كلية العلوم بتونس
FACULTE DES SCIENCES DE TUNIS

MNS2023 Tunisia

Carthage, 14-18 October 2023

9th Conference of the Mediterranean Neuroscience Society

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PROGRAMME

MNS2023, Carthage, Tunisia, 14th - 18th October

The Official Venue of MNS2023 is

HOTEL "Carthage Thalasso Resort" Gammarth, Tunis

Conference proceedings

9th Mediterranean Neuroscience Society Conference 2023 Tunisia MNS2023

WELCOME LETTER

Dear Colleagues,

It is a great pleasure and honour to welcome you to the 9th Mediterranean Neuroscience Society (MNS) Conference which takes place from 14th to 18th October 2023, in beautiful Carthage in Tunisia, a UN ESCO World Heritage Site and certainly one of the most beautiful places in the Mediterranean, We look forward to welcoming researchers, scientists, clinicians, students, educators, local and regional authorities, as well as civil society organisations in the neurosciences field and those interested in any aspect of research on brain function.

The COVID-19 pandemic has revealed vast inequities between populations and scientific research and technological development have become more necessary than ever for a better future and better equality. Also, a place to connect scientists from all around the world and let them share their research discoveries and experiences with the scientific community, particularly from developing countries or minorities now more than ever is needed. In this context, we hope that scientific interest in developing countries can be expanded particularly in neuroscience and the impact of MNS conferences is certainly in favor of the idea.

The 9th MNS Conference aims to promote knowledge and foster closer these mutual ties between Mediterranean neuroscientists and neuroscientists at large and with your participation MNS will succeed.

As with previous MNS conferences, communications at the meeting will include high-quality Keynote and Symposia speakers and we would very sincerely thank President Giuseppe Di Giovanni and all the members of the MNS council for their work and commitment, especially to those most involved in the organization of the Conference. We also thank IBRO and FENS for their invaluable support. Their great teamwork will surely make this meeting one of the best.

Finally, we hope you enjoy the chance to learn and network at MNS2023 as you will also have the opportunity to visit Carthage with its history stretching back nearly three millennia, the capital Tunis and the elegant village of Sidi Bou Said where the blue and white houses are the best of traditional Tunisian architecture.

Sincerely,

MNS2023 Conference Chairs

Olfa Masmoudi
Taoufik Ghrairi

Giuseppe Di Giovanni
MNS President

Mediterranean Neuroscience Society (MNS)

The MNS has been created to support and help strengthen all initiatives that bring together Mediterranean neuroscientists.

The previously successfully held Mediterranean Conferences of Neuroscience were organized in Montpellier in 1997**,** Marrakech in 2006, Alexandria in 2009**,** Istanbul in 2012, Pula – Sardinia in 2015, St. Julian – Malta in 2017, Marrakech in 2019, and Dubrovnik 2022. The aforementioned MNS conferences gathered scientists from all Mediterranean countries and offered a rich program with lectures, symposia, poster sessions, and social events. These meetings have proved to be highly beneficial, not only for the scientific exchanges but also in terms of training opportunities for students and young researchers. Research on brain function in health and disease is among the priorities for today's societies, and several indicators put the Mediterranean research area among strategic issues for the European Union (EU).
Many South-North collaborations and networks have emerged in recent years through bilateral and multi-lateral actions, supported by the EU or by international and national actions, whether for setting up teaching curricula (Tempus programs), or by building human potential (Horizon programs). Many other initiatives of cooperation (e.g. Neurobridges) have seen the light of day, initiated by groups of motivated individuals, believing in the importance of scientific cooperation as a way to alleviate political distress between cultures.

Objectives of the MNS

The MNS works towards three main objectives:

- Strengthen exchanges between Mediterranean neuroscientists.
- Promote education in the neurosciences and increase public awareness of progress made.
- Sustain scientific, training and networking events, such as, in particular, the biennial Mediterranean Neuroscience Conference.

To reach these objectives, the MNS's policy is to work in close cooperation with existing national and international Neuroscience Societies. In particular, we are proud member of the International Brain Research Organization – IBRO and also act in synergy with the Federation of European Neuroscience Societies – FENS.

ORGANIZED UNDER THE AUSPICES AND SUPPORT OF

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Prof Nouria Lakhdar-Ghazal (Mohammed V University of Rabat) - Member
Prof Said Glai (National Institute of Neurology, University Tunis El Manar) - Member
Dr Yosra Hamdi (University of Tunis El Manar, Tunisia) - Member
Prof Marc Landry (University of Bordeaux, FR) - Honorary Member
Prof Christina Dalla (University of Athens, Greece) - Honorary Member
Prof Khalid El Lali (IAV Hassan II, Morocco) - Member
Prof Fatiha Chigr (Université Sultan Moulay Slimane, Morocco) - Member
Prof Patrizia Campolongo (Sapienza University of Rome, Italy) - Member
Dr Liana Fattore (IN-CNR, Italy) – Member

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INFORMATION FOR SPEAKERS AND CHAIRPERSONS

The role of the chairpersons is to monitor speaking and discussion times and to lead the discussions. Chairpersons control the switch between presentations. Each presentation is 20 min followed by 5 min Q/A section.

Use a presentation in the **16:9** format. The Chairperson is responsible to collect all the presentations of their symposium. It is advisable that the Chairpersons use their own PC in which the presentations of the single speakers are saved for the Symposium.
All speakers must submit their presentations to the Chairperson and Secretary at ***info@medneuroscisociety.org*** before the 14th of October

Multimedia Considerations and Slide Preparation
Presenters: Make your presentations compatible with on-site audio/visual specifications.

Each room will be equipped with a laptop which has Windows 11.
VGA and HDMI cables will be available, as well as adapters for PCs (not Macbooks)
Rooms: Carthage 1 and 3: 16:9 widescreen format.
Room: Carthage 2 and Majless: 1:1 screen format.

...Before Traveling (Recommended)…

It is highly recommended to send your presentation before the 14th of October by email to your chairperson/s and cc info@medneuroscisociety.org **specifying in the SUBJECT SYMPOSIUM NUMBER AND SYMPOSIUM PRESENTATION (e.g. S33.2 Symposium n 32 presentation n 2).**

For the Chairpersons:
Please note you are responsible for collecting all the presentations of your Symposium in a file on a USB memory stick and loading it on one of the Conference computers in the Conference Room before the start of the session. Another option is to use their own personal PCs with all the presentations saved.

Please note that the conference computers in the session halls are being supplied with Office 2020.
If combining video films with PowerPoint, please make sure to check it with your chairperson before the start of the session.
Alternatively, you may supply your own laptop computer. In such a case please be aware if it has a VGA socket for external signal or take with you VGA to HDMI adaptor.

Important note for Macintosh users
In order to use MAC presentations, you may use your own Macintosh laptop computer. In such a case please confirm you provide it with a **VGA adaptor** for external signal.

POSTER INFORMATION

Poster Presentations

Whole-day poster presentations will take place in the Poster Area from Saturday 14th of October until Tuesday 17th of October. Authors are requested to be in attendance at their poster for discussion, as scheduled below:

Saturday, 14th October 2023

17:20 – 17:40 h **Poster session**

Sunday, 15th October 2023

10:50 – 11:10 h and 17:10 – 17:30 h **Poster sessions**

Monday, 16th October 2023

10:50 – 11:10 h **Poster session**

Tuesday, 17th October 2023

10:50 – 11:10 h and 17:10 – 17:30 h **Poster sessions**

Please find your board number by locating your abstract on the programme book. You should display your poster on the board number assigned to you.

Poster dimensions: 84.1 cm x 118.9 cm, Portrait format.

Posters can be affixed by double-sided adhesive tape, available at the Poster Assistance desk onsite.
Posters should be mounted on Saturday, 14th October 2023, at 12:00 p.m.
Removal: Posters can be removed on Tuesday, 17th October 2023 afternoon, after the final poster session.
The organizers cannot be responsible for posters not being removed by the above-stated time.

Programme

Saturday, October 14th 2023

12:00-18:00 REGISTRATION

13:30-14:20 Opening Ceremony

Olfa Masmoudi (TN), Taoufik Ghrairi (TN) and Giuseppe Di Giovanni (MT)

(Carthage room I)

14:20-15:30 **ALBA Network**

ALBA's mission: Dubravka Svob Strac, Zagreb, Croatia

Osborne Almeida, Munich, Germany "A Bag of Thoughts on Diversity, Equity & Inclusivity"

Chair: Christina Dalla

(Carthage room I)

15:30-17:20 **SYMPOSIA 1-3**

S1 "***Stress and glucocorticoids: memory functions and implications for psychiatric disorders***"
(Carthage I room)
CHAIRS: **Gina Lorena Quirarte (MX), Giulia Federica Mancini (IT)**

- **S1.1 Giulia Federica Mancini** (Sapienza University, IRCCS Santa Lucia Foundation, Rome, Italy): "Early-life stressful experiences in the susceptibility/resilience for psychiatric disorders development later in life"
- **S1.2 Gina Lorena Quirarte** (Instituto de Neurobiología Queretaro, Universidad Nacional Autónoma de México, México): "Glucocorticoids-induced effects on memory functions of the striatum"
- **S1.3 Carrie Cuttler** (Washington State University, Pullman, WA, USA): "A translational examination of the effects of cannabis use on diurnal cortisol rhythms"
- **S1.4 Patrizia Campolongo** (Sapienza University, IRCCS Santa Lucia Foundation, Rome, Italy): "Arousal and stress effects on cannabinoid modulation of aversive memory: Insights into Post-Traumatic Stress Disorder Susceptibility"
- **S1.5 Tanja Jovanovic** (Wayne State University, Detroit, MI, USA): "Fear Conditioning and Extinction in Children with Trauma: Associations with Brain and Behavior"

S2 "*Parkinson's disease as a conundrum: specific synucleinopathy or circuitry disease?*"
(Carthage II room)

CHAIRS: **Alessandro Stefani (IT), Salvatore Galati (CH)**

- **S2.1 Matteo Conti** (University of Rome Tor Vergata, Rome, Italy): "Functional connectivity in PD patients"
- **S2.2 Marta Sciascia** (Neurocenter of Southern Switzerland, Lugano, Switzerland): "The Impact of sleep mediated downscaling process on theta wake activity in Parkinson's disease"
- **S2.3 Alain Kaelin** (Università della Svizzera Italiana, Lugano & University of Bern, Switzerland): "Update on "peripheral" biomarkers in PD**"**
- **S2.4 Di Maio Roberto** (University of Pittsburgh, USA): "Exploring oxidative signalling in Parkinson's disease: uncovering complex pathways and potential therapeutic avenues"

S3 "*Senescence: Friend or foe for neurodevelopment, cancer and neurodegeneration*"
(Carthage III room)
CHAIRS: **Isabel Varela-Nieto (ES), Manuel Collado (ES)**

- **S3.1 José Marco-Contelles** (Institute of General Organic Chemistry, CSIC -Madrid, Spain): "Contilisant, a small molecule designed for Alzheimer's disease therapy"
- **S3.2 Dubravka Svob Strac** (University Psychiatric Hospital Vrapce, Zagreb, Croatia): "Potential protective role of dhea(s) in cellular and animal models and subjects with dementia"
- **S3.3 Isabel Varela-Nieto** (Institute for Biomedical Research Alberto Sols, CSIC-UAM & CIBERER): "Cellular senescence from early inner ear development to age-associated hearing diseases"
- **S3.4 Manuel Collado** (Health Research Institute of Santiago de Compostela, IDIS): "Time flies: Cellular senescence in aging CNS of Drosophila melanogaster"

17:20-17:40 **COFFEE BREAK**

17:40-18:40 **SONA Keynote Lecture**

Amadi Ihunwo - University of the Witwatersrand, Johannesburg, South Africa, Secretary General of the Society of Neuroscientists of Africa (SONA):
"***Neurogenesis in avian species: a comparative approach*"**
CHAIR: Giuseppe Di Giovanni, MT
(Carthage room I)

19:00-21:00 **Welcome Cocktail**

Sunday, October 15th 2023

9:00-10:50 SYMPOSIA 4-7

S4 "*Cells, Molecules, Circuits and Behaviors: The Future of Therapeutics in Substance Use Disorders*" (Carthage I room)
CHAIRS: **Kathryn A. Cunningham (USA), Marco Diana (IT)**

- **S4.1 Kathryn A. Cunningham** (University of Texas Medical Branch, Galveston, Texas, USA): "Mining 5-HT2A receptor ligand discovery for substance use disorders"
- **S4.2 John Neumaier** (University of Washington, Seattle, Washington, USA): "Neurocircuit control of oral fentanyl self-administration engages a novel role for the lateral habenula: Implications for SUD therapeutics"
- **S4.3 Lauren M. Slosky** (University of Minnesota Medical School, Minneapolis, MN, USA): "β-Arrestin-biased allosteric modulators of neurotensin receptor 1 for the treatment of cocaine use disorder"
- **S4.4 Liana Fattore** (CNR Institute of Neuroscience, National Research Council, Cagliari, Italy): "Dual 5-HT2B antagonist-5-HT1A agonist for methamphetamine use disorder"
- **S4.5 Noelle Anastasio** (University of Texas Medical Branch, Galveston, Texas, USA): **"**The nociceptin receptor as a target for opioid use disorder" therapeutics

S5 "*Understanding the online and offline representation of complex stimuli: From behavioural performance to neural mechanisms*" (Carthage II room)
CHAIRS: **Carlo Sestieri (IT), Valerio Santangelo (IT)**

- **S5.1 Emiliano Macaluso** (Université Claude Bernard Lyon 1, Bron, France): "Memory retrieval after the encoding of complex and naturalistic episodes"
- **S5.2 Marco Sperduti** (Université Paris Cité, Paris, France): "The impact of editing on time perception for movie scenes"
- **S5.3 Carlo Sestieri** (University of Chieti, Italy): "Cognitive mechanisms supporting temporal memory for movie scenes**"**
- **S5.4 Valerio Santangelo** (University of Perugia, Italy): "The representation of perceptual saliency of task-relevant objects in complex visual scenes"

S6 "*Neurotransmitter dynamics and actions in neuro-astroglial networks*" (Carthage III room)
CHAIR: **Dmitri Rusakov (UK)**

- **S6.1 Marta Navarrete** (Cajal Institute, Madrid, Spain): "Catching neuron-astrocyte engrams"
- **S6.2 Robert Zorec** (University of Ljubljana, Lubljana, Slovenia): "Noradrenergic signalling and vesicle dynamics in reactive astrocytes"
- **S6.3 Nathalie Rouach** (College de France, Paris, France): "A neuroglial circuit for maternal behaviors"
- **S6.4 Dmitri Rusakov** (University College London, UK): "Brian rhythm regulation by extracellular GABA waves"

S7 "*New insights in Parkinson's disease and other motor disorders*" (Majles room)
CHAIRS: **Leonidas Stefanis (GR), Rosario Moratalla (ES)**

- **S7.1 Aurora Zilli** (Sapienza University of Rome, Italy): "Antibiotic-induced leaky gut syndrome promotes parkinsonism in mice: protective effects of rifaximin"
- **S7.2 Alessandro Stefani** (University of Rome Tor Vergata, Rome, Italy): "Gut microbiota dysbiosis in Parkinson's disease patients: not only an early feature but a potential biomarker of disease severity and progression"
- **S7.3 Rosario Moratalla** (Cajal Institute, Spain): "The origin of comorbid anxiety and depression in Parkinson's disease"
- **S7.4 Ali Jahanshahi** (Maastricht University, The Netherlands): "Wireless deep brain stimulation in freely moving mice with nonresonant powering of magnetoelectric nanoparticles"
- **S7.5 Wolters Anouk** (Maastricht University, The Netherlands): "The application of magnetic nanodiscs for neuromodulation"

10:50-11:10 COFFEE BREAK

11:10-13:00 SYMPOSIA 8-11

S8 "*Emerging trends in New Psychoactive Substances (NPS): From preclinical evidences to clinical perspectives*" (Carthage I room)
CHAIRS: **Matteo Marti (IT), Liana Fattore (IT)**

- **S8.1 Eef Theunissen** (Maastricht University, The Netherlands): "Cognitive, psychomotor and psychotomimetic effects of a synthetic cannabinoid"
- **S8.2 Jakub Wojcieszak** (Medical University of Łódź, Poland): "Perinatal treatment with MDPV impairs cognitive functions in the adulthood of male but not female C57BL/6J mice"
- **S8.3 Sabrine Bilel** (University of Ferrara, Italy): "*In silico*, *in vitro* and *in vivo* pharmacological characterization of emerging novel synthetic opioids: focus on sex differences"
- **S8.4 Gunes Unal** (BoğaziçI University, Istanbul, Turkey): "Enhancing the antidepressant effect of ketamine via alternative routes of administration"

S9 "*The role of the amygdala in modulating negatively and positively valenced states*" (Carthage II room)
CHAIRS: **Andrew Holmes (USA), Maria Morena (IT)**

- **S9.1 Bernard Balleine** (University of NSW, Sydney, Australia): "Amygdala-cortical control of striatal plasticity"
- **S9.2 Valentina Vozella** (The Scripps Research Institute, La Jolla, CA, USA):"Role of endocannabinoids in the amygdala control of stress and alcohol drinking"
- **S9.3 Maria Morena** (Sapienza University & IRCSS Santa Lucia Foundation, Rome, Italy): "Amygdala regulation of stress effects on fear memory processes**"**
- **S9.4 Cyril Herry** (INSERM & University of Bordeaux, Bordeaux, France): "Decoding fear in prefrontal-amygdala circuits"
- **S9.5 Andrew Holmes** (National Institute on Alcohol Abuse and Alcoholism, Rockville, MD, USA): "Amygdala astrocytes gate the transformation of memory into action"

S10 "*Neurobiology of Social Cognition in Animal Kingdom*" (Carthage III room)
CHAIR: **Giulia Salamanca (IT)**

- **S10.1 Giulia Salamanca** (University of Bologna, Italy): "Where do the atypical long-range somatostatin projections go in the brain? A neuroanatomical study"
- **S10.2 Francesco Papaleo** (Italian Institute of Technology, Genoa, Italy): "Cortico-Cortical Transfer of Socially Derived Information Gates Emotion Discrimination"
- **S10.3 Julia Sliwa** (Sorbonne University, Institut du Cerveau, ICM, Inserm, CNRS, Paris, France): "Comparing human and monkey neural circuits for processing social scenes"
- **S10.4 Gernot Ernst** (University of Oslo, Norway): "A translational perspective on opioids and social behaviour: from rodents to humans"

S11 "*Ion channels and receptors in myelin-forming glia cells*" (Majles room)
CHAIRS: **Valerio Magnaghi (IT)**

- **S11.1 Wenjing Sun** (The Ohio State University, Columbus, OH, USA):"New insights into activity-dependent myelination"
- **S11.2 Maria Kukley** (University of Sciences and Technology Houari Boumediène, Algiers, Algeria):"Glutamate receptors in the oligodendrocyte lineage cells: what is new?"
- **S11.3 Aleksandra Rutkowska** (Medical University of Gdańsk, Poland): "Can we stimulate remyelination in vivo? A glance at GPR183 as novel therapeutic target"
- **S11.4 Valerio Magnaghi** 15niversityy of Milan, Italy): "NKCC1 and GABA-A-receptor regulation of chloride flux in peripheral nerve: are Schwann cells engaged?"

13:00-14:00 LUNCH

14:00-15:20 SPECIAL Event (SE): Neuroscience and Law: Lobes and Robes

(Carthage I room)

- **SE.1 Marie Lamarche** (Law clinic, Faculty of Law and Political Sciences, Bordeaux, France) **& Cédric Brun** (Bordeaux-Montaigne University, Bordeaux, France): "The Legal and Ethical Implications of Neuroscience Discoveries: A Framework for Balancing Societal Interests and Individual Rights"
- **SE.2 Ahmed Elkahwagy** (Faculty of Law, Alexandria University, Alexandria, Egypt) **& Thomas Boraud** (University of Bordeaux, CNRS Bordeaux, France): "The contribution of neuroscience to Criminal Law"
- **SE.3 Nihal Elbanna** (Faculty of Law, Alexandria University, Alexandria, Egypt)**& Marc Landry** (University of Bordeaux, CNRS Bordeaux, France): "Do we need a legal framework for neuromarketing?"

WORKSHOP EJN Wiley/FENS Workshop on Publishing)

(Carthage II room)

Bernard Balleine, EJNS Editor

POSTER SESSION within Coffee breaks

15:20-17:10 SYMPOSIA 12-15

S12 "*Non-neuronal mechanisms of motivated behavior*" (Carthage I room)
CHAIR: **Debra Bangasser (USA)**

- **S12.1 Debra Bangasser** (Georgia State University, Atlanta, GA, USA): "Early resource scarcity causes lasting effects on cognition and non-neuronal cortical cells"
- **S12.2 Pavel Ortinski** (University of Kentucky, Lexington, KY, USA): "Cocaine self-administration increases voltage-gated signaling in accumbens astrocytes"
- **S12.3 Jared Young** (University of California, San Diego, CA, USA): "Impact of HIV on motivation and risk-taking: Activated microglia as a potential treatment target"
- **S12.4 Michael Scofield** (University of South Carolina, Columbia, SC, USA): "Ca2+ Activity Profiles of Cortical Astrocytes During Conditioned Reward Seeking"
- **S12.5 Jill Turner** (University of Kentucky, Lexington, KY, USA): "Microglia Regulate Sex- and Region-Specific Blood-Brain Barrier Integrity During Nicotine Withdrawal"

S13 "*Diverse Neurobiological Actions of Cannabinoids in the Brain*" (Carthage II room)
CHAIRS: **Matthew Hill (CA), Roberto Colangeli (IT)**

- **S13.1 Roberto Colangeli** (Università Politecnica delle Marche, Ancona, Italy): "2-AG-mediated control of GABAergic plasticity in physiological and pathological condition"
- **S13.2 Matthew Hill** (Hotchkiss Brain Institute, University of Calgary, Canada): "Endocannabinoid signaling governs stress induced activation and termination of neural activity within corticotropin releasing hormone neurons in the paraventricular nucleus of the hypothalamus"
- **S13.3 Stephanie Borgland** (University of Calgary, Canada): "Sex differences in effects perinatal cannabis exposure on metabolism and emotional behaviour in adult offspring"
- **S13.4 Ryan McLaughlin** (Washington State University, WA, USA): "Using rodent models to identify behavioral and biological predictors of problematic cannabis use"

S14 "*Interplay of estrogens, antidepressants and behavior: classical and rapid effects*" (Carthage III room)
CHAIR: **Nikolaos Kokras (GR)**

- **S14.1 Polymnia Georgiou** (University of Wisconsin Milwaukee, Milwaukee, WI, USA):"Estrogen Receptor β Modulates Depressive phenotypes via an Amygdala-Nucleus Accumbens Pathway"
- **S14.2 Elena Choleris** (University of Guelph, Ontario, Canada): "Hormone regulation of brain circuits of social cognition in male and female mice"
- **S14.3 Nikos Kokras** (National and Kapodistrian University of Athens, Greece): "How to integrate sex in preclinical research of antidepressants: the role of estrogens"
- **S14.4 Panos Zanos** (University of Cyprus, Nicosia, Cyprus): "Mechanism of action of rapid acting antidepressants"
- **S14.5 Charis Brakatselos** (University of Ioannina, Greece):"Targeting affective disorders: synergies of cannabidiol and antidepressants"

S15 "*Brain extracellular matrix: organization, remodelling, and functions in health and disease*" (Majles room)
CHAIRS: **Tommaso Pizzorusso (IT), Alexander Dityatev (DE)**

- **S15.1 Tommaso Pizzorusso** (Institute of Neuroscience, CNR, Pisa, Italy): "An Atlas of Perineuronal Net Distribution and Colocalization with Parvalbumin in the Adult Mouse Brain"
- **S15.2 Alexander Dityatev** (German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Germany): "Neuromodulatory and neuroinflammatory mechanisms of ECM remodelling"

- **S15.3 Juan Nacher** (University of Valencia, Spanish Research Network on Mental Health (CIBERSAM), Spain): "Perineuronal nets as emerging targets for the treatment of neuropsychiatric disorders"
- **S15.4 Laure Verret** (Toulouse University and Research Center on Animal Cognition (CRCA-CBI), France): "Experience-dependent perineuronal net remodelling and memory in AD mice"

17:10-17:30 **COFFEE BREAK**

17:30-18:30 **Keynote Lecture**

Rajita Sinha (Yale School of Medicine, CT, USA)
"*Stress, Drugs, and Relapse: How can neuroscience help us in improving addiction treatment?*"

CHAIR: Liana Fattore
(Carthage room I)

