNC) - Department of Physiology and Biophysics, Institute of Biological Sciences, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, MG, Brazil, [2]Department of Electronics Engineering, Engineering School, UFMG, Belo Horizonte, MG, Brazil, [3]Graduate Program in Neurosciences, Institute of Biological Sciences, UFMG, Belo Horizonte, MG, Brazil.

Rationale: In neuroscience, the extracellular electric potential recordings have led to the understanding of how oscillatory neural activity may reflect important underlying processes involved in both local circuitry processing and large-scale neuronal integration. In addition, diseases (e.g. Epilepsy and Alzheimers's) often display very characteristic aberrant electrographic behavior, making longitudinal electrophysiological recordings a biomarker-of-choice for long-term evaluation, highlighting unexpected non-physiological states that lead to disease manifestation. Although ideal regarding their predictive and/or diagnostic potential, recordings over long periods present challenges inherent to embedded electronics, signal storage and processing as well as the prohibitive cost for high-quality bioelectric-signal acquisition. The main goal is to introduce an affordable system for large-scale longitudinal recording, based on high-efficiency/quality signal acquisition chips and low cost microcontrollers.

Methods: MicroMAP (Multichannel Acquisition Pack), was developed combining the Intan RHD family of microchips with an Arduino DUE, a powerful low cost microcontroller with 32-bit and 84 MHz processor. The system consists of 3 components: (1) analog-to-digital converter (Intan RHD family), to digitize and amplify the electrographic signals; (2) graphical user interface (GUI), programmed in Python based on the PyQt5 library; (3) microcontroller

control routine, which mediates the communication between the first and second components, ensuring that the samples are recorded at regular and uninterrupted intervals.

Results: The first stage of system validation consisted of recording electrocardiography activity from a Male Rattus norvegicus (Wistar), weighing 300g (CEUA: 116/2021) using in parallel the MicroMAP and the OpenEphys, a commercially established acquisition system. Ten recordings with different filter configurations and sampling frequencies (1kHz and 2kHz) were stored, each with a maximum duration of 5 minutes. Finally, the signals were compared by correlating the average signal of the 0.2 ms windows around the peak of each cardiac cycle. All recordings based on MicroMAP were benchmark-tested against an industry gold-standard OpenEphys, showing a mean and standard deviation of Pearson's product-moment correlation coefficients of 0.9996 ± 0.0003. In addition, we developed a very effective GUI for setting up sampling, real-time signal viewing, and storing the collected data. Data is stored in a format that is completely interchangeable with standard analysis packages such panda-python or matlab.

Conclusion: As perspectives, the final implementation will be carried out in long-term recordings in rats submitted an acute focal model of temporal lobe epilepsy (kainic acid into Hippocampus CA3) followed by longitudinal long-term recordings during epileptogenesis prior to spontaneous and recurring seizures. The MicroMAP may also be coupled to electrical deep-brain stimulation protocols for both closed-loop treatment (seizure prediction and abortion) and studying the mechanisms underlying seizure propagation. MicroMAP represents an open source alternative and is also a low-cost option to commercially available devices. The system development can be followed through the following link: https://github.com/mcjpedro/micromap.

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28 - Effects of gestational exposure to crack cocaine on lymphoid organs in lactating rats and their offspring

Authors: COUTINHO, A.B[1], SANTOS, Y.M.O[1], OLIOSI, E.B[1], LINS, M.P[1], PACHECO, A.L.D[1], SIQUEIRA, E.S[1], REITER, M.M.J.H[1], SOUZA, F.M.A[1], SILVA, B.R.M[1], OLIVEIRA, K.L.S[1], TORRES, R.G.D[1], SILVA, F.S[1], CASTRO, O.W[1], MELO, I.S[1]*

[1]Institute of Biological Sciences and Health, Federal University of Alagoas (UFAL), Maceio, AL, Brazil.

Rationale: Crack cocaine use during pregnancy can compromise the health of both mother and child since the metabolites of crack combustion can cross the placental barrier and cause complications, central nervous system (CNS) malformations, cell damage, and immunological alterations. In addition, treatment with cannabidiol (CBD) has gained greater scientific interest as an alternative in the treatment of neuropsychopharmacological diseases. Therefore, our aim was to evaluate the effects of gestational exposure to crack cocaine and treatment with CBD on the lymphoid organs of lactating rats and their offspring.

Methods: Pregnant Wistar rats (*Rattus norvegicus* [n= 29, 200-300g, 2-3 months old]) were exposed to air or crack cocaine (200 mg, for 10 min) throughout the 5th - 21st of day of pregnancy, according to a protocol approved by the UFAL Ethics Committee (Protocol nº. 28/2021). After lactation, the lactating rats (n=11) were euthanized to collect the lymphoid organs, divided into 2 experimental groups: control (exposed to air) and crack (exposed to crack cocaine). The animals' offspring were treated orally with CBD oil (10 mg/kg) or 0.9% saline solution (VEH) for 20 days, forming the four experimental groups (n=5 animals for each group) of females and males: CTRL+VEH, CTRL+CBD, CRK+VEH and CRK+CBD (N=40). After lactation or treatment, the thymus and spleen of lactating rats and their offspring were collected and weighed, and their cellularity counted. Finally, we assessed the subpopulations of B, T CD4+ and CD8+ lymphocytes by flow cytometry. Statistical analysis was performed using unpaired t test or two-way ANOVA followed by Tukey's post-hoc test, presented as mean ± SEM with $p < 0.05$.

Results: We observed a reduction in the relative weight of the spleen of lactating rats, which was reflected in the lower cellularity of splenocytes and subpopulations of CD8+ T lymphocytes. However, there was no change in the weight or cellularity of the thymus. Regarding the offspring, there was a reduction in weight when exposed only to crack cocaine.

Similarly, animals exposed to crack and treated with CBD showed a reduction in weight compared to control. We also observed that exposure to crack decreased the number of splenocytes in female rats. However, crack exposure increased the number of thymocytes and CBD treatment blocked this increase only in male rats. Finally, the relative weights of the thymus and spleen remained unchanged.

Discussion/Conclusion: Our study argues that exposure to crack cocaine alters the number of thymocytes and splenocytes in a sex-dependent manner, and that treatment with cannabidiol attenuates some of these effects. The deleterious effects of crack on the lymphoid organs should also be the subject of research since the immune system of users is possibly deficient and requires treatment. However, our data are preliminary, and further studies should be carried out to elucidate the mechanisms involved in the modulation of thymus and spleen cells after exposure to crack.

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Conflicts of Interest Disclosure: The authors declare that the they have no conflicts of interest.

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29 - Modulation of Hippocampus-Prefrontal Cortex Oscillatory Synchrony through Dopaminergic Activation

Authors: Oliveira-Júnior. B. A.[1], Nandakumar, N. S.[2], Leite. J. P.[1], Ruggiero. R. N[1]

[1]Department of Neuroscience and Behavioral Sciences, Ribeirão Preto Medical School, USP, SP, Brazil; [2]Department of Neurology (Division of Neuroscience), University of Iowa, Iowa City, IA, USA

Rationale: The synchronization of oscillations is proposed to enable dynamic and adaptable communication between distant brain regions. The hippocampus-prefrontal cortex (HPC-PFC) pathway exhibits synchrony modulation during various cognitive demands, including spatial working memory. Although the mechanisms underlying this modulation remain unclear, it is suggested that dopaminergic neurotransmission is one of the potential modulatory factors. However, there is limited evidence regarding dopamine's role in

modulating HPC-PFC synchrony, and the specific receptors involved in this process are unknown. In this context, we aimed to investigate the dopaminergic involvement in HPC-PFC synchrony, particularly focusing on phase synchrony while evaluating the receptor specificity and dose-dependency of these effects.

Methods: We conducted experiments on forty-two male Sprague Dawley rats, aged seven weeks. To record local field potential and neuronal firing, we surgically implanted stereotrodes in the hippocampus (HPC) and in the prefrontal cortex (PFC), or a silicon probe in the PFC. Rats were divided into groups and given varying doses of dopaminergic receptor agonists: apomorphine (i.p.), dopamine (i.c.v.), SKF-38393, or quinpirole (i.c.v.). The effects of each drug on HPC-PFC oscillatory dynamics were evaluated using spectral power, spectral coherence, and phase synchrony measures. We used a Student t-test to compare before and after drug administration periods, and significance was set at $p<0.05$. The study was conducted with ethical approval from the local animal experimentation ethics committee (Ribeirão Preto Medical School, USP; protocol number: 74/2021).

Results: Our results reveal that a 500 nmol dose of dopamine induces theta phase synchronization within the HPC-PFC pathway ($t(12)=2.682$, $p=0.019$). Similarly, a 3 mg/kg dose of apomorphine shifts the brain's oscillatory state from delta to theta ($t(4)=3.400$, $p=0.027$). However, we found that the selective activation of D1 and D2 dopamine receptors using SKF and quinpirole did not replicate these effects. It is noteworthy that a 0.75 mg/kg dose of apomorphine elicits oscillatory patterns characterized by predominant delta oscillations ($t(3)=5.418$, $p=0.012$), in contrast to the theta oscillations induced by a higher apomorphine dose. Additionally, we noted an increase in delta coherence that occurred between 30 to 40 minutes following the administration of dopamine (100 nmol, ($t(7)=2.153$, $p=0.068$), apomorphine (0.75 mg/kg, $t(3)=3.004$, $p=0.057$), and quinpirole (both concentrations; 1µg, $t(5)=3.960$, $p=0.010$; 10µg, $t(5)=5.814$, $p=0.002$).

Conclusions: Our study shows that dopaminergic activation has dose- and time-dependent effects on oscillatory dynamics in the HPC-PFC pathway during urethane anesthesia. Both apomorphine and D2 receptor agonism mediate these effects, but only full dopaminergic agonism induces theta phase synchrony in HPC-PFC circuits.

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NEUROSCIENCE AND EPILEPSY ABSTRACTS

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EPILEPSY ABSTRACTS

30 - Epileptogenesis in a two-hit model of epilepsy: contributions of inhibitory synapses and gutmicrobiota

Authors: Fernanda Marcelia dos Santos[1], Thais Martins de Lima[1], Thalita Sbeghen[1], Michele Bertoni Mann[2], Ana Paula Varela[2], Luiz Filipe Mendes[1], Flávio Kessler[1], Jeverson Frazzon[2], José Cláudio Fonseca Moreira[1], Norberto Garcia-Cairasco[3], Maria Elisa Calcagnotto[1]

[1]Department of Biochemistry, ICBS, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, RS, Brazil, [2]Institute of Food Science and Technology, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, Brazil, [3]Department of Physiology, Ribeirão Preto Medical School - Universidade de São Paulo (FMRP-USP), Ribeirão Preto, SP, Brazil.

Rationale: The interplay between excitation and inhibition is crucial to neuronal network function in the brain and in particular to control seizure activity in epilepsy. One of the important causes of refractory epilepsy is Developmental Cortical Malformation (DCM). Impairment of GABAergic system have been observed in humans and animal models with epilepsy associated with DCM and can contribute to epileptogenesis in DCMs. Changes in the gut microbiome have been explored to understand epileptogenesis in patients with epilepsy, since it is able to produce neuroactive metabolites and also neurotransmitter affecting the brain through several pathways. Here, we evaluated the spontaneous inhibitory postsynaptic currents (sIPSC) in pyramidal cortical neurons and characterized gut microbiome in a two-hit animal model of epilepsy (WAR- DCM).

Methods: Newborn Wistar (WIS) and Wistar Audiogenic Rat (WAR) rats were randomized and the DCM was induced in the right somatosensory cortex by freeze-lesion (FL) (WIS-SHAM, WIS-DCM, WAR- SHAM, WAR-DCM). In the postnatal period of P35-45 we collected stool samples and recorded sIPSC by whole-cell patch-clamp in visually pyramidal cortical neurons. The sIPSC were recorded in pyramidal cells of the paramicrogyral cortex and in distant cortical areas from the microgyria, and in the contralateral somatosensory cortex from DCM animals (paramicrogyral cortex: WIS-SHAM=5 cells,4 animals ; WIS-DCM =3 cells,3 animals ; WAR-SHAM=4 cells, 3 animals; WAR-DCM=4 cells, 3 animals; distant cortical areas: WIS-DCM=4 cells, 2 animals; WAR-DCM=5 cells, 3 animals; contralateral somatosensory cortex: WAR-

SHAM=4 cells, 4 animals; WAR-DCM=4 cells, 4 animals). The sIPSC parameters were analyzed using Mini Analysis 6.0.7 software. For the gut microbiota evaluation, 16s rDNA were amplified from stool samples and them sequenced by the Illumina MiSeq platform. The relative abundances were obtained using phyloseq, Metacoder and EdgeR packages in R, the sequencing data were checked and aligned using SILVA database (N=6 per group). To compare the results we used two-way ANOVA followed by Tukey considering $p \leq 0.05$. (CEUA#40836).

Results: Paramicrogyral cortex of WAR-DCM animals presented pyramidal cells with faster decay time sIPSCs when compared to WAR Sham ($F(1,12)=7.852$, $p=0.0160$). WAR-DCM animals presented pyramidal cells with faster sIPSCs decay time and rise time in the contralateal cortex when compared to paramicrogyral pyramidal cells $F(1,13)=33.26$, $p=\leq 0.0001$; ($F(1,13)=5.353$,$p=0.0377$). In addition, pyramidal cells in the contralateal cortex of WAR-DCM had faster sIPSCs decay time and rise time than contralateral cortex of WAR-Sham animals ($F(1,13)=15.80$, $p=0,0016$; ($F(1,13)=18.43$, $p=0.0009$). The gut microbiota of WAR animals had predominance of Firmicutes, while Wistar had gut microbiota composition distributed in Firmicutes, Bacteriodota, Actinobacteriota, Desufobacterota and Proteobacteria. The phyla composition showed to be smaller in WAR-DCM.

Conclusion: The preliminary data showed that the faster kinetic of sIPSCs in pyramidal cells of WAR-DCM could indicate a decreased cortical inhibition contributing to the epileptogenesis and the qualitative results from gut microbiota suggested dysbiosis in WAR animals even more intense in WAR-DCM. However, quantitative analysis are essential to clarify these results.

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31 - Evaluation Of The Physicochemical Characteristics Of Nanoemulsions Carrying The Neuropeptide Neurovespin For The Treatment Of Epilepsy

Authors: Marques, F.V.B.S.[1], Morais, S.S.[2], Monge-Fuentes, V.[1], Ombredane, A.S.[2], Souza, A.C.B.[1], Lima, L.S.[1], Joanitti, G.A.[2], Mortari, M.R.[1].

[1]Laboratory of Neuropharmacology, Institute of Biological Sciences, Department of Physiological Sciences, UnB, Brasília/DF; [2]Laboratory of Nanobiotechnology, Institute of Biological Sciences, Department of Genetics and Morphology, UnB, Brasília/DF.

Indroduction: Epilepsy is conceptualized as a neurological disorder qualified by a persistent predisposition of the brain to generate spontaneous and recurrent seizures. Despite the use of antiepileptic drugs in order to control and prevent seizures, their prolonged use causes a considerable risk of morbidity. Currently, arthropod venom has been considered an important source of neuroactive compounds. The peptide Neurovespin, bioinspired from social wasp venom, in acute models of seizures, showed great promise, inducing a potent anticonvulsant effect, as well as no detectable adverse effects so far. In order to minimize any inherent problem with peptides and to enable the use of these molecules as drugs, one of the main optimization strategies has been structural modifications of peptides and the improvement of the delivery system (nanosystems).

Objective: Evaluation of the physicochemical characteristics of nanoemulsions carrying the neuropeptide Neurovespine developed for the treatment of epilepsy.

Methodology: Neurovespin peptide was synthesized by Biointech Biotecnologia Ltda, its purity evaluation performed at the Laboratory of Neuropharmacology and the development of the conjugate delivery systems, characterization and stablity (nanoemulsion + Neurovespin) at the Laboratory of Nanobiotechnology. The peptide was encapsulated in one type of nanoemulsion (oil-in-water type) and characterized in terms of its physicochemical properties, such as mean hydrodynamic diameter (HD), zeta potential and polydispersity index (PDI), from readings in the dynamic light scattering and electrophoretic mobility apparatus, Zetasizer Nano ZS90.