18:30-19:30 **MNS GENERAL ASSEMBLY**

CHAIR: Giuseppe Di Giovanni, MT

Monday, October 16st 2023

9:00-10:50 SYMPOSIA 16-19

S16 "*The intertwining of inflammatory pathways in the central nervous system: physiological versus pathological implications*" (Carthage I room)
CHAIRS: **Amira Zaky (EG), Youssef Anouar (FR)**

- **16.1 Youssef Anouar** (INSERM, University of Rouen Normandy, France):
- "Role of a selenoprotein in neuroprotection: application to Parkinson's disease after intranasal"
- **16.2 Nermeen Z. Abuelezz** (Misr University for Science and Technology Giza, Egypt): "MicroRNAs as Potential Orchestrators in Alzheimer's related inflammatory Pathology: An experience from Egypt"
- **16.3 Marc Landry** (University of Bordeaux; IMN, CNRS, France): "Analgesic effects of the relaxin family peptides in inflammatory pain"
- **16.4 Amira Zaky** (Alexandria University, Alexandria, Egypt): "Implication of the pleiotropic APE1/Ref-1 Redox activity in pain sensitization mechanism"
- **16.5 Elena Lucarini** (University of Florence, Italy): "Efficacy and pharmacodynamic profile of Brassicaceae constituents in the management of chronic pain"

S17 "*From neuronal plasticity to glia protection: mapping the path of resilience and vulnerability to stress*" (Carthage II room)
CHAIRS: **Marta Valenza (IT), Carla Nasca (USA)**

- **S17.1 Barbara di Benedetto** (University of Regensburg Regensburg, Germany): "Molecular and morphological signatures of astroglial responses to social and emotional dysfunctions"
- **S17.2 Benedetta Bigio** (New York University School of Medicine, New York, NY, USA): Computational approaches and exosomes to identify modifiable targets for stress-related disorders"
- **S17.3 Roberta Facchinetti** (Sapienza University of Rome, Italy): "Molecular changes of glia and neurons in the maladaptive response to acute stress are prevented by a single administration of ketamine in a rodent model of PTSD"
- **S17.4 Laura Musazzi** (University of Milano Bicocca, Milan, Italy): "Mechanisms of resilience and vulnerability to chronic mild stress in rats: a role for inflammation?"
- **S17.5 Carla Nasca** (New York University School of Medicine, New York, NY, USA): "Epigenetic mechanisms of neuroplasticity to stress: emerging role of mitochondria"

S18 *"New Perspectives in Mechanisms of Neurodegeneration"* (Carthage III room)
CHAIR: **Alexia Polissidis (Greece)**

- **S18.1 Aaron Gitler** (Stanford University, CA USA): "Two New ALS Targets (and one New Drug)"
- **S18.2 Hilal Lashuel** (Ecole Polytechnique Fédérale de Lausanne, Switzerland): "Unraveling the Complex Role of Protein Aggregation in Parkinson's Disease; From mechanisms to diagnostics and therapeutic strategies"
- **S18.3 Siham Boumhaouad** (Mohammed V University of Rabat, Rabat, Morocco):"The Impact of Melatonin on Diurnal Variation of Extracellular Dopamine in CBA/CaJ and C57BL/6 Mice: A Comparative Study"
- **S18.4 Harry Alexopoulos** (National and kapodistUniversity of Athens, Greece): "Drosophila Melanogaster AsA Model System For Drug Discovery In Neurodegenerative Disorders"
- **S18.5 Alexia Polissidis** (Biomedical Research Foundation Academy of Athens, Deree – American College of Greece)**:** Alpha-synuclein-induced stress sensitivity renders the Parkinson's disease brain susceptible to neurodegeneration

S19 "*New insights into activated kinases, multiple sclerosis and receptors mechanisms*" (Majles room)
CHAIR: **Lamia Bouslama-Oueghlani (FR)**

- **S19.1 Lamia Bouslama-Oueghlani** (Sorbonne University, Paris, France): "Pak1 inactivation triggers myelin formation through actin disassembly in oligodendrocytes"
- **S19.2 Meriam Belghith** (Institut Pasteur de Tunis, Tunisia): "The fine tuning of infiltrated t cells in multiple sclerosis"
- **S19.3 Erika Pintér** (University of Pécs, Pécs, Hungary): "Determination of the binding sites of organic polysulfides on human trpa1 by mutant variants of the receptor"
- **S19.4 Rafika Ben Laamari** (Institut Pasteur de Tunis, Tunisia):"Study of the Correlation between Herpesvirus Infection and T CD8+ Effector Cells in Patients with Multiple Sclerosis and Neuro-Behçet's Disease"

10:50-11:10 COFFEE BREAK

11:10-13:00 SYMPOSIA 20-23

S20 "Novel approaches in preclinical neuroscience" (Carthage I room)
CHAIR: **Christina Dalla (GR) and Olfa Masmoudi-Kouki (TN)**

- **S20.1 Christina Dalla** (National and Kapodistrian University of Athens, Greece): "Sex as a biological variable in preclinical neuropsychopharmacology"
- **S20.2 Panagiotis Politis** (Biomedical Research Foundation of the Academy of Athens, Greece): "Gene regulation networks in nervous system cancers: identification of novel pharmacological targets"

- **S20.3 Yosra Hamdi** (University of Tunis El Manar, Faculty of Sciences of Tunis, Tunisia): "Cytoprotective and Neurotrophic Effects of neuropeptide ODN and PACAP in *in vitro* and in vivo Models of Neurodegenerative Diseases"
- **S20.4 Rafael Madonado** (University Pompeu Fabra, Barcelona, Spain): "Involvement of gut microbiota and epigenetic factors in food addiction"

S21 "*Fighting neurological diseases from the intestine: impact of enteric microbiota, immune and nervous system on the gut-brain axis*" (Carthage II room)
CHAIRS: **Luisa Seguella (IT), Lorenzo Di Cesare Mannelli (IT)**

- **S21.1 Matteo Fornai** (University of Pisa, Italy): "Intestinal epithelial barrier at the crossroads between the microbiota-gut-brain axis and neurodegenerative disorders."
- **S21.2 Giuseppina D'Alessandro** (Sapienza University of Rome, Italy): "Gut microbiota alterations affect glioma growth and innate immune cells."
- **S21.3 Malvyne Derkinderen** (UMR Inserm, Faculté de Médecine, Nantes, France): "Can probiotics modulate gut inflammation and induce gut-brain axis remodelling?"
- **S21.4 Aitak Farzi** (Otto Loewi Research Center, Medical University of Graz, Austria): "Gut-brain communication in bipolar disorder."
- **S21.5 Jacques Gonzales** (Michigan State University, East Lansing, USA): "Early life adversity disrupts intestinal function by remodeling the enteric nervous system."

S22 "*The role of nitric oxide signaling in brain pathologies. Therapeutic implications and their limit*. (Carthage III room)
CHAIR: **Joanna M. Wierońska (PL)**

- **S22.1 Vicente Felipo** (Centro de Investigación Príncipe Felipe, Valencia, Spain): "Differential role of nitric oxide signaling in the deleterious effects of acute and chronic hyperammonemia"
- **S22.2 Nikolaos Pitsikas** (University of Thessaly, Volos, Greece): "Nitric oxide (NO) donors. Potential candidates for the treatment of anxiety disorders?"
- **S22.3 Joanna M Wierońska** (Maj Institute of Pharmacology Polish Academy of Sciences, Poland): "The role of nitric oxide dependent pathways in the procognitive activity of metabotropic glutamate receptors ligands"
- **S22.4 Fella Tounsi** (Mouloud Mammeri University of Tizi Ouzou, Algeria): "The role of nitric oxide signaling in brain pathologies. Therapeutic implications and their limits."
- **S22.5 Paulina Bastian** (Medical University of Gdansk, Poland): "2-methoxyestradiol – mediated control of nNOS and Heat Shock Proteins affects DNA in glioblastoma cells"

S23 "*Novel insights into alpha-synuclein pathology and toxicity in neurodegenerative diseases*" (Majles room)
CHAIR: **Arianna Bellucci (IT)**

- **S23.1 Luigi Bubacco** (University of Padua, Italy): "Dopamine metabolites initiate αSynuclein-mediated impaired proteostasis and degeneration in neuronal projections"
- **S23.2 Leonidas Stefanis** (University of Athens Medical School, Athens 11527, Greece): **"**Alpha-synuclein interplay with protein degradation systems"
- **S23.3 Sarah-Anna Hescham** (Maastricht University Medical Center, The Netherlands):"Magnetothermal nanoparticle technology alleviates parkinsonian-like symptoms in mice."
- **S23.4 Arianna Bellucci** (University of Brescia, Italy): "Synaptic alpha-synuclein microaggregates in synucleinopathies: engine of neurodegeneration and key therapeutic targets"

13:00-14:00 LUNCH

14:00-15:50 SYMPOSIA 24-28

S24 "*Sex differences in translational mechanisms of fear-based disorders*" (Carthage I room)
CHAIR: Raül Andero Galí (ES)

- **S24.1 Joanna Dabrowska** (Rosalind Franklin University of Medicine and Science, Chicago, IL, USA): "The integration of interoceptive signals and defensive behaviors via oxytocin receptor-expressing neurons in the bed nucleus of the stria terminalis (BNST)"
- **S24.2 Arnau Ramos Prats** (Medical University of Innsbruck, Austria): "Sex differences in mglu5 receptor-mediated control of negative valence in mice"
- **S24.3 Hanna Hörnberg** (Max Delbrück Center for Molecular Medicine, Berlin, Germany): Sex differences in translational mechanisms of fear-based disorders"
- **S24.4 Raül Andero Galí** (Autonomous University of Barcelona, Spain): "Sex differences in neural mechanisms of the NK3 receptor modulating fear"

S25 "*Non-neuronal cells as guardians of CNS homeostasis: relevance in brain development and diseases*" (Carthage II room)
CHAIRS: Mariagrazia Grilli (IT); Roberta Facchinetti (IT)

- **S25.1 Marta Valenza** (Sapienza University of Rome, Italy): "The role of astrocytes in mediating oligodendrocyte maturation and function: evidence with co-ultramicronized palmitoylethanolamide/luteolin in models of beta-amyloid toxicity"
- **S25.2 Rosa Chiara Paolicelli** (University of Lausanne, Switzerland): "The Alzheimer's disease risk gene Inpp5d modulates synaptic pruning by microglia in the developing hippocampus"

- **S25.3 Mariagrazia Grilli** (University of Piemonte Orientale, Novara, Italy): "Multifaceted non-neuronal dysfunction as a novel pharmacological target in neurodevelopmental and neuropsychiatric disorders**"**
- **S25.4 Neibla Priego** (Spanish National Cancer Research Centre (CNIO), Madrid, Spain): "TIMP1 mediates astrocyte-dependent local immunosuppression in brain metastasis"

S26 "*Dissecting the complexity of neurodevelopmental disorders: from pathophysiology to novel therapeutic approaches*" (Carthage III room)
CHAIRS: Antonia Manduca (IT) and Anna Maria Tartaglione (IT)

- **26.1 Marco Segatto** (University of Molise, Italy): "Disruption of cholesterol homeostasis in Rett syndrome: a new role for BET proteins"
- **S26.2 Elena Martín-García** (Universitat Pompeu Fabra, Barcelona, Spain): "THC exposure during adolescence increases impulsivity-like behavior in adulthood in a WIN 55,212-2 self-administration mouse model"
- **S26.3 Tibor Stark** (Masaryk University, Brno, Czech Republic): "Role of the endocannabinoid system in the pathophysiology and treatment of schizophrenia: the emerging potential of preventive approach"
- **S26.4 Anna Maria Tartaglione** (Italian National Institute of Health, ISS, Rome, Italy): "Enhanced expression of endogenous retroviruses in Autism Spectrum Disorder: bystander or key player?"

S27 "*Therapeutic Use of Cannabinoids in Neurodegenerative Disorders*" (Majles room)
CHAIRS: Alessia Ligresti (IT) & Eva De Lago (ES)

- **S27.1 Alessia Ligresti** (National Research Council of Italy (ICB-CNR, Italy): "Targeting cannabinoid receptor 2 in neurodegenerative diseases: recent efforts from a medicinal chemistry perspective"
- **S27.2 Julian Romero** (Universidad Francisco de Vitoria, Madrid, Spain): "Cannabinoid modulation of microglial function in the context of neuroinflammation"
- **S27.3 Eva De Lago** (Universidad Complutense de Madrid, Spain): "Preclinical development of cannabinoid-based therapies in pathologies related to TDP-43 dysregulation: Amyotrophic lateral sclerosis and frontotemporal dementia"
- **S27.4 Mario Van Der Stelt** (Leiden University, The Netherlands): "Controlling and Visualizing Lipid Signaling in the Brain"

S28 "*Chemical and Molecular Tools to Understand the Brain in Health and Disease*" (Carthage VII)

CHIARS: Ismail Ahmed (USA) & Hilal Lashuel (CH)

- **S28.1 Ismail Ahmed** (New York University School of Medicine, NY, USA): "Optopharmacological tools for spatiotemporal control of neurohormone signaling and social behavior"
- **S28.2 Eleonora Palma** (Sapienza University of Rome): "The imbalance between pro-epileptogenic and protective cytokines in human epilepsies"
- **S28.3 Leena Ali Ibrahim** (Harvard Medical School, MA, USA): "Developmental dynamics of bottom-up and top-down input integration onto L1 interneurons in the sensory cortex"
- **S28.4 Ines El Bini Dhouib** (Pasteur Institute of Tunisia, Tunisia): "Insights into Parkinson's with Potassium Channels at the Forefront"
- **S28.5 Hilal Lashuel** (Swiss Federal Institute of Technology Lausanne, Switzerland): Post-translational Modifications in Parkinson's disease and Synucleinopathies: From mechanisms to novel targets and therapeutic opportunities

15:50-16:50 Keynote Lecture

RUTGERS

Tracey Shors (Rutgers University, Piscataway, New Jersey, USA): "*Everyday trauma – and how not to ruminate on it so much*"

CHAIR: Christina Dalla

(Carthage room I)

18:00- 23:00 Visit to Sidi Bou Said and Social Dinner with a Show at Dar Zarrouk Restaurant

Tuesday, October 17st 2023

9:00-10:50 SYMPOSIA 29-31

S29 "*Clinical, behavioral and neurodevelopmental effects of stress life span: can we identify biomarkers of vulnerability?*" (Carthage I room)
CHAIR: **Annamaria Cattaneo (IT)**

- **S29.1 Annamaria Cattaneo** (University of Milan, Italy): "Inflammatory biomarkers for an early screening of vulnerability and for a personalized intervention"
- **S29.2 Valentina Zonca** (King's College London, UK): "Impairment of social behavior is associated with a different transcriptomic profile of the Habenula in vulnerable and resilient rats exposed to prenatal stress"
- **S29.3 Hannah Juncker** (Amsterdam University Medical Center, The Netherlands): "From maternal psychopathology to child neurodevelopment: the role of early-life nutrition, mechanisms and promising targets for intervention"
- **S29.4 Claudio D'Addario** (University of Teramo, Italy): "Impact of stress on mental health: epigenetic biomarkers"

S30 "*Precipitants of brain (mal) plasticity and pathology in the new era of precision medicine*" (Carthage II room)
CHAIR: **Ioannis Sotiropoulos (GR)**

- **S30.1 Farida Sohrabji** (Texas A&M University School of Medicine, TX, USA): "The expected and the unexpected: neuroprotective effects of estrogens for stroke diverge dependent on reproductive age"
- **S30.2 Ioannis Sotiropoulos** (Institute of Biosciences & Applications, RCSR Demokritos, Greece): "The stressed brain: a gate along the path from depression to Alzheimer's disease"
- **S30.3 Lisa Galea** (Centre for Addiction and Mental Health, Toronto, ON, Canada): "Sex differences in Negative Cognitive Bias**"**
- **S30.4 Iva D. Tzvetanova** (European University Cyprus, Cyprus): "Oligodendroglial Support of Axonal Function in Health and Disease"

S31 "*Preclinical study of the mechanism of action of psychedelics*" (Carthage III room)
CHAIRS: Nasser Haddjeri (FR), Philippe De Deurwaerdère (FR)

- **S31.1 Bruno P Guiard** (Centre de Recherches sur la Cognition Animale (CRCA), Toulouse, France): "Influence of the context of administration in the psychopharmacological profile of the psychedelic 5-MeO-DMT"

- **S31.2 Amel Bouloufa** (University of Lyon, France): "The prototypical hallucinogen LSD produces rapid antidepressant effects via 5-HT2B receptor activation"
- **S31.3 Jasmine J Butler** (University La Charité, Berlin, Germany): "The 5-HT2A receptor agonist TCB-2 disrupts the correlative links between numerous classical neurotransmitters in the mouse brain"
- **S31.4 Danilo De Gregorio** (San Raffaele University, Milan, Italy): "Role of LSD in anxiety and social behavior"

S32 "*Neurobiology of alcohol and opiates use disorders*" (Majles room)
CHAIR: **Sami Ben Hamida (FR)**

- **S32.1 Mickael Naassila** (Université de Picardie Jules Verne, Amiens, France): "Effectiveness of psychedelics on alcohol use disorders"
- **S32.2 Eric Augier** (Center for Social and Affective Neuroscience, CSAN, Sweden): "the GABA transporter GAT-3 and GABAergic transmission in the CeA: a common role in alcohol and drug use disorder?"
- **S32.3 Emmanuel Darq** (Interdisciplinary Cluster for Applied Genoproteomics (GIGA-R), Belgium):"Unveiling the consequences of adolescent alcohol exposure on prefrontal cortex maturation"
- **S32.4 Sami Ben Hamida** (Université de Picardie Jules Verne, Amiens, France): "mPFC and alcohol related-behaviors"

10:50-11:10 COFFEE BREAK

11:10-13:00 SYMPOSIA 33-36

S33 "*EpiEpiNetwork MNS Symposium: Next steps on epilepsy research: from brain dysfunction and immunity to comorbidities*" (Carthage I room)
CHAIRS: **Sandra H Vaz (ES); Tatiana P. Morais (MT)**

- **S33.1 Gabriele Ruffolo** (Sapienza University of Rome, Italy): "GABAergic neurotransmission: a common hallmark of neurodevelopmental impairment"
- **S33.2 Cristina Limatola** (Sapienza University of Rome, Italy): "GABAergic modulation by immune cells and effects on memory"
- **S33.3 Marco Ledri** (Lund University Hospital, Sölvegatan, Sweden): "Early postnatal transplantation of human stem cell-derived GABAergic interneurons alters the adult epileptic phenotype of Cntnap2 knock-out mice"
- **S33.4 Sandra Vaz** (Universidade de Lisboa, Portugal): "Cognitive comorbidities of absence seizures"
- **S34.5 Tatiana Morais** (Malta University, Malta): "Absence Seizures Comorbidities and Their Pharmacological Modulation"

S34 "*Regulation of cognitive control from rodents to primates and humans*"
(Carthage II room)
CHAIR: **Radwa Khalil (DE)**

- **S34.1 Emiliano Macaluso** (Université Claude Bernard Lyon 1, Bron, France): "Combining external and internal signals for attentional selection : from simple visual displays to active behavior in complex virtual environments"
- **S34.2 Zakria Ouhaz** (University of Oxford, UK): "Unravelling the contribution of the mediodorsal thalamus in reward-guided decision making: insights from rodents and primates' studies"
- **S34.3 Sarah Bou Sader Nehme** (Holy Spirit University of Kaslik, Lebanon): "Neuroinflammatory Mechanisms of Pain Hypersensitization In A Mouse Model Of Attention-Deficit/Hyperactivity Disorder (ADHD)**"**
- **S34.4 Ilona Kotlewska** (Jagiellonian University, Kraków, Poland): "Evidence for two sources of EEG theta-band activity during proactive action control: midfrontal and right lateral-prefrontal"
- **S34.5 Radwa Khalil** (Constructor University, Bremen, Germany): "Inhibitory control and creative performance in humans"

S35 "*Molecular targets in alcoholism and associated neuropsychiatric disorders*"
(Carthage III room)
CHAIR: **Mohamed Kabbaj (USA)**

- **S35.1 Mohamed Kabbaj** (Florida State University, FL, USA):"Effects of ketamine on alcohol drinking in rats"
- **S35.2 Mickael Naassila** (Université de Picardie Jules Verne, Amiens, France): "Targeting epigenetic mechanisms to treat alcohol use disorder: insights from animal models"
- **S35.3 Stefania Maccari** (Campus Cité Scientifique, CNRS, Lille, France): "Perinatal stress and alcohol drinking on sleep cycle: role of metabotropic receptors"
- **S35.4 Nazzareno Cannella** (University of Camerino, Italy): "A reverse translational approach to evaluate individual variability in treatment response in alcoholism"

S36 "*New insights in brain homeostasis*" (Majles room)
CHAIR: **Thiriet Nathalie (FR)**

- **S36.1 Thiriet Nathalie** (INSERM, University of Poitiers, Poitiers, France): "Acute and chronic cocaine and nicotine change the expression of genes involved in cholesterol homeostasis in the rat dorsal striatum"
- **S36.2 Mélodie Devère** (INSERM, Normandie University, Rouen, France): "The chemogenetic activation of a novel key subpopulation of neurons, expressing 26rfa and orexins, elucidates part of the fine and complex hypothalamic regulation of glucose and energy homeostasis"

- **S36.3 Laila Berroug** (Sultan Moulay Slimane University. Beni Mellal, Morocco): "Sex-specific neurobehavioral and biochemical effects of developmental exposure to malathion in offspring mice"
- **S36.4 Meriem Laaroussi** (Sultan Moulay Slimane University. Beni Mellal, Morocco): "Chronic exposure to inorganic mercury affects neurobehavioral and oxidative stress in female mice"

13:00-14:00 LUNCH

14:00-15:20 Experimental Design and Reporting by NC3Rs (Carthage I room)

Nathalie Percie du Sert, Esther Pearl & Stephen Turnock

NC 3Rs National Centre for the Replacement Refinement & Reduction of Animals in Research

15:20-17:10 SYMPOSIA 36-39

S37 "*The "invisible" disability: neurological disorders including chronic pain and epilepsy*" (Carthage I room)

CHAIR: **Katarzyna Starowicz (PL) & Livio Luongo (IT)**

- **S37.1 Katarzyna Starowicz** (Maj Institute of Pharmacology Polish 28cademy of Sciences, Kraków, Poland): "Therapeutic potential of endocannabinoids for the treatment of chronic pain and associated cognitive impairment"
- **S37.2 Livio Luongo** (University of Campania Luigi Vanvitelli, Naples, Italy): "Potential role of the hydroxyl carboxylic acid receptor type 2 (HCAR2) in microglia pathophysiology and pain implications"
- **S37.3 Cristiano Bombardi** (University of Bologna, Bologna, Italy): "5-HT2CR endocannabinoids interaction in absence epilepsy"
- **S37.4 Rosmara Infantino** (University of Campania Luigi Vanvitelli, Naples, Italy): "Old skulls tie new tricks: the therapeutic potential of the novel cannabimimetic substance Δ9-Tetrahydrocannabiphorol in the Central Post-Stroke Pain"
- **S37.5 Alon Friedman** (Dalhousie University, Halifax, Canada): "Neuro-glia-vascular interactions in health and disease: Time for translation"

S38 "*Maternal environment during perinatal life affects offspring brain development and life-long brain functions*" (Carthage II room)
CHAIR: **Marialetizia Rastelli (FR) & Sebastien Bouret (FR)**

- **S38.1 Laura Dearden** (University of Cambridge, UK): "Early life programming of obesity via a hypothalamic miRNA involved in fatty acid sensing"
- **S38.2 Oumaima Essaidi** (Sultan Moulay Slimane University, Beni Mellal, Morocco): "Prenatal restraint stress affects maternal behavior, early neurobehavioral response and oxidative stress in mice pups"
- **S38.3 Roberta Haddad-Tovolli** (Institut d'Investigacions Biomèdiques August Pi i Sunyer, IDIBAPS), Barcelona, Spain): "Neuronal circuits underlying maternal dietary habits and the programming of offspring health**"**
- **S38.4 Stefania Maccari** (University of Lille, France): "The intergenerational inheritance of early life stress is transmitted by maternal oxytocin"

S39 "*Neural Cell Metabolism in Health and Disease*" (Carthage III room)
CHAIR: **Natalie Rasgon (USA)**

- **S39.1 Mark Rasenick** (University of Illinois College of Medicine, Chicago, IL, USA) : "A biosignature for depression and antidepressant response: Roles of G proteins, lipid rafts, and the cytoskeleton"
- **S39.2 Nina Vardjan** (University of Ljubljana, Slovenia): "Lipid droplet homeostasis under stress and ageing"
- **S39.3 Robert Zorec** (University of Ljubljana, Slovenia): "Astroglial mechanisms of neurodegeneration and viral infection"
- **S39.4 Natalie Rasgon** (Stanford University School of Medicine, USA): "A neuroglial circuit for maternal behaviour"

S40 "*New insights in neuroprotection, learning and memory mechanisms*" (Majles room)
CHAIR: **Aldo Donizzetti (IT) & James Olopade (NG)**

- **S40.1 Aldo Donizetti** (Universita' degli studi di Napoli Federico II, Naples, Italy): "*In vitro* model of synaptic activity for the investigation of molecular mechanisms of synaptic plasticity and neuroprotection"
- **S40.2 Taoufik Ghrairi** (University of Tunis El-Manar, Tunisia):"Characterization of neurotrophic potentials of Imine Analogs of Trans-Resveratrol"
- **S40.3 James Olopade** (University of Ibadan, Nigeria): "Surveillance of neurotropic viruses in Nigeria: What are plans to develop novel therapies?"
- **S40.4 Georgios S. Kogias** (Louisiana State University, New Orleans, LA, USA):"Activation of cerebellar PCs disrupts reconsolidation of associative emotional memory"
- **S40.5 Latifa Dorbani-Mamine** (University of Science and Technology Houari Boumediene. Bab Ezzouar, Algeria): "Cellular and molecular aspects of neurotoxicity induced in rats and rabbits by pesticides: thiamethoxam and voliam-targo"

17:10-17:30 **COFFEE BREAK**

17:30-18:30 Keynote Lecture

Daniele Piomelli (University of California, Irvine, CA, USA)
"*The long-term impact of cannabis use in adolescence: it's time to take a fresh look*"

CHAIR: Patrizia Campolongo
(Carthage I room)

Wednesday, October 18st 2023

9:00-9:50 Keynote Lecture

Riadh Gouider (Razi Hospital, Faculty of Medecine of Tunis & University of Tunis El Manar, Tunis, Tunisia):
"How Homozigosity impact our clinical neurology practice"

CHAIR: Olfa Masmoudi
(Carthage I room)

9:50-11:10 SYMPOSIA 41-43

S41 "*Preclinical and clinical novel insights on the mechanisms underlying human obesity and eating disorders*" (Carthage I room)
CHAIR: **Mariangela Pucci (SW), Paola Fadda (IT)**

- **S41.1 Mariangela Pucci** (Karolinska Institute, Huddinge, Sweden): "Preclinical and clinical evidence of dopaminergic system regulation in Binge Eating"
- **S41.2 Maria Scherma** (University of Cagliari, Italy): "Neurobiological and molecular mechanisms implicated in the development of anorexia nervosa: focus on the experimental model of Activity-Based-Anorexia (ABA)"
- **S41.3 Marianna Rania** (University Magna Graecia of Catanzaro, Catanzaro, Italy): "Feeding the gut, feeding the host: insights on the interplay between gut microbiome and eating behaviours in eating disorders and obesity**"**
- **S41.4 Florijan Jalsevac** (Universitat Rovira i Virgili, Tarragona, Spain): "Profile of Bitter Taste Receptors in the Jejunum of Morbid Obese Patients that undergo Bariatric Surgery"
- **S41.5 Bourdy Romain** (CNRS/Université de Strasbourg, France): "Endocannabinoid system regulations in the reward system in obesity and binge eating disorder"

S42 "*Sensory alterations in autism: From preclinical models to human studies*" (Carthage II room)
CHAIR: **Ourania Semelidou (FR)**

- **S42.1 Ryan Stevenson** (Western University, London, Ontario, Canada): "Sensory phenotypes in Autism: From neural networks to clinical profiles"
- **S42.2 Aline Lefebvre** (Institut Pasteur, UMR 3571 CNRS, University Paris Diderot, Paris, France): "Tackling hypo and hyper sensory processing heterogeneity in Autism: from clinical stratification to genetic pathways"

- **S42.3 Benjamin D. Auerbach** (University of Illinois, Urbana, Illinois, USA): "Auditory Hypersensitivity and Processing Deficits in a Rat Model of Fragile X Syndrome"
- **S42.4 Ourania Semelidou** (Inserm, Bordeaux, France): "Altered detection of tactile stimuli in a mouse model of autism during a translational task"

S43 "*Understanding the role of neuronal integrative processing through oligomeric receptor complexes in health and brain disorders*" (Carthage III room)
CHAIR: **Dasiel O. Borroto-Escuela (SW)**

- **S43.1 Fang Liu** (University of Toronto, Canada): "Dual effects of α7nAChR-NR2A receptor complex on nicotine addiction and major depression"
- **S43.2 Ramon Fores-Pons** (University of Malaga, Malaga, Spain): "The mGlu5 receptor protomer-mediated dopamine D2 receptor trans-inhibition is dependent on the adenosine A2A receptor protomer: implications for Parkinson's disease"
- **S43.3 Dasiel O. Borroto-Escuela** (Karolinska Institutet, Stockholm, Sweden): "Dysfunctional serotonin heteroreceptor complexes as novel targets for the treatment of Major Depressive Disorders"

11:10-11:30 COFFEE BREAK

11:30-12:30 AWARDS & CONCLUSION (Carthage I room)

Olfa Masmoudi (TN), Taoufik Ghrairi (TN) and Giuseppe Di Giovanni (MT)

Journal Neuroscience Methods Elsevier Best Paper Awards

CNS Neuroscience and Therapeutics Wiley Best Paper Awards

The Receptors Springer/Nature Best Paper Awards

Announcement MNS2025

POSTERS

During coffee breaks (14. 15,16, 17/10/2023)

P1 Fattore Liana,
Psychiatric disorders and Comorbidities caused by pollution in the Mediterranean area

P2 Galip Yiğit Ünlü
Role of Cannabinoids in Neuropsychiatric Comorbidities in Absence Seizures

P3 Olfa Masmoudi
Study of the protective effect of PACAP on brain development and oxidative stress in mice exposed in utero to glyphosate

P4 Olfa Masmoudi
Neuroprotective effects of neuropeptides PACAP and ODN against prenatal glyphosate exposure induced oxidative damage and neurotoxicity

P5 Taoufik Ghrairi
Biological Activities of Cumin and Nutmeg Essential Oils on N2A cells: Focus on Cytotoxic Effects

P6 Soltesova Prnova Marta
Sorbitol accumulation in ZDF rat's brain as new link between diabetes and Alzheimer's disease?

P7 Sabrine Bilel
In silico, *in vitro* and *in vivo* pharmacological characterization of emerging novel synthetic opioids: focus on sex differences

P8 Pavlina Pavlidi
Sex-specific effects of GPER1 modulation on behavioral and neurochemical profiles: Investigating GPER1 as a therapeutic target for mood and anxiety

P9 Valérie Lemaire
Neurochemical analysis of the brain monoamine status of CD mice, a genetic mouse model of Williams-Beuren syndrome

P10 Martina Vincenzi
Emerging value of olfactory neuronal Prokineticin-2 as novel target in Parkinson's disease

P11 Roberta Misasi
Chronic stress on neuronal cells converges on TDP43 endogenous cleavage and aggregation

P12 Daniel Venturi
Marine-derived extracts: effects of Polycarpa aurata and Sidnyum elegans in an *in vitro* model of cisplatin-induced neurotoxicity

P13 Taoufik Ghrairi
Characterization of neurotrophic potentials of Imine Analogs of Trans-Resveratrol

P14 Philippe De Deurwaerdère
Distribution of tissue monoamines across the brain of young and old 3xTg-AD mice, a mouse model of Alzheimer's disease

P15 Ramon Fores-Pons

The mGlu5 receptor protomer-mediated dopamine D2 receptor trans-inhibition is dependent on the adenosine A2A receptor protomer: implications for Parkinson's disease

P16 Hassina Belblidia

Maternal deprivation effects on recognition memory and depressive-like behavior in adolescent NMRI male mice

P17 Said Galai

Comparison between muscular biopsy and fibroblast as cell model to investigate mitochondrial activities in the neurometabolic disease "Melas Syndrome"

P18 Hela Mrizak

Increased MOP expression in the Ventral Tegmental Area mediates higher heroin self-administration and motivation expressed by marchigian sardinian alcohol preferring rats compared to non-preferring Wistars

P19 Francesca Mercante

Investigation on the interplay between salivary microbiota and exosomal microrna in binge eating disorder

P20 Alexandra Séverac

Using fNIRS for studying self-motion perception induced by galvanic vestibular stimulation according to gravity

P21 Irene Palenca

High-fat diet negatively affects the mucosal barrier function in the duodenum and trigger crucial changes along the gut-brain axis glial cells involved in anxiogenic and depressive-like behaviours

P22 Maria Antonietta Casu

Neuroprotective activity of MT-POM in the LRRK2 genetic model of PD in drosophila melanogaster

P23 Maria Jesus Oset-Gasque

QN6: A new 8-Hydroxyquinolylnitrone for the therapy of diseases of aging and stroke

P24 Malqui Hafsa

Prenatal and postnatal exposure to inorganic mercury affects neurodevelopmental behavioral parameters in mice offspring

P25 Giuseppina Cantarella

Inflammatory response in the retina in a mouse model of Alzheimer's disease is restrained by targeting the miRNA-155/TNFSF10 network

P26 Nathalie Thiriet

Acute and chronic cocaine and nicotine change the expression of genes involved in cholesterol homeostasis in the rat dorsal striatum

P27 Charalampos Brakatselos

Impaired fronto-striatal excitation/inhibition balance underlies the repeated ketamine-induced schizophrenia-like bio-phenotype: The modulatory role of cannabidiol.

P28 Alexandra Polyzou

Evidence suggesting that PLPPR3 tunes neuronal responses to Lysophosphatidic Acid.

P29 Benedetta Di Cesare

Chronic intranasal administration of URB597 reverts short-term memory deficits in a rat model of metabolic syndrome

P30 Éva Dr Szőke
Cyclodextrins decrease TRP ion channel activation via lipid raft disruption
P31 Basili Franzin Silvia
Genetically modified Lactobacillus paracasei subsp paracasei F19 producing oleoylethanolamide (OEA) relieves peripheral and central symptoms associated with metabolic diseases
P32 Youna Vandaele
Role of cholesterol homeostasis in the dorsomedial striatum on the balance between habitual and goal-directed control
P33 Tunde Toth
Investigation of the role and diagnostic, prognostic value of PACAP-38 in multiple myeloma
P34 Olivera Nesic-Taylor
Engaging Kenyan Communities in Dementia Research
P35 Fella Tounsi
The impact of Thiamethoxam on oxidative stress level in hypothalamic pituitary axis in Wistar rat.
P36 Wassila Benhacene
Impact of type 2 diabetes on the organization and plasticity of the supraoptic and paraventricular hypothalamic nuclei in wistar rats subjected to high-calorie diet
P37 Ikram Abdellaoui
Dystrophins distribution in the median eminence of adult mice: effects of osmotic stimulation and reversibly normal hydration.
P38 Madina Sifi
Implication of Dp and α1-syntrophin in cellular plasticity and reversibility during water stress in wistar rats
P39 Cristiana Valle
The impact of intense endurance exercise on SOD1G93A ALS mouse model
P40 Alberto Ferri
The metabolic modulator Trimetazidine ameliorates mitochondrial dysfunction in Amyotrophic Lateral Sclerosis SOD1G93A cell models via autophagy activation
P41 Eleonora Riccardi
Behavioral correlates of fear memory in an animal model of Post-Traumatic Stress Disorder: Ultrasonic vocalizations and sex differences
P42 Nabat Yoann
Neurobiological vs judiciary truth
P43 Andrea Tamás
Examination of pituitary adenylate cyclase-activating polypeptide in Parkinson's disease focusing on correlations with motor symptoms
P44 Dora Reglodi
A new potential therapeutic target in inflammatory retinopathy
P45 Al-Mashhadani Sada
Octadecaneuropeptide promotes the migration of astrocyte via ODN metabotropic receptor and calcium signaling pathway
P46 Cherif Amine
Effects of binge alcohol exposure on the hippocampus in adolescent and adult mice

P47 Sarah Bou Sader Nehme

Neuroinflammatory Mechanisms of Pain Hypersensitization in a Mouse Model of Attention-Deficit/Hyperactivity Disorder (ADHD)

P48 Oumaima Essaidi

Prenatal restraint stress affects maternal behavior, early neurobehavioral response and oxidative stress in mice pups

P49 Meriem Laaroussi

Chronic Exposure to Inorganic Mercury Affects Neurobehavioral and Oxidative Stress in Female Mice

Keynote lectures

KL1

Neurogenesis in avian species: a comparative approach

Amadi Ogonda Ihunwo

School of Anatomical Sciences, Faculty of Health Sciences, university of the Witwatersrand, Johannesburg, South Africa

The brains of several species of birds from different taxonomic orders exhibiting different behavioural repertoires were studied to determine the active neurogenic regions, migratory routes of migrating neuroblasts and regions of integration of new neurons. The birds belonged to these taxonomic orders: *Columbifomes* (domestic pigeons; racing homer and utility carneau pigeons); *Psittaciformes* (Congo African grey and Timneh grey parrots); *Struthioniformes* (common ostrich), *Casuariiformes* (emu) and the Japanese quail (Coturnix japonica). Free floating immunohistochemical methods against proliferating cell nuclear antigen (PCNA) which labels proliferating cells and doublecortin (DCX) which stains immature neurons. High levels of cell proliferation in the *olfactory bulb*s and subventricular zones (SVZ) of the lateral ventricles in the telencephalon with the SVZ as the primary neurogenic zone contributing new neurons in the adult telencephalon; immature neurons are localised in high density in the olfactory bulb and the subdivisions of the telencephalon, but in low densities in the *subtelencephalic* regions except in the ratite birds (common ostrich and emu) where moderate densities were observed in the cerebellar cortex. Distribution of DCX positive neurons showed region specificity within the subdivisions of the telencephalon across all species with high densities in the medial and lateral regions of the pallial and subpallial regions, but devoid in the core areas; species-specific distribution of DCX positive neurons was observed in the hippocampus and song control systems and cerebellum of the ratite birds suggesting behavioural specialisations. Migratory routes of immature neurons were not clearly defined across species except in the ratites where three distinct bundles of migrating neuroblasts were observed in the telencephalon. Neuroblasts migrated from the dorsal and ventral poles of the SVZ of the lateral ventricle into the hyperpallium and medial striatum respectively. The peak period for cell proliferation in the Japanese quail is between 5-6 weeks post-natal stage.

KL2

Stress, Drugs, and Relapse: How can neuroscience help us in improving addiction treatment?

Rajita Sinha

Yale University School of Medicine

Stress and trauma have long been known to increase addiction risk and relapse. How does this happen? What are the critical neural circuits that promote and sensitize stress-related reward motivation? This presentation will focus on specific chronic drug related adaptations

in brain and peripheral circuits that impact compulsive motivation and relapse risk. It will also identify chronic stress related neuroplasticity in resilient coping and self-control circuits that increase risk of developing addictive disorders. The effects of steroid hormone dysfunction due to chronic stress and chronic drug misuse will be described and how they related to stress motivational neural circuitry, drug craving and related clinical outcomes will be discussed. Finally, pharmacological rescue of neural and endocrine alterations with noradrenergic and neurosteroid manipulations and their effects on drug craving and drug use outcomes will be shown. Implications of reversing key drug-related targeting stress dysfunctional circuits for addiction prevention and treatment development will also be presented.

KL3

EVERYDAY TRAUMA -- AND HOW NOT TO RUMINATE ON IT SO MUCH

Tracey J. Shors

Behavioral and Systems Neuroscience in the Department of Psychology, Center for Collaborative Neuroscience at Rutgers University

Everyone experiences trauma. Whether it's a specific harrowing event or a series of stressful moments that accumulate over time, trauma can echo and etch itself into our brains. In her lecture, neuroscientist Dr. Tracey Shors will discuss how our brains are inclined to ruminate on painful memories and how this process can interfere with our everyday lives, while making still more memories. She will also present effective tools for reducing repetitive thoughts that reinforce our everyday traumas. By understanding how our brains ruminate on the past, while training them with new mental and physical skills, we are better equipped to leave our pasts behind and live in a brighter future.

KL4

THE LONG-TERM IMPACT OF CANNABIS USE IN ADOLESCENCE: IT'S TIME TO TAKE A FRESH LOOK

Daniele Piomelli

University of California, Irvine, CA, USA

The use of cannabis is common in adolescence, a time when neocortical networks that underpin cognition are still developing and may be especially vulnerable to the effects of cannabis' intoxicating constituent, Δ9-tetrahydrocannabinol (THC). Epidemiological surveys suggest that exposure to cannabis during the teenage years may be associated with impairments in cognition and affect, which continue into adulthood even after use of the drug has stopped. Increased risk of developing schizophrenia has also been documented. Some of these findings have been questioned but, supporting their relevance, laboratory studies in rodents indicate that adolescent treatment with THC causes lasting dysregulations in memory, emotion and reward-seeking behavior. In this lecture, I will describe a realistic mouse model of low-intensity adolescent exposure to cannabis and its application to investigate the lasting impact of this drug on brain microglia function and systemic energy metabolism.

Symposia

S1 Stress and glucocorticoids: memory functions and implications for psychiatric disorders

CHAIR: Gina Lorena Quirarte[1], Giulia Federica Mancini[2]

[1] *Universidad Nacional Autónoma de México, Querétaro, México*
[2] *Leiden University Medical Center, Leiden, The Netherlands*

Glucocorticoids (GCs) are stress-hormones regulating many processes within the body as well as within the brain, such as learning and memory functions. Stress-induced GCs release triggers many responses responsible for the activation of the homeostatic and behavioral strategies to cope with it. However, when GCs levels are very high, stress response can be exacerbated and may lead to the development of maladaptive features (e.g., psychiatric disorders). The present symposium will provide novel important tiles in the big mosaic of the stress/glucocorticoids research field.

S1.1
Glucocorticoids-induced effects on memory functions of the striatum.

Quirarte, G.L., Serafin, N., Fuentes-Ibañez, A., Siller-Pérez, C., Ponce-Lina R., Pegueros-Maldonado, R., Prado-Alcalá, R.A.

Laboratorio de Aprendizaje y Memoria, Depto. de Neurobiología Conductual y Cognitiva, Instituto de Neurobiología Campus Juriquilla, UNAM, Querétaro, Qro., 76230 México.

Glucocorticoids, such as corticosterone (CORT) in rodents, are stress hormones secreted by the adrenal glands during emotional events. They play a crucial role in memory consolidation and retrieval by acting upon glucocorticoid receptors in various brain regions, with their effects depending on the timing of administration and stressor intensity. Data from our laboratory demonstrated that CORT administration into the dorsal striatum (DS) facilitates memory consolidation and impairs retrieval; these effects, which can be blocked by concurrent administration of a β-blocker into the basolateral amygdala (BLA), indicate that noradrenergic activation in the amygdala is required to enable striatal glucocorticoid actions on memory. Importantly, we have described that the activation of glucocorticoid receptors in the medial or lateral region of the striatum hinders or enhances consolidation, depending on the type of memory (spatial or procedural, respectively), consistent with human findings that stress facilitates a shift toward stimulus-response memory and habit formation. These findings indicated that spatial and procedural memory functions involve different portions of the DS

and that the enhancing and impairing effects of glucocorticoids on consolidation and retrieval of procedural memory are mediated through glucocorticoid actions. This evidence contributes to the study of the effects of stress on habit formation, which becomes altered to produce maladaptive behaviors in different psychopathologies and drug abuse.

S1.2

Early-life stressful experiences in the susceptibility/resilience for psychiatric disorders development later in life

Giulia F. Mancini[1,2], Onno C. Meijer[2], Patrizia Campolongo[3]

[1] Department of Physiology and Pharmacology, Sapienza University of Rome, Rome, Italy
[2]Dept. of Endocrinology, Leiden University Medical Center, Leiden, The Netherlands
[3]Neurobiology of Behavior Laboratory, Santa Lucia Foundation, Rome, Italy

Exposure to stress is a predominant environmental risk factor for psychiatric disorders. However, not all individuals experiencing stressful events will eventually develop a mental disease, and it may be due to a combination of numerous factors, including previous life experiences. Literature data indeed demonstrated that experiencing early-life adverse events can interfere with neurodevelopmental trajectories, which may result in altered susceptibility/resilience for the later psychiatric disorders development. In this talk I will discuss whether and how early-life stress may affect the stress response in adult rats. In particular, I will present data demonstrating that different early-life stressors show different programming effects on emotionality and cognitive functions, and that the exposure to such stressors may alter the ability to cope with a second challenge increasing (or decreasing) vulnerability for psychiatric disorders development later in life. Since sex hormones are known to affect the stress response system, I will also discuss sex differences involved in these processes.
Investigating the programming effects of early-life stress exposure and the related neurobiological underpinnings could pave the way to the development of novel and precision-medicine based prophylactic and/or therapeutic interventions for psychiatric diseases in humans.

S1.3

Arousal and stress effects on cannabinoid modulation of aversive memory: Insights into Post-Traumatic Stress Disorder Susceptibility

Patrizia Campolongo

Department of Physiology and Pharmacology, Sapienza University of Rome, P.le A. Moro 5, 00185 Rome, Italy

Neurobiology of Behavior Lab, Santa Lucia Foundation, Via del Fosso di Fiorano 64, 00143 Rome, Italy

Emerging evidence demonstrates that the level of stress associated to the environmental conditions plays a crucial role in modulating cannabinoid effects on emotional behaviors. Therefore, in this talk I will discuss to what extent the level of stress, associated to the level of training-induced emotional arousal, might have implications on cannabinoid effects on memory performances in rats.
In particular, I will present data demonstrating that variations in the level of emotional arousal, associated to the experimental conditions, shape cannabinoid effects on memory functions. Given that, I will present results indicating that exogenous manipulation of the endocannabinoid system might differentially affect memory processes, thus being in certain conditions protective with regard to the development of long-term behavioral alterations partially resembling those seen in PTSD patients.

S1.4
A Translational Examination of The Effects of Cannabis Use on Diurnal Cortisol Rhythms

Carrie Cuttler, Nicholas C. Glodosky, and Ryan J. McLaughlin

Washington State University, Pullman, WA, USA

Stress is the most reported reason for cannabis use. Our research has revealed perturbed cortisol/corticosterone (CORT) reactivity in cannabis-using humans and rodents trained to self-administer cannabis. However, little is known about whether cannabis use impacts diurnal CORT rhythms. Thus, we examined whether healthy cannabis-using humans exhibit a dysregulated diurnal CORT slope, and whether we can recapitulate this effect in a rat model of cannabis use. We further examined whether diurnal CORT dysregulation predicts heightened levels of depression typically reported by human cannabis users, as well as the acute effects of cannabis use on changes in salivary CORT concentrations.
Eighty humans (40 users, 40 non-users) and 64 rodents are being tested to address these objectives. Humans complete the Beck Depression Inventory and collect saliva samples repeatedly throughout the day in their natural environments. Cannabis users collect additional saliva samples immediately before and after using cannabis. Long Evans rats were trained to self-administer 150 mg/ml cannabis (69.9% THC extract; n = 48) or vehicle (n = 16) vapor. Blood samples were collected at the beginning and end of their active cycle both before and after 22 days of daily cannabis vapor self-administration.
Preliminary results (15 users, 25 non-users) indicate that human cannabis users have flatter diurnal CORT slopes relative to non-users. Depression scores were elevated in cannabis users, but depression was not significantly correlated with diurnal CORT slopes. Results further indicate that CORT significantly decreased following acute cannabis use in participants' natural environments. CORT analyses in rodents are still ongoing.

S1.5

Fear Conditioning and Extinction in Children with Trauma: Associations with Brain and Behavior

Tanja Jovanovic, John McClellan France, Lana R. Grasser, Anaïs F. Stenson

Department of Psychiatry and Behavioral Neurosciences, Wayne State University, Detroit, MI, USA

Threat-related circuitry has been shown to be dysregulated in adults with posttraumatic stress disorder (PTSD), manifesting in amygdala hyperactivity and impaired fear extinction. The developmental trajectories of these phenotypes are not yet clear, as threat regulation brain regions mature more slowly relative to amygdala. In our studies, we investigated fear conditioning and extinction using fear-potentiated startle (FPS) in children with a history of trauma exposure. We examined several factors related to fear extinction, such as contingency awareness, trauma load, PTSD symptom severity, and amygdala reactivity using functional magnetic resonance imaging (fMRI). In two separate studies (Study A: n=62, 9-year-old children with civilian trauma; Study B: n=71, 7-17 year-old children with refugee trauma) we found that impaired fear extinction was associated with PTSD symptoms. Among children exposed to urban violence in Study A, those who did not extinguish the association between the CS+ and the US had higher PTSD symptoms compared to the children who demonstrated awareness of the change in contingency during extinction, F=4.48, p=0.04. In Study B, children who had PTSD had higher FPS to the CS+ during extinction compared to children without PTSD, F=6.25, p=0.02. In a subset of children from Study A that had completed fMRI, amygdala reactivity was positively associated with FPS during extinction, r=0.56, p=0.002). Taken together, these studies show that the same threat circuitry phenotypes observed in adults with PTSD are already seen in pre-adolescent children, supporting the use of fear conditioning methods in early detection of risk in children with trauma exposure.