Results: The mean hydrodynamic diameter (HD), with values of 126.3 ± 2.594 (White) and 160.0 ± 1.804 (NeuroNE), showed within the size range up to 200nm, referring to the size of nanovehicles for delivery to the brain by the intranasal route in animal models. The polydispersity index (PDI) obtained values of 0.256 ± 0.008 (White) and 0.317 ± 0.038 (NeuroNE), also within the range of 0.08-0.700, representing a more homogeneous population of nanogotules, with low polydispersity. With respect to surface charge, the data showed slightly positive charges, 1.46 ± 0.477 (White) and 1.10 ± 0.502 (NeuroNE), favoring the trigenimal pathway, i.e., enabling a slower translocation of nanogoticles in this pathway.

Conclusion: With this, a possible increase in the therapeutic efficacy of the nanoencapsulated peptide is expected, maintaining its pharmacological safety and aiming at a more effective treatment against drug-resistant epilepsy.

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32 - Alterations of potassium and calcium currents are related with generation of epileptic bursts

Authors: Diogo L. M. Souza[1], Paulo R. Protachevicz[2], Conrado F. Bittencourt[1], En- rique C. Gabrick[1], Lucas E. Bentivoglio[1], Jos´e D. Szezech Jr.[1,3], Antonio M. Batista[1,3], Iberê L. Caldas[2], Salvador Dura-Bernal[4,5], Rodrigo F. O. Pena[6], Fernando S. Borges[4,7]

[1]Graduate Program in Science, State University of Ponta Grossa, Ponta Grossa, PR, Brazil; [2]Institute of Physics, University of São Paulo, São Paulo, SP, Brazil; [3]Department of Mathematics and Statistics, State University of Ponta Grossa, Ponta Grossa, Brazil; [4]Department of Physiology and Pharmacology, State University of New York Downstate Health Sciences University, Brooklyn, New York, USA; [5]Center for Biomedical Imaging and Neuromodulation, The Nathan S. Kline Institute for Psychiatric Research, New York, USA; [6]Department of Biological Sciences, Florida Atlantic University, Jupiter, Florida, USA; [7]Center for Mathematics, Computation, and Cognition, Federal University of ABC, S˜ao Bernardo do Campo, SP, Brazil.

Rationale: The ionic channels play a crucial role in neuronal activities. Each channel in the neuron membrane contributes in a different way to the generation of action po- tentials. Potassium, sodium and calcium currents are not only related to a single neuron- cell electrophysical activity but also to the transition from asynchronous spike to high- synchronous burst states in neuronal networks. Alterations in ionic channels are associated with certain brain disorders. Therefore, understanding the role of different ionic channels at a network level is essential.

Methods: Many works have demonstrated that each channel plays a fundamental role in neuronal networks. In this work, we consider a network in which each neuron is described by a conductance-based model of cortical regular spiking. The model parameters are taken from whole-cell patch-clamp recordings. First, we investigate the influence of the slow-potassium and calcium channels in a single neuron cell. Second, the

impact of those ionic channels is studied in a high- synchronous state for different synaptic couplings and current.

Results: Our results show that the slow-potassium current is associated with the high-synchronous states and also with the transitions of firing patterns spike-to- burst. The bistable dynamics is related to such transition, where physiological asynchronous spikes and pathological synchronous bursts coexist. We show that the high and low threshold calcium currents are strongly related to the parameters necessary for the neuronal network to achieve a bistable state.

Conclusions: Ionic channels are of great importance within a network. They play main roles to reach and avoid high-synchronous and bistable states. It has been observed that the channels are strongly related to firing pattern transition. Considering our findings, we propose that pharmacological interaction with slow-potassium, high- and low-threshold calcium channels can hinder the high-synchronous burststate.

33 - Oscillatory pattern of *in vitro* cortical activity in wistar audiogenic rats with microgyria

Authors: Thais Martins de Lima[1]; Querusche Klippel Zanona[1]; Gabriela Lazzarotto[1]; José Antonio Cortes[2]; Norberto Garcia-Cairasco[2]; Maria Elisa Calcagnotto[1].

[1]Department of Biochemistry, ICBS, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre. RS, Brazil; [2]Department of Physiology, Ribeirão Preto Medical School - Universidade de São Paulo (FMRP-USP), Ribeirão Preto, SP, Brazil.

Rationale: Developmental Cortical Malformation (DCM) is one of the major causes of refractory epilepsy, mainly in children. Neuronal network reorganization can play a role in brain oscillation changes and epileptogenesis in DCM.

Methods: To study the modification pattern of cortical oscillations in DCM during development (juvenile (ID1) and adolescence (ID2)), we use the two-hit model consisting of freeze-lesion (FL)-induced microgyria in neonatal Wistar Audiogenic Rats (WAR) (P0-P1) to boost epileptogenesis as demonstrated previously. The FL was performed in the right somatosensory cortex of WAR and Wistar animals (Wistar Sham: n= 6 ID1 e n= 6 ID2; Wistar DCM: n= 5 ID1 e n= 6 ID2; WAR Sham: n= 6 ID1 e n= 8 ID2; WAR DCM: n= 6 ID1

e n= 5 ID2). *In vitro* Local Field Potentials (LFP) in the cortical area of the left and right hemispheres were performed for each animal under normal ACSF slice perfusion (baseline) and modified ACSF with 4-aminopyridine (4AP) and $0Mg^{2+}$to elicit ictal and interictal epileptiform activities. Background activity was analyzed during the baseline and interictal periods. The frequency bands were decomposed by a customized MATLAB routine in delta (1-4Hz), theta (4-12Hz), beta (12-30Hz) and slow gamma (SG) (30-50Hz). The normalized power of each frequency band was obtained using a mathematical equation (100*(log10(interictal)-log10(basal))/log10(basal)). The statistical analysis was made using Generalized Estimation Equation (GEE). (CEUA Approval # 37310).

Results: The normalized cortical power of delta was higher in the DCM groups (Wistar and WAR) when compared to Wistar-Sham at ID1, independently of hemisphere ($p<0.005$). The normalized cortical power of theta was higher in the DCM groups (Wistar and WAR) and WAR-Sham when compared to Wistar-Sham, independently of hemisphere or age ($p<0.005$). The normalized cortical power of beta was higher in the WAR-DCM in the ipsilateral hemisphere when compared to both Wistar and WAR Sham groups ($p<0.005$). In addition, the normalized cortical power of SG in WAR-DCM contralateral to the microgyria was higher when compared to Wistar-Sham, independently of age ($p<0.05$), while in the Wistar-DCM group it was lower in the right, when compared to the left hemisphere, independently of age ($p<0.0005$).

Discussion/ Conclusion: The data showed that the microgyria induced the increment in the slow cortical oscillation detected in juvenile rats, suggesting epileptogenesis in course. Animals with DCM and WARs without microgyria (WAR-Sham) had increased power of theta, while WAR-DCM showed increased power of beta in the cortex. Lower power of theta oscillation was found in patients with epilepsy and the increment in power of delta and theta oscillations was described in patients with absence seizures. WAR-DCM animals also showed higher power of SG oscillations in the contralateral hemisphere, which could be related to the ongoing secondary epileptogenesis. These preliminary data reinforce that the two-hit model (WAR-DCM) could be a reliable model to study epileptogenesis during development.

Financial Support: CAPES, CNPq, FAPESP

34 - Preclinical Efficacy Of Cannabigerol For The Treatment Of Early-Life Seizures.

Authors: Lillian Soares Pinto[1,2], Matheus Silva de Oliveira[2], Rafaella Terêncio Ferreira[2], Rúbia Aparecida Fernandes[2], José Alexandre de Souza Crippa[4], Fabrício Araújo Moreira[3], Victor Rodrigues Santos[1,2].

[1]Graduate Program in Cell Biology, [2]Department of Morphology, [3]Department of Pharmacology, Institute of Biological Sciences, UFMG, Belo Horizonte/MG. [4]Department of Neuroscience, Ribeirão Preto Medical School, FMRP, USP, Ribeirão Preto/SP.

Introduction: Epilepsy stands as a chronic neurological disorder marked by epileptic seizures, which can be categorized as either focal or generalized. Although medications like phenobarbital and valproic acid exist to manage seizures, they prove insufficient in fully suppressing all epileptic seizures and might even lead to neuronal death in immature brains. A promising remedy emerges in the form of Cannabigerol (CBG), a minor constituent of *Cannabis sativa*, recognized for its anti-inflammatory and neuroprotective effects. Among its known mechanisms of action, CBG regulates the endocannabinoid system, thereby implying a significant role in controlling neuronal excitation.

Objective: To evaluate CBG's anticonvulsant efficacy using neonate rodent model of seizures induced by Pentylenetetrazole (PTZ).

Methods: The experimental protocols were approved by the Ethics Committee in Animal Research at UFMG (CEUA-261/2022). Neonate Wistar rats aged 10 days (P10, n=12 per group) were employed. CBG was mixed with a vehicle solution containing 2% Tween 20 and 0.9% saline, administered intraperitoneally (IP) 60 minutes prior to 100 mg/kg subcutaneous (SC) PTZ injection. CBG concentrations of 10 mg/kg, 30 mg/kg, and 100 mg/kg were tested. Following PTZ administration, the animals were observed for approximately 15 minutes in transparent acrylic boxes. Statistical analysis utilized Graphpad Prism 8, and the Kruskal-Wallis test was employed to ascertain seizure latency, types, severity, and duration.

Results: Animals administered 30 mg/kg and 100 mg/kg of CBG exhibited significantly extended latency for both the first seizure onset ($P=0.0001$) and the most severe seizure ($P=0.0002$), compared to the control group. In terms of the loss of straightening reflex duration, indicative of seizures, the 30 mg/kg and 100 mg/kg CBG-treated animals displayed notably shorter durations ($P<0.0001$) than the control group. The number of tonic-clonic seizures, which represent the most severe seizure behavior, showed no significant variance

between CBG-treated and vehicle groups (P=0.3034). Likewise, no noteworthy distinctions emerged in the occurrence of spasm behaviors (Jerks) across groups (P=0.6900).

Conclusion: These findings suggest that CBG exhibits a dose-dependent anticonvulsant effect in neonatal seizures, modeled by P10 treatment in the PTZ-induced seizure animal model.

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35 - Isoflurane Anesthesia: A New Possibility For *Status Epilepticus* Cessation In The Pilocarpine Model Of Temporal Lobe Epilepsy?

Authors: Resende, M.C.S., Lima, L.S., Azevedo, C.V.I.B., Martins G.S., Guedes, I.T.L., Marques, F.V.B.S., Mortari, M.R..

Departamento de Ciências Fisiológicas, Instituto de Ciências Biológicas, Universidade de Brasília, Brasília/DF.

Rationale: The pilocarpine model of temporal lobe epilepsy is widely utilized by research groups throughout the world, replicating relevant pathophysiological mechanisms such as hippocampal sclerosis and hardly controlled epileptic seizures. Despite successfully mimetizing the neurological condition, this model comes with significantly high mortality rates. It is evident that induction of *status epilepticus* (SE) by pilocarpine injection itself might lead to death, but ineffective termination of seizures is also a significant cause of mortality. A variety of drugs, such as diazepam, phenobarbital and thiopental, are used for this rescue. However, our group observed that the interruption of SE by thiopental administration was not accomplished for a significant number of animals. Given that, we here propose the utilization of isoflurane – a volatile general anesthetic agent that influences GABAergic neurotransmission – for SE cessation.

Objective: The objective of this study was to compare the effectiveness of isoflurane and thiopental forSE cessation in the pilocarpine model of temporal lobe epilepsy in mice.

Methodology: Swiss mice were injected with scopolamine butylbromide (4 mg/kg, intraperitoneally) for reduction of pilocarpine peripheral adverse effects. 20 minutes later, they were administered with pilocarpine (150 mg/kg, intraperitoneally) for induction of SE. After 180 minutes, seizures of surviving animals were interrupted either with an

intraperitoneal injection of sodium thiopental (40 mg/kg, intraperitoneally, n = 39) or with inhalation anesthesia with isoflurane (n = 71). For statistical analysis, a Mann-Whitney test was applied to the data. This project was approved by *Comitê de Ética no Uso Animal da Universidade de Brasília*, under the protocol 23106.104582/2020-71.

Results: 9 of the 39 animals that underwent SE termination with thiopental survived. This means that only 23% of them survived the 180 minutes of SE and its termination. In regards to the SE cessation with isoflurane, 52 of the 71 mice, 73%, that went through the cessation survived. These results demonstrate that the rate of survival for SE termination with isoflurane is statistically higher when compared to SE termination with thiopental (p = 0,0105).

Discussion and Conclusions: There was a significant difference between the effectiveness of the rescues with thiopental and isoflurane, demonstrating that isoflurane might be an interesting strategy for rescuing animals in SE. This may be due to isoflurane's lipophilicity, which contributes to its swift diffusion through the central nervous system. It also has a short half-life period, which contributes to good drug monitoring, and it does not interact with other substances. Furthermore, isoflurane's mechanism of action might also be one of its advantages. In conclusion, SE termination with isoflurane appears to have considerable advantages over the one with thiopental in regards to the pilocarpine model of temporal lobe epilepsy in mice.

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Conflicts of Interest Disclosure: The authors declare that they have no conflicts of interest that could have appeared to influence the work reported in this paper.

36 - The Lateral Hypothalamic Neurons And Postictal Antinociception

Authors: Felipe Ribeiro de Oliveira, Renato Leonardo de Freitas, Rafael Carvalho Almada, : Norberto Cysne Coimbra

Laboratório de Neuroanatomia & Neuropsicobiologia, Departamento de Farmacologia, Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo, Ribeirão Preto, 14049-900, São Paulo, Brasil

The postictal state is commonly followed by comorbidities between epilepsy, headache, anxiety and depression. Post-ictal antinociception is an additional phenomenon observed in both laboratory animals and humans, characterized by an increase in the pain perception threshold after tonic-clonic seizures. There is evidence that the lateral hypothalamus (LH) participates in the pain modulation response. The aim of this study was to investigate the role of the LH in both the post-ictal antinociception and the severity of seizures. Wistar Hannover male rats (n= 7-8 per group) were submitted to stereotactic surgery to implant a guide cannula in the lateral hypothalamus. Five days after surgery the tail flick latency (TFL) baseline was recorded in each rat submitted to the tail-flick test, followed by microinjection of either lidocaine (2%) or vehicle solution (0.9% NaCl/0.2 μL) in LH. Five minutes after the microinjection, either pentylenetetrazole (54 mg/kg) or vehicle was intraperitoneally administered to evoke tonic-clonic seizures in rats. The animals were then placed in a circular arena to record the seizures frequency, latency and Racine's index. The TFL was recorded immediately after the end of the last seizure (time 0), and again 10-minute intervals during 120min. Seizure severity was recorded using the Racine's index of severity latter modified by de Freitas et al. (2009). The data were submitted to a repeated measure two-way analysis of variance (ANOVA) after Shapiro-Wilk normality test. Data related to the severity of seizures were submitted to a one-way ANOVA followed by Tukey's post hoc test. $P < 0.05$ was considered statistically significant. PTZ caused tonic-clonic seizures, with a significant enhancement of Racine's index as compared to control, in all animals, followed by significant increase in TFL recorded immediately after seizures and at 10, 20, 40 and 80min after seizures (Tukey's post hoc test, $p < 0.05$ in all cases) suggesting post-ictal analgesia. Microinjections of lidocaine in LH caused a significant increase in postictal antinociception at 60 and 70 min when compared to the control group (Tukey's post hoc test, $p < 0.05$ in both cases). In fact, the lateral hypothalamus sends projections to nuclei directly related to post-ictal analgesia, such as the periaqueductal grey matter, nucleus raphe magnus, dorsal raphe nucleus, gigantocellularis reticular nuclei and locus coeruleus. We hypothesize that these connections are inhibitory or recruit inhibitory interneurons to can explain the antinociceptive effect of decreasing activity of LH neurons by lidocaine causing enhancement of postictal antinociception. Interestingly, the pretreatment of LH with lidocaine had no influence on seizures severity. These findings suggest the involvement of LH neurons in the modulation of

postictal antinociception and that seizures severity and postictal antinociception can be at least partially independent phenomena.