S2

Parkinson's disease as a conundrum: specific synucleinopathy or circuitry disease?

CHAIR: *Salvatore Galati,[1] Alessandro Stefani[2]*

[1] Istituto di Neuroscienze Cliniche della Svizzera Italiana, Lugano

[2] Dip Medicina dei Sistemi, Università di Roma Tor Vergata

Parkinson's disease (PD) is characterized by the degeneration of dopamine neurons and the simultaneous derangement of multiple systems, which may involve extra-dopamine sites and circuitries. The clinical presentation of PD, including non-motor domains, is powerfully shaped by the complex interplay between neurodegeneration and consequent network changes. This symposium will evaluate recent investigations that target the interplay between cortical and subcortical structures. Pioneering studies revealed that the pathological synchronization of

the beta band in basal ganglia stations and in the cortex correlated with akinesia in both primate models and patients. Recent investigations using neuroimaging techniques have explored PD brain connectivity in terms of predictors, markers, and prognosis. However, our understanding of PD based on electrophysiological or molecular tools is relatively scarce. During the symposium, Alessandro Stefani will present an innovative functional analysis based on high-resolution EEG recordings in PD patients. He will discuss how an abnormal ratio between beta and gamma bands may serve as a disease marker and lead to putative phenotypic stratification or change the clinical indication to deep brain stimulation (DBS). Moreover, he will explore whether connectivity changes along different PD stages and how different connectomic features, such as PD gender or specific PD phenotypes, play a role. Marta Sciascia will discuss the relevance of standard EEG and expose a wide range of cortical correlates of sleep alteration, particularly delta and theta distribution patterns, which represent intriguing facets of the PD motor spectrum. The symposium will also focus on a recently validated tool presented by Alain Kaelin, which applies an innovative flow cytometric multiplex bead-based platform to investigate plasma-derived extracellular vesicles. This tool contributes to differentiating PD patients from those with atypical parkinsonism. Finally, Roberto Di Maio will present comprehensive mechanistic evidence supporting the central role of oxidative stress in driving PD-related nigrostriatal degeneration. Overall, this symposium will provide a comprehensive overview of recent investigations into the interplay between cortical and subcortical structures and provide insights into the diagnosis and treatment of Parkinson's disease.

S2.1

Functional connectivity in Parkinson's disease patients: EEG studies

Matteo Conti[1], Vincenza D'Angelo[1], Alessandro Stefani[2]

[1]*Neurology Unit, Department of Systems Medicine, University of Rome "Tor Vergata", Rome, Italy*
[2]*Parkinson Centre, Department of Systems Medicine, University of Rome "Tor Vergata", Rome, Italy*

Functional connectivity (FC) is a promising approach for investigating Parkinson's disease (PD) pathophysiology. In recent years, we have studied resting-state FC abnormalities in PD patients using a refreshed high-density EEG tool. Data are recorded with 64-channels EEG system and a source-reconstruction method is used to identify brain-region activity. FC was calculated using the weighted phase-lag index in θ, α and β bands. Statistical analysis was conducted using a network-based statistical approach.

PD patients show hypoconnected networks in θ and α band and a hyperconnected network in the β one, involving sensorimotor-frontal areas. The θ-FC network is negatively related to NM scores and α-FC to the MDS-UPDRS-III gait sub-score; the β-FC and β-FR network are positively linked to the bradykinesia subscore. Further, we explored the possible differences in FC in a cohort of early-stage PD patients but featuring or not REM sleep behavior disorder (pRBD). Intriguingly, RBD may represent a marker of the so-called PD "body-first" subtype.PD

patients showed hypoconnected networks in theta and alpha band, involving prefronto-limbic-temporal and fronto-parietal areas. When comparing the PDpRDB- and PDpRBD+ subgroups, we found a lower FC in the alpha frequency band in PDpRBD-, which involved a network composed by temporo-parietal, frontal and sensorimotor areas (t=2.5, p=0.025).

Abnormalities of frequency-specific FC changes in PD are involved in the pathophysiology of specific motor and NM PD symptoms, including bradykinesia and cognition. Moreover, compared to "brain-first" PD, the body-first subtype demonstrates specific EEG-FC dysfunctions in the α band, likely reflecting an involvement of the cholinergic system.

S2.2

The Impact of sleep mediated downscaling process on theta wake activity in Parkinson's disease

Marta Sciascia,[1] Ninfa Amato,[1] Alain Kaelin,[1,2] Salvatore Galati[1,2]

[1]*Neurocenter of Southern Switzerland*
[2]*Università della Svizzera Italiana*

The process of slow wave sleep (SWS) is essential in the brain's ability to adapt and change. During SWS, slow wave activity (SWA) plays a significant role in scaling down synaptic strength. The amount of SWA during SWS, which usually occurs in the first part of the night, serves as a primary electrophysiological marker for the homeostatic process.
Previous research has suggested that there is a connection between levodopa-induced dyskinesia (LID) in Parkinson's disease and impairment in this mechanism (1).
However, this association could be due to either an impaired SWA-mediated downscaling mechanism or a lower build-up process. Our previous research favors the former hypothesis. We are currently studying the build-up process during wake to confirm this.
As part of our study, we recruited three different PD groups: de novo (n = 8), advanced (n = 12), and dyskinetic (n = 6), and compared them to healthy volunteers (n= 3).
All participants underwent a physical and neurological examination and received inertial sensors to monitor their sleep-wake cycle for a week before a PSG recording was taken.
On the day of PSG recording, subjects underwent to short waking recordings, during which they also performed a go/no-go task, the first in the morning and the second 9 hours later.
Our findings showed changes in theta activity in the morning amount in Parkinsonian patients, indicating an intrinsic alteration in the sleep-mediated mechanism of synaptic downscaling.
Overall, our study is a valuable effort in clarifying the relationship between sleep and the onset of LID. It also opens up possibilities for innovative therapies that enhance SWA in PD.

(1) Amato N, Manconi M, Möller JC, Sarasso S, Stanzione P, Staedler C, Kaelin-Lang A, Galati S. Levodopa induced dyskinesia in Parkinson disease: Sleep matters. Ann Neurol. 2018 Dec;84(6):905-917. doi: 10.1002/ana.25360. Epub 2018 Nov 29. PMID: 30328147.

S2.3

Update on peripheral biomarkers in Parkinson Disease

Alain Kaelin-Lang and Giorgia Melli

Neurocenter Of Southern Switzerland, 6900-Lugano

Parkinson disease is still defined as a clinical entity based on motor symptoms such as bradykinesia linked with the dopaminergic denervation. It is, however, well known that motor symptoms are occurring at an advanced stage of the neurodegenerative process. There is an urgent need for both clinical and biological biomarkers of the disease at an early stage allowing for early diagnosis. It is however difficult to gain direct access to the brain pathology. Hence, there is a quest for peripheral biomarkers such as from blood or from peripheral tissues. On the other hand, studies in both genetic and sporadic cases have demonstrated a heterogeneity of the biological processes leading to alpha-synuclein accumulation in the brain. The heterogeneity of the pathogenesis probably underlies the heterogeneity of the disease manifestation and of the clinical progression. It is thus likely that Parkinson disease is not the consequence of one single pathological process but due to several mechanisms leading to a final similar syndrome. In this regard, biomarkers would also help understand and classify the different forms of the diseases based on biological parameters, such as, for example, level of neuroinflammation or of mitochondrial dysfunction. Finally, the lack of an animal model reflecting the human pathology does not allow easily the identification of new therapeutic targets. Looking at the pathology in human with biomarkers could help better understand and identify innovative targets for more efficacious neuroprotective therapy. This is urgently needed after the lack of efficacy of several antibodies targeting alpha-synuclein in recent clinical studies. We will review current knowledge on peripheral biomarkers with an emphasis on our work on inflammation and skin biopsies.

S2.4

Exploring oxidative signaling in Parkinson's disease: uncovering complex pathways and potential therapeutic avenues

Roberto Di Maio

Pittsburgh Institute for Neurodegenerative Diseases, Department of Neurology, University of Pittsburgh

Parkinson's disease (PD) is an increasingly common age-related movement disorder with a gene-environmental complex etiology affecting millions of people worldwide. While the exact mechanisms behind the selective loss of nigrostriatal cells in PD remain elusive, several key pathogenic features have emerged, shedding light on this debilitating condition. These include oxidative stress, aberrant LRRK2 kinase activity, α-synuclein misfolding and aggregation, mitochondrial dysfunction, and persistent neuroinflammation.

One area of recent research garnering significant attention is the role of nicotinamide adenine dinucleotide phosphate oxidases (NOXs) in PD-related nigrostriatal degeneration. Among the

brain's various NOX isoforms, NOX2, the most abundant, has surfaced as a potential key player in PD pathogenesis and progression.
Our groundbreaking studies have provided comprehensive mechanistic evidence supporting the central role of oxidative stress in driving PD-related nigrostriatal degeneration. Our investigations have unveiled a critical feedforward loop in PD pathogenesis characterized by a complex interplay between mitochondrial reactive oxygen species (ROS) increased LRRK2 kinase activity, induction of α-synuclein post-translational modifications and impaired mitochondrial import. In the context of this intricate web of interactions, neuronal NOX2 plays a critical role in enhancing this PD-related pathogenic cascade.
Our research has profound implications. By unraveling the intricate mechanisms involving NOX2 in PD, we have made significant strides in advancing our understanding of this devastating neurological disorder. Our findings offer promise for the development of novel therapeutic approaches urgently needed to alleviate the growing burden of PD on individuals and society.

S3

Senescence: Friend or foe for neurodevelopment, cancer and neurodegeneration

CHAIR: Isabel Varela-Nieto[1], Manuel Collado[2]

[1] *Institute for Biomedical Research Alberto Sols, CSIC-UAM & CIBERER Arturo Duperier 4, Madrid 28029, Spain*
[2] *Health Research Institute of Santiago de Compostela, IDIS Clinical University Hospital,Santiago de Compostela 15706, Spain*

The "Senescence: Friend or Foe in Neurodevelopment, Cancer, and Neurodegeneration" symposium at MNS2023 explores the multifaceted role of cellular senescence in various aspects of neuroscience and disease. Four engaging talks shed light on the implications of senescence in Alzheimer's disease therapy, dementia prevention and treatment, inner ear development and age-associated hearing diseases, as well as the aging central nervous system (CNS) using Drosophila melanogaster as a model organism.

"Contilisant: A Potential Alzheimer's Disease Therapy"

José Marco-Contelles

Contilisant, a promising neuroprotective compound, exhibits properties conducive to Alzheimer's disease treatment. This presentation highlights its potential as a lead compound for AD therapy, including its non-toxic nature, ability to cross the blood-brain barrier, and favorable in vitro pharmacological properties. Excitingly, Contilisant demonstrates efficacy in restoring cognitive function in relevant animal models.

"DHEA(S) in Dementia: A Potential Protective Role"

Barbara Vuic

Delving into the realm of neurosteroids, this talk explores the neuroprotective potential of dehydroepiandrosterone (DHEA) and its sulfate form (DHEAS) in dementia. Research covers both cellular and animal models, shedding light on the viability of these neurosteroids in Alzheimer's disease and vascular dementia. Beneficial effects of DHEA/S suggest new avenues for dementia prevention and treatment.

"Cellular Senescence in Inner Ear Development and Age-Associated Hearing Diseases"

Isabel Varela-Nieto

This presentation uncovers the role of cellular senescence in inner ear development and its association with age-related hearing loss (ARHL). Insights into tissue remodeling and differentiation during otic development are discussed, along with the impact of chronic oxidative stress on cochlear hair cells. The potential involvement of Nrf2 and downstream targets in ARHL is explored, along with the intriguing link between cellular senescence and inner ear tumors.

"TIME FLIES: Cellular Senescence in Aging CNS of Drosophila melanogaster"

Presenter: Manuel Collado

Introducing Drosophila melanogaster as an alternative model to study aging-related cellular senescence, this talk examines senescent cells in the central nervous system of aging flies. Preliminary findings reveal increased senescence markers in neurons of old flies, which can be eliminated using senolytic compounds. This novel perspective on senescence in Drosophila opens doors for cost-effective and ethical research into aging and senescence mechanisms.

S3.1
Contilisant, A Small Molecule Designed for Alzheimer's Disease Therapy

José Marco-Contelles,[a] Francisco López-Muñoz,[b,c] and María Jesús Oset-Gasque[d,e]

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[b] Faculty of Health, Camilo José Cela University, Villanueva de la Cañada, Madrid, Spain
[c] Neuropsychopharmacology Unit, "Hospital 12 de Octubre" Research Institute, Madrid, Spain
[d] Department of Biochemistry and Molecular Biology, Faculty of Pharmacy, Complutense University of Madrid, Plaza Ramón y Cajal s/n, Ciudad Universitaria, 28040 Madrid, Spain
[e] Instituto de Investigación en Neuroquímica. Universidad Complutense de Madrid. Ciudad Universitaria, 28040 Madrid, Spain

Contilisant is a neuroprotective, non-toxic, antioxidant, permeable ligand, able to cross the blood-brain-barrier, showing satisfactory *in vitro* pharmacological properties on selected biological targets (hChEs, hMAOs, hH3R, and hS1R) involved in the progress of Alzheimer's disease (AD), being able to restore the cognitive impairment in appropriate in *in vivo* AD animal models, comparing very favorably with donepezil, a drug in the clinics for AD patients tretament.[1,2] Thus, these data suggest that *Contilisant* is a new "lead-compound" for AD therapy, ready to enter in the pre-clinical phase.[3]

1. *J. Marco-Contelles et al. Angew. Chem. Int. Ed.* ***2017****, 56, 12765.*
2. *J. Marco-Contelles et al. J. Med. Chem.* ***2018****, 61, 6937.*
3. *J. L.Marco Contelles, F. López Muñoz, H. Stark, S. Hagenow, R. R. Ramsay, "Nuevos compuestos con capacidad antioxidante que combinan la inhibición de las enzimas monoamino oxidasas y colinesterasas y la*

S3.2 Potential Protective Role Of Dhea(S) In Cellular And Animal Models And Subjects With Dementia

Barbara Vuic[1], Tina Milos[1], Matea Nikolac Perkovic[1], Gordana Nedic Erjavec[1], Lucija Tudor[1], Marcela Konjevod[1], Ana Knezovic[2], Jelena Osmanovic Barilar[2], Adrienn Szabo[3], Szidonia Farkas[3], Dora Zelena[3], Suzana Uzun[4], Oliver K~~ozumplik[4], Ninoslav~~ Mimica[4], Dubravka Svob Strac[1]

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The neurosteroids dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) have been studied for their neuroprotective potential in dementia. We have investigated potential neuroprotective effects of these neurosteroids on the survival and viability of primary mouse neurons, as well as the human SH-SY5Y neuroblastoma cells. As *in vitro* models of Alzheimer's disease (AD) and vascular dementia, we have exposed these cells to the toxic Aβ oligomers or to the oxygen-glucose deprivation (OGD), respectively. In animal research, we have utilized both genetic and pharmacologically induced mouse model of AD. The triple-transgenic AD (3xTg-AD) mouse and C57BL/6 control mice were chronically treated with DHEAS using subcutaneously implanted osmotic pumps. The pharmacologically induced AD model was established by intracerebroventriculary injecting the C57BL/6 mice with Aβ oligomers and chronically administered with DHEA via intraperitoneal injection. Various cognitive and behavioral tests were performed on both models and analyzed using Noldus EthoVision XT software. Human subject research enrolled patients with dementia and individuals with mild cognitive impairment (MCI) (comparative group). Dementia diagnosis was determined according to DSM-V criteria and cognitive symptoms were evaluated by MMSE (Mini mental state examination). DHEA(S) plasma concentrations were determined by ELISA, whereas genotyping for rs2637125 in the S*ULT2A1* gene, coding for enzyme that catalyzes the formation of DHEAS from DHEA, was conducted using qPCR. The obtained results demonstrated beneficial effects of DHEA/S and suggested these neurosteroids as new options for the prevention and treatment of dementia. The research has been supported by CSF project IP-2019-04-6100.

S3.3

Cellular senescence from early inner ear development to age-associated hearing diseases

Isabel Varela-Nieto

Institute for Biomedical Research Alberto Sols CSIC-UAM & CIBERER-ISCIII, Madrid, Spain

Cellular senescence participates in tissue repair, cancer, aging, and embryonic morphogenesis. The embryonic development of the organs requires tissue reshaping that is highly regulated at the genetic level. During the earliest stages of otic development, the otocyst contains most of the molecular cues to form the adult inner ear. Developmental senescence is here regulated by transforming growth factor β2 and insulin-like growth factor-1 to modulate tissue remodeling and differentiation of the vertebrate inner ear. Age-related hearing loss (ARHL) is the most widespread neurodegeneration affecting the elderly population. ARHL has been associated to chronic oxidative stress in cochlear hair cells leading to loss of mitohormesis, cellular senescence and apoptosis in auditory hair cells in animal models. A role for the regulation of Nrf2 and downstream targets in cochlear cells has been proposed as central to ARHL. Finally, ageing is associated to the appearance and progression of tumors in the inner ear, specifically vestibular schwannomas that present spontaneous senescent traits, opening a window for the development of new treatments based on targeting cellular senescence.

This work was supported by PID2020-THEARPY and BenBedPhar-COST grants.

S3.4

TIME FLIES: Cellular senescence in aging CNS of Drosophila melanogaster

Manuel Collado

National Center for Biotechnology (CNB-CSIC), Campus Universidad Autónoma de Madrid, Madrid, Spain. Health Research Institute of Santiago de Compostela (IDIS), Santiago de Compostela, Spain

There is a need for in vivo models to study the contribution of cell senescence to aging and to test antiaging interventions based on the elimination of senescent cells. Models based on mice are expensive, complex and time consuming, and ethical issues represent a limitation. We think that Drosophila melanogaster could represent a cheap, simple, and short-lived alternative animal model.

Drosophila is a widely used animal model to study aging. Of all the defined aging hallmarks shared in Drosophila, cell senescence has not been studied yet. However, this process has been described after oncogene induction, chromosomal instability, and mitochondrial defects in flies. Given the conservation of this cellular response in different contexts it is tempting to speculate that cell senescence might also be involved during aging.

Our preliminary results show that it is possible to detect increased levels of SABG activity (the most widely used marker of cell senescence) in neurons of the central nervous system of old flies, both at the ganglion and the brain. These positive cells can be removed by treatment with a known senolytic compound, ABT263, reinforcing their senescent identity.

S4

Molecules, Circuits and Behaviors: The Future of Therapeutics in Substance Use Disorders

CHAIR: Kathryn A. Cunningham[1], Marco Diana[2]

[1] *Chauncey Leake Distinguished Professor Center for Addiction Research John Sealy School of Medicine University of Texas Medical Branch Galveston, Texas 77555-0615* [2] *University of Sassari, Dept Chemistry and Pharmacy, Sassari, Italy*

The United Nationals World Drug Report estimates that abused drugs account for 355 million years of "healthy" life lost due to disability and premature deaths worldwide (2022). In the U.S. alone, 107,000 people died of abused drug overdoses and over 40 million people were diagnosed with a past year substance use disorder (SUD) in 2020. The diagnosis of SUDs is based upon the primary abused drug and diagnostic criteria (DSM-5/IDC-10), including hazardous and uncontrollable substance use, withdrawal/tolerance, social/interpersonal problems use, and craving (i.e., urge to use the substance). However, each of these behavioral features of SUDs are rooted within expanding dysfunction in discrete brain circuits, indicating that distinct molecular and cellular targets regulate different aspects of SUDs. Major preclinical and clinical advances in understanding SUDs have been made, however, very few marketed medications have emerged to amplify the success of psychosocial modalities to treat SUDs. Given the growing levels of SUDs, a key goal is to maximize therapeutic options. Opioid receptor agonists (e.g., buprenorphine, methadone) are a viable option for opioid use disorder (OUD), but carry their own risk for misuse and overdose. Pharmacotherapeutics for psychostimulant (e.g., cocaine, methamphetamine) disorders are lacking and an important unmet need. The present panel will consider contemporary approaches in this arena, highlighting ongoing efforts to develop innovative therapeutics to facilitate extended recovery from opioid and psychostimulant use disorders.

Dr. Cunningham will present the scientific rationale, models, and prospects for advancing psychedelics and 5-HT2 receptor molecules for cocaine (CUD) and opioid use disorders (OUD). She will discuss progress in chemical biology, in vitro pharmacology and in vivo targeting of cocaine and opioid-related behaviors. Dr. Neumaier will explore the molecular mechanisms involved in the critical role of lateral habenula in opioid seeking and voluntary abstinence within the context of future therapeutics. Dr. Slosky will focus on pharmacologically targeting the neuropeptide neurotensin (NTS) and its high-affinity neurotensin receptor 1 (NTSR1) for CUD therapeutics. She will outline the rational for this novel target and present data to demonstrate that an allosteric β-arrestin-biased NTSR1 agonist is remarkably efficacious in suppressing cocaine intake with a limited predicted side effect profile. Dr. Fattore will demonstrate that the functional interplay between the serotonin 5-HT1A and 5-HT2B receptors controls the mesocorticolimbic system. She will introduce the concept that a unique 5-HT2B antagonist-5-HT1A agonist is a highly desirable therapeutic agent for the treatment of methamphetamine use disorder. Rafel Maldonado's talk unveiled that food addiction involves a loss of behavioral control over eating, with unknown mechanisms. Their research uncovered

similar miRNA patterns in animal and human brains, shedding light on potential contributors to this disorder. Additionally, shared gut microbiota signatures in extreme food addiction cohorts suggest prospects for innovative biomarkers and interventions.

S4.1

Mining 5-HT_{2A} and 5-HT_{2C} Receptor Ligand Discovery for Cocaine Use Disorder

Kathryn A. Cunningham,

Center for Addiction Sciences and Therapeutics and Department of Pharmacology and Toxicology; John Sealy School of Medicine, University of Texas Medical Branch, Galveston, Texas, USA

Cocaine was involved in nearly 20% of USA drug overdose deaths while ~1.4 million people reported current cocaine use disorder (CUD) in 2020. CUD is a debilitating health condition, but we lack effective pharmacotherapies to facilitate CUD recovery. The serotonin 5-HT_{2A} receptor (5-HT_{2A}R) and 5-HT_{2C}R are key modulators of meso-corticoaccumbens circuitry involved in enduring CUD relapse vulnerability. Psychedelics are 5-HT_{2A}R agonists attracting attention as potential neurotherapeutics, including for CUD. We are employing fragment-based discovery approaches to discover small molecules as positive allosteric modulators (PAMs) for the 5-HT_{2A}R or 5-HT_{2C}R as well as dual 5-HT_{2A}R/5-HT_{2C}R PAMs. We have synthesized novel chemical entities with on-target properties, acceptable pharmacokinetic and brain penetration parameters as well as negligible displacement of orthosteric sites of ~50 GPCRs and transporters. *In silico* analyses suggest binding to less conserved, extracellular sites vs. the orthosteric 5-HT site. Efficacy profiles of PAMs in unconditioned and conditioned behavior assays are consistent with more constricted agonist-like actions vs. a full orthosteric agonist. This talk will focus on serotonin target-phenotype relationships engaging mPFC circuitry and molecular targets which precipitate CUD risk, particularly engaging 5-HT_{2A}R and 5-HT_{2C}R neurobiology. The goal is to maximize efficacy of PAMs as targeted therapeutics to reduce relapse risk in CUD.

S4.2

Neurocircuit control of oral fentanyl self-administration engages a novel role for the lateral habenula: Implications for SUD therapeutics

John F. Neumaier and Kevin R. Coffey

University of Washington and Puget Sound VA Health Care System

The widespread availability of synthetic opioids has led to an epidemic of opioid abuse and overdose. Fentanyl produces rapid and intense euphoria followed by severe withdrawal and emotional distress—these synergize to promote relapse. We developed a new model of fentanyl seeking in outbred male and female rats using volitional oral self-administration that can be readily applied in labs without intravascular access. Using a traditional two lever operant procedure, rats learned to take oral fentanyl vigorously, escalated their intake across sessions, and readily reinstated responding to conditioned cues after extinction. We observed

both individual and sex differences in self-administration. During a behavioral economics task,

rats displayed classical demand curves and maintained a preferred intake across a wide range of fentanyl concentrations. Oral self-administration was also neatly patterned, with distinct "loading" and "maintenance" phases of responding within each session. Using our deep-learning software DeepSqueak, we analyzed thousands of ultrasonic vocalizations (USVs), which are innate expressions of current emotional state in rats. Rats produced 50 kHz USVs during "loading" then shifted quickly to 22 kHz calls despite ongoing "maintenance" oral fentanyl taking, reflecting a transition to a negative emotional state. Using fiber photometry, we found that the lateral habenula was differentially engaged during drug-cues and drug-consumption depending on affective state, with increased activation in response to drug cues during the negative affective maintenance phase. Together, these results indicate rapid progression from positive to negative reinforcement occurs even within an active drug taking session, revealing a within-session manifestations supporting the opponent process theory.

S4.3

β-Arrestin-biased allosteric modulators of neurotensin receptor 1 for the treatment of psychostimulant use disorders

Lauren M. Slosky

Department of Pharmacology, University of Minnesota, Minneapolis, MN, USA

Neurotensin receptor 1 (NTSR1) is an endogenous modulator of brain dopamine signaling. Small molecule NTSR1 agonists have been pursued for more than 40 years as potential therapeutics for dopamine-associated psychiatric disorders, including psychostimulant addictions. While such compounds remained elusive, characterization of NTSR1's diverse physiological effects made apparent that desired dopamine neuromodulatory action may be accompanied by unwanted effects, including hypotension and hypothermia. As a G protein-coupled receptor (GPCR), NTSR1 signals through the canonical activation of G proteins and engages β-arrestins to mediate distinct cellular signaling events. Because of the limited historical success identifying NTSR1 agonists using G protein-based screens, a collaborative effort was initiated to identify small molecule NTSR1 ligands using a β-arrestin-based screen. From this screen, and subsequent medicinal chemistry optimization, we developed a lead series of allosteric NTSR1 modulators, typified by the compound SBI-553. SBI-553 not only exhibits β-arrestin activity on its own, but also extends profound β-arrestin bias to the endogenous ligand by selectively antagonizing G protein signaling. SBI-553 is active in animal models of psychostimulant use but lacks the thermoregulatory and cardiovascular side effects characteristic of balanced NTSR1 agonism. These findings indicate that the dopamine neuromodulatory action of NTSR1 may be selectively preserved in β-arrestin biased ligands, thus providing a strategy to develop safer NTSR1-targeting anti-addiction therapeutics with more directed pharmacological action. Our research team recently developed a new lead compound from this series, a molecule termed SBI-810. SBI-810 has a

similar pharmacodynamic profile to SBI-553 but exhibits a more favorable pharmacokinetic profile in non-human primates.

S4.4

Dual 5-HT2B antagonist/5-HT1A agonist for methamphetamine use disorder

Liana Fattore

CNR Institute of Neuroscience-Cagliari, National Research Council of Italy

Methamphetamine (METH) is a potent, addictive psychostimulant and among the most extensively abused drugs worldwide, with an overwhelming majority of patients (nearly 85%) who went through rehabilitation program that reverted to abuse. Beside the mesolimbic dopaminergic system, chronic METH use significantly impacts on the brain serotonin transmission, with serotonin 5-HT_{2B} and 5-HT_{1A} subtype receptors playing crucial, although different, roles in its mechanism of action. This study tested the hypothesis that a new promising compound, DDD-024, which elicits 5-HT_{2B} antagonist and 5-HT_{1A} agonist activities simultaneously in the brain, could be effective in treating METH abuse. This talk will illustrate results from a series of studies in rats showing how DDD-024 (1-15 mg/kg, i.p.) is able to reduce (*i*) intravenous METH self-administration (i.e., drug-taking behavior), and (*ii*) drug-induced reinstatement of responding after extinction (i.e., drug-seeking behavior) in a dose-dependent and sex-specific manner. Importantly, DDD-024 (*iii*) did not affect food self-administration, which confirms its specificity of action, and did not significantly alter (*iv*) motor activity and (*v*) anxiety-like behaviors in male and female rats, thus excluding possible interfering side effects. Finally, (*vi*) DDD-024 did not sustain self-administration behavior when made available to rats, suggesting that it does not induce positive reinforcing effects and, hence, is devoid of abuse liability, at least at doses used in these studies. Altogether, results showed that this new dual serotoninergic compound is able to reduce intake of, and craving for, METH in male and female rats without inducing rewarding properties *per se* or altering significantly motor activity or anxiety states.

S5

Understanding the online and offline representation of complex stimuli: From behavioural performance to neural mechanisms.

CHAIR: Carlo Sestieri[1], Valerio Santangelo[2]

[1] *University of Chieti, Chieti, Italy*

[2] *University of Perugia, Perugia, Italy*

The last decades have seen a great improvement in our understanding of the mechanisms supporting "online" (i.e., perceptual/ attentional) and "offline" (i.e., mnemonic) representation of external stimuli. Much of the research in cognitive neuroscience relies on a reductionist approach that favors the use of simplified, artificial stimuli, emphasizing the need for experimental control over possible confounding variables. However, the human brain has evolved to make sense of a complex world and guide behavior based on multidimensional information. Accordingly, there is now a growing consensus on the necessity to use more ecological and naturalistic stimuli to better capture the functioning of these fundamental cognitive processes in real-life. At the same time, the use of novel methodological and analytic approaches allows us to study ecological brain function while maintaining experimental control. This symposium aims at providing new insights into this line of research, presenting recent findings from behavioral and neuroimaging experiments that make use of complex stimuli, from everyday life pictures and videos to cinematographic movies and virtual reality, to unravel the cognitive processes and the neural underpinnings involved in the online and offline representation of ecological stimuli.
Specifically, in this symposium will be presented: neuropsychological studies concerning the assessment of episodic and prospective memory in cognitive and pathological aging using virtual reality (Valentina La Corte); data on the impact of editing on time perception for movie scenes (Marco Sperduti); data on the cognitive mechanisms supporting temporal memory for movie scenes (Carlo Sestieri); data on the representation of perceptual saliency of task-relevant objects in complex visual scenes (Valerio Santangelo).

S5.1
Memory retrieval after the encoding of complex and naturalistic episodes

Emiliano Macaluso

Université Claude Bernard Lyon 1, Centre de Recherche en Neurosciences de Lyon, Bron, France

Rich contextual associations characterize episodic memory, but the majority of the paradigms that are routinely used to investigate this fundamental brain function still rely on relatively simple and stereotyped conditions. Here, I will present human behavioral and imaging studies that targeted the multi-dimensional nature of episodic memory following encoding in naturalistic contexts (i.e. commercial movies, large scale virtual environments and encoding in the real world using a dedicated mobile-phone application). The imaging results showed that, together with classical memory-related regions in the medial temporal and medial prefrontal cortex, the precuneus plays a key role during the retrieval of memories with episodic characteristics. Analyses of effective connectivity highlighted that the interaction between the precuneus and the medial temporal cortex specifically supports this type of memories. Behavioral data using mobile-phones in the real world confirmed the importance of contextual information for episodic retrieval, even when the events are encoded within vast

spatio-temporal contexts. Overall, the results fit with the proposal that the medial parietal cortex instantiates situational models coding for prior personal experiences and provide us with a new perspective about the functioning of memory in naturalistic, life-like conditions.

S5.2

The impact of editing on time perception for movie scenes

Klara Kovarski[1] & Marco Sperduti[2]

[1]LaPsyDÉ, Université Paris Cité, CNRS, Paris, France, [2]Laboratoire Mémoire, Cerveau and Cognition, (LMC2 UPR 7536), Université Paris Cité, 92100 Boulogne-Billancourt, France

Filmmakers use different techniques (e.g., camera movements, editing) to shape viewers' experience. In particular, editing can be used to handle the temporal unfolding of events represented in a movie. Nevertheless, little is known about how different editing types impact viewers' time perception. We tested this question in two studies. The firs study was conducted on-line on 90 volunteers. The second study was a pre-registered conceptual replication study conducted in an experimental setting on 60 participants. We asked participants to judge (Study 1) or reproduce (Study 2) the duration of a movie excerpts containing either continuous editing, action discontinuity editing or no editing. In both studies, we reported that scenes containing continuous editing were perceived as longer than the other two scene types. Moreover, scenes containing action discontinuity editing were perceived as longer than scenes with no editing. Our contribution adds information on how different types of events (visual continuous or discontinuous cut) modulate time perception and gives important insight on how studying movie editing could be pertinent for our understanding of time perception in real life. Moreover, the present findings are of interest to better apprehend how film editing, and in general cinema formalisms (camera movements etc.), influences time perception by providing valuable clues as to how time perception is impacted by natural phenomena producing similar visual consequences (e.g. eye movements, blinks). We will discuss our results in light of recent proposals suggesting that tracking changes in low-level perceptual processing provides a basis for human time perception.

S5.3

The temporal representation of complex narratives.

Carlo Sestieri*, Matteo Frisoni*, Monica Di Ghionno*, Federica Procida*, Annalisa Tosoni*

** Department of Neuroscience, Imaging and Clinical Sciences & ITAB Institute for Advanced Biomedical Technologies, University G. d'Annunzio of Chieti-Pescara, Via dei Vestini 31, 66100 Chieti, Italy*

Remembering when events took place is crucial to episodic memory. In a series of studies, we used complex audio-visual material and a sensitive measure of temporal memory precision to investigate the temporal representations of past events. Participants indicated the position

of short video clips extracted from a previously encoded movie on a visual analog scale representing the movie duration. We found that memory for time performance reflects the use of a general narrative template. For example, removing different parts from the movie resulted in a systematic under- or over-estimation of the clip's position, as if participants made room for missing information. These findings are consistent with a reconstructive account of temporal memory based on an automatic adaption of narrative time to a standard template. Direct support for the reconstruction hypothesis comes by temporally scrambling the narrative at encoding. In this condition, temporal judgments are systematically distorted as a function of direction/amount of discrepancy between story and viewing time, consistent with a spontaneous chronological reorganization of the encoded material. We further demonstrate that participants can gradually build an effective temporal representation of a narrative also from sparse inputs by exploiting chronologically, but not randomly, arranged cues. Finally, we demonstrate that temporal memory precision is associated with oscillatory neural activity in high-beta/low-gamma frequency. Crucially, this activity appears to encode a temporal representation of the event, as suggested by the significant correlation between indices of behavioral and neural distance. We conclude by highlighting the importance of cinematic experience for the study of human memory.

S5.4
The representation of saliency in complex visual scenes and cinematographic movies

Valerio Santangelo

Department of Philosophy, Social Sciences & Education, University of Perugia, Italy
Functional Neuroimaging Laboratory, IRCCS Santa Lucia Foundation, Rome, Italy

Elaboration of “salient” stimuli is typically prioritized among concurrent stimuli that compete for processing resources. In two fMRI studies, we investigated the brain representation of saliency. In Study 1, we used multivoxel pattern analysis (MVPA) to investigate whether a neural signature of perceptual-related salience (PRS; defined as local discontinuity in line orientation, intensity contrast, and colour opponency) is detectable in key regions involved with visual object processing, namely, the lateral occipital cortex (LOC), the fusiform gyrus (FG), and the primary visual cortex (V1). Two categories of objects were embedded in real-world scenes, located either at the point of maximal or minimal salience. We presented sequences of scenes, and participants were asked to perform a 1-back task to ensure attention to the task-relevant object category. MVPA revealed distinguishable patterns of brain activity for maximal vs. minimal salience in the LOC, but not in the FG and V1 (where only the task-relevant category was decodable), supporting a LOC specialization of representing PRS of attended objects in complex scenes. In Study 2, we computed both PRS and semantics-related salience (SRS; i.e., the variation of interesting/meaningful points in movie scenes) of cinematographic movies, and used these parameters to model BOLD signals and time-varying measures of network centrality related to movie watching. SRS signals were found to overcome PRS signals in predicting activity and network centrality measures in

sensory- and attention-related regions. Overall, the findings of both studies contribute to characterize the functioning of perceptual and attentional mechanisms using highly complex and ecological material.

S6

Neurotransmitter dynamics and actions in neuro-astroglial networks

CHAIR: Dmitri Rusakov

UCL Queen Square Institute of Neurology, University College London

The symposium will focus on the cellular and molecular mechanisms underpinning homeostasis, release, and receptor actions of neurotransmitters and neuromodulators among the interacting cellular networks of brain neurons and astrocytes. The presented findings will also illustrate how these mechanisms could contribute to pathological changes in the brain and affect the traits of animal behaviour. Dr Navarrete will describe their recent experiments unveiling the pathways-specific signalling between glutamatergic circuits and astrocytes using a battery of newly developed methods pertaining to calcium-sensitive photoactivatable ratiometric imaging. Mr Odii will present and discuss his data, revealing spatial juxtaposition of synaptic proteins (Bassoon, Homer1, PSD95, VGLUT) and astroglial signalling molecules in the contiguous microscopic environment of excitatory and inhibitory synapses, by using 3D multi-colour super-resolution (stochastic localisation) microscopy imaging. Prof Zorec will describe their recent multi-disciplinary experiments that employ new methods of high-resolution recording, to show how the noradrenergic receptor signalling regulates the dynamics of vesicular exocytosis in reactive brain astrocytes. Dr Rouach will present evidence that connexin-30 dependent morphological plasticity of astrocytes regulates the level of oxytocin and thus modulates interaction of adult females with pups, thus unveiling an important mechanism contributing to maternal behaviour. Prof Rusakov will focus on the role of volume transmitted extracellular waves of the inhibitory neurotransmitter GABA in pacing neural network rhythms in the hippocampus, in particular during epileptiform activity, as uncovered by combining sniffer patch and multiple-cell recordings, neural network modelling, and a newly developed genetically encoded GABA sensor. The speakers come from a diverse community of neuroscientists, across the various levels of academic seniority, and will present and discuss their published as well as unpublished findings.

S6.1
Catching Neuron-Astrocyte Ensembles

Marta Navarrete

Cajal Institute, CSIC Madrid, Spain

To understand how complex cell circuits process information, it is necessary to use techniques that can precisely target and modulate the activity of the involved elements. Neuro-astrocyte networks are highly complex, and understanding their involvement in circuit modulation and behavior requires state-of-the-art complementary tools. Although most genetic tools have focused on neuronal activity, my talk will introduce adapted tools that can dissect active astrocyte circuits with spatio-temporal precision, such as CaMPARI$_{GFAP}$ and Astro-Light. Additionally, I will present our recent data on mapping the functional astrocytic circuitries in the Nucleus Accumbens (NAc), which reveal the existence of specific astrocyte circuits in this region. Finally, we will show that activating the astrocyte ensemble related to a specific reward can shift behavior towards that option through optogenetic stimulation. Overall, the cutting-edge data I will present supports the idea that NAc astrocytic networks play a critical role in integrating information.

S6.2
Vesicle dynamics in reactive astrocytes

Robert Zorec

University of Ljubljana, Medical Faculty, Ljubljana, Slovenia

Astrocytes are neuroglial cells that maintain homeostasis in the central nervous system (CNS). This involves the release of chemical messengers by exocytosis, a universal process of eukaryotic cells, consisting of the merger between the vesicle membrane and the plasmalemma, playing a key role in cell-to-cell communication, through the release of transmitters. There are a number of barriers a vesicle needs to pass to discharge vesicle content to the extracellular space. At the pre-fusion site vesicles need to be transported to the sites on the plasmalemma where the merger may begin. Cytoskeleton was considered an important barrier and was thought to be disintegrated to allow vesicle access to the plasmalemma [1]. However, later cytoskeletal elements were considered to promote the vesicle merger with the plasmalemma and fusion-pore expansion [2]. In reactive astrocytes, which are undergoing morphological, molecular, and functional remodeling in response to pathologic events, revealed an overexpression of cytoskeletal nanofilaments [3], shown to affect vesicle delivery to the plasmalemma [4]. In addition to the cytoskeleton as a barrier to

vesicle content discharge, recent studies indicated that vesicle cholesterol accumulation during ageing [5] and disease [6] may affect the release of
transmitters and altering the astrocyte homeostatic functions.

1. *Aunis & Bader; J Exp Biol, 1988.**139**:253.*
2. *Burgoyne & Morgan; Physiol Rev, 2003.**83**(2):58.*
3. *Escartin, et al., Nat Neurosci, 2021.**24**(3):312-325.*
4. *Vardjan, et al., J Neuroinflammation, 2012.**9**:144.*
5. *Roh, et al., Nat Metab, 2023.**5**(3):398.*
6. *Rituper, et al., Cell Calcium, 2022.**101**:102503.*

S6.3
A neuroglial circuit for maternal behavior

Grégory Ghézali, Julien Moulard, Isabelle Arnoux, Astrid Rollenhagen, Carl Meinung, Nadia De Mota, Pascal Ezan, Anthony Laugeray, Vidian de Concini, Alexis Bemelmans, Inga Neumann, Arnaud Menuet, Catherine Llorens-Cortes, Joachim HR Lübke, Nathalie Rouach

Center for Interdisciplinary Research in Biology, Collège de France, CNRS, INSERM, Labex Memolife, Université PSL, Paris, France

The hypothalamic supraoptic nucleus is a unique brain region where neurons release neuropeptide hormones such as oxytocin and is characterized by a strong structural neuroglia plasticity occurring during physiological processes. Oxytocin has a role in a number of functions and behaviors, including reproductive and osmoregulatory functions, cognition and social behavior. However there is still limited evidence supporting a role for astrocytes in the neuroendocrine control of social behaviors. Here I will show that astrocytes contribute to maternal behavior via a mechanism controlling structural plasticity of neuroglial interactions in the supraoptic nucleus and oxytocin levels.

S6.4
Brian rhythm regulation by extracellular GABA waves

Dmitri A. Rusakov

UCL Queen Square Institute of Neurology, University College London

The knowledge of network mechanisms that pace cyclical brain activity is particularly important for understanding the machinery of rhythmic epileptiform discharges. Such rhythms have traditionally been considered as the result of interneuronal network activity driven by synaptic GABAergic connections. However, intense firing of interneurons could also elevate the concentration of extracellular GABA over relatively large tissues volumes. The latter would transiently increases tonic conductance of GABA receptors thus altering the excitability of multiple cells that are not necessarily connected synaptically, with the underlying dynamics remaining poorly understood. We employed a patch-clamp GABA

'sniffer' and a novel optical GABA sensor iGABASnFR2 to monitor extracellular GABA in slices of the mouse hippocampus during periodic epileptiform discharges. We found that such discharges were preceded by the transient waves of extracellular GABA, suggesting a cycle of GABA-driven network inhibition and disinhibition. High-resolution imaging of astroglia-expressed iGABASnFR2 has revealed that cyclic GABA elevations were spatially heterogeneous on the scale of several microns. Finally, weakening GABA uptake could slow down extracellular GABA fluctuations, which in turn decelerated rhythmic electrical activity. Thus, the extracellular dynamics of extrasynaptic, volume-transmitted GABA appears to play a key role in pacing rhythmic activity in brain networks.

S7 *New insights in Parkinson's disease and other motor disorders*

CHAIRS: **Leonidas Stefanis (GR), Rosario Moratalla (ES)**

This symposium, titled "New Insights in Parkinson's Disease and Other Motor Disorders," brings together leading experts in the field to present groundbreaking research shedding light on various aspects of Parkinson's disease and related motor disorders. The symposium features four distinct presentations, each offering unique insights into the pathogenesis, treatment, and associated factors of these conditions.

1. Antibiotic-Induced Leaky Gut Syndrome Promotes Parkinsonism in Mice: Protective Effects of Rifaximin

Presented by Aurora Zilli, et al. This presentation explores the connection between antibiotic-induced leaky gut syndrome and the development of Parkinsonism in mice. Researchers investigate the potential role of Rifaximin, a non-absorbable antibiotic known for its impact on intestinal dysbiosis, in preventing gut permeability alterations and colonic mucosal damage. Their findings suggest that Rifaximin may have protective effects on PD-related neuropathological changes, highlighting its potential as a therapeutic tool for PD patients.

2. Gut Microbiota Dysbiosis in Parkinson's Disease Patients: Not Only an Early Feature but a Potential Biomarker of Disease Severity and Progression

Presented by Alessandro Stefani, et al. This presentation examines gut microbiota alterations in Parkinson's disease patients throughout the course of the disease. The research compares microbiota composition among different stages of PD and identifies progressive changes in microbial diversity and the prevalence of pro-inflammatory families. The findings suggest that gut microbiota dysbiosis may serve as a biomarker for disease progression and prognosis.

3. The Origin of Comorbid Anxiety and Depression in Parkinson's Disease

Presented by Rosario Moratalla, et al. This presentation focuses on unraveling the origin of comorbid anxiety and depression in Parkinson's disease. Using a mouse model, the researchers investigate the involvement of specific neuronal populations, such as the dorsal

raphe and locus coeruleus, in the emotional symptoms that often precede motor impairment in PD patients. Their findings establish a causal link between alpha-synuclein accumulation in these neurons and emotional symptoms, providing valuable insights into the early stages of Parkinson's disease.

4. Wireless Deep Brain Stimulation in Freely Moving Mice with Nonresonant Powering of Magnetoelectric Nanoparticles. Presented by Ali Jahanshahi, et al. This presentation delves into the development of injectable, magnetoelectric nanoelectrodes that wirelessly transmit electrical signals to the brain in response to an external magnetic field. Unlike traditional DBS approaches, this wireless method does not require genetic modification of neural tissue and allows for free movement during stimulation. The research demonstrates its potential for modulating deep brain targets and influencing behavior in mice, highlighting its promise as a less invasive neural modulation technique.

Together, these presentations provide a comprehensive overview of the latest advancements in Parkinson's disease research, showcasing innovative approaches to treatment, the role of gut microbiota, and the origins of emotional comorbidities associated with the disease. This symposium promises to provide attendees with a deeper understanding of these complex motor disorders and their underlying mechanisms.

S7.1

Antibiotic-induced leaky gut syndrome promotes parkinsonism in mice: protective effects of Rifaximin.

Aurora Zilli [1], Alessandro Del Re[1], Irene Palenca[1], Silvia B. Franzin[1], Giuseppe Esposito [1], Luisa Seguella[1]

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Parkinson’s disease (PD) is the second most common neurodegenerative disorder of aging characterized by dopaminergic neurons dead in the substantia nigra and altered α-synuclein (α-syn) aggregation. Aggregates of misfolded α-syn are also detected outside the central nervous system (CNS) within the submucosal (SMP) and myenteric plexus (MP) of the enteric nervous system (ENS) in pre-motor stage of the disease. This is associated with gastrointestinal dysfunction and intestinal hyperpermeability (leaky-gut syndrome) in PD patients that precede motor symptoms onset by years. Leaky-gut syndrome might promote a pro-inflammatory/oxidative milieu within the ENS and lead to enteric glial activation. Enteric glia modulates the intestinal homeostasis and respond to any perturbation of it. Our prelimary data display that glia derived from myenteric plexuses increase their expression of S100β and GFAP following α-syn fibrils exposure, suggesting potential glial involvement in PD-related neuropathology. We tested whether leaky-gut syndrome elicits PD-like motor dysfunction and neuropathological changes within the ENS and their prevenction by Rifaximin treatment. Rifaximin, a non-adsorbable antibiotic, clinically used to ameliorate intestinal dysbiosis has been identified as a powerful anti-leaky gut compound. Our results showed how

Rifaximin prevents intestinal permeability alterations and colonic mucosal damage induced by antibiotic treatment in mice. Showed effectiveness to prevent the occurrence of PD-related neuropathological changes (i.e. upregulation of LRRK-2 and α-syn) in SNE, probably by preventing the passage of luminal noxiae at the tissue level. Rifaximin increased motor coordination performances (RotaRod and pole test) in antibiotic-treated mice, self-candidating as a possible pharmacological tool impacting PD course even in humans.

S7.2

Gut microbiota dysbiosis in Parkinson's disease patients: not only an early feature but a potential biomarker of disease severity and progression.

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Objective: To investigate gut microbiota alterations in Parkinson's disease (PD) along disease progression.

Background: Gut microbiota dysbiosis is an hallmark in PD1. However, it is unclear whether microbiota alterations represent a pathogenetic starting point or also a consequence of disease2 Methods: At first, we compared fecal samples from 3 groups: de novo PD patients (dnPD); advanced PD(advPD), defined by H&Y stage≥3 and healthy controls (HC, cohabitants). The second research line followed longitudinally a cohort of dnPD for 2 years, divided into 2 groups: the "eubiotics" group and the "dysbiotics" one.

Microbiota compositions was studied through 16rRNA amplicon sequencing and classified to taxonomic rank through bioinformatic analysis. Results: In the transactional study, we compared samples from 30 dnPD, 38 advPD and 79 HC,observing a progressive reduction both in alfa and beta diversity moving. A progressive reduction in Bacteroidaceae, Lacnospiraceae, Family XIII, Prevotellaceae, Ruminococcaceae, Rikenellaceae families (from HC to dnPD and to advanced PD) was observed; whilst a reverse trend occurred for Enterobacteriaceae and Lactobacillaceae families. Consistently with genera, Roseburia, Lacnospira, Butyricicoccus, Faecalibacterium genus decreased moving from HC to dnPD and to advPD and a reverse trend in Lactobacillus genus. In the longitudinal study, patients belonging to the "dysbiotic" group showed a faster disease progression.