37 - Effects Of Acetyl-L-Carnitine On Acute Pentylenetetrazole-Induced Seizure In Zebrafish

Authors: Amanda Patelli-Alves[1], Rafael Chitolina[1,2], Carlos G. Reis[1,2], Thailana Stahlhofer-Buss[1], Amanda Linazzi[1], Leonardo Marensi Bastos[1], Radharani Benvenutti[3], Matheus Marcon[4], Ana P. Herrmann[5], Angelo Piato[1,2]

[1]Laboratório de Psicofarmacologia e Comportamento (LAPCOM), Departamento de Farmacologia, ICBS, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, RS, Brazil. [2] Programa de Pós-graduação em Neurociências, ICBS, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, RS, Brazil. [3] School of Pharmacy and Biomolecular Sciences, RCSI University of Medicine and Health Sciences, Dublin, Ireland. [4] Departamento de Bioquímica, Farmacologia e Fisiologia, Instituto de Ciências Biológicas e Naturais, Universidade Federal do Triângulo Mineiro (UFTM), Uberaba, MG, Brazil, [5] Laboratório de Neurobiologia e Psicofarmacologia Experimental (PsychoLab), Departamento de Farmacologia, ICBS, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, Rio Grande do Sul, Brazil.

Rationale: Acetyl-L-carnitine (ALC) is a dietary supplement that plays an important role in β-oxidation through the transport of fatty acids across the mitochondrial membrane. Several studies have shown that ALC prevents epileptic seizures, increases antioxidant enzyme levels, and decreases the expression of oxidative stress and apoptosis markers in acute seizure models and kindling models in rodents. Nevertheless, the current literature remains unclear about the external validation and limited by species-specific bias. Considering the promising potential therapeutics of ALC for epilepsy treatment, this study aims to investigate the effects of acute exposure to ALC on pentylenetetrazole (PTZ)-induced seizures in larvae and adult zebrafish.

Methods: In this study were used 100 larvae, obtained from mating wild-type zebrafish (*Danio rerio*) from the colony of the Instituto de Ciências Básicas da Saúde (UFRGS), and 160 adult (1:1 male:female) wild-type zebrafish, obtained from a local commercial supplier (CEUA/UFRGS n° 35823). At 6 days post-fertilization (dpf), larvae were randomly allocated and exposed (for 18 hours) to the treatments (n= 17-20): control (water), 18 μM diazepam (DZP) or 0.1, 1 and 10 mg/L ALC. On the next day, larvae were submitted to the

PTZ-induced seizure test (10 mM for 10 minutes) and recorded to quantify the seizure scores reached in 30-seconds intervals as well as the latency to reach larvae seizure stages 2 and 3 (whirlpool swimming behavior and clonus-like seizure followed by loss of posture, respectively). Adult fish were randomized to the treatments groups as described above (n=16) and exposed to the treatment for 40 minutes. Next, fish were recorded in the PTZ-induced seizure test (20 minutes) to quantify the seizure stage reached every 30-seconds intervals and latency to reach seizure stages 4 and 5 (clonic and tonic seizure-like stages in adult fish, respectively). All analyses were performed using BORIS® software by researchers blinded to the treatment groups.

Results: In larvae, only the 1 mg/L ALC and the diazepam were able to prevent epileptic seizures, decreasing the seizure intensity ($p<0.05$ and $p<0.0001$, respectively; effect size -0.84 and -2.59, respectively) and increasing the latency to reach the clonus-like seizure stage ($p<0.05$ and $p<0.0001$). In adults, only diazepam decreased the seizure intensity ($p<0.05$, effect size -1.11) and increased the latency to reach the clonic seizure-like stage ($p=0.001$). All parameters were analyzed by one-way ANOVA/Tukey's post hoc. The normality and homogeneity of variances were confrmed for all data sets using D'Agostino-Pearson and Levene tests, respectively.

Discussion/Conclusions: These findings corroborate with the current literature, showing an antiepileptic property of ALC in zebrafish larvae. These results seem to be associated with an inverted U-shaped concentration-response curve of this compound. The lack of effect in adults may be explained by shorter treatment periods and developmental stage differences, but this remains to be empirically tested in further studies. Additional investigations are thus warranted with different experimental designs, including treatment duration and a wider range of concentrations.

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Conflicts of interest: The authors declare no conflicts of interest.

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Keywords: acetyl-L-carnitine; epilepsy; zebrafish; animal model.

38 - Epilepsy Abstracts: The study of the effects of cannabidiol and its derivatives on the astrocyte's glutamate-glutamine cycle in experimental models of epilepsy

Authors: Milton Kennedy Aquino Júnior[1], Natália Barboza da Silva[1], Thaís Santos de Almeida Lima[2], Marina Prado Rubinho[1], Marina Fiuza Silva[1], Kauê Shindi Dias Nakamura[1], Claudio Viegas Junior[1], Graziella Reis Franco[1], Mikaela Lucinda de Souza[1], Lillian Soares Pinto[3], Victor Rodrigues Santos[3], Fabricio de Araújo Moreira[3], Nathalia Peixoto[4], Marília Gabriela Alves Goulart Pereira[1]

[1]Federal University of Alfenas, [2]University of São Paulo, [3]Federal University of Minas Gerais, Brazil; [4]George Mason University, USA.

Introduction: Epilepsy is a neurological disorder characterized by the periodic occurrence of unpredictable seizures, caused by hyperexcitability of brain neurons. Some current evidence suggests that astrocytes participate in the development of this condition, especially when related to excess excitotoxic glutamate. The adverse effects of traditional antiepileptic drugs, as well as their ineffectiveness in refractory cases, led to the search for alternative treatments for epilepsy, such as the use of Cannabidiol (CBD), a non-psychotropic compound of *Cannabis sativa*. It is believed that some CBD derivatives are equally effective in mitigating epileptic symptoms, making further studies in the area necessary in order to improve the epilepsy treatment.

Rationale: The use of different approaches and experimental models to search for new possible molecules with therapeutic potential for epilepsy are essential for the understanding of epileptogenic mechanisms and the search to improve the quality of life of patients with epilepsy.

Methods: For the *in vitro* experiments (animal ethics committee approval 0004/2021), the primary culture of hippocampal astrocytes were used with 0.5 x 10^5 cells per well (n=5 per group). Initially, we performed the cell viability test (MTT) to 28 compounds derived from cannabidiol molecule and it was selected 4 compounds with IC50 up 30mM (PQM 245, 291, 302, 309). For quantification intra and extracellular glutamate and glutamine concentrations by HPLC, the wells were treated with cannabidiol derivatives by 30min and subsequently performed the stimulus with 1mM glutamate. GFAP immunohistochemistry for the analyzed groups was also performed. The *in vitro* experiments were carried out under the approval of the ethics committee (226/2022). For the *in vivo* tests, 40 *wistar* rats aged 11 days were used. The

animals were treated with cannabidiol derivatives (30mg/Kg/i.p) 1 hour before the stimulus performed with Pentylenetetrazole (100mg/Kg/s.c). The latency and duration of seizures, and the loss of posture, were analyzed in the first 15 minutes after the stimulus.

Results: The compounds selected through the MTT test were 245 (IC_{50}=46,94mM), 291 (IC_{50}=55,38mM), 302 (IC_{50}=41,53mM) and 309 (IC_{50}=34,64mM). After quantification of glutamate and glutamine by HPLC, we observed that compounds 245, 291 and 309 showed glutamate uptake similar to the group treated with cannabidiol (0,07 μg/μL) and that compound 309 showed the highest release of glutamine in the extracellular environment compared to the others (0,06μg/μL). Cannabidiol and compounds 245 and 302 reduced astrogliosis compared to the glutamate group ($p<0.001$), while compound 309 showed no difference. The statistics of *in vivo* tests with compounds 245, 291, 302 and 309 are currently being worked on.

Discussion/Conclusions: The glutamate is the main excitatory neurotransmitter, which in high concentrations in the extracellular environment can cause excitatory neuronal death. Preliminary results suggest that the cannabidiol derivatives analyzed in the study may affect the control of neuronal excitotoxicity.

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39 - ARC Immunoreactive Neurons and Network Synchronization: Implications for the Epilepsy Control

Authors: P. R. Protachevicz[1], F. S. Borges[2,3], E. C. Gabrick[4], G. S. V. Higa[3,5], J. D. Szezech Jr.[4,6], I. L. Caldas[1], A. M. Batista[4,6], A. H. Kihara[3]

[1]Institute of Physics, University of São Paulo, São Paulo, SP, Brazil; [2]Department of Physiology and Pharmacology, State University of New York Downstate Health Sciences University, Brooklyn, NY, USA; [3]Center for Mathematics, Computation, and Cognition, Federal University of ABC, S˜ao Bernardo do Campo, SP, Brazil [4]Graduate in Science Program - Physics, State University of Ponta Grossa, Ponta Grossa, PR, Brazil; [5]Institute of Chemistry, University of São Paulo, São Paulo, SP, Brazil; [6]Department of Mathematics and Statistics, State University of Ponta Grossa, Ponta Grossa, PR, Brazil.

Rationale: Neuronal synchronization is essential for effective brain communication and learning, however, abnormal alterations in connectivity result in hyper-synchronized states associated with epileptic seizures. In this regard, the activity- regulated cytoskeleton-associated protein (ARC) is pointed in synaptic alterations related to epilepsy. For this reason, we investigated how ARC immunoreactive neurons (IAINs) can influence neuronal network dynamics, particularly on firing pattern and synchronization levels, aiming to understand their role in both the generation and suppression of activities associated with epilepsy.

Methods: The research used ARC immunofluorescence analysis in hippocampal sections to characterize IAINs after the induction of the epileptic status in rodents. On the basis of this, a neuronal network model consisting of adaptive exponential integrate-and-fire neurons (AdEx) was developed to investigate the influence of such IAINs on the emergence of intermittent activities. This model was chosen for its ability to replicate both the spiking and burst firing activities observed in neuronal networks. This model simulated intermittent behaviors, considering the impact of IAINs connectivity as the increase in strength and the number of connections. Optogenetics, a technique involving light-sensitive channels, was employed to control neuron activity, particularly focusing on IAINs' effects using different light stimuli.

Results: Our model revealed intriguing insights into the relationship between IAINs and neuronal network behavior. Increasing the fraction and synaptic conductance of excitatory IAINs resulted in synchronized burst firing within the network. Furthermore, these alterations favored the emergence of intermittent firing patterns, characterized by transitions be- tween synchronous bursts and asynchronous spikes, reminiscent of the up and down states of neural activity. Notably, this intermittent synchronization pattern has strong relevance to epileptic activities, prompting us to employ the in- stantaneous coefficient of variation to quantify the intermittency of spike and burst patterns over time. As the strength of IAINs' connections increased, hyper-synchronized burst events became more prevalent, with durations extending beyond tens of minutes. Power-law and exponential distributions were used to fit the temporal characteristics of these events, which can be associated for

example with mild-to-moderate and severe epilepsy. In this context, the optogenetic control of high synchronous bursts was effective when targeting IAINs but not non-IAINs.

Conclusions: This study unravels the possible intricate relationship between IAINs and neural network dynamics implicated in epilepsy. The observed correlation between elevated synapse connectivity exemplified by IAINs and the initiation or mitigation of hyper-synchronized activities presents a promising therapeutic avenue. Abnormal neuronal connectivity, as observed in IAINs, can lead to epileptic seizure patterns. This study demonstrates that IAINs can contribute significantly to the emergence of hyper-synchronized activities. In addition, the research highlights the potential of optogenetics, particularly in targeting IAINs, for controlling epileptic seizures. Understanding the intricate relationship between neuronal connectivity, firing patterns, and synchronization sheds light on potential therapeutic strategies for epilepsy treatment. The proposed model provides insights into the mechanisms underlying epileptic network dynamics and offers a foundation for future studies aiming to develop novel interventions for epilepsy management.

40 – Combined Administration of Phenobarbital and Cannabidiol Impacts Neuronal Death in the Amygdala of Developing Wistar Rats

Authors: FREITAS, L. G. R.[1]; RIBEIRO, J. V. M.[1]; SANTOS, V. R.[1]

[1]Laboratório de Neurobiologia, Department of Morphology, Federal University of Minas Gerais.

Rationale: The amygdala plays a significant role in epilepsy by contributing to the initiation, propagation, and control of seizures. It serves as a focal point for the generation of abnormal electrical activity in the brain. The amygdala plays a crucial role in emotional processing, fear, and the processing of punishments and rewards. The amygdala's involvement in processing emotions, fear, and stress also influences seizure thresholds and propagation. Meanwhile, phenobarbital and cannabidiol are frequently used in clinical practice to treat epilepsy, including cases involving developmental stages. Thus, it is imperative to analyze the impact of these drugs on the development of this pivotal brain region.

Methods: Wistar mice received intraperitoneal administration of either 75mg/kg of phenobarbital, 30mg/kg of cannabidiol, or a combination of both drugs on the seventh day of

life. Additional groups received doses of 2mg/kg, 20mg/kg, and 200mg/kg of cannabidiol to assess dose dependency cell death. Control groups received saline or a vehicle. Subsequent to drug administration, cardiac perfusion was performed followed by brain extraction. The brains were sectioned and stained with Fluorojade C to detect dying neurons. Quantification of stained neurons was achieved using fluorescence microscopy and QuPath software.

Results: Comparatively, the combined administration of phenobarbital and cannabidiol (30mg/kg each) induced a higher rate of neuronal death in the amygdala when contrasted with groups receiving either drug alone. No significant difference in neuronal death was observed between the phenobarbital and cannabidiol (30mg/kg) groups. Furthermore, neuronal death in groups administered saline or the vehicle was not significantly different from those treated with phenobarbital or cannabidiol (30mg/kg) alone, but it significantly differed from the combined administration group. Varying doses of cannabidiol (2mg/kg, 20mg/kg, 200mg/kg) did not exhibit dose-dependent effects, and these groups did not significantly differ from the saline or vehicle groups. However, a significant difference in neuronal death was evident between these groups and the combined phenobarbital and cannabidiol (30mg/kg) group.

Conclusion: The combined administration of phenobarbital and cannabidiol appears to correlate with heightened neuronal death in the cerebral amygdala of developing rodent. These data suggest a potential relationship between the combined use of these drugs and increased neuronal death, supporting the notion of their impact on the comprehension and expression of fear at the subcortical level. This research project declares no conflict of interest.

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41 – The impact of excess glutamate on astrocytic components of the glutamate-glutamine cycle: induction of epileptogenesis

Authors: Marina Prado Rubinho[1]; Milton Kennedy Aquino Junior[1]; Gabriel Alberto de Carvalho Barbosa[1]; Leonardo Trisciuzzi[1]; Nariany Renata Mateus de Oliveira[1]; Maria Eduarda Tavares de Lima[1]; Jessica Oliveira[3]; Kris Simone Tranches Dias[1]; Jéssica Rodrigues Pedro[1]; Marcos Vinicios Salles Dias[2]; Nathalia Peixoto[3]; Marilia Gabriella Alves Goulart Pereira[1]

[1]Department of Biochemistry, Federal University of Alfenas, Alfenas, Minas Gerais, Brazil ; [2]Institute of Natural Sciences, Federal University of Alfenas, Alfenas, Minas Gerais, Brazil ; [3]Neural Engineering Lab, George Mason University, Fairfax, Virginia, United States.

Rationale*:* The maintenance of glutamate concentration below neurotoxic levels depends on the glutamate-glutamine cycle. Although some studies indicate that specific changes in this cycle can trigger seizures in animals, no in vitro studies establish a direct relationship between the inhibition of transporters and/or enzyme and the process of excitotoxicity observed in epilepsy.