Conclusions: According to our results, the progression of the PD correlates, regarding gut microbiota with: progressive impoverishment of biodiversity, loss of homeostatic taxa and prevalence of pro-inflammatory Families. Dysbiosis of gut microbiota, in PD, may represent a biomarker of disease progression and a negative prognostic factor.

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S7.3
The origin of comorbid anxiety and depression in Parkinson's disease

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Parkinson's disease is a progressive neurodegenerative disorder whose symptoms appear in a longitudinal temporal pattern along the neuropathological burden. Preceding motor impairment, most patients suffer anxiety/depression, the most common and disabling emotional comorbidities. Although their anatomical bases are not well established, some studies point out that the locus coeruleus and the dorsal raphe nucleus are affected at early parkinsonian stages, when these symptoms appear.

To determine the involvement of the dorsal raphe and locus coeruleus in these emotional comorbidities, we use a mouse model that specifically accumulates pathologic human alpha-synuclein under the TH promoter in dopamine and norepinephrine neurons. We tested for emotional signs, along with histological, electrophysiological, functional, and molecular approaches to identify the neuronal populations involved.

We show for the first time that alpha-synuclein accumulation in the dorsal raphe dopamine neurons or in the locus coeruleus norepinephrine neurons alters catecholamine signaling on the target areas, bed nucleus of stria terminalis (BNST) and central amygdala (CeA) and reduces general dorsal raphe activity, causally linking these neuronal dysfunctions with the emotional symptoms present at early stages of Parkinson's disease.

Key Words: Parkinson's disease, anxiety, depression, dopamine, serotonin, dorsal raphe-nucleus.

S7.4

Wireless deep brain stimulation in freely moving mice with nonresonant powering of magnetoelectric nanoparticles

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Key words: Magnetoelectric Nanoparticles; Deep Brain Stimulation; Wireless

Devices that electrically modulate the deep brain have enabled important breakthroughs in the management of neurological and psychiatric disorders. Such devices are typically centimeter-scale, requiring surgical implantation and wired-in powering, which increases the risk of hemorrhage, infection, and damage during daily activity. Recently, several remotely powered devices have emerged that could enable less invasive neuromodulation. The most clinically promising of these do not rely on transgenesis of neural tissue, but instead directly create electric signals to achieve neuromodulation. However, it has not yet been possible to scale down such devices sufficiently to enable complete implantation in the brain while still achieving deep-brain neuromodulation. Herein, we present injectable, magnetoelectric nanoelectrodes that wirelessly transmit electrical signals to the brain in response to an external magnetic field. Importantly, this mechanism of modulation requires no genetic modification of neural tissue and allows animals to freely move during stimulation. Using these nanoelectrodes, we demonstrate neuronal modulation in vitro and in deep brain targets in vivo. We also show that local thalamic modulation promotes modulation in other regions connected via basal ganglia circuitry, leading to behavioral changes in mice. This work demonstrates the potential of magnetoelectric materials as nanoelectrodes for wireless electrical modulation of deep brain targets. Herein, we have shown that we can stimulate Magnetoelectric Nanoparticles (MENPs) with a magnetic field to remotely generate electric polarization of the MENPs. We have shown evidence that non-resonant frequency magnetic stimulation of MENPs locally modulates neuronal activity in vitro and in vivo. We have also demonstrated that this modulation is sufficient to change animal behavior and to modulate other regions of the cortico-basal ganglia-thalamo-cortical circuit. Future work will be key to optimizing magnetoelectricity based neural devices and understanding the abilities and limitations of this technology. Magnetoelectric materials present a versatile platform technology for less invasive, deep brain neuromodulation.

S7.5

The application of magnetic nanodiscs for neuromodulation.

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Deep brain stimulation (DBS) is a neurosurgical technique based on electrodes' stereotactic implantation, delivering current in specific subcortical structures. It is usually indicated to decrease symptoms in neurological disorders, such as Parkinson's disease. The reversibility of DBS supports its ethical status, and in patients with severe debilitating diseases who are resistant to medical and psychotherapeutic treatment, DBS can offer symptomatic relief. Despite its significant benefits, however, DBS technology has seen limited advancements. It necessitates wired and long-term implants and requires battery replacement surgeries. As a result, many patients are reluctant to undergo DBS when surgery is warranted.

Researchers have explored minimally invasive and wireless neuromodulation techniques using nanotechnology for these reasons. One approach explores magnetothermal DBS, employing magnetic nanoparticles and alternating magnetic fields (AMF) to excite neurons through heat. While promising in mouse models, this method requires complex power electronics, offers limited temporal precision, and raises concerns about prolonged neuronal heating.

Our study investigates magnetomechanical DBS as an alternative. It employs anisotropic magnetic nanodiscs in low-magnitude AMFs, using less complex equipment. These nanodiscs convert magnetic energy into mechanical energy, activating mechanosensitive proteins like PIEZO1. We aim to establish proof of concept for magnetomechanical DBS as a wireless alternative to traditional DBS, potentially making treatment more accessible to a broader range of patients.

S8

Emerging trends in New Psychoactive Substances (NPS): From preclinical evidence to clinical perspectives.

CHAIR: Matteo Marti[1], Liana Fattore[2]

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The symposium "Emerging Trends in New Psychoactive Substances (NPS): From Preclinical Evidences to Clinical Perspectives" brings together a multidisciplinary group of researchers to delve into the latest insights surrounding the use of New Psychoactive Substances (NPS). These substances, often found in synthetic forms, have become a pressing concern in the realm of public health due to their unpredictable effects and potential risks. The symposium explores four distinct facets of this complex issue through a range of research endeavors.

Abstract 1: Cognitive, Psychomotor, and Psychotomimetic Effects of a Synthetic Cannabinoid

Dr. Eef Lien Theunissen from the Faculty of Psychology at the University of Maastricht, Netherlands, presents findings on the acute effects of JWH-018, a synthetic cannabinoid with potency exceeding that of natural cannabis. Through placebo-controlled studies on cannabis-experienced individuals, the research uncovers the detrimental cognitive, psychomotor, and psychotomimetic effects of JWH-018 inhalation. These results underscore the grave public health risks associated with synthetic cannabinoids.

Abstract 2: Treatment with 3,4-Methylenedioxypyrovalerone (MDPV) during Infancy and Its Impact on Adult Cognitive Function

A team led by Katarzyna Kuczyńska at the Medical University of Lodz, Poland, investigates the long-term consequences of exposing mice to 3,4-Methylenedioxypyrovalerone (MDPV) during their developmental stages. The study reveals sex- and dose-dependent impairments in spatial working memory and novel object recognition in adult mice exposed to MDPV during infancy. This research highlights the need for a comprehensive understanding of the enduring effects of NPS exposure.

Abstract 3: Pharmacological Characterization of Novel Synthetic Opioids and Sex Differences

Researchers led by Sabrine Bilel at the University of Ferrara, Italy, delve into the pharmacodynamic profiles of two fentanyl analogues, Butyrylfentanyl (BUF) and 4-Fluoro-Butyrylfentanyl (4-FBUF). Using in vitro, in silico, and in vivo methods, the study elucidates the opioid receptor efficacy, toxicity, and cardiotoxicity of these substances. Notably, the research uncovers sex differences in the cardio-

respiratory impairments induced by these synthetic opioids, emphasizing the importance of gender-specific considerations.

Abstract 4: Enhancing the Antidepressant Effect of Ketamine via Alternative Routes of Administration

Dr. Gunes Unal from Boğaziçi University, Turkey, explores the novel application of ketamine, a non-competitive NMDAR antagonist, in the treatment of depressive disorders. The study demonstrates the antidepressant effects of ketamine through alternative routes of administration, such as oral and transdermal delivery, offering insights into the potential for extended therapeutic effects with minimized side effects. This research highlights innovative approaches to managing depressive disorders beyond traditional monoaminergic antidepressants.

In summation, this symposium offers a comprehensive view of the NPS landscape. It reveals the acute risks associated with synthetic cannabinoids, the lasting cognitive impacts of early NPS exposure, the pharmacological profiles of synthetic opioids with attention to gender-specific effects, and innovative methods for optimizing the therapeutic potential of ketamine. These insights collectively contribute to a better understanding of NPS and inform strategies for mitigating their harm and advancing clinical care.

S8.1
Cognitive, psychomotor and psychotomimetic effects of a synthetic cannabinoid

Eef Lien Theunissen

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For over a decade, synthetic cannabinoids (SCs) have been used recreationally, yet placebo-controlled studies examining their effects are scarce. SCs, such as JWH-018, have a much higher potency than natural cannabis and are associated with an increased risk for adverse events. We aimed to investigate the acute effects of low doses of JWH-018 on cognition, psychomotor performance, and subjective responses.

Three placebo-controlled, within-subjects studies were performed in healthy cannabis-experienced volunteers. Participants inhaled the vapor of 2 and 3 mg of JWH-018 (study 1), 75µg JWH-018/kg bodyweight (study 2), and 75µg JWH-018/kg bodyweight plus a booster dose on an as-needed basis to reach a minimum level of intoxication (study 3). Participants were monitored for at least 4,5 hours, while psychomotor, cognitive, and subjective effects were measured. This included measures for eye-hand coordination, divided attention, and inhibition. Subjective experiences such as the subjective high, dissociative states (CADSS), psychedelic symptoms (Bowdle), mood (POMS), and cannabis reinforcement (SCRQ) were also evaluated.

The inhalation of JWH-018 resulted in impaired performance on tracking, divided attention, inhibition tasks, despite a sometimes suboptimal drug administration. JWH-018 caused psychedelic and dissociative effects and induced feelings of confusion. Additionally,

participants with high levels of subjective intoxication exhibited the most pronounced impairment and psychedelic effects.

These findings demonstrate that a low dose of JWH-018 induces pronounced psychotomimetic symptoms and causes acute cognitive and psychomotor impairment in healthy participants. Therefore, it is concluded that intoxication with SCs poses a severe risk to public health.

S8.2

Treatment with 3,4-methylenedioxypyrovalerone (MDPV) during infancy results in dose- and sex- dependent impairment of spatial working memory and novel object recognition in adult mice

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During recent years we have witnessed emergence and raise of prevalence of New Psychoactive Substances (NPS). Synthetic cathinones (SC) are one of the most prominent groups of NPS. They mimic properties of old psychostimulant drugs, such as cocaine or methamphetamine. 3,4-Methylenedioxypyrovalerone (MDPV) is an example of SC, which due to its high potency at inhibition of reuptake of dopamine and norepinephrine produces strong psychostimulant effects in humans and laboratory animals. Apart from numerous studies on acute effects and addictive properties of MDPV, little is known about its long-term harms. To assess the effects of MDPV exposure on the developing brain, we treated male and female C57BL/6J mice with MDPV and bromodeoxyuridine (BrDU) between postnatal days 11 and 20, which is a period of development of hippocampus. At 12 weeks of age mice were examined using a battery of behavioral tests measuring different types of memory. Afterwards the animals were sacrificed and their hippocampi were isolated for assessment of protein expression using Western blot and for detection of BrDU using immunohistochemistry. Exposure to MDPV caused sex- and dose- dependent impairment of spatial working memory measured with Y-maze spontaneous alternation test and of novel object recognition. However, no impairment in hippocampus-dependent spatial learning and memory were detected using Morris water maze paradigm. Similarly, we did not detect impairment of hippocampal neurogenesis nor expression of synaptic proteins: synaptophysinand PSD95. In conclusion, administration of MDPV to growing mice resulted in persistent cognitive impairments, but they were not related to disruption of hippocampal development.

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S8.3

In silico, in vitro and in vivo pharmacological characterization of emerging novel synthetic opioids: focus on sex differences.

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Novel Synthetic Opioids, in particulars fentanyl derivatives (FENS), have been implicated in many cases of intoxication and death with overdose worldwide. The aim of this study is to investigate the pharmaco-dynamic profiles of two fentanyl (FENT) analogues: Butyrylfentanyl (BUF) and 4-Fluoro-Butyrylfentanyl (4-FBUF). *In vitro*, we measured FENS opioid receptor efficacy, potency, and selectivity and their capability to promote the interaction of the mu receptor with G protein and β-arrestin 2. *In silico*, we evaluated the ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) profiles of BUF and 4-FBUF. *In vivo*, we evaluated the cardio-respiratory changes using the Electrocardiography (ECG) and plethysmography in female and male mice injected with BUF or 4F-BUF (0.1-6 mg.kg i.p.). Opioid receptor specificity was investigated using naloxone (NLX; 6 mg/kg i.p.) pre-treatment. Moreover, we investigated the possible role of stress in increasing cardiotoxicity in mice using the CRF-1 antagonist Antalarmin (10 mg/kg). In vitro, FENT, BUF and 4F-BUF mimicked the maximal effects of dermorphin displaying the following rank of potency: FENT= 4-FBUF> BUF. 4-FBUF displayed lower maximal effects behaving as a partial agonist. FENT and BUF behaved as partial agonists for the β-arrestin 2 pathway, whereas 4-FBUF did not promote β-arrestin 2 recruitment. *In silico* ADMET prediction revealed higher toxicity risk of 4F-BUF respect to BUF. *In vivo*, our results revealed sex difference in the cardio-respiratory impairments inducedby BUF and 4-FBUF. The pre-treatment with NLX partially reduced the cardio-respiratory impairments while the pre-treatment with NLX in combination with Antalarmin totally prevented the impairments induced by BUF and 4-FBUF. These findings reveal the risks associated with the use of FENS and the importance of studying the pharmaco-dynamic properties of these drugs considering sex differences. Moreover, our study shed light on the role of stress in potentiating the toxic effects of opioids.

S8.4

Enhancing the Antidepressant Effect of Ketamine via Alternative Routes of Administration

Gunes Unal

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Pharmacological treatment of depressive disorders has traditionally been based on drugs that target monoaminergic systems. Relatively delayed onset and limited efficacy of these monoaminergic antidepressants gave rise to development of *atypical antidepressants* that exert their effects via other neurochemicals. The antidepressant use of ketamine, a non-competitive NMDAR antagonist that blocks the transmembrane ion channel of the receptor, attracted attention due to its fast onset. Intravenous (IV) administration of racemic ketamine and intranasal esketamine proved effective in depressed patients with suicidal thoughts as well as those with treatment-resistant depression. Ketamine, through its different mechanisms of action, leads to diverse cognitive and behavioral effects in a dose-dependent manner. Alternative routes of ketamine administration have been tested to extend its therapeutic effects while minimizing cognitive side effects. We have shown that *ad libitum* administration of oral ketamine in Wistar rats produced antidepressant effects in the forced swim test without altering general locomotor activity or impairing working memory performance. Sustained administration of oral ketamine also prevented anhedonia assessed by the sucrose consumption test. We repeated the therapeutic effects of low-dose oral ketamine in a novel transdermal application. A shea butter-based 5% (w/w) ketamine ointment applied to the dorsal skin of rats prior to forced swim test led to an antidepressant-like behavior compared to a drug-free vehicle. These findings show that the ameliorative effects of ketamine or its enantiomers are not restricted to acute IV injections at high doses, but extends to sustained delivery of seemingly subtherapeutic doses via alternative methods.

S9

The role of the amygdala in modulating negatively and positively valenced states

CHAIR: Andrew Holmes[1], Maria Morena[2]

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The amygdala is a primary hub in the brain that receives and processes sensory information, and through communication with different brain structures ascribes valence to external stimuli and drives behavior. As such, the amygdala is activated by stress, identifies threatening and rewarding stimuli, and plays a critical role in the regulation of aversive memory and reward processing. A compelling body of clinical evidence implicates the amygdala in disorders ranging from anxiety to post-traumatic stress disorder, to substance use disorders.

Recent advances in the field have provided a deeper understanding of the neural circuits and signal molecules subserving the regulation of these processes.

This symposium will bring together leading experts in the field to provide novel evidence on how the amygdala regulates negative and positive valenced states in both physiological and pathological processes spanning multiple levels of neural organization, from molecular and cellular mechanisms at one end, to circuits, networks, behavior, and disease at the other. Dr. Balleine will discuss the mechanisms by which the amygdala regulates neural plasticity in the striatum. Dr. Vozella will present data on how endocannabinoid signaling in the amygdala regulates stress and alcohol drinking behavior. Dr. Morena will discuss the neurobiological mechanisms by which the amygdala regulates the impact of stress on fear memory extinction and generalization. Dr. Herry will present novel data on neural circuitry involved in the prefrontal cortex-amygdala regulation of fear. Dr. Holmes will discuss the involvement of amygdala astrocytes in the regulation of fear memory dynamics.

The amygdala is recognized as a central node within brain systems subserving an array of higher-order behaviors that are disturbed in various mental disorders. This symposium will provide new insights on how the amygdala regulates positive and negative emotional behavior and provide future direction for research in this field and potential implications for the treatment of psychiatric disorders, such as stress- and trauma-related disorders and addiction.

S9.1

Amygdala-cortical control of striatal plasticity

Bernard W. Balleine

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The amygdala has been found to play an essential role in striatal function both via its direct connections and indirectly through its contribution to two distinct circuits involving midbrain- and prefrontocortical-striatal projections. Interestingly, whereas the former midbrain circuit appears to regulate general reward predictions and reinforcement processes, the latter prefrontal circuit has been associated with the influence of the sensory-specific features of reward on goal-directed action. Here I present recent data from experiments examining the role of this amygdala-cortico-striatal circuit in the learning and performance of goal-directed actions; specifically, in: (i) the plasticity in dorsal striatum supporting goal-directed learning; and (ii) the selection and performance of actions driven by stimuli associated with the outcomes of specific actions.

S9.2

Role of endocannabinoids in the amygdala control of stress and alcohol drinking

Valentina Vozella

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Chronic stress during adolescence increases the susceptibility to many neuropsychiatric diseases in adulthood, including anxiety-like and alcohol drinking behaviors. Social isolation is a profound stressor with increasing human relevance, especially during the COVID-19 pandemic, when millions of adolescents faced prolonged periods of isolation. The central nucleus of the amygdala (CeA) is activated by stress and its dysfunction is implicated in anxiety, chronic stress, and alcohol use disorder. The endocannabinoid system is abundantly expressed in the CeA, a primarily GABAergic nucleus that acts as a hub for negative emotional responses. Here we investigated how social isolation during the developmental period of adolescence impacts alcohol drinking behaviors in male and female rats and how the synergistic effect of social isolation stress and alcohol drinking can cause long-lasting behavioral effects and neuronal activity changes. We then explored the potential role of the endocannabinoid system, using lipidomic and pharmacological approaches. First, we found that social isolation increased alcohol preference in adolescent rats when compared to group-housed controls. Next, we found that socially isolated rats develop higher anxiety and irritability-like behaviors in adulthood, in a sex-specific manner. Finally, we observed altered basal presynaptic GABA release and blunted 2-AG signaling in the CeA of adult rats that underwent social isolation during adolescence. These findings suggest mechanisms that may underlie social isolation-induced maladaptation to alcohol drinking and stress-related behavioral responses and propose endocannabinoid system as potential therapeutic target.

S9.3

Amygdala regulation of stress effects on fear memory processes

Maria Morena

Sapienza University of Rome & Santa Lucia Foundation, Rome, Italy

The amygdala represents a central node in the brain activated by stress and plays a primary role in regulating traumatic memory by integrating information from different brain regions, including the hippocampus, which is highly involved in processing contextual information and is essential in supporting contextual fear extinction and overgeneralization. Altered fear memory processing represents the hallmark symptom of Post-Traumatic Stress Disorder (PTSD), as PTSD patients present excessive recall of traumatic memory, become resistant to fear extinction, and generalize fear responses to non-threatening stimuli, among other symptoms. PTSD patients experience heightened levels of stress which further interfere with

correct extinction of traumatic memory and exacerbate fear generalization. Thus, understanding the exact mechanisms by which stress affects traumatic memory processing remains of crucial importance for the identification of novel therapeutic targets for the treatment of cognitive symptoms of PTSD.
Findings will be presented on how the amygdala communicates with cortico-limbic brain regions to modulate different phases of traumatic memory and how stress influences these processes in rodents.
Collectively, findings presented here help to elucidate the neural underpinnings of the fine-tuned regulation of limbic neurocircuitry involved in modulating the impact of stress on fear memory processes, thus opening the avenue to investigate novel potential therapeutic interventions to treat memory alterations associated with trauma-related psychopathologies.

S9.4
Decoding fear in prefrontal-amygdala circuits

Cyril Herry

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Coping with threatening situations requires both identifying stimuli predicting danger and selecting adaptive behavioural responses in order to survive. The dorsomedial prefrontal cortex (dmPFC) is a critical structure involved in the regulation of threat-related behaviour. Yet, it is still unclear how threat-predicting stimuli and defensive behaviours are associated within prefrontal networks to successfully drive adaptive responses. Here, we used a combination of extracellular recordings, neuronal decoding approaches, pharmacological and optogenetic manipulations to show that threat representations and the initiation of avoidance behaviour are dynamically encoded in the overall population activity of dmPFC neurons. Our data indicate that although dmPFC population activity at stimulus onset encodes sustained threat representations driven by the amygdala, it does not predict action outcome. In contrast, transient dmPFC population activity prior to action initiation reliably predicts avoided from non-avoided trials. Accordingly, optogenetic inhibition of prefrontal activity constrained the selection of adaptive defensive responses in a time-dependent manner. These results reveal that the adaptive selection of defensive responses relies on a dynamic process of information linking threats with defensive actions, unfolding within prefrontal networks.

S9.5

Amygdala astrocytes gate the transformation of memory into action

Andrew Holmes, Olena Bukalo

Laboratory of Behavioral and Genomic Neuroscience

Astrocytes are increasingly implicated as dynamic participants in complex neural and associated behavioral processes. However, the role of astrocytes in regulating amygdala-mediated processes, such as fear memory and extinction, remains unclear. This presentation will describe recent studies from our laboratory designed to assess the role of astrocytes in the basolateral amygdala in cued fear memory. The results of experiments involving population-level and cellular-resolution calcium imaging of astrocytes and neurons will be discussed. The effects of chemogenetic manipulation of basolateral amygdala astrocytes on fear memory will also be shown. Taken together, the findings presented will offer new insights into the role of astrocytes in amygdala-mediated fear memory.

S10

Neurobiology of Social Cognition in Animal Kingdom

CHAIR: Giulia Salamanca

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The symposium titled "Neurobiology of Social Cognition in Animal Kingdom" brought together four distinct perspectives on the intricate workings of neural circuits and social cognition in both animal models and humans. Giulia Salamanca and her colleagues presented a neuroanatomical study focused on atypical long-range somatostatin projections originating from the medial prefrontal cortex (mPFC) and anterior cingulate cortex (ACC) in mice. Their research unveiled the intricate pathways of these projections spanning across various brain regions, shedding light on the intricate network facilitating rapid communication between them.

In a complementary investigation, Daniel Dautan and his team delved into the realm of emotion recognition, a critical aspect of social cognition. They revealed an evolutionarily conserved long-range inhibitory/excitatory brain network connecting the mPFC and retrosplenial cortex (RSC), orchestrated by somatostatin (SOM) projections. Their findings illuminated the central role of this network in emotion recognition and its potential as a target for addressing emotion discrimination deficits in mouse models relevant to psychiatric vulnerability.

Julia Sliwa's research transcended species boundaries as she explored the neural circuits responsible for processing social scenes in both humans and macaque monkeys. Using functional Magnetic Resonance Imaging, her work identified a network centered on the prefrontal cortex, emphasizing its evolutionary significance in decoding social interactions and actions of peers directed towards objects.

Shifting the focus to the opioid system, Gernot Ernst provided insights into its ancient origins and multifaceted roles in pain physiology, social behavior, and reward systems. While the μ-opioid system influences pain mitigation and social bonding in mammals, he highlighted the contrasting responses observed in rodents and primates when manipulating this system pharmacologically. Furthermore, Ernst's studies in humans revealed the variable effects of opioids, influenced by prior exposure and childhood adversity, emphasizing the need for a nuanced understanding of the opioid system.

S10.1

Where do the atypical long-range somatostatin projections go in the brain? A neuroanatomical study

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The atypical long-range somatostatin projections belong to a subtype of somatostatin-expressing (SOM) inhibitory interneurons in the cerebral cortex[1,2]. These long-range interneurons are characterized by axon trees that span two or more cortical and sub-cortical regions, providing fast communication between the innervated areas[3]. Little is known about the circuits that extend throughout the brain starting from the medial prefrontal cortex (mPFC) and the anterior cingulate cortex (ACC). To answer the question we processed the brains from six SOM-Cre line mice in which the virus AAV5-EF1a-DIO-eYFP.WPRE.hGH was injected respectively into the mPFC (three mice) and in ACC (three mice). Using immunofluorescence we performed the rostrocaudal evaluation by processing 30μm thickness coronal sections of the whole brain and mapping the areas in which the long-range projections spread. The interested areas were: telencephalon (in particular neocortex, olfactory system, septum, hippocampal region, and amygdaloid complex), diencephalon (in particular thalamus and hypothalamus) and brainstem (mesencephalon, pons, and medulla oblongata).

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S10.2

Cortico-Cortical Transfer of Socially Derived Information Gates Emotion Discrimination

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Emotion recognition and consequent reaction are important for a healthy animal life. However, it is unclear how cell-specific long-range circuits might process socially derived information for reliable emotion recognition. Here, we reveal an evolutionary conserved long-range inhibitory/excitatory brain network mediating these socio-cognitive processes. We show the involvement of long-range somatostatin (SOM) projections from the medial prefrontal cortex (mPFC) to the retrosplenial cortex (RSC), and an excitatory feedback loop from the RSC to mPFC. Anatomical tracing in mice highlighted the existence of a subpopulation of SOM GABAergic neurons projecting from the mPFC to the RSC. Optogenetics manipulations and Ca^{2+} imaging fiber photometry in mice, together with human functional imaging, demonstrated the specific participation of this inhibitory/excitatory mPFC-RSC network in emotion recognition. Notably, mPFC-to-RSC SOM projections are dysfunctional in mouse models relevant to psychiatric vulnerability and can be targeted to rescue emotion discrimination deficits. Our findings demonstrate a cortico-cortical circuit subtending emotion recognition.

S10.3

Comparing human and monkey neural circuits for processing social scenes

Julia Sliwa

Paris Brain Institute – ICM, CNRS, Sorbonne Universite, INSERM

Recognizing agents, their actions, and their interactions is essential for understanding the world around us. Using functional Magnetic Resonance Imaging, we discovered in the

macaque monkey brain a network of areas centered on the medial and ventrolateral prefrontal cortex that is selectively engaged in social interaction analysis. Its extent and location suggest that this function is an evolutionary forerunner of human mind-reading capabilities [1,2]. A comparative fMRI investigation in humans additionally revealed which neural strategies adapted to the needs of each species, and emphasized human interest in understanding actions of our peers directed towards objects. Together these studies show how our primate brains continuously decode the complex visual scenes unwinding in front of us: both the nature of material entities, such as individuals and objects, and their immaterial interactions.

1. *Deen B, Schwierdzik C, Sliwa J, Freiwald WA (2023). Systems for social understanding in the primate brain. Annual Review of Neuroscience. 10.1146/annurev-neuro-102522-121410*
2. *Sliwa J, Freiwald WA (2017). A dedicated network for social interaction processing in the primate brain. Science 356 (6339), 745-749. 10.1126/science.aam6383.*

S10.4

Opioid effects in animals and humans: What opioids (sometimes) do

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The opioid system appeared 450 million years ago and appears highly preserved. It plays a role not only in pain physiology but also in social behaviour and generally in the reward system. Socially bonded mammals exhibit affiliative behaviours in response to alleviating negative emotions and pursuing pleasurable experiences. The activity of the μ-opioid transmission system influences these two distinct motivational states. Within the brain, the μ-opioid receptor (MOR) system is pivotal in mitigating pain and reinforcing reward-related behaviours. This system is also intricately involved in processing social rewards and forming affiliative bonds among various mammalian species. However, it is noteworthy that manipulating the μ-opioid system through pharmacological interventions has produced contrasting outcomes in rodents and primates. In rodents, administering MOR agonists generally enhances social motivation, while MOR antagonists tend to diminish it. Comparatively, studies involving primates have demonstrated the opposite response pattern. New studies of our lab have shown that in humans, the opioid effects are highly variable and are influenced by earlier use of opioids. Only one of three opioid-naïve patients feel better after application of oxycodone on the operation theatre, but patients with previous opioid exposure reported improved well-being. Patients with higher levels of childhood adversity reported significantly less liking of the effects. Understanding the role of the opioid system needs new approaches and attention to the details.

S11
Ion channels and receptors in myelin-forming glia cells

CHAIR: Valerio Magnaghi

Department of Pharmacological and Biomolecular Sciences Università degli Studi di Milano Milan Italy

The myelin-forming glia cells encompass the oligodendrocytes and the Schwann cells. Recently, there has been an explosion of interest in studying the signaling pathways responsible for interaction of the myelin-forming glia with neurons and other glial cells. This reflects the ability of the myelin-forming glia to sense and respond to neuronal activity, their crucial role in regulating neuronal functions and homeostasis. The myelin-forming glia cells express a large set of voltage-gated and un-gated K+, Na+, Ca2+, Cl- ion channels, and receptors for neurotransmitters. The remarkable variety of the mechanisms through which the myelin-forming glial cells interact with neurons and other types of glia make us wonder how ion channels and receptors contribute to this complexity.

Overall, the symposium addresses the functional role of ion channels and receptors in the myelin-forming cells, that is oligodendrocytes and Schwann cells, in physiological and pathophysiological conditions, considering their contribution to the neuron-glia cross talk and neuronal homeostasis. This is timely because functions of ion channels and receptors in the myelin-forming glia have rarely been discussed under the angle of variety. We want to emphasize this point by focusing on specific functions of ion channels and receptors, also discussing their cross-talk. Thus, we should boost the understanding of the functional role of ion channels and receptors in the myelin-forming glia in physiology and pathophysiology, and inspire new ideas for future research.

S11.1
New insights into activity-dependent myelination

Wenjing Sun

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Accumulating data demonstrate that neuronal activity positively regulates myelination in the central nervous system (CNS). However, the underlying mechanisms are not fully understood. Recent studies highlighted the critical role of axonal vesicle release in instructing myelin formation, and synaptic transmission from neurons to oligodendrocyte precursor cells (OPCs) may be essential to instructing OPC proliferation, differentiation, and the subsequent myelination. Alpha2delta (A2d) subunits of voltage-gated calcium channels (VGCCs) positively regulate the plasma membrane expression and the biophysical properties of VGCCs, including those controlling synaptic vesicle release. In addition, A2d subunits are not only expressed by

neurons but also by OPCs. We show here that A2d subunits regulate myelin formation, indicating that voltage-gated calcium channel subunits might be novel molecular mediators for activity-dependent myelination, thereby providing a molecular entry point for further investigating cellular and molecular mechanisms controlling the multi-step myelin formation process.

S11.2
Glutamate receptors in the oligodendrocyte lineage cells: what is new?

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Receptors for α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPARs) are ligand-gated ionotropic receptors for glutamate which are expressed by neurons and glial cells in the central and peripheral nervous system.
It is well known that AMPARs in neurons are the key players in synaptic signaling and synaptic plasticity. But functional role of AMPARs in the oligodendrocyte lineage cells is significantly less understood. Many studies have been focusing on AMPARs as mediators of excitotoxic damage and death of oligodendroglial cells, emphasizing that blocking AMPARs reduces damage and increases survival of these glial cells during pathological conditions. At the same time, the functional role of AMPARs in the oligodendrocyte lineage cells during physiological conditions is being discussed much less frequently, and often this topic simply remained in the shadow.
In my talk, I want to discuss two important questions: (1) What is the functional role of AMPARs in oligodendrocyte lineage cells during physiological conditions? I will focus on the recent findings from our and other labs regarding the role of AMPARs in proliferation, differentiation, and survival of oligodendroglial cells in animals in vivo; (2) Is it true that the only function of AMPARs during pathological conditions is to mediate cell damage and death? I will emphasize recent findings from the literature regarding beneficial role of AMPAR during pathologies, and present my own thoughts on why we need new ideas and experiments on this topic.

S11.3
Unveiling Novel Targets for Remyelination in Multiple Sclerosis: A Path to CNS Repair

Aleksandra Rutkowska[1] and Bartosz Karaszewski[1,2]

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Remyelination in the CNS is a complex process dependent on oligodendrocytes and their progenitors, microglia, astrocytes, neurons and peripheral immune cells. Demyelination has

been observed in a range of CNS conditions including stroke, multiple sclerosis, dementia, infection and brain trauma, to name just a few. Irrespective of the cause of demyelination, remyelination begins almost immediately and follows the same steps. In multiple sclerosis, remyelination often fails for a number of factors, most of which are modulated by the glial cells. We identified a novel target for remyelination, which is expressed and highly functional in astrocytes, microglia and oligodendrocytes. Importantly, this target is a key immune modulator in the CNS and the peripheral immune system, an important aspect in the pathophysiology of MS.

Funding:
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S11.4

NKCC1 and GABA-A-receptor regulation of chloride flux in peripheral nerve:are Schwann cells engaged?

Valerio Magnaghi

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Schwan cells (SCs) in vitro and in vivo express GABA receptors, i.e. GABA-A and GABA-B receptors, which mediate autocrine/paracrine actions in proliferation, differentiation, axonal sorting and myelination, likely during PNS development. Recently, we reported that the peripheral axons of dorsal root ganglia (DRG) neurons, especially the unmyelinated nociceptive C-fibres, are depolarized by GABA, causing increased electrical excitability. The axonal GABA-A receptor mediates depolarizing Cl- fluxes, which are involved in nociceptor peripheral computation. The magnitude and time course of GABA-A responses are coupled to the Na+/K+/Cl- cotransporter (NKCC1) activity and secondary to the Cl- ion conductance. We showed that the SCs are the main source of peripheral GABA, which is endogenously secreted in peripheral nerves in the range of tens of nanomolar. However, the identification of the mechanisms and triggers for the tonic GABA release by SCs is still a challenge.
The complete GABA machinery was studied in rat SCs culture and ex vivo sural nerves. We found GABA transaminase (GABA-T) and GABA transporters (GAT-1 and GAT-3) in SCs. Although the vesicular GABA transporter (VGAT) has also been found, the process does not appear Ca++-dependent. Thus, the involvement of other anion channels (e.g. ClC, VRAC, etc.) has been hypothesized.
Overall, our findings shed light on a new functional role of GABA and ion channels in peripheral SCs-axon crosstalk, with relevance to the mechanisms underlying the physio-pathological control of C-fibres and pain perception. (This study was supported by PRIN 2017BJJ5EE).

S12
Non-neuronal mechanisms of motivated behavior

CHAIR: Debra Bangasser

Georgia State University, USAA

There is mounting evidence that glial cell dysfunction occurs in disorders characterized by altered motivational states, such as mood and substance use disorders (SUDs). Yet how environmental stimuli such as stress and drug taking impact glia, and how glia, in turn, mediate behavioral outputs is less understood. The speakers in this symposium will address this gap and highlight emerging roles for glia in motivated behavior. First, Dr. Debra Bangasser will discuss how early life adversity affects cortical astrocyte morphology and motivation for opioids. Next, Dr. Pavel Ortinski will share results of experiments that investigate how astrocyte potassium channels in the nucleus accumbens impact cocaine self-administration. Then, Dr. Jared Young will discuss how Human Immunodeficiency Virus (HIV) impacts activated neuronal microglia and subsequent measures of effortful motivation and risky decision making, with the potential benefit of nicotine use. Dr. Michael Scofield will discuss how heroin self-administration impacts cortical astrocyte Ca^{2+} signaling, morphology, and astrocyte-synapse interaction. Finally, Dr. Jill Turner will share insights into genomic mechanisms by which glia shape the affective phenotypes that emerge during withdrawal from drugs of abuse. Together these studies highlight how mechanistic understanding of glial contributions to motivated behavior can advance novel therapeutic development for treating affective disruptions and SUD.

S12.1
Early resource scarcity causes lasting effects on cognition and non-neuronal cortical cells

Debra Bangasser

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Experiencing early trauma increases risk for substance use disorder. However, early adversity that is not overwhelming can promote later resilience to disease. Our laboratory models brief early life scarcity using the Limited Bedding and Nesting (LBN) manipulation, in which rat dams and pups are reared in a low-resource environment during the pups' first week of life. We find that LBN promotes later resilience to adult addiction-related behaviors, reducing impulsivity, risky decision-making, and morphine self-administration. These behaviors rely on glutamatergic transmission in the medial orbitofrontal (mOFC) and medial prefrontal (mPFC) cortex, which is regulated by astrocytes. Thus, we assessed whether astrocyte morphology, which affect their function, was altered by LBN. LBN causes an increase in the surface area and volume of astrocytes in the mOFC and mPFC of adult males and females relative to

control-raised rats. We next used bulk RNA sequencing of OFC tissue to assess transcriptional changes that could affect astrocyte morphology. LBN caused sex-specific changes in differentially expressed genes. However, Park7, which encodes for the protein DJ-1 that alters astrocyte morphology, was increased by LBN across sex. Pathway analysis revealed that OFC glutamatergic signaling is altered by LBN in males and females, but the gene changes in that pathway differed across sex. This may represent a convergent sex difference where glutamatergic signaling, which affects astrocyte morphology, is altered by LBN via sex-specific mechanisms. Collectively, these studies highlight that astrocytes may be an important cell type that mediates the effect of early resource scarcity on adult brain function.

S12.2

Cocaine self-administration increases voltage-gated signaling in accumbens astrocytes

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Dopaminergic signaling in the nucleus accumbens shell (NAc) regulates neuronal activity relevant to reward-related learning, including cocaine-associated behaviors. Although astrocytes respond to dopamine and cocaine with structural changes, the impact of dopamine and cocaine on astrocyte functional plasticity has not been widely studied. Specifically, behavioral implications of voltage-gated channel activity in the canonically non-excitable astrocytes are not known. We characterized potassium channel function in NAc astrocytes following exposure to exogenous dopamine or cocaine self-administration training under short (2hr/day) and extended (6hr/day) access schedules. Electrophysiological, Ca^{2+} imaging, mRNA, and mass spectrometry tools were used for molecular characterization. Behavioral effects were examined after NAc targeted microinjections of channel antagonists and astroglial toxins. Exogenous dopamine was found to increase activity of currents mediated by voltage-gated (K_v7) channels in NAc astrocytes. This was associated with a ~5-fold increase in expression of *Kcnq2* transcript level in homogenized NAc micropunches. Matrix-assisted laser desorption/ionization mass spectrometry revealed increased NAc dopamine levels in extended access, relative to short access, animals. K_v7 inhibition selectively increased frequency and amplitude of astrocyte intracellular Ca^{2+} transients in NAc of extended access animals. Inhibition of K_v7 channels in the NAc attenuated cocaine-seeking in extended access animals only, an effect that was occluded by microinjection of the astrocyte metabolic poison, fluorocitrate. These results establish behavioral relevance of voltage-gated K^+ channel signaling in NAc astrocytes, support cocaine-induced regulation of astrocyte potassium channels, and suggest novel mechanisms of neuroglial interactions relevant to drug use.

S12.3

Impact of HIV on motivation and risk-taking: Activated microglia as a potential treatment target

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HIV diagnosis is no longer fatal as a result of the advent of antiretroviral therapy (ART). People living with HIV (PLH) continue to exhibit cognitive deficits however, known as HIV Associated Neurological Disorders (HAND), that includes amotivated states. In addition, despite zero virologic levels resulting from ART administration, PLH also continue to exhibit neuroinflammation as measured using PET imaging via levels of activated microglia, which may contribute to these behavioral deficits. PLH smoke cigarettes at higher rates (40%) than the general population (16%), and since nicotine can induce pro-cognitive and anti-inflammatory effects, the directional impact of long-term nicotine on such neuroinflammation and behaviors relevant to HAND requires determination. The envelope glycoprotein (gp)120 drives entry of HIV into neurons and can induce inflammation. Thus, we determined the impact of chronic nicotine administration on mice over-expressing gp120 (tg) and their wildtype (WT) littermates, on motivation, reinforcement learning, and neuroinflammation.

Male and female gp120 tg and WT littermate mice (n=120), were bred from heterozygous breeding pairs and trained to respond in 5-hole operant chambers. Mice were baseline tested in effortful motivation using the progressive ratio breakpoint task (PRBT), then counterbalanced into 3 groups (by sex and gene), and implanted with osmotic minipumps containing vehicle or one of two doses of nicotine (14 or 40 mg/kg/day). Mice were then tested in the PRBT on days 24/25, then in the probabilistic reversal learning task (PRLT) on days 26/27, after which brains were removed for inflammatory histopathology.

No gene effect or sex*gene interaction [Fs<1, ns], was observed on breakpoint (motivation from PRBT), but a trend sex effect was observed [$F(1,118)=3.9$, $p=0.051$]. In the PRBT, males exhibited a higher breakpoint than females [$F(1,117)=7.2$, $p=0.009$]. No gene, nicotine, gene*nicotine, or sex*gene*nicotine interactions (Fs<1, ns) were observed. In the PRLT, on % target responses, a sex effect [$F(1,118)=4.8$, $p=0.031$], was observed, though no gene effect [$F(1,118)=2.41$, $p=0.123$], or drug [$F(2,118)=1.49$, $p=0.230$], was observed. Importantly, a gene*drug interaction was observed [$F(2,188)=4.0$, $p=0.022$]. *Post hoc* analyses revealed that nicotine did not affect WT mice ([F<1, ns), but increased the %target responses of gp120 mice [$F(2,58)=4.9$, $p=0.011$], at both 14 and 40 mg/kg/day vs. vehicle ($p=0.008$ and 0.013 respectively). No sex*gene interactions were observed in any measure. Nicotine increased the lose-shift ratio of gp120 tg mice when responding at the non-target [$F(2,58)=4.08$, $p=0.022$], at both 14 and 40 mg/kg/day vs. vehicle ($p<0.015$ and $p=0.026$ respectively). A nicotine trend interaction effect was observed [$F(2,21)=3.3$, $p=0.056$], revealing that nicotine at the highest dose reduced Iba1 levels. Although no interaction was seen with genotype, gp120 transgenic

mice exhibited higher levels of Iba1 vs. WT mice, with nicotine exerting a greater effect in gp120 mice, consistent with tobacco-induced reduction in PET-measured neuroinflammation in our PLH PET imaging studies.

Thus, chronic nicotine treatment improved reinforcement learning in the gp120 tg model relevant to HAND, driven by increased punish-sensitivity. Furthermore, this mechanism may relate to nicotine-induced lowering of neuroinflammation as measured by Iba1 staining. Studies are ongoing to determine whether PWH that smoke exhibit normalized reinforcement learning using the PRLT, and neuroinflammation using positron emission tomography.

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S12.4
Ca^{2+} Activity Profiles of Cortical Astrocytes During Conditioned Reward Seeking

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Findings from rodent models of heroin **self-administration (SA)** and cue-induced heroin seeking demonstrate that chronic opioid exposure leads to maladaptive corticostriatal plasticity mechanistically linked to the persistent vulnerability to relapse that characterizes OUD. Emerging data support the hypothesis that discrete neuronal ensembles encode specialized information pertaining to reward-associated cues, and reward delivery to drive reward seeking behaviors. Despite these advances, very little is known about how dorsal medial prefrontal cortex (dmPFC) neuronal ensembles are refined to control drug seeking. We hypothesize that astroglia are critical mediators of this synaptic plasticity. With astrocyte-specific expression of Ca^{2+} indicators, two-photon Ca^{2+} imaging, and various head-fixed conditioned reward seeking paradigms we have analyzed activity of individual astrocytes, longitudinally, through both sucrose and heroin seeking paradigms in the dmPFC**.** Using a custom python pipeline, recordings are motion corrected and individual astrocytes are selected and analyzed for Ca^{2+} activity during the head-fixed behavior. To visualize these data, individual astrocyte cell $\Delta F/F$ responses are aligned to cue presentation and/or lever responding and reward delivery. We find that dmPFC astrocytes respond with temporal precision to sucrose or heroin reward delivery, and that response timing and magnitude is refined during training. We also find that astrocytes still respond within to the absence of reward delivery when training paradigms are altered. These data speak to a potential role for astrocyte-mediated neuronal synchronization in response to reward conditioned stimuli and for cortical astrocytes in the mechanisms underlying conditioned reward seeking.

S12.5
Microglia Regulate Sex- and Region-Specific Blood-Brain Barrier Integrity During Nicotine Withdrawal

Dr. Jill Rebecca Turner

University of Kentucky, College of Pharmacy, Department of Pharmaceutical Sciences

Smoking is the largest preventable cause of death and disease in the United States, with <5% successful quit attempts. Microglia activation and pro-inflammatory neuroimmune signaling in reward neurocircuitry is implicated in nicotine withdrawal symptomology. Microglia are integral regulators of blood brain barrier (BBB) functionality as well; however, whether the effects of nicotine withdrawal on microglia function impact BBB integrity is unknown. Mice were treated with chronic nicotine (12mg/kg/day) and subjected to 48h nicotine withdrawal. Regional BBB permeability, along with the mRNA and protein expression of tight junction proteins was assessed. PLX5622 chow was used to deplete microglia to evaluate the role of microglia in regulating BBB integrity and nicotine withdrawal symptomology. Female mice had higher baseline BBB permeability in the prefrontal cortex (PFC) and hippocampus as compared to males. Nicotine withdrawal further exacerbated the BBB permeability selectively in the PFC of females. These effects were concurrent with PFC alterations in a subset of tight junction proteins, alongside increased pro-inflammatory responses following nicotine withdrawal in females. Depletion of microglia via PLX5622 treatment prevented all these molecular effects as well as attenuated withdrawal-induced anxiety-like behavior in female mice. These results are the first to show sex differences in the regional BBB permeability during nicotine withdrawal. This represents a possible link to both the reduced smoking cessation success in women as well as their increased risk for smoking-related neurovascular disorders. Furthermore, these findings open an avenue for sex-specific therapeutics targeting microglia and BBB dysfunction during nicotine withdrawal in women.

S13
Diverse Neurobiological Actions of Cannabinoids in the Brain

CHAIR: Matthew Hill[1], Roberto Colangeli[2]

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[2]*Dept. of Experimental and Clinical Medicine, Università Politecnica delle Marche, 60126 Ancona, Italy*

Cannabinoids are known to have a diverse impact on homeostatic processes in the brain ranging from the modulation of synaptic plasticity to the organization of complex behavioral processes such as feeding and emotional state. This symposium will bring together leading experts in the field of cannabinoids to provide novel data on how cannabinoids can modulate both discrete neuronal processes and complex behavioral outputs.

Dr. Colangeli will be talking about the physiological role of endocannabinoid signaling on plasticity at inhibitory synapses and how the reorganization of endocannabinoid signaling in

the epileptic brain may contribute to the negative neurobiological consequences associated with seizure activity. Dr. Hill will discuss how endocannabinoid regulation of CRH neurons in the hypothalamus governs activation and termination of the stress response. Dr. Borgland will present novel data regarding the impacts of perinatal cannabinoid exposure on metabolic processes and feeding behavior. Dr. McLaughlin will discuss novel work exploring behavioral and neurobiological predictors of cannabis self administration.

Collectively, this symposium will provide new insights on the influence of both exogenous and endogenous cannabinoids on neuronal processes and homeostatic behavioral processes. These data will foster discussions regarding implications of cannabinoids during various developmental periods and for the treatment of neurological and psychiatric conditions.

S13.1

2-AG-mediated control of GABAergic plasticity in the epileptic brain

Roberto Colangeli

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Persistent alteration of neuroplasticity is an important hallmark of the pathophysiology of epilepsy and contributes to the negative neurobiological consequences associated with seizure activity. The endocannabinoid (eCB) system finely shapes synaptic activity by performing a tight control of neurotransmitter release and both exogenous and endogenous cannabinoids acutely dampen neuronal hyperexcitability and seizure expression. Conversely, data on pathologic long-term remodeling of the eCB signaling following seizure activity are less consistent across studies. We previously found that repeated seizures in the amygdala cause a persistent maladaptive downregulation of anandamide (AEA) signaling in the BLA, which drives aberrant excitatory synaptic function and altered emotional behavior. Here, we provide evidence that repeated seizure activity in the amygdala is associated with enduring alterations of GABAergic synaptic plasticity in the BLA and these synaptic alterations were mimicked by the disruption of 2-AG signaling in sham rats by inhibiting 2-AG synthesis. We report a new mechanism by which seizures persistently alter neurophysiology and synaptic functionality of brain regions involved in seizure activity, pinpointing the eCB system as a chief target for the development of new therapeutic options for seizure related disorders.