Methods: To determine the relationship of transporters and enzyme of the glutamate-glutamine pathway of astrocytes with the pathogenesis of epilepsy in an *in vitro* model, primary cultures of astrocytes and co-cultures of astrocytes and neurons from the hippocampus of Wistar rats were incubated with glutamate (1 mM) and/or inhibitors of glutamate transporters or the enzyme glutamine synthetase. Astrocytes were evaluated for expression of glial fibrillary acidic protein (GFAP), GLAST and GLT-1 transporters, and GS enzyme. The functional analysis was performed by the dosage of glutamate and glutamine by HPLC. Neuronal electrical activity was verified by plating the co-culture in the microelectrode matrix, and neurodegeneration analysis was performed using Fluoro-Jade.

Results*:* Glutamate 1 mM increased the expression of GFAP in astrocytes, while the association with the GLAST transporter inhibitor significantly reduced the expression of the protein, and the inhibition of GLT-1 or the GS enzyme did not cause changes. Inhibition of GLAST, GLT-1 and GS promoted a significant reduction in the expression of the GLAST transporter. In the case of neurons, astrocytic inhibition of GLAST and GS resulted in less neurodegeneration when compared to inhibition of GLT-1. In the *in vitro* model of excitotoxicity, the inhibition of the glutamate-glutamine cycle reduced the expression of GLAST, GLT-1, and GS, while glutamate increased the expression of transporters and decreased GS. Glutamate caused an increase in the number of spikes and induced neurodegeneration.

Discussion/Conclusions: We can affirm that excess glutamate causes changes in the glutamate-glutamine cycle that cause an increase in glutamate levels, initiating a continuous process of

disturbance of homeostasis that proves the participation and the relationship of the glutamate-glutamine cycle with the epileptogenic process.

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Conflict of interest: The authors declare that they have no conflicts of interest.

Keywords: Glutamate-glutamine cycle. Glutamate. Astrocytes. Excitotoxicity. Epilepsy.

42 – Physiological Mechanisms Underlying The Generation Of Fast Rip-Ples (FR) Associated With Epilepsy

Authors: Fernando S. Borges[1,2], Guilherme V. Higa[2,3], Joao V.S. Moreira[1], Salvador Dura-Bernal[1,4]

[1]Department of Physiology and Pharmacology, State University of New York Downstate Health Sciences University, Brooklyn, New York, USA; [2]Center for Mathematics, Computation, and Cognition, Federal University of ABC, São Bernardo do Campo, SP, Brazil; [3]Institute of Chemistry, University of São Paulo, São Paulo, SP, Brazil; [4]Center for Biomedical Imaging and Neuromodulation, The Nathan S. Kline Institute for Psychiatric Research, New York, USA

Rationale: Patients with drug-resistant epilepsy often require surgery to reduce their seizure burden. Intracranial electrode implantation is used in the planning of these surgeries, where electrophysiological biomarkers, such as fast ripples (FR), are needed to identify the epileptogenic zone. Therefore, it is important to better understand the neurophysiological mechanisms responsible for generating fast ripples.

Methods: Several lines of evidence suggest that alteration of the reversal potential of $GABA_A$ and/or modulation of synaptic strengths are related to FR generation. First, we analyzed neocortical FR in intracranial EEG recordings of patients with epilepsy during non-REM sleep. Second, we built a biophysically and anatomically accurate computational

model of the primary somatosensory cortex (S1) to investigate how FR are generated when the $GABA_A$ reversal potential becomes depolarizing and after changes in synaptic strengths.

Results: Our results showed that simulated local field potentials (LFPs) exhibit characteristics similar to those of human cortical recordings, including low- and high-frequency oscillations and FR rate. Furthermore, we described how the different cell types and populations contribute to the generation of FR. Finally, we demonstrated that the FR rate increases when the $GABA_A$ reversal potential is depolarized and/or the excitatory synaptic connectivity of L5 is strengthened.

Conclusions: Our detailed model reproduced physiological properties and the rate of occurrence of FR of human records during non-REM sleep. The results obtained provide insight into the neurophysiological mech- anisms underlying fast ripples, including the specific cortical cell types, neural populations, and inter- actions across scales responsible for their generation.

43 – Epilepsy Abstracts: Study of the action of Angiotensin 1-7 in epilepsy: focus on theneuromodulation of glutamate metabolism in astrocytes

Authors: Jéssica Rodrigues Pedro[1], Isabela Maia de Carvalho[1], Andrey Costa Sartori[1], Marina PradoRubinho[1], Marilia Gabriela Alves Goulart Pereira[1]

[1] Federal University of Alfenas, Minas Gerais, Brazil.

Introduction: Epileptogenesis is directly related to the imbalance between excitatory and inhibitory neurotransmitters, mainly glutamate and GABA, respectively. In this scenario, astrocytes play a fundamental role, reducing the toxicity of excess glutamate in the synaptic cleft, through reuptake by astrocytic glutamate transporters (GLAST and GLT-1) and the regulation of intracellular glutamate-glutamine by glutamine synthase (GS).

Rationale: Several evidence suggest that the deregulated cerebral renin-angiotensin system may be implicated in neurodegeneration, where we can mention Angiotensin II, which is classically

the most studied metabolite. Angiotensin 1-7 [Ang-(1-7)], another RAS peptide, has a possible neuroprotective role, mainly in the neuromodulation of glutamate metabolism in astrocytes. The action of this peptide suggests that it may be useful in the development of therapeutic agents. For this, we studied transporters and enzyme involved in glutamate metabolism, using the *in vitro* model of epilepsy.

Methods: To carry out the experiments, we performed a primary culture of astrocytes isolated from fresh hippocampus and cortex, collected from neonatal rats (CEUA 0004/2021) and to perform the *in vitro* epilepsy model, we used excess extracellular glutamate (1mM). Cells were incubated with Ang-(1-7) (1nM) and the Mas receptor antagonist A779 (10 μM). Then, they were fixed and submitted to immunofluorescence for GFAP (glial fibrillary acidic protein), glutamate transporters and GS. The values obtained with the quantification of the fluorescent signal were plotted and analyzed using the Graph-Pad Prism program (GraphPad, San Diego, CA).

Results: In the hippocampal region, in physiological condition, statistically there was no difference between the groups in the expression of GLAST and GLT-1. In the situation with glutamate excess, observed a decrease, around 50%, in the expression of both glutamate astrocytic transporters by Ang-(1-7) compared to the group treated only with glutamate ($p<0,05$). This effect is completely

reversed with A779, therefore Ang-(1-7) regulation is via Mas receptor. In the cortical region, under physiological conditions, in the group treated with Ang-(1-7) in relation to the control, it is possible to verify that there was a decrease of about 50% in the expression of GLAST and GLT-1 ($p<0.05$). Still in the cortex, with glutamate excess, we observed that there was an increase in the expression, about 100%, of the two transporters when treated with Ang-(1-7) compared with glutamate excess ($p<0.05$). In the cortex, the use of A779 was not able to reverse any effect caused by Ang-(1-7), indicating that, in this region, this peptide acts through another receptor. Regarding the enzyme glutamine synthetase (GS), the results demonstrate no effect of Ang-(1-7) in its regulation, in any of the regions or conditions.

Discussion/Conclusions: The data obtained in the present study showed that Ang-(1-7) can alter the components of the glutamate-glutamine pathway in astrocytes and that this action is

different between the hippocampus and the cerebral cortex, as well as the effects are dependent on the conditions physiological/pathological.

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44 - Exploring Seizure Dynamics In Focal Temporal Lobe Epilepsy Using Vector-EEG

Authors: Moreira, J.P.C.[1,2], Mourão, F.A.G.[1,3], Guarnieri, L.O.[1,2], Mendes, E.M.A.M.[1,2,3], Moraes, M.F.D.[1, 2, 3]

[1]Núcleo de Neurociências (NNC) - Department of Physiology and Biophysics, Institute of Biological Sciences, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, MG, Brazil. [2]Department of Electronics Engineering, Engineering School, UFMG, Belo Horizonte, MG, Brazil. [3]Graduate Program in Neurosciences, Institute of Biological Sciences, UFMG, Belo Horizonte, MG,Brazil

Rationale: Although Epilepsy is commonly viewed as a syndrome, given its multiple causes and manifestations, a surprisingly consistent abnormally activated circuit is recruited during the ictogenesis process of any given patient. Therefore, the dynamics of seizures in terms of spatiotemporal propagation is paramount for diagnosis, seizure prediction and treatment. Despite advances in neural dynamics recording techniques, the temporal resolution of deep brain electrical activity is indisputable, in spite of its lacking spatial resolution. In fact, the spatial origin of neuronal activity is bound, among other aspects, by the number of electrodes, the electrode size and the cerebral substrate in which the electrodes are implanted. The Vector-EEG technique proposed here aims to enhance spatially derived information and provide a high temporal precision vector as well as magnitude and direction related to the dipoles foci during the neural activity. The main goal is to apply Vector-EEG to investigate the dynamics of seizures in an animal model of focal temporal lobe epilepsy, induced by kainic acid (KA) in the CA3 region of the Hippocampus.

Methods: A total of 16 Teflon-coated stainless steel wires were used to design 4 sets of 4 spatially distributed electrodes for bilateral recordings in the Amygdala complex and the CA1 Hippocampus. Stereotaxic surgery was performed in an 8-week-old Wistar rat (~250 g) for electrodes implantation in addition to a guide cannula in the left CA3 hippocampus (CEUA:

116/2021). After a recovery period, a 3 steps protocol followed: (1) 30 minutes of basal recording; (2) administration of kainic acid to induce seizures; (3) 2 hours of seizure recording. The data were collected and stored at a sampling rate of 2kHz by a Intan RHD2132 analog-to-digital converter connected to an OpenEphys system. Vector-EEG was applied to 4 segments with similar electrographic signatures during seizure episodes (~1.5s) and 4 baseline segments for each seizure segment for comparison.

Results: The Vector-EEG graphical representation showed a clear difference between the basal and the seizure state. In the latter, repetitive trajectories are visible for each electrographic epileptiform signature-pattern, with increasingly higher trajectory-magnitude in sequentially distributed discharges. Vectors from different recorded sites are consistent with what would be expected from unilateral KA injection, indicating an evolution of circuitry propagation. The anatomical distribution is also evident, distinguished by vector clusters that depict the directionality of the main activity sources. The Euclidean distance summation between 2 vectors was used as a comparative metric and those involving seizure-epochs averaged 3 +/- 3.5 greater than the basal epochs only.

Discussion: In spite of the need for more appropriate metrics in order to better quantify Vector-EEG trajectories and correlate data from different recorded sites, there is a notable improvement in spatial neuro-dynamics information during ictogenesis. Different recorded sites show very distinct trajectory profiles, showing an emerging cyclic trajectory pattern throughout the epileptic seizure episodes. The Vector-EEG magnitude increased during consecutive trajectory cycles, suggesting a higher neural recruitment alongside a propagation of the ictogenic process throughout recruited neural networks.

Funding: This study was financed by the Fundação de Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) and the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq).

46 - Behavioral Characterization Of Intense Sound Stimulation And Audiogenic Seizures In Animal Models Of Neurodevelopmental Disorders

Authors: Magalhães, L.C.[1]; Campos, D.M. [1]; Nava, J.M. [1], Barbosa, G.R. [1], Garcia-Cairasco, N. [2], Barbosa, L.A.O. [1]; Tilelli, C.Q. [1]

[1]Federal University of São João del-Rei (UFSJ), Divinópolis, MG, Brazil.; [2]University of São Paulo (USP), Ribeirão Preto, SP, Brazil.

Rationale: Autism spectrum disorders (ASD) are associated with sound hypersensitivity, epileptic seizures, and sleep deprivation, with low levels of melatonin hormone. This work aims to investigate the relationship between maternal melatonin, ASD, and epilepsy, through behavioral characterization under intense sound stimulation (ISS). **Methods:** Dams (9-12 weeks old) were divided into five groups: pinealectomized rats with (MEL, n=3) and without (PTX, n=4) melatonin supplementation (0.5 mg/kg in drinking water, 18h00-06h00), rats subjected to a surgical procedure without pineal removal (SHAM, n=3), rats injected intraperitoneally with sodium valproate (500 mg/kg) on the 13th day of gestation (ASD model, VPA, n=5), and rats injected with saline (CTL, n=4) on the 13th day of gestation. Litter was pruned to 8 pups at the 3rd postnatal day and remained with their mothers until 22 days old. Only part of the litter was used for the experiments described here (SHAM, n=7; PTX, n=8; MEL, n=5; CTL, n=10; VPA, n=13). ISS (3 min of 120 dB complex wave stimulation) occurred in 35-45 days old rats. They were put in a cylindric (30 cm diameter) acrylic chamber inside a sound-proof box. Rats were observed 2 min pre-ISS, 3 min during ISS and 2 min post-ISS. Data were processed statistically after tested for normality using ANOVA followed by Tukey post-hoc (JASP 0.17.3, University of Amsterdam) and χ^2test (Excel 2308, Microsoft). Results are presented as mean +/- SEM. Statistical significance was set for $p \leq 0.05$. UFSJ ethics committee approval: protocol 011/2018.

Results: The behaviors presented were grouped in 6 categories: stress/attention (ATT: freezing, piloerection), coping (CPG: grooming, nibling), exploratory behavior (EXP: sniffing, walking), stress/flight (FG: running, withdrawing), ictal (ICT: seizures), and post-ictal (PICT: post-ictal immobility and death). ANOVA showed interaction effect between phases (pre, during, or post-ISS) and behavioral category ($F_{(10,648)}=45.82$; $p<0.001$). EXP was more prevalent during the pre-ISS (102.0+/-3.6s) than both ISS (45.6+/-5.4s) and post-ISS (32.1+/-5.4s) phases ($t_{(10)}=11.26$, pre vs ISS and -12.28, post vs pre; $p<0.001$). CPG behavior was more prevalent during ISS (111.7+/-7.2s), followed by post-ISS (77.8+/-6.3s) and then by pre-ISS (11.4+/-3.6s) ($t_{(10)}=12.15$, post vs pre, -7.31, post vs ISS, and -19.46, pre vs ISS; $p<0.001$). An interaction between group, phase and behavioral category was also detected ($F_{(40,648)}=1.465$; $p=0.035$). During ISS, CPG behavior was less prevalent in VPA group (77.6+/-14.9s) than in CTL group (126.7+/-16.3s) ($t_{(40)}=-5.12$;

p=0.002). After ISS, CPG was more prevalent in PTX group (109+/-8.6s) than in MEL group (90.8+/-20.9s) ($t_{(40)}$=4.45; p=0.045). More VPA rats presented ATT behavior during ISS than CTL ($\chi^2_{(1,\ n=23)}$=7.26; p=0.007). More rats in experimental groups (VPA, PTX) presented ICT behaviors during ISS than all control groups (SHAM, MEL, CTL) ($\chi^2_{(1,\ n=41)}$=4.43; p=0.035). Post-ISS, EXP was presented by less PTX rats, compared to SHAM and MEL ($\chi^2_{(2,\ n=18)}$=5.90; p=0.05).

Discussion/Conclusion: Neurodevelopmental disorders caused by VPA intra-uterine exposure or melatonin absence during pre- and early post-natal development can induce increased susceptibility to seizures and reduced capacity to cope with ISS. Additional investigations will allow for better characterization of these effects, with electroencephalography, biochemical stress markers and repeated stimulation protocols.

Keywords: Autism, Melatonin, VPA, Pinealectomy, Epilepsy, Behavior, Stress, Coping, Neurodevelopment.

Financial Support: Students received scholarships from UFSJ, FAPEMIG and CNPq. UFSJ provided animals, laboratory structure, and most materials and equipment. LAOB and CQT purchased some materials and equipment.

47 – Sex-Dependent Long-term Behavioral Consequences of Early-Life Seizure

Authors: Beatriz Eiris Pereira[1]; Tamiris Prizon[1], João Pereira Leite[1], Rafael Naime Ruggiero[1]

[1]Department of Neuroscience and Behavioral Sciences, Ribeirão Preto Medical School, University of São Paulo.

Rationale: Seizures during development are associated with the subsequent development of epilepsy and diverse neuropsychiatric comorbidities. Depressive symptoms frequently surface, establishing depression as one of the most prevalent psychiatric comorbidities. Nevertheless, a deficiency of robust animal models designed to investigate depressive behavior in epilepsy persists. Our hypothesis suggests that, akin to human studies, female rats may exhibit a greater propensity for the prevalence of depressive symptoms. Moreover, delving into sexual

dimorphism in this context has the potential to enhance our understanding of epileptogenesis and its comorbidities.

Materials and Methods: On postnatal day 11 (P11), the experimental groups received Lithium Chloride (LiCl, 127 mg/kg, i.p.), followed by methylscopolamine (1 mg/kg, s.c.) and pilocarpine (80 mg/kg, s.c.). Inclusion criteria relied on Racine Scale seizure severity, requiring at least a class 3 seizure. After 2 hours of continuous seizures, status epilepticus (SE) was halted with Diazepam (5 mg/kg, i.p.). At P55, female rats' estrous cycles were analyzed. Behavioral assessments started at P60 and included exploratory activity (Open Field Test), anxiety (Elevated Plus Maze Test), depression (Forced Swim Test), and psychosis (Prepulse Inhibition of Startle Reflex). Sensory-motor filtering was tested using sound stimuli. Dopaminergic system sensitivity was probed with Apomorphine (1.5 mg/Kg). Data analysis was conducted using X-plo-Rat software, while statistical analyses relied on GraphPad Prism 9, incorporating one-way Student's t-tests or ANOVA tests as appropriate (Protocol 066/2021 of Ethics Committee on Animal Experimentation of FMRP- USP).

Results: We found that in the Open Field Test (OF), there were no significant differences among groups in exploratory behavior ($p=0.34$; $F(3,276) = 1.11$). In the Elevated Plus Maze (EPM), SE females spent more time in the closed arm compared to CTRL females ($p=0.024$; $t(32) = 2.36$) and also more time in the central area than CTRL males and SE males ($p=0.0095$; $F(3,60) = 4.17$). SE females predominantly employed a diving strategy ($p=0.021$; $t(32) = 2.41$). In the Forced Swim Test (FST), SE females exhibited increased immobility time ($p=0.0013$; $F(3, 68) = 5.81$) and reduced swimming time ($p=0.0065$; $F(3, 68) = 4.44$) compared to other groups. For the Startle Reflex, males displayed heightened responsiveness to aversive sound stimuli compared to CTRL and SE females ($p=0.0003$; $F(3,69) = 7.27$), but no differences in the sensory-motor filter. Regarding Apomorphine (APO) administration, SE males covered a significantly greater distance than SE females ($p=0.02$; $t(32) = 2.39$), suggesting potential hyperdopaminergic state in males.

Conclusion: This study investigated the impact of SE during development revealing that females exposed to SE exhibit behavioral changes indicative of depression and anxiety-like symptoms, whereas males display an altered sensorimotor profile, potentially associated with dopaminergic alterations. These findings underscore the necessity for further research to understand sexual

dimorphism as consequences of early-life seizures and epilepsy. Notably, our results advocate for the utilization of female subjects as a valuable model for investigating depressive phenotypes in epilepsy.

Financial Support: CAPES, CNPq, and FAPESP.

Conflicts of Interest Disclosure: The authors declare that they have no conflicts of interest.

Acknowledgements: Renata Caldo Scandiuzziand Antônio Renato Meirelles

48 – Evaluation Of The Impact Of Multimodal Early Life Stress On PTZ-Induced Seizures In Mice

Authors: Ferreira, R. T. [1], Souza, J. H. R. [1], **Melo, M. A. A.** [1], Godoy, L. D. [2], Santos, V. R. [1]

[1] Department of Morphology, Institute of Biological Sciences, Federal University of Minas Gerais, Brazil; [2] Physiology Department, Ribeirão Preto School of Medicine, University of São Paulo, Brazil

Introduction: Epilepsy is a chronic disease that affects thousands of individuals worldwide. Research has presented compelling evidence that stress can act as a trigger through complex neurobiological mechanisms involving alterations in brain electrical activity and neurotransmitter regulation, modifying stress response systems. In this study, we focused on analyzing the behavior of mice of the C57/BL6 strain during seizures, observing the latency, duration and phases of the epileptic seizure. We used a multimodal stress protocol that involved repeating and alternating daily stressors, gradually inducing maladaptive plasticity. In particular, animals that experienced stress early in life had worsened epileptic seizures and decreased latency.

Objective: The aim of this project is to evaluate the influence of early life stress on the latency, duration and types of PTZ-induced epileptic seizures.

Methods: The experimental protocols described in this study were approved by the Ethics Committee in Animal Research of UFMG (CEUA-226/2022). Pups of C57/BL6 mice were

submitted to stress from the 1st to the 9th postnatal day (n=9 stressed group and n=7 control). The multimodal protocol for early life stress (ELS) included alternating periods of separation of mother and pair in an acrylic box with internal separations for 60 minutes, containment with agitation at 30 rpm in falcon tubes with holes for 60 minutes on an agitator, and exposure to cold in beakers for 10 minutes. On the 10th postnatal day, subcutaneous doses of 80 mg/kg and 100 mg/kg of the seizure-inducing drug, pentylenetetrazole (PTZ), were administered to animals in the stressed group and to animals that did not suffer stress, as a negative control. The PTZ was diluted in saline solution. The animals were marked with colored adhesive tape on the tail according to the concentration of the drug and differentiating between control and stress animals. Subsequently, they were placed in acrylic boxes and observed for about 20 minutes, with a camera placed above the boxes. The videos were analyzed and the initial data collected stored in a spreadsheet with the parameters to be analyzed. The data will be transformed into statistical data using GraphPad Prism 8 to evaluate various crisis parameters, including seizure types, duration,severity, and latency.

Results: After preliminary analyses, it was observed that in the group of control animals the latency time was approximately five minutes longer compared to the group of stressed animals. In addition, the stressed animals had longer seizures of about 15 minutes and continuous, while the control animals lasted about 10 minutes and were able to return from the seizure at least once. The stressed group also showed loss of straightening reflex more significantly. When the stressed group showed decreased latency and worsening of seizures, this indicates a potential association between stress in early life and increased susceptibility to epileptic seizures.

Conclusions: The results showed how crucial it is to understand the relationship between early life stress and epilepsy. We have determined that animals subjected to the Early Life Stress (ELS) protocol exhibited a notable decrease in latency time for seizures.

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49 – NMDA Receptors On Parvalbumin Interneuron Hypofunction Led To Intense StatusEpilepticus And Behavioral Impairment.

Authors: Medeiros, A.C. [1], Ruggiero, R. N. [1] Leite, J. P. [1]

[1] Department of Neurology, School of Medicine of Ribeirão Preto, University of São Paulo, Brazil.

GABAergic interneurons (IN) expressing parvalbumin (PV+) play a key role in gamma oscillation generation and information processing. These IN undergo a prolonged period of maturation and integration into cortical circuits during adolescence (period of high plasticity) and are critically involved in cognitive development. Their activity involves NMDA receptors and genetic mutations of these receptors are associated with several neurological developmental disorders such as epilepsy and schizophrenia. Moreover, the reorganization of different neuronal microcircuits may be the key to understanding neurological disorders and comorbidities. In this sense, we hypothesize that dysfunction of NMDA receptors in PV IN increases susceptibility to status epilepticus (SE), depending on the age at which the insult occurs, and favors the appearance of behavioral and cognitive impairments associated with morphological and functional alterations. Mice with ablation of the NR1 subunit in IN PV+ (PVCre NR1f/f) were used in a pilocarpine model (CEUA protocol: 1055/2022). The SE was induced in animals at 17 days postnatal age and morphological changes were followed 48h after SE and in adult life by an analysis of neuronal (NeuN), microglial (lba1), and astrocytic (GFAP) density. Adults were submitted to tests to evaluate depressive-like behavior (tail suspension and sucrose preference tests), anxiety-like behavior (plus maze and open field test), and psychotic-like behavior (pre-pulse inhibition). We also performed a novel object recognition test to assess cognitive impairment. Data were analyzed according to distribution and the value of $p < 0.05$ was used as the criterion for statistical significance. Mice PVCre NR1f/f at P17 had a more intense and longer SE compared to PVCre NR1+/+. It was observed that there was an increase in the number of GFAP+ cells in dCA1 ($F_{3, 16} = 34.72$; $p< 0,05$), dCA3 ($F_{3, 16} = 7.854$; $p < 0.05$), and prelimbic cortex (PrL) ($F_{3, 16} = 39.18$; $p < 0.05$). Also, a decrease of PV+ cells in *dentate girus* (DG) ($F_{3, 8} = 6,114$; $p< 0.05$), dCA1 ($F_{3, 8} = 28.70$; $p< 0.05$), dCA3 ($F_{3,16} = 7.854$; $p<0.001$) and PrL ($F_{3, 8} = 13.37$; $p< 0.05$). In relation to Iba immunolabelling, it was observed

an increase of positive cells in the PrL ($F_{3, 15} = 2.855$; $p<0.05$), dorsal ($F_{3, 15} = 15.09$; $p<0.05$), and ventral hippocampus ($F_{3, 15} = 8.986$; $p<0.001$). The same analysis in adult life shows that GFAP labeling is higher in the PrL ($F_{3, 14} = 18.71$; $p<0.001$), dCA3 ($F_{3, 18}= 10.06$; $p<0.001$), vCA1 ($F_{3, 18} = 8.649$; $p<0.001$), and vDG ($F_{3, 18} = 24.23$; $p<0.001$). Also, an increase of PV-positive cells in PrL, dCA1 ($F_{3, 18} = 5.204$; $p<0.001$), dDG ($F_{3, 18} = 13.07$; $p<0.001$), and ventral hippocampus ($F_{3, 18} = 8.507$; $p<0.001$). Regarding Iba+ cells, was observed an increase in PrL ($F_{3, 18} = 24.71$; $p<0.001$) and dorsal hippocampus ($F_{3, 18} = 59.58$; $p<0.001$). Furthermore, our data show that these adult mice have behavioral alterations related to depression, anxiety, and cognitive impairment. Our data suggest that mice with hypofunction of NMDA receptors in the IN PV+ were considered more intense SE. In addition, animals present more diverse alterations in relation to morphology. In adulthood, this condition persists, and behavioral changes and cognitive impairment are added. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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50 – Lack of N-Methyl-D-aspartate Receptor Subunit NR1 in Parvalbumin-Interneurons intensifies seizure and depressive-like behaviors in Amygdala rapid kindling

Authors: José Luiz Liberato[1*], Leonardo Rakauskas Zacharias, Danilo Benette Marques, Tamiris Prizon[1], Rafael Naime Ruggiero [1], João Pereira Leite[1]

[1] Department of Neuroscience and Behavioral Sciences, Ribeirão Preto Medical School, University of São Paulo,Ribeirão Preto, SP, Brazil.

Rationale: The progression of Temporal lobe epilepsy (MTLE) seizures affects populations of GABAergic-interneurons (IN) and the functional/morphological connectivity between the hippocampus (HPC) and the Prefrontal Cortex (PFC), which could explain the high prevalence of psychiatric disorders in MTLE patients. However, the pathophysiology underlying the comorbidity between MTLE and psychiatric disorders is still poorly explored, and the role of parvalbumin-interneurons (PV-INs) in epileptogenesis is still controversial and much debated. Thus, this study investigated the role of PV-IN malfunction in the HPC-PFC microcircuitry on the process of epileptogenesis and associated comorbidities, such as depression-like, anxiety-like, and psychosis-like.

Methods: Adult male mice C57BL6 and PV-Cre/NR1$^{f/f}$ (selective ablation of the NMDA receptor NR1) were implanted with bipolar electrodes in the basolateral-amygdala (BLA) and with monopolar-electrodes in the HPC and PFC to induce Rapid Kindling through electrical stimuli (BLA-RK) and recording local field potential (LFP), respectively. The BLA-RK protocol consisted of applying ten daily stimulations, 20-min apart from each other, with biphasic pulse trains of 0.1-ms duration each and frequency of 50-Hz, for 10s, through 3-days. The mice's behavior was assessed in the open field (OF), elevated plus maze (EPM), sucrose preference (SPT), tail suspension (TST), and prepulse- inhibition (PPI) tests. *The Ribeirão Preto Medical School Animal Use Ethics Committee (CEUA-FMRP-USP) approvedthis study (# 33/2019).*

Results: We found no significant difference in the OF exploration and TPS test between groups of mice. However, PV- Cre/NR1$^{f/f}$ spent less time in the open arms of the EPM, took longer immobility time in TSC, and showed no deficits in the PPI test compared to C57BL6 mice. Also, PV-Cre/NR1$^{f/f}$ mice exhibit a lower threshold for the onset of after- discharges (AD) and the emergence of secondary ADs in the HPC, indicating the spread of epileptiform activity beyond the stimulus region. Furthermore, the analyses of the spectral power density (PSD) showed a decrease in the power of frequencies above 10Hz on the first day of stimulations in PV-Cre/NR1$^{f/f}$, an increase

in the gamma- power in the mCPF on the third day of BLA-RK. After BLA-RK, the PV-Cre/NR1$^{f/f}$ exhibited an unexpected increase in the consumption of sucrose solution, and in the immobility time in TSC, in comparison to C57BL6 mice. We did not observe significant impairment in the other behavioral tests assessed.

Conclusions: Our findings indicated that the PV-IN malfunction is related to an increase in the susceptibility of AD onset and duration, and also provides further evidence of the PV-IN role in the depression-like comorbidity in the RK model of epileptogenesis.

51 – Preliminary Characterization Of BD-15 Effects On Pilocarpine-Induced Status Epilepticus: A Possible Neuroprotective Molecule

Authors: Barbosa, G.R.[1]; Camilo, M.E.P. [1], Teixeira, F.S. [1], Garcia-Cairasco, N. [2], Moraes, M.F.D.M. [3]; Villar, J.A.F.P. [1], Barbosa, L.A.O. [1], Carvalho, L.E.D. [1]; Tilelli, C.Q. [1]

[1]Federal University of São João del-Rei (UFSJ), Campus Centro-Oeste D. Lindu, Divinópolis, MG, Brazil; [2]University of São Paulo (USP), Ribeirão Preto, SP, Brazil; [3]Federal University of Minas Gerais (UFMG), Belo Horizonte, MG, Brazil

Rationale: Epilepsy is a severe neurological condition with worldwide high prevalence. Some of the patients present with uncontrollable seizures, despite adequate pharmacological treatment. Mesial temporal lobe epilepsy (MTLE) represents about 30% of such cases. One of the important issues to be evaluated in epilepsy research is the possible prevention of epilepsy condition aggravation, though the use of neuroprotective agents. Our group has been working on the study of new drugs, derived from cardiotonic steroids. One of those drugs is called BD-15, and has been shown neuroprotective characteristics, when used in central nervous system ischemia. We aimed to study the effects of BD-15 in the pilocarpine model of MTLE.

Methods: Male wistar rats (n=17), approximately 70 days old, were injected with scopolamine (1 mg/kg) and, after 30 min, pilocarpine (PILO; 300 mg/kg). Animals that entered status epilepticus (SE) were allowed to seize during 90 min and then were injected with diazepam (5 mg/kg) and ketamine (50 mg/kg). Thirty min after diazepam/ketamine injection,

they received the first of 3 doses of BD-15 (0.1 mg/kg; BD15), which was given every 24 hours, thereafter. Control animals were injected with similar volume of saline (SAL) instead of BD-15. Rats were monitored and hydrated for several days, until they were able to feed and drink by themselves. Body weight was measured before pilocarpine treatment and every 24 hours for 7 days. Data were processed statistically using Student *t* test, after tested for normality (JASP 0.17.3, University of Amsterdam). Results are presented as mean +/- SEM. Statistical significance was set for p value equal to or lower than 0.05. UFSJ ethics committee approval: protocol 9007230322.