S13.2

Endocannabinoid signaling governs stress induced activation and termination of neural activity within corticotropin releasing hormone neurons in the paraventricular nucleus of the hypothalamus

Gavin N. Petrie, Robert J. Aukema, Samantha L. Baglot, Tamas Fuzesi, Georgia Balsevich, Wouter Driever, Mario van der Stelt, Jaideep S. Bains, Matthew N. Hill

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Activation of the hypothalamic pituitary adrenal (HPA) axis involves release of corticotropin-releasing hormone (CRH) from the paraventricular nucleus of the hypothalamus (PVN) which increases circulating corticosterone (CORT). CRH neurons in the PVN (CRH^{PVN}) are also implicated in several stress-induced behaviors, such as grooming. The endocannabinoid (eCB) is involved in many arms of the stress response, although circuit mechanisms of how it regulates stress are poorly understood. The following studies utilize cellular, neuroendocrine and behavioral measures together to capture a broad picture of how tonic and phasic eCB signaling regulates the stress response.
Systemic administration of a CB1 receptor antagonist/inverse agonist (AM251), neutral antagonist (NESS0327) and AEA synthesis inhibitor (LEI401) all elevated cellular activity in the PVN, circulating CORT and homecage grooming behaviors, suggesting a role for AEA as the tonic regulator of the stress response. Intra-PVN AM251 administration increased stress-like grooming and circulating CORT, providing evidence for local tonic eCB signaling in gating the stress response in the absence of a stressor.
Pharmacological blockade of 2-AG degradation, but not AEA, with JZL184 accelerated the behavioral recovery following a footshock stressor. Intra-PVN JZL184 infusions recapitulated the behavioral effects of systemic administration. Systemic JZL184 administration also enhanced CRH^{PVN} recovery following return to homecage, providing a putative mechanism of the augmented stress recovery.
Overall, these data identify AEA as a tonic gatekeeper of the stress response in the absence of a threat and 2-AG as providing a phasic response to a stressful stimulus, shutting the stress response down during recovery.

S13.3
Sex differences in effects perinatal cannabis exposure on metabolism and emotional behaviour in adult offspring.

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Cannabis use during pregnancy has increased over the last decade. The active ingredient, delta-9-tetrahydrocannabinol (THC), can cross the placenta to influence numerous aspects of neurodevelopment. There is significant evidence of low birthweight in cannabis exposed offspring. Low birthweight is associated with catch-up growth leading to possible metabolic abnormalities. However, it is unknown if low birthweight or perinatal cannabis exposure (PCE) can influence metabolic processes in the offspring. We examined how PCE influenced diet-induced obesity and emotional behaviour in adult offspring. Dams received oral cannabis (5 mg/kg THC) or vehicle from GD1.5-PD10. At 7 weeks, offspring were placed on a 12-week high

fat diet (HFD) or control diet and then assessed for metabolic and behavioural profiles. There was no effect of PCE on bodyweight, food intake, glucose tolerance or fasting glucose. Adiposity was lower in PCE HFD female mice compared to vehicle HFD mice. Furthermore, while vehicle female mice had reduced insulin sensitivity after HFD exposure, insulin sensitivity was not altered in PCE HFD mice. Consistent with this, amylin, c-peptide, GLP, insulin and leptin were increased in vehicle HFD female exposed mice, but not in PCE HFD mice, suggesting that PCE reduces HFD-induced changes in metabolic signaling in adult female offspring. Finally, there were sex-dependent effects of PCE on the elevated plus maze in control diet but not HFD exposed mice, such that PCE-control diet male mice had decreased duration in open arms. Taken together, these results indicate that PCE reduces the metabolic response to HFD and increases anxiety-like behaviour.

S13.4

Identifying predictors of response-contingent cannabis vapor administration in rats

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Approximately 9% of first-time cannabis users will become dependent, yet there are no FDA-approved pharmacotherapies for managing cannabis use disorder (CUD). This is partly due to flawed diagnostic nosology resulting in an impoverished understanding of mechanisms that give rise to CUD, as well as a lack of translational preclinical models of cannabis use. To this end, we have validated a model of cannabis use that uses response-contingent delivery of vaporized cannabis extracts in rats, and we used this model herein to identify predictors of motivation to work for vaporized cannabis. To accomplish this, we conducted a battery of behavioral assays in female and male Long Evans rats (N=48) prior to initiation of cannabis administration and characterized endophenotypes using endpoints that correspond to the behavioral dimensions of the NIMH Research Domain Criteria. We then used linear regression to determine whether performance predicted the number of cannabis vapor deliveriesearned during a progressive ratio test after 21 days of vapor administration.

Preliminary results indicate that sex, high social grooming during adolescence, and higher break points for sucrose reinforcement during adulthood each significantly predicted willingness to work for cannabis vapor. Greater reliance on visual cue-based decision-making strategies and more difficulty shifting away from cue-based strategies during an attentional set-shifting task were also significant predictors of vaporized cannabis administration. Ongoing studies are exploring whether circulating endocannabinoid content predicts rates of responding for vaporized cannabis and whether chronic cannabis administration alters

components of the endocannabinoid system in brain regions that critically contribute to these endophenotypes.

S14

Interplay of estrogens, antidepressants and behavior: classical and rapid effects

CHAIR: Nikolaos Kokras

Dep. of Pharmacology, Medical School, National and Kapodistrian University of Athens and First Psychiatric Clinic, Medical School, National and Kapodistrian University of Athens

Several neuropsychiatric disorders, such as depression and anxiety disorders are overall more prevalent in women than in men. Novel studies take into consideration the importance of studying sex differences and aim to develop rapid-acting neuropsychopharmacological treatments. Therefore estrogens' receptors, cannabinoids and NMDA receptor modulators, such as ketamine are currently under investigation worldwide. In this symposium, five female and male researchers from Greece, Cyprus, USA and Canada will present their findings in this exciting topic of research.

Dr. Georgiou will present novel data on the role of estrogen receptor beta (ERβ) in the development of stress susceptibility in both male and female mice. Using behavioral, pharmacological and molecular approaches was demonstrated that absence of ERβ is associated with stress susceptibility in male but not female mice following exposure to a mild stressor. Overall, her findings provide evidence for an estrogen-based mechanism underlying stress susceptibility and suggest a novel therapeutic strategy utilizing brain selective estradiol for treating depression.
Dr. Choleris will present her research on mechanisms underlying the rapid effects of estrogens on the brain and cognition. She will present several studies elucidating some molecular and neurotransmitter systems that interplay with the rapid actions of estrogens infacilitating social cognition and neuroplastic changes in neurons.

Dr. Kokras will present methodological approaches that can be used for the consideration of female subjects in neuroscience and neuropsychopharmacology. He will particularly talk about sex differences in models of depression, stress response and antidepressant activity. Furthermore, he will present the effects of estrogen depletion by aromatase inhibition in both male and female rats and the role of the estrogen membrane GPER1 receptor in the brain. It is possible that GPER1 activation mimics the rapid-acting antidepressant effect of ketamine or augments the effects of serotonergic antidepressants drugs.

Dr. Zanos will show new data from mouse behavioral pharmacology, western blot quantification of hippocampal synaptoneurosomal protein levels, and *ex vivo* hippocampal slice electrophysiology, demonstrating for the first time that NMDA receptor activation (and not inhibition) is necessary for the beneficial effects of ketamine and other putative rapid-

acting antidepressant compounds. He suggests that promoting NMDA receptor activation-dependent LTP-like processes *in vivo* may prove to be a novel and effective rapid-acting antidepressant strategy.
Dr. Brakatselos will talk about cannabidiol (CBD), which is a non-psychotomimetic component of Cannabis sativa plant that has shown a variety of pharmacological properties, while its underlying mechanism of action remains unknown. CBD's antidepressant profile is not sufficiently characterized although novel therapeutic strategies are needed for identification of new targets and development of new antidepressant drugs. He we will present data concerning the characterization of CBD's antidepressant profile, including its rapid-acting action and its potential synergy with a classical selective serotonin reuptake inhibitor, and ketamine, the only approved rapid-acting antidepressant.

S14.1
Estrogen Receptor β Modulates Depressive phenotypes via an Amygdala-Nucleus Accumbens Pathway

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In susceptible populations, stress is a major risk factor for the development of mental disorders, including depression. Estradiol, often considered a female hormone, is distributed in the male brain via aromatization of testosterone. The role of estrogen receptors (ERs) in male stress susceptibility and depression is not well understood. Here, we used behavioral, pharmacological and systems neuroscience approaches to elucidate the role of estradiol and ERs in both sexes in stress susceptibility and depression-like behaviors. We found thatabsence of ERβ is associated with susceptibility to stress in male but not female mice. No effect of ERα was observed both in male and female mice. Moreover, we show that the activity of ERβ-projecting neurons from the basolateral amygdala to nucleus accumbens is reduced in hypogonadal male mice subjected to stress, while activation of this circuit reverses stress-induced maladaptive behaviors and inhibition induces stress susceptibility. Activation of the ERβ-projecting neurons from the basolateral amygdala to nucleus accumbens isrewarding in male, but not female, mice. We identified that absence of estradiol, but not testosterone per se, underlies stress susceptibility and that brain-selective delivery of

estradiol prevents the development of depression-related behaviors. Intra-basolateral amygdala administration of an ERβ-specific agonist reversed the induction of stress susceptibility in hypogonadal male mice. Our findings provide evidence for an estrogen-based mechanism underlying stress susceptibility and offer an unexpected therapeutic strategy for treating male depression.

S14.2

Hormone regulation of brain circuits of social cognition in male and female mice

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Estrogens and androgens and their interplay with neuromodulators and/or neurotransmitter profoundly affect brain structure and function through genomic and rapid mechanisms. We have been investigating brain regions and networks of rapid hormone facilitation of social and non-social cognition. In the Dorsal Hippocampus 17β-estradiol (E2) and its receptors rapidly facilitate different types of short-term memory (object, location, and social) in males and females. Conversely, in regions of the social brain network, we showed that estrogens either specifically facilitate social cognition or affect social and non-social cognition differently. In the Paraventricular and Supraoptic nuclei of the hypothalamus E2 rapidly facilitates social (and not object) recognition short-term memory in female (and not male) mice in a manner that is dependent upon Oxytocin Receptors (OTR) in the Medial Amygdala. We then showed a similar E2/OTR interplay within the Medial Amygdala in the rapid facilitation of social recognition. Similarly, social (but not object or location) recognition and socially learned short-term memory were rapidly facilitated by E2 in the Medial Prefrontal Cortex of female mice. We also investigated a male network were Vasopressin (AVP) dependent social recognition in the Lateral Septum is modulated by estrogens (but not androgens) and their receptors in the Bed Nucleus of the Stria Terminalis (BNST). Conversely, in the BNST androgen and estrogens inhibit non-social cognition (object recognition). Overall, we have been elucidating a network of brain regions where hormones rapidly regulate social and non-social cognition in male and female mice in interplay with neuropeptide systems.
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S14.3

How to integrate sex in preclinical research of antidepressants: the role of estrogens

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Depression exhibits sex differences in its epidemiology, presentation, and treatment. Central to these disparities may be a hypothalamous-pituitary-adrenals (HPA) axis dysfunction. Our experiments with the Forced Swim Test (FST) reveales enhanced corticosterone levels in both sexes. Across various experimental models of depression, our studies suggest differential involvement of the HPA axis in the stress responses between sexes. Interestingly, the male behavioral response under stress correlates well with the HPA activation, a finding not replicated in females. Given these results, it's plausible that unrecognized sex differences have undermined the success of HPA axis-targeted drugs in clinical trials. As we delve deeper into the neurobiological aspects of depression, estrogens stand out for their pivotal role in mood and cognitive regulation. Our investigations into the effects of estrogen depletion by aromatase inhibition revealed that letrozole treatment diminishes noradrenaline levels and the dopaminergic ratio in the hippocampus and prefrontal cortex of both sexes while amplifying the serotonergic ratio in the hippocampus. Recent discoveries indicate that neuroestrogens play a role in mood regulation, and we posit that rapid neuroestrogen signaling, coupled with the G protein-coupled estrogen receptor 1 (GPER1), may influence mood, HPA axis function, and antidepressant efficacy. Considering these intricate interactions and sex-based variations, it's essential to prioritize sex inclusivity in preclinical neuroscience research. Such an approach will not only deepen our scientific knowledge but also pave the way for more holistic therapeutic interventions.

This research has been supported by the Hellenic Foundation for Research and Innovation (HFRI-FM17-1676)

S14.4

NMDA receptor activation underlies rapid antidepressant efficacy of ketamine

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Ketamine is a well-known open-channel NMDA receptor (NMDAR) antagonist, although the relevance of its actions on the NMDAR to its rapid antidepressant actions is unclear. It is known that its antidepressant properties depend on mechanisms convergent with strengthening of excitatory synapses. Since synaptic NMDA receptor activation is implicated in inducing long-term potentiation (LTP) and enhancing synaptic strength, here we explored the relevance of NMDA receptor activation to ketamine's antidepressant actions. To investigate NMDA receptor activation's necessity for rapid antidepressant effects, we conducted behavioral pharmacology experiments, quantified hippocampal protein levels, and

performed hippocampal electrophysiology in mice. Findings indicated an inverted U-shaped dose-response relationship for ketamine in behavioral tests, suggesting excessive NMDA receptor inhibition may impede its antidepressant properties. Antidepressant-like effects, up-regulation of hippocampal AMPA receptor subunits, and hippocampal metaplasticity induced by ketamine were abolished by pre-treatment with non-antidepressant NMDA receptor antagonists. Other putative rapid-acting antidepressant drugs, including (2R,6R)-hydroxynorketamine (a ketamine metabolite), MRK-016 (a GABAAα5 negative allosteric modulator), and LY341495, exhibited antidepressant-like actions that were hindered by NMDA receptor inhibition. Additionally, ketamine demonstrated synergy with an NMDA receptor positive allosteric modulator in inducing antidepressant-relevant behavioral actions, and the NMDA receptor subunit GluN2A was necessary and sufficient for these effects. In conclusion, our findings suggest a common downstream effector mechanism involving NMDA receptor activation for rapid-acting antidepressant compounds, regardless of their initial targets. These findings highlight strategies promoting NMDA receptor signaling or enhancing NMDA receptor-dependent LTP-like synaptic potentiation as effective, next-generation interventions for depression.

S14.5

Targeting affective disorders: synergies of cannabidiol and antidepressants.

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The neurobiological underpinnings of repeated ketamine (KET) model of schizophrenia remain poorly understood. Cannabidiol (CBD), a non-addictive phytocannabinoid has been reported to present antipsychotic potential, but the mechanisms involved remain elusive. This study aims to investigate the KET-induced bio-phenotype, and the potential therapeuticeffect of CBD by emphasizing on the glutamatergic system, and network function.

After a repeated subanesthetic KET exposure, rats received a 5-day long treatment with CBD. Subsequently, they underwent behavioral analyses exploring positive, negative, and cognitive symptomatology. HPLC-ED provided estimates of GABA and glutamatergic activity, NMDA and AMPA receptors have been quantified using western blot, and specific interneuron densities have been calculated using immunohistochemistry. LFPs have been recorded from sevoflurane-anesthetized rats' mPFC (medial prefrontal cortex), simultaneously with dorsomedial striatum (DMS), and ventral hippocampus (VH).

KET-treated rats displayed a schizophrenia-related behavioral bio-phenotype, with a parallel impairment in glutamatergic neurotransmission and excitation/inhibition balance in the PFC and DMS. CBD was able to ameliorate positive, negative, and cognitive symptomatology, while also positively modulated the excitation/inhibition imbalance with the concomitant reduced interneuron densities in the PFC.

Current findings characterize further the schizophrenia-like bio-phenotype induced by repeated KET and enrich our understanding of the antipsychotic potential of CBD.

S15

Brain extracellular matrix: organization, remodeling, and functions in health and disease

CHAIR: Prof. Tommaso Pizzorusso[1], Alexander Dityatev[2]

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The symposium titled "Brain Extracellular Matrix: Organization, Remodeling, and Functions in Health and Disease" featured four insightful talks by different speakers.

Tommaso Pizzorusso et al. presented an "Atlas of Perineuronal Net Distribution and Colocalization with Parvalbumin in the Adult Mouse Brain." They introduced a comprehensive atlas illustrating the distribution of perineuronal nets (PNNs) across over 600 regions of the adult mouse brain, providing valuable insights into their correlation with parvalbumin (PV) cells. This research emphasized the significance of PV expression as a predictor of PNN aggregation and shed light on the role of PNNs in cortical layers and their connection patterns.

Alexander Dityatev et al. explored "Neuromodulatory and Neuroinflammatory Mechanisms of ECM Remodeling." Their study elucidated how the neural extracellular matrix (ECM) influences memory precision and cognitive flexibility through its impact on neuronal excitability, connectivity, and plasticity. They discussed the pivotal role of various signaling mechanisms, including those involving serotonin receptors and dopamine receptors, in ECM remodeling. Additionally, they highlighted the role of microglial phagocytosis and ECM recycling in perisynaptic ECM remodeling, connecting these mechanisms to conditions like epilepsy, schizophrenia, and dementia.

Juan Nàcher et al. focused on "Perineuronal Nets as Emerging Targets for the Treatment of Neuropsychiatric Disorders." They delved into the specialized regions of the extracellular matrix known as PNNs, emphasizing their influence on the connectivity and plasticity of fast-spiking parvalbumin expressing (PV+) interneurons. Their presentation explored the impact of psychiatric disorders on PNNs and inhibitory circuits, drawing from both animal models and postmortem tissue analysis of patients with conditions like schizophrenia, bipolar disorder, and major depression. This research highlighted PNNs as promising targets for understanding inhibitory circuit physiology and the etiology of certain psychiatric disorders.

Laure Verret et al. discussed "Experience-Dependent Perineuronal Net Remodeling and Memory in AD Mice." They highlighted the causal link between impaired function of parvalbumin (PV) GABAergic interneurons, brain network activity, and cognitive impairment in Alzheimer's disease (AD) mice and patients. Their research focused on PNNs surrounding PV cells and their role in preserving memories and strengthening synapses. Two strategies were presented to restore PNNs in AD mice, involving enriched environments and neuregulin-1 (NRG1) injections, both of which demonstrated positive effects on cognitive performance. These findings suggested that PV/PNN remodeling contributes to the observed improvements in the AD model.

In summary, the symposium provided valuable insights into the organization, remodeling, and functions of the brain extracellular matrix, with a focus on perineuronal nets and their implications in various neurological and psychiatric conditions. The research presented by these speakers collectively advanced our understanding of the intricate role played by the ECM in brain health and disease.

S15.1

An Atlas of Perineuronal Net Distribution and Colocalization with Parvalbumin inthe Adult Mouse Brain

Tommaso Pizzorusso[1,2]

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Perineuronal nets (PNNs) surround specific neurons in the brain and are involved in various forms of plasticity and clinical conditions. However, our understanding of the PNN role in these phenomena is limited by the lack of highly quantitative maps of PNN distribution and association with specific cell types. Here, we present the first comprehensive atlas of PNN distribution (in Allen Brain Atlas coordinates) and colocalization with parvalbumin (PV) cells for over 600 regions of the adult mouse brain. Data analysis showed that PV expression is a good predictor of PNN aggregation. In the cortex, PNNs are dramatically enriched in layer 4 of all primary sensory areas in correlation with thalamocortical input density, and their distribution mirrors intracortical connectivity patterns. Gene expression analysis identified many PNN correlated genes. Strikingly, PNN anticorrelated transcripts were enriched in synaptic plasticity genes, generalizing PNN role as circuit stability factors. Overall, this atlas offers novel resources for understanding the organizational principles of the brain extracellular matrix.

S15.2

Neuromodulatory and neuroinflammatory mechanisms of ECM remodeling

Alexander Dityatev

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Neural extracellular matrix (ECM) plays the pivotal role in regulation of memory precision and cognitive flexibility via the control of neuronal excitability, connectivity and plasticity [1,2]. Excessive up- and downregulation of ECM may be detrimental for learning and memory, and hence it is crucial to maintain the appropriate levels of ECM. Neural ECM is formed and remodeled in a manner dependent on neuronal activity and activation of neuromodulatory systems. Signaling via 5-HT7 receptors promotes activation of MMP9 and cleavage of CD44 (the major receptor to the neural ECM backbone, hyaluronic acid), triggering elongation of dendritic spines [3]. Activation of D1-like dopamine receptors results in ADAMTS4/5-mediated cleavage of ECM proteoglycans, including brevican and aggrecan [4]. Presynaptically released protease neurotrypsin cleaves the ECM molecule agrin, a small fragment of which promotes the formation of dendritic spines during learning in a Hebbian-like manner and also regulates the number of presynaptic boutons. In addition to ECM proteolysis, recent studies highlight the importance of microglial phagocytosis and integrin-based ECM recycling in the remodeling of perisynaptic ECM [5,6]. The presented signaling mechanisms are expected to shape diverse forms of learning and memory and be involved in the pathophysiology of epilepsy, schizophrenia, mental retardation and dementia.

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S15.3
Perineuronal nets as emerging targets for the treatment of neuropsychiatric disorders

Juan Nàcher[1,2,3]

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The perineuronal nets (PNNs) are specialized regions of the extracellular matrix, frequently found surrounding the soma and proximal dendrites of fast-spiking parvalbumin expressing (PV+) interneurons. Their appearance overlaps the maturation of neuronal circuits and the closure of critical periods in different regions of the brain, setting their connectivity and reducing abruptly their plasticity[1]. In the presentation I will review recent evidence of the impact of PNNs presence on the input and output connectivity of PV+ neurons and their

physiology[2]. I will also talk about the influence of psychiatric disorders on PNNs and on the inhibitory circuits in which they are involved. For this I will revise recent results from our laboratory on animal models involving adverse experiences, particularly in early life[3]. Additionally, I will present results about alterations in PNNs and inhibitory networks in postmortem tissue from patients with schizophrenia, bipolar disorder or major depression[4]. The focus of the presentation will be the cerebral cortex, but I will also explore other brain regions, such as the thalamus, in which PNNs have a relevant presence. Together, all the data available point to PNNs as promising targets to understand the physiology of inhibitory circuits involving fast-spiking cells, and to unveil the etiopathology of certain psychiatric disorders CNS[5].

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S15.4
Experience-dependent perineuronal net remodeling and memory in AD mice

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We and others have established a causal link between impaired function of parvalbumin (PV) GABAergic interneurons, aberrant brain network activity, and cognitive impairment in both Alzheimer's disease (AD) mice and patients (1). PV cells can be surrounded by a specific form of extracellular matrix, the perineuronal net (PNN), which is dependent on lived experiences and subsequent neuronal activity. PNNs play a crucial role in maintaining the PV cell network by strengthening existing synapses (2), and protecting memories from being erased (3). In this talk, we will present two strategies that successfully restored PNNs around PV cells and improved cognitive deficits in the Tg2576 model of AD. Firstly, a temporary stay in an enriched environment during early adulthood restores PV expression and PNNs in the hippocampus of Tg2576 mice (4), resulting in long-lasting beneficial effects on their cognitive performance. Secondly, a single local injection of neuregulin-1 (NRG1), a growth factor involved in the experience-dependent maturation of PV cells, is sufficient to restore both PV/PNN levels and memory performance (5). These findings suggest that the remodeling of PV/PNNs is responsible for the positive impact of these strategies in the AD model.

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4. *Cattaud et al., Neurobiol Aging (2018)*

5. *Rey et al., iScience (2022)*

S16

Intertwining of inflammatory pathways in the central nervous system: physiological versuspathological implications

CHAIR: Amira Zaky[1], Youssef Anouar[2]

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The central nervous system (CNS) has a unique relationship with the immune system known as CNS immune privilege. It maintains dynamic bi-directional communication with the immune system due to the protection conferred by the blood-brain barrier. It lacks lymphatic vessels and is devoid of dendritic cells, and the parenchyma cells do not express major histocompatibility complex (MHC) class-I antigen-presenting molecules. Neurons of the CNS play pivotal role in modulation of the function of glial cells and T lymphocytes. They sample, detect, and eliminate debris or apoptotic neurons by phagocytosis, but this ability is considerably decreased in a pro-inflammatory context. Microglia is involved in multiple processes such as neurogenesis, synapse elimination in a complement-dependent manner, or synapse plasticity. Neurodegenerative diseases share the fact that they derive from altered proteins that undergo an unfolding process followed by formation of β-structures and a pathological tendency of certain proteins to self-aggregate in neuronal cells. It is postulated that these protein unfolding events are the molecular alterations that trigger several neurodegenerative disorders. Most interestingly, these events occur as a result of neuroinflammatory cascades involving alterations in the cross-talks between glial cells and neurons as a consequence of the activation of microglia and astrocytes. An accumulation of a large amount of unfolded or misfolded polypeptides resulting from the number of pathogenetic sources such as mutations, inefficient folding, error in synthesis, may cause cell toxicity, as defense mechanisms enable to withstand. One of such molecules that assist protein homeostasis is molecular chaperons. Numerous studies support that amyloid-β peptide (Aβ) aggregation is mainly responsible