Results: One rat died soon after PILO injection, therefore was not included in the results. Eight animals did not develop SE. Nine rats developed SE and were divided in groups BD15 (n=5) and SAL (n=4). Three rats died after 24-72 hours from PILO injection (2 from BD15 group and 1 from SAL group). Among the survivors, although there was no body weight difference in the day of induction ($t_{(4)}$=0.44; p=0.683), and all lost weight from day of induction to the day after ($t_{(8)}$=2.46; p=0.039), weight was recovered better by BD15 group (317+/-6.6g) compared to SAL group (288.9+/-6.2g) during the following week ($t_{(40)}$=3.10; p=0.004).

Discussion/Conclusion: Although we only have preliminary data, there is evidence for a protective effect of BD-15 in the context of PILO-induced SE, as the surviving rats from BD15 group recovered their weight more efficiently than the SAL group. We are currently incrementing the evaluation, with SE characterization, daily global neurologic test and chronic video recording for spontaneous seizures detection. These evaluations will provide a better understanding of BD-15 role as a possible neuroprotective molecule.

Keywords: epilepsy, status epilepticus, pilocarpine, BD-15, neuroprotection.

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52 - Knock-out of NR1 subunit of NMDA receptors in Parvalbumin Interneurons is associated with enhancement of intrinsic excitability of cortical pyramidal neurons

Authors: Zacharias, LR[1,2]; Benites, NM[2]; Liberato, JL[1]; Leite, JP[1]; Lopes-Aguiar, C[3]; Leão, RM[2]

[1]Departamento de Neurociências e Ciências do Comportamento - Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo – USP; [2]Departamento de Fisiologia - Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo – USP; [3]Departamento de Fisiologia e Biofísica - Instituto de Ciências Biológicas - Universidade Federal de Minas Gerais.

Rationale: Recent research has underscored the role of N-methyl-D-aspartate Receptors (NMDAR) within parvalbumin interneurons in regulating the balance of cortical circuits. Our prior work (Guyon et al., Journal of Neuroscience, 41, 2944, 2021) revealed that the knock-out of NR1 subunit of NMDAR in these interneurons leads to altered dynamics of electrophysiological oscillations, emerged from asynchronous activity of prefrontal cortical pyramidal neurons (PNs). However, the underlying mechanisms remain unclear. Recent studies show that mice lacking NMDAR in inhibitory interneurons during development reach adulthood with altered morphological and intrinsic properties of PNs linked to excitatory-inhibitory (E/I) imbalance. We hypothesize that the emergence of aberrant activity (observed in Guyon et al. 2021) is thus not only linked to disruptions in the E/I balance but also to inherent modifications within the PNs. To probe the mechanisms driving this behavior, we conducted current-clamp experiments on PNs of mice lacking the NR1 subunit of NMDAR in parvalbumin interneurons, assessing intrinsic properties and response to current injections.

Methods: To knock out the NR1 subunit of NMDAR in parvalbumin interneurons, we crossbred PV-Cre knock-in mice (control group) and mice carrying floxed NR1 alleles, leading to PV-Cre/NR1f/f mice (NR1 group). We conducted whole-cell patch clamp recordings in PNs from layer 2/3 of the medial prefrontal cortex (mPFC) slices (300 µm). NR1 mice (n = 19 cells from 6 individuals) and PV-Cre mice (n = 17 cells from 6 individuals) were deeply anesthetized with isoflurane and quickly decapitated to obtain viable coronal slices. The intrinsic properties of the PNs were assessed through current clamp recordings, employing step currents ranging from -200 pA to 700 pA with 50 pA steps. Spike initiation parameters such as rheobase current, access resistance, latency and threshold, and width and maximum amplitude of the action potential were extracted from the first detected spike. The frequency-stimulus relationship (FI curve) was

established by analyzing spike frequencies across the applied stimuli. Protocols were approved by the FMRP Ethics Committee (CEUA 1150/2022).

Results: Our findings revealed that, apart from alterations in action potential amplitude ($p = 0.007$, t-value = -2.85, unpaired t-test), the intrinsic properties of PNs remained largely unaltered in the NR1 mice compared to the control group. However, NR1 mice exhibited a significantly higher frequency of action potentials across stimuli than the control group ($p = 0.0003$, Wald $\chi^2 = 13.3$, GLM comparison).

Discussion/Conclusion*:* The distinctive firing pattern observed might indicate changes in the intrinsic excitability of PNs, suggesting that the aberrant dynamics of cortical circuits in the NR1 group (as previously observed in Guyon et al. 2021) not only emerge from the altered excitability of parvalbumin interneurons but also from intrinsic modification of the PNs. However, other intrinsic properties, such as rheobase current or membrane resistance, remain similar to control animals. To comprehensively understand the extent of these modifications and their contribution to the dynamics of mPFC circuits, further experiments will be conducted to evaluate additional parameters of intrinsic excitability of PNs and direct synaptic communication between PNs and parvalbumin interneurons.

Financial Support: CAPES, CNPq, and FAPESP.

53 – Investigating the Link between Alzheimer's Disease and Epilepsy: An Electroencephalographic Study on Spontaneous and Audiogenic Seizures in the Streptozotocin-Induced Alzheimer's Disease Model

Authors: Gabriel Servilha-Menezes[1], José Antônio Cortes de Oliveira[1], Flavio Del Vecchio[1], Suélen Santos Alves[1,2], Rui Milton Patrício da Silva-Junior[1,3], Norberto Garcia-Cairasco[1,2].

[1] Department of Physiology, Ribeirão Preto Medical School - University of São Paulo (FMRP-USP), São Paulo, Brazil. [2] Department of Neurosciences and Behavioral Sciences, Ribeirão Preto Medical School - University of São Paulo (FMRP-USP), São Paulo, Brazil. [3] Hospital Clínic Barcelona, Institut d'Investigacions Biomèdiques August Pi Sunyer (IDIBAPS), University of Barcelona, Barcelona, Spain.

Rationale: Epilepsy and Alzheimer's disease (AD) are highly prevalent and severe neurological disorders affecting tens of millions of individuals worldwide. Despite the vast amount of human and financial resources invested in the search for new therapies, both diseases have no cure, which leaves a large percentage of patients with very limited prospects for health and quality of life improvements whenever therapy fails. A growing body of evidence has demonstrated a likely bidirectional association between epilepsy and AD, which provides a new vantage point for research looking for new therapeutic approaches and a better understanding of these complex diseases. As a focus of our recent work, our goal was to investigate central insulin resistance as a possible link between epilepsy and AD.

Methods: In order to assess the effect of AD and the role of impaired brain insulin signaling on seizure susceptibility, we used the intracerebroventricular streptozotocin (STZ-icv; N=4) induced rat model of sporadic AD and citrate buffer vehicle controls (VEH; N=5) to record video-electroencephalographic (video-EEG) before and after drug injection (animal ethics committee approval; CEUA-1114/2022R3). On days 7 and 14 after STZ or vehicle icv-injection, we also recorded video-EEG before, during and after two sessions of acoustic stimulation (AS), a trigger for audiogenic seizures in susceptible animals. As a validatory step of the model and to assess learning and memory, the animals were also subjected to Barnes Maze (BM) test starting on the 21st day after icv-injection.

Results: Seizure-like electroencephalographic activity without motor manifestation was observed in VEH and STZ-icv immediately after vehicle or drug injection. Outside AS, behavioral and electrographic spontaneous seizures were observed in animals of the STZ-icv group but not VEH animals. On the 7th day after injection, 40% of both groups displayed audiogenic seizures following AS. On the 14th day after injection, 20% of the VEH group and 100% of the STZ-icv group displayed audiogenic seizures during AS ($p=0.0397$ Fisher's exact test). The mean score in the categorized severity index (cSI), a behavioral measurement for mesencephalic seizure intensity, was 1 for the VEH group and 5 for the STZ-icv group ($p=0.0397$; Mann-Whitney test). In the BM test we observed that STZ-icv produced a negative effect on spatial memory as detected by an increase in latency for escape during the training phase ($p=0.0002$; Mixed-effect analysis), a higher number of errors ($p=0.0474$; Mixed-effect

analysis) and a decrease in the occupation of the target quadrant in the probe trial (p=0.0195; Unpaired t test).

Discussion/Conclusions: The STZ-icv model was initially developed to study the role of central insulin resistance in AD as it impairs insulin signaling in the brain while also producing several other of the more commonly described alterations of AD. Our results, therefore, provide additional evidence of an association between Alzheimer's disease and epilepsy in the STZ-icv model, which suggests that central insulin resistance may be a key link between both conditions. Further research is needed to better understand the molecular mechanisms underlying this complex association and to help develop new strategies for preventing or reversing these conditions.

Acknowledgements: This study was supported by the São Paulo Research Foundation (FAPESP-Brazil) grant: 19/05957-8 (NGC); Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES-Brazil – Finance Code 001 (GSM, NGC); National Council for Scientific and Technological Development (CNPq-Brazil), grant: 305883/2014-3; National Institutes for Science and Technology (INCT-Brazil) – "Translational Medicine," grant: 14/50891-1 (FAPESP-Brazil) and 465458/2014-9 (CNPq-Brazil); NGC holds a CNPq 1A Research Fellowship (#309397/2018-9).

Keywords: Epilepsy, Alzheimer's Disease, Audiogenic Seizures, Electroencephalography.

54 – Impaired Hippocampal-prefrontal synchrony underlies cognitive deficits following Early-Life Seizure

Authors: D'Agosta, R.[1], Prizon, T.[1], Zacharias, L.R.[1]; Marques, D.B.[1], Leite, J.P.[1], Ruggiero, R.N.[1]

[1]Department of Neuroscience and Behavioral Neuroscience, Ribeirão Preto Medical School, University of São Paulo, SP-Brazil.

Rationale: Early-life Status Epilepticus (SE) is associated with epilepsy and cognitive deficits, yet the neurophysiological changes driving these effects are unclear. Understanding the impact

of epileptogenic processes on cognition is crucial for the development of better treatments. We hypothesized that these deficits may stem from altered neural dynamics within critical fronto-limbic circuits. Our objective was to investigate the hippocampal-prefrontal-thalamic oscillatory network during a working memory task in the T-maze in rats that experienced SE during development.

Methods: We used 25 Sprague Dawley male rats divided into two experimental groups: the control group (CTRL, N=13) and the experimental group with SE induced by pilocarpine (PILO, N=12). This study received approval by the Animal Use Ethics Committee (CEUA) under protocol number 1151/2022. Rats were submitted to an SE protocol 12 days after birth (P12), starting the experiment at P11 with lithium chloride treatment (LICl, 127 mg/kg, i.p.), and 18-20 hours later, we administered methylscopolamine (1 mg/kg, s.c.) to all animals. After 30 minutes, saline (0.9% NaCl, s.c.) was injected in the CTRL group, and pilocarpine (80 mg/kg, s.c.) in the PILO group. SE was interrupted after 2 hours with diazepam (5 mg/kg, i.p.). After 50 days, each animal was trained to find a reward (0.5 mL of 20% weight/volume sucrose solution) until reaching 70% of correct answers per day for 3 days. Next, the trained animals underwent stereotaxic surgery for the implantation of stereotrodes in the prefrontal cortex (PFC), middle dorsal thalamus (MD), and dorsal hippocampus (DH). After recovery, rats were re-trained until criteria was once again reached. Finally, the animals were submitted to the random delay test using intervals of 30, 60, and 90 seconds, with 12 attempts daily, for ten days, in the paradigm *delayed non-match-to-sample*.

Results: In the T-maze task, rats subjected to SE performed less correct choices when compared to the CTRL group (Two-way repeated measures ANOVA treatment × delay interaction: $F(1,23)=11.44$, $p=0.002$). This difference was particularly pronounced at longer delays, as shown by Sidak's multiple comparisons *post-hoc*, specifically 60 seconds, (t-test: $t(69)=2.95$, $p=0.012$), and 90 seconds (t-test: $t(69)=2.61$, $p=0.032$). We found that SE rats showed significantly lower HPC-PFC theta (5-12 Hz) coherence at the decision point than CTRL animals, specifically during correct trials at delays of 60 seconds ($t(7)=-2.565$, $p=0.037$), and 90 seconds ($t(7)=-3.203$, $p=0.015$). Importantly, these effects were independent of alterations in theta oscillatory power ($t(7) =-1.209$, $p=0.265$) Also, we found strong correlation between HPC-PFC theta coherence at decision making and working memory accuracy (Pearson's correlation, $r(6)=0.760$ $p=0.028$).

Conclusion: In conclusion, our findings indicate that early-life seizures result in working memory impairments, implying cognitive deficits in adulthood linked to decreased HPC-PFC synchrony. This study offers valuable insights into how early-life seizures impact cognitive processing and maycontribute to comorbidity symptoms.

55 - Modulation of recruitment from primary to secondary epileptic focus with different patterns of electrical stimulation in Wistar Audiogenic Rats

Authors: Valentim-Lima, E.[1]*; Guarnieri, L.O.[1]; Mourão F.A.G.[1]; Moraes, M.F.D.[1]

[1]Programa de Pós Graduação em Neurociências, Núcleo de Neurociências, Departamento de Fisiologia e Biofísica, Instituto de Ciências Biológicas (ICB), Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, Brazil.

Rationale: Epilepsy is characterized by an abnormal predisposition of the brain in present epileptic seizures. Moreover, individuals afflicted by this, not only experience epileptic seizures, but also can develop comorbidities such as anxiety. The knowledge about that has advanced in conjunction with neuroscience, through studies that aided in elucidating how different brain regions communicate and how this process can either facilitate or disrupt the spread of epileptic activity from one region to another. It is established that electric stimulation applied to a specific brain region at regular intervals can induce hypersynchronization, thereby enhancing communication between two or more regions. Conversely, when such stimulation is applied at irregular intervals, it creates greater difficulty in communication, consequently disturbing the propagation of epileptic activity to other brain regions. Hence, the primary objective of our study is to investigate if electric stimulation, administered in both periodic and non-periodic patterns, can modulate the recruitment of a secondary epileptic focus in Wistar Audiogenic Rat (WAR). Additionally, we aim to ascertain whether these stimulation patterns can induce anxiety like behavior in these rat strain.

Methods: For the experiments, Wistar (n = 10) and WAR (n = 18) female animals, aged 6 weeks, were subjected to three consecutive days of sound stimulation at 110dB for one minute

each day. The Wistar animals that exhibited seizures at this stage were excluded from the subsequent phases. Following this stimulation, the animals were then divided into three groups: Wistar, WAR Low Audiogenic Response (WAR LAR) (WAR below 0.61 in Mesencephalic seizure severity indexes scale of Garcia-Cairasco et al. 1996), and WAR High Audiogenic Response (WAR HAR) (higher 0.61 of the same scale). All animals were then subjected to stereotaxic surgery for bilateral electrode implantation in the basolateral amygdala. After a one-week recovery period following the surgery, each group was further subdivided into three subgroups based on the type of stimulus to be applied: Sham, periodic (constant interpulse intervals of 250 µs, and non-periodic (randomized interpulse intervals). The experiment consisted of 20 consecutive days of sound stimulation at 110dB, with the sound modulated at 4Hz, with or without an electric stimulation also at 4Hz, 100µs of wave length and 50 µA for a duration of one minute. Alongside the sound stimulation, the animals received electrical stimulation in the amygdala corresponding to their respective groups. To assess potential alterations in the anxious-like behavior, all groups were evaluated on day 1, day 11, and day 20 of stimulation, one hour prior to the implementation of the protocol described above. After the final stimulus, the animals were euthanized, and their brains were removed to verify the correct electrode position.

Results: Regarding brainstem seizures, we observed that WAR LAR had the lowest scores throughout the days in the non-periodic group, while the Wistar periodic group had longer seizure durations, with no difference in the other groups. Similarly, WAR HAR showed slightly longer seizure durations in the periodic group compared to the sham group, with the non-periodic group having the shortest seizure durations. In WAR HAR, seizure durations were longest in the sham group, followed by the periodic and non-periodic groups. As for limbic seizures, WAR LAR experienced an increase in severity and duration over time, while the non-periodic group had lower severity and shorter durations. WAR HAR had higher severity only in the sham group, with both stimulation groups exhibiting low scores for limbic seizures. The duration of limbic seizures followed a similar pattern to the severity. In the EPM test, the Wistar groups had higher numbers of entries into open and closed arms, spent more time in open arms, and had a higher frequency of head dipping. Electric stimulationdid not yield any differences in the analyzed parameters.

Discussion/Conclusion: According to our preliminary data, in animals with high sound sensitivity and high brainstem seizure indices, such as in the case of WAR HAR, the type of electrical stimulation does not seem to matter for limbic seizures. Both periodic and non-periodic stimulation are capable of reducing severity and duration while increasing latency to the onset of these seizures. This may indicate that an established epileptic circuitry in the amygdala may have a different oscillation frequency, and thus both 4 Hz stimulations may have an inhibitory effect. On the other hand, when animals exhibit low brainstem seizure indices during sound stimulus, as in the case of WAR LAR, there is evidence that periodic stimulation promotes hyper-synchronization between the amygdala and the inferior colliculus, increasing the severity and duration, and decreasing the latency of limbic seizures, while non-periodic stimulation seems to desynchronize both structures. Anxiety is a common comorbidity of epilepsy. According to our preliminary data, the type of electrical stimulation used does not appear to interfere with anxiety-related behavior. Therefore, our preliminary data suggest that periodic stimulation may induce hyper- synchronization and non-periodic stimulation desynchronization between the amygdala and the inferior colliculus in animals whose sound stimulus generates less severe seizures. However, in animals experiencing more severe seizures in response to the sound stimulus, both electrical stimulations lead to desynchronization of these structures. It is important to note that these data are preliminary, and more animals are needed to conduct a more comprehensive analysis of these indications.

Funding: We thank CAPES, CNPQ and FAPEMG for supporting our research.

56 - Machine Learning Resampling Techniques do not Improve Seizure Prediction using EEG Recordings

Authors: Ruggiero, R.N.[1]; Oliveira-Júnior[1], B.A.; Leite, J.P[1].

[1]Department of Neuroscience and Behavioral Neuroscience, Ribeirão Preto Medical School, University of São Paulo, SP-Brazil.

Rationale: Accurate seizure prediction using machine learning is essential for enhancing patients' quality of life and ensuring timely medical interventions. However, a common

challenge arises from imbalanced data distributions between the majority (interictal states) and minority classes (seizures). This imbalance can significantly impact the predictive performance of machine learning models. To address this challenge, various resampling techniques have been developed. While numerous models have been created and validated the practical implementation of these models in clinical practice remains limited. This study aims to address this gap by focusing on the performance evaluation of different resampling techniques in the context of stereo-electroencephalography (SEEG)data analysis.

Methods: We employed two distinct datasets, the Melbourne-University AES- MathWorks-NIH Seizure Prediction Challenge and the American Epilepsy Society Seizure Prediction Challenge, containing invasive EEG recordings. Attributes were categorized as "short" (extracted every minute) or "long" (extracted from 10-minute segments). Short attributes included total energy normalized by band, while long attributes encompassed correlation coefficients, eigenvalues of the correlation matrix, statistical moments in the time domain, maximum frequency, root mean square, total energy in the spectrum, entropy, mobility, complexity, and Higuchi fractal dimension. For handling class imbalance, we applied four approaches: original data (no resampling), Synthetic Minority Over-sampling Technique (SMOTE), random undersampling, and SMOTEENN (a hybrid of over-sampling and under-sampling). Classification employed four algorithms: K-nearest neighbors (KNN), logistic regression (LR), random forests (RF), and multi-layer perceptron (MLP). Model performance evaluation involved partitioning the dataset into training (80%) and testing (20%) subsets using stratified random sampling to maintain class distribution. Additionally, we conducted 10-fold cross-validation on the training data to assess model robustness.

Results: When used in the training data the resampling algorithms contributed to enhanced training performance when analyzing F1 value ($F(3,36)=30.96$, $p<0.0001$, Tukey HSD post-hoc $p<0.05$ for original x SMOTE, Under e SMOTEENN). Using AUC as the metric, we observed superior performance in models using SMOTE and SMOTEENN resampling techniques when compared to the dataset with imbalanced data and the dataset with undersampling ($F(3,36)=23.85$, $p<0.0001$, Tukey HSD post-hoc $p<0.05$ for imbalanced and UNDER vs. SMOTE and SMOTEENN). However, when evaluating the models on a new data (the test data), no significant differences among the models were observed, whether using the F1 score

(F(3,36)=0.48, p=0.7) or AUC (F(3,36)=2.23, p=0.13) as evaluation metrics. These results suggest that resampling techniques can lead to overfitting, without effective learning occurring when the data is highly distinct.

Conclusion: These results suggest that caution should be exercised when employing resampling techniques, which are widely utilized in medical literature, particularly in the field of seizure prediction. Contrary to expectations, correcting for outcome imbalance through resampling methods may not necessarily improve model performance. In fact, it can lead to models with pronounced miscalibration, undermining their clinical utility.

57 - Behavioral And Mesolimbic Electrophysiological Alterations In An Animal Model Of Postictal Psychosis

Authors: Prizon, T.[1]; Rossignoli, M.T.[1].; Marques, D.B.[1]; Leite, J.P.[1]; Ruggiero, R.N.[1]

[1] Department of Neuroscience and Behavioral Neuroscience, Ribeirão Preto Medical School, University of São Paulo, SP-Brazil.

Introduction: Temporal lobe epilepsy is the most common type of focal epilepsy. It presents a high prevalence of psychosis, indicating that alterations on limbic circuits are essential for the development of psychiatric symptoms. Experimental evidence suggests that seizures can generate a hyperdopaminergic state through indirect activation of mesolimbic pathways. This dopaminergic activation is linked to the emergence of behavioral alterations that are relevant to postictal psychosis. We hypothesized that psychotic symptoms after an epileptic seizure are related to a hyperactivity of the hippocampus (HPC) -ventral tegmental area (VTA) pathway. We investigated if the HPC-VTA circuit was involved with psychotic-like behaviors in an experimental model of postictal psychosis induced by afterdischarges (AD).

Materials and Methods: Adult male Sprague-Dawley rats (n=8) were chronically implanted with recording electrodes in the dorsal CA1 and stimulation electrodes in the ventral hippocampus. Once recovered from surgery, rats were tested in the prepulse inhibition of the acoustic startle (PPI, background noise of 67 dB, with pulses of 120 dB and pre-pulses of 71, 77 and 83 dB). After 24 h, we established the stimulation threshold (minimum current to evoke at least a 5 s AD) induced by a 10s, 50 Hz train stimulation (squared pulses of 0.1 ms duration,

150-350 µA, protocol used in all experiments). In the next day, AD was evoked, and rats were immediately reexposed to the PPI. In a second experiment, rats were chronically implanted with multielectrode arrays to record multi-unit activity in the Nacc and VTA during the hippocampal kindling protocol (10 stimulations for 3 consecutive days, n=1). Between 3 and 4 days after the afterdischarge, the locomotion and social interaction of the animals were evaluated. All procedures were approved by the Committee on Ethics in the Use of Animals (102/2020).

Results: Rats presented a reduction in PPI after AD (Student paired t-test and p-value FDR corrected for multiple comparisons, 71 dB: $t(7)= 2.447$, $p=0,044$; 77dB: $t(7)= 2.875$, $p=0,06$; 83dB: $t(7)=2.589$, $p=0,045$). In the second experiment, we observed, over the course of days, that kindling generated the emergence of stereotyped behaviors such as wet-dog shakes, rearing, face-washes, and hyperlocomotion. These stereotyped behaviors were accompanied by an increase in neuronal firing rate of Nacc (n=9, 0.694 ± 0.095 Z-score) and VTA (n=3, 0.261±0,246 Z-score). Also, chronically, there appear to be no differences. in locomotion ($p= 0.69$; $t(9)=0.40$), time in center or border ($p=0.28$; $t(10)=1.12$), and social behavior ($p=0.10$; $t(3)=2.29$).

Conclusion: Our results suggest that the induction of afterdischarges (ADs) led to stereotyped behaviors and sensorimotor gating deficits, accompanied by heightened activity in the VTA-Nacc pathway. These findings hint at a potential connection between the overactivity of mesolimbic dopaminergic projections and postictal behavioral abnormalities.

Financial Support: CNPq (Process 164165/2018-5) and FAPESP (Process 2016/17882-4)

Conflicts of Interest Disclosure: The authors declare that they have no conflicts of interest.

Acknowledgments: Renata Caldo Scandiuzzi, Daniella Cristina Borges Ribeiro and Antônio Renato Meirelles.

58 - Hippocampus dynamics after post-discharge threshold induction by kindling in C57BL6 during the object recognition test

Authors: Braga, L.A.S.[1],Ruggiero, R.N.[1], Rossignoli, M.T[1], Leite, J.P.[1],

[1]Department of Neuroscience and Behavioral Neuroscience, Ribeirão Preto Medical School, University of São Paulo, SP-Brazil.

Introduction: Epileptic seizures are frequently related with memory and cognitive deficits. Comprehending the underlying neurophysiological alterations related with seizures effects is essential to the development of specific therapeutic interventions. Hence, we aimed to investigate the impact of induced electrical temporal lobe seizures in the process of memory formation and consolidation and the underlying oscillatory activity ofhippocampus.

Materials and Methods: Twenty male C57BL/6 mice were divided into two groups: the memory consolidation group (CS), containing 10 mice and memory formation (FR), containing 10 mice . Protocol 1069/2022R2 was approved by the Ethics Committee for the Use of Animals (CEUA). Four monopolar recording electrodes were implanted in the CA1 region of the dorsal hippocampus for electrophysiological recording, and one bipolar electrode was used to stimulate the CA1 region of the ventral hippocampus. The recovery period was 7 days. The ventral hippocampus was stimulated punctually during the object recognition test. This experiment will be carried out on two separate days. On each day, the CS and FR groups of animals are randomly exposed to electrical stimulation. The intensity of the electrical stimulation is equal to the after-discharge threshold (AD) or lower than the post-discharge threshold (SHAM). The animals are chosen at random. The FR group undergoes AD induction two hours pre-training (six-hour before test). In contrast, the CS group receives the AD stimulation two hours post-training (four hours pre-test).

Results: In the FR group, the AD mice showed greater performance during novel object exploration. To delve deeper into the possible electrophysiological origins, and how they can be attributed to changes in hippocampal networks, we recorded high-quality local field potentials from the hippocampus throughout the task. We are currently conducting ongoing research on electrophysiological signals.

Conclusion: Our study indicates that seizures affect object recognition memory. To understand the functional role of hippocampal seizures in object recognition memory, we are currently examining electrophysiological data.

59 - Impacts of Proline-Rich Region Mutations in Tau on Epileptic Activity and Sleep in Murine Models of Epilepsy

Authors: Mariane Vicente[1], Rahil Vaknalli[1], Ashley Anderson[2], Joshua Stepter[1], Nane Onanyan[1], Anushka Narasani[1], Sahana Ravishankar[1], Ava Western[1], Stanley Thayer[2] and Keith Vossel[1]

[1]University of California, Los Angeles, Mary S. Easton Center for Alzheimer's Research and Care atUCLA; [2]University of Minnesota

Background: In transgenic mouse models of Alzheimer's disease, the genetic removal of tau has been shown to effectively alleviate seizures, memory decline, and premature mortality. However, the precise mechanisms underlying these positive effects remain unclear. To address this, we conducted experiments to investigate the hypothesis that mutations within the proline-rich domain of tau, known to impact its interactions with SH3-containing proteins, might play a pivotal role in preventing epileptic activity in epilepsy models.

Methods: Our study utilized two distinct mouse lines: 1) AxxA6, which featured proline-to-alanine substitutions within the 6th PxxP motif of tau, and 2) R221A, characterized by anarginine-to-alanine substitution at the amino acid corresponding to position 221 in the human 2N4R tau isoform. As a reference, we employed tau knockout mice. To induce epileptic activity, we administered kainic acid intraperitoneally at a dose of 25 mg/kg. We subsequently assessed the latency to different seizure severity levels (SSL) over a 3-hour period, ranging from grade 1 to grade 8. Additionally, we crossed AxxA6 and R221A mice with the Kv1.1 knockout (Kcna1–/–) epilepsy model. For mice aged between 5 and 8 weeks, we conducted 24-hour epidural video-electroencephalography and electromyography. To complement these in vivo observations, we also performed ex vivo slice electrophysiology. Specifically, we measured burst frequency in the CA3 region following the application of picrotoxin and 4- aminopyridineto the bath.

Results: Tau knockout mice exhibited significantly delayed onset of seizure stages compared to wildtype mice (WT) following kainic acid injections ($p<0.05$, One-way ANOVA), consistent with previous findings. Notably, heterozygous AxxA6 mice displayed reduced susceptibility to seizures (n=4-6 per genotype; SSL 4-8: approximately 9.5 seconds vs. WT: 4.5 seconds, $p<0.05$, One-Way ANOVA). Furthermore, the heterozygous R221A tau variant led to a significant decrease in mortality among Kcna1 KO mice ($p<0.05$). In Kcna1 KO mice, epileptic spikes averaged 22 spikes per hour (AxxA6 n=4, R221A n=7), while AxxA6 (both homozygous and heterozygous) tau variants markedly reduced epileptic activity to approximately 2 spikes per hour ($p<0.05$, One-Way ANOVA, with statistical outliers excluded). Additionally, Kcna1 KO mice exhibited a higher percentage of time spent in the awake state during both light and dark phases compared to WT mice (n=5, $p<0.05$, t-test). Importantly, the AxxA6 and R221A tau variants did not significantly alter the sleep-wake cycle in Kcna1 KO mice. Furthermore, Kcna1 KO mice demonstrated an increased burst frequency in the CA3 region, while heterozygous and homozygous R221A tau variants effectively reduced bursting frequency ($p<0.05$, One-Way ANOVA).

Conclusion: The AxxA6 and R221A tau lines show partial reduction in seizure susceptibility in models of epilepsy compared to the tau knockout line. The tau protein variants do not affect regulation of the sleep-wake cycle in the Kcna1 model.

Funding/Financial support: National Institutes of Health (NIH): NS033310, AG058820, AG075955, R56 AG074473.

International Symposium

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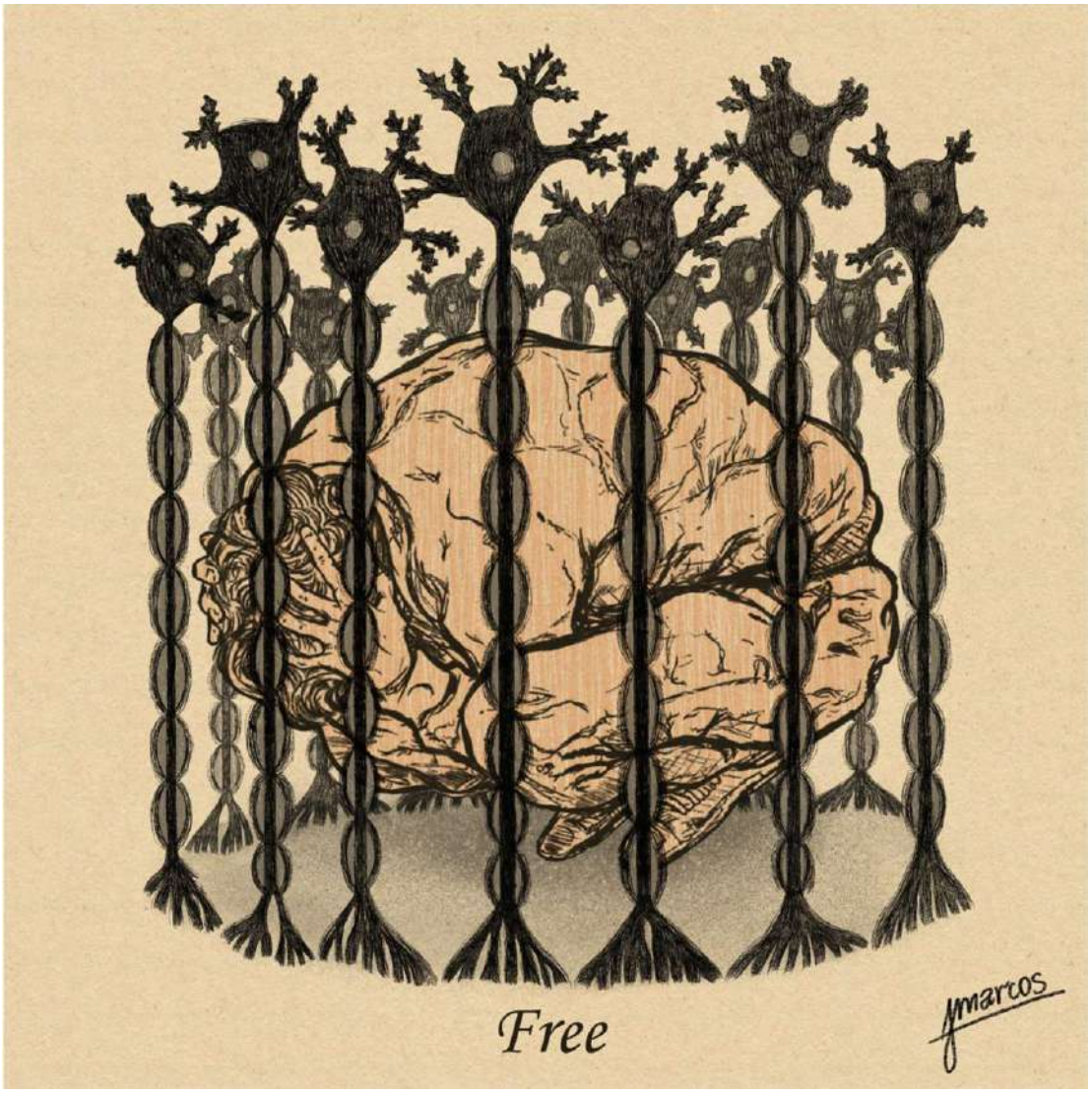
NEUROSCIENCE-VISUAL ARTS ABSTRACTS

60 - ASPECTS OF DISABILITY

Crispim Antonio Campos

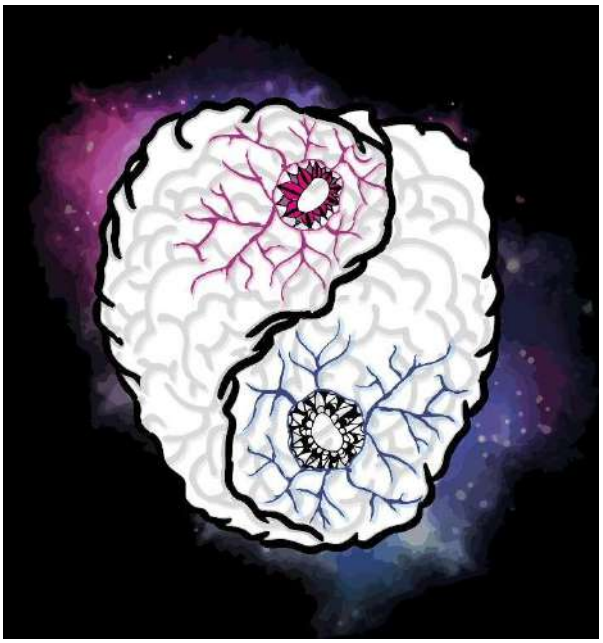
Legend: Work prepared on the occasion of a Post Doctorate in Sociology at the University of Leeds - England in 2013-2014 from seminars, colloquiums, and reports from people with disabilities.

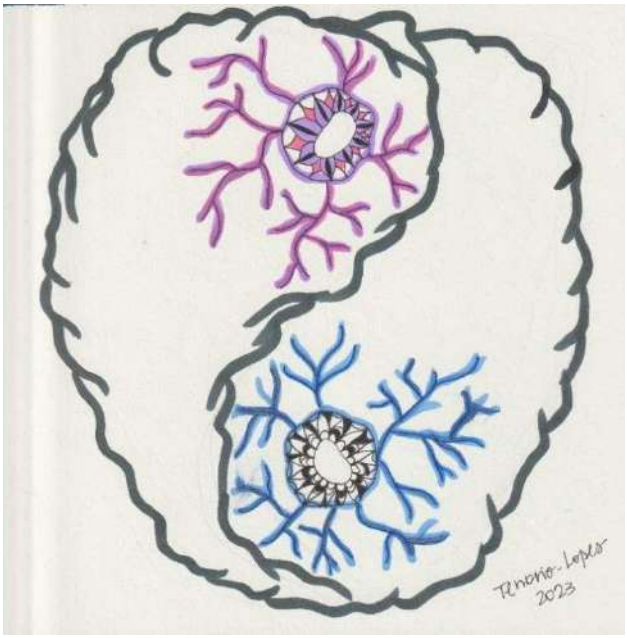


61 – FREE

João Marcos Lima Garcia

Legend: Humans consider themselves unique, so they based the entire theory of existence on their uniqueness and on the concept of free will to live their decisions and emotions, however, everything is just a big fallacy. All the social and sensory systems that we create are just sketches of the chemicals that permeate the synaptic clefts of millions of neurons interconnected by electrical impulses that simply code our existence to reduce it to human scale, in order to make it comprehensible. Thus, a prison was created with bars of unlimited potential: the brain, whether in conditions of homeostasis (limiting, enslaving thoughts) or prison neuropathologies (Alzheimer's).



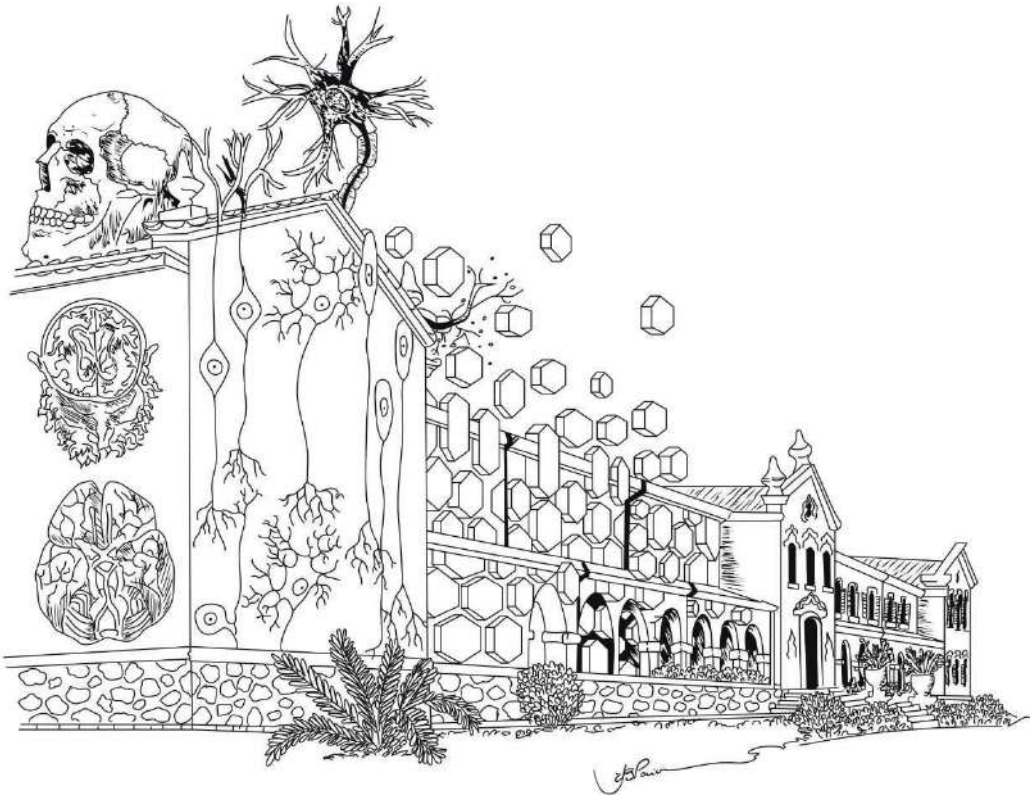


62 - DEEP DIVE INTO OURSELVES: A PERSONAL AND UNIQUE ROADMAP TOWARD EQUILIBRATING OUR EMOTIONSAND MANIFESTING HEALTH

Luana Tenorio-Lopes and Leonardo de Assis

Department of Animal Morphology and Physiology, FCAV, São Paulo State University, Jaboticabal, Brazil

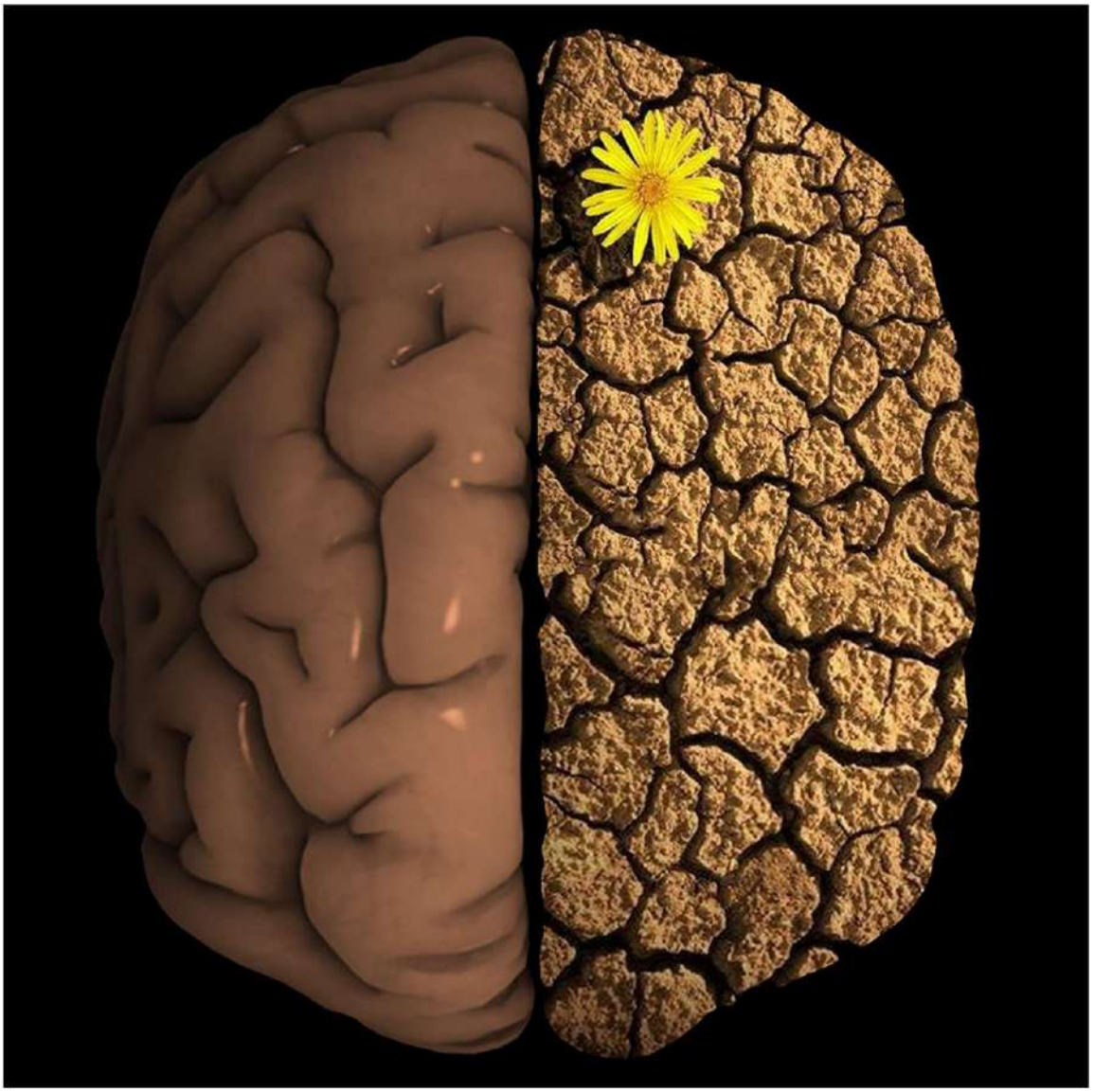
Legend: As a researcher, I am interested in investigating how several forms of stress experienced during early life, can impact the neural control of breathing and behaviour in adulthood. In this context, from my perspective, each being is a result of a set of unique and personal experiences that directly influence the manifestation of health or disease states. This understanding is important in terms of guiding scientists and health professionals to work toward the development and application of personalized and multidisciplinary therapeutic strategies that help patients restore their natural equilibrium state, represented in the image by the Yin-Yang symbolism.



63 - KNOWLEDGE BREAKS DOWN WALLS

Yara Bezerra de Paiva

Legend: Hand drawning and after digital converter, for the International Brain Bee – The Neuroscience Competition for Teens (Committee of Ribeirão Preto – FMRP – USP). Author: Yara Bezerra de Paiva. 2020.



64 - NEUROSCIENCE & RESILIENCE

Danilo Benette Marques

Legend: This artwork exploits the aesthetic parallel between the human brain and a barren landscape to draw parallels between neuroscience and resilience. The solitary blooming flower, a symbol of thriving amidst adversity, besides reminding us of the inherent human capacity for adaptation, is a metaphor for the rising yet far less explored facet of neuroscience that is the investigation of natural adaptive processes rather than focusing on disease and vulnerability. The flower's deliberate forefront placement mirrors the pivotal role of the prefrontal cortex in stress coping. Crafted from publicly-sourced internet pictures and edited in Adobe Photoshop CC 2015.

65 - THE DREAM GROUNDED IN SCIENCE

Gabriel Skiba

Legend: A child fulfills their desire to wear a sneaker, touched by its colorful em forms design. He said that was a superhero's sneaker. And guess what? It really is! All-star sneakers, personalized by the artist and biologist from Morretes, Giorgia Azeredo.

FIRE DEPARTMENT – 193
MILITARY POLICE – 190
FIRST AID – 192

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Phone: +55 (16) 3605-5025
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MILITARY POLICE

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FROM BUS STATION: 4 KM
Take the Bus Line N904 Oeste 2/HC-USP

PLAZA INN MASTER

www.plazainn.com.br

TO UNIV. OF SÃO PAULO: 4 KM

Walking distance: 50 minutes
Or take the Bus Line: Cidade Universitaria on the Florencio de Abreu Street.

YOU ARE IN DOWNTOWN

FROM AIRPORT: 9 KM
Take an Uber!

FROM BUS STATION: 1 KM

Walking distance: 10 minutes
Take an Uber!

STREAM PALACE HOTEL

www.streampalacehotel.com.br

TO UNIV. OF SÃO PAULO: 5 KM

Walking distance: 60 minutes
Or take the Bus Line:

- Cidade Universitária on the Florêncio de Abreu Street.
- Hospital das Clínicas in the Praça XV.

YOU ARE IN DOWNTOWN

FROM AIRPORT: 9 KM
Take an Uber!

FROM BUS STATION: 1,5 KM

Walking distance: 20 minutes
Take an Uber!

MONREALE HOTEL

www.monrealehotels.com

TO UNIV. OF SÃO PAULO: 5 KM

Walking distance: 60 minutes

Or take the Bus Line:

- Cidade Universitária on the Florêncio de Abreu Street.
- Hospital das Clínicas in the Praça XV.

YOU ARE IN DOWNTOWN

FROM AIRPORT: 9 KM
Take an Uber!

FROM BUS STATION: 1 KM

Walking distance: 12 minutes
Take an Uber!

Once on University of São Paulo Campus, you can take the University Bus. The University Bus schedule is available in the site: www.pcarp.usp.br

RESTAURANTS

CONVÍVIO RESTAURANTE FEA
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CONVÍVIO RESTAURANTE MEDICINA
Av. Bandeirantes, 3900 – Ribeirão Preto/SP

INVICTA
Av. do Café, 1881 - Ribeirão Preto/SP.
Phone: +55 (16) 3236-1365

LAVECCHIA VILLA
Av. do Café, 1545 – Vila Amélia – Ribeirão Preto/SP
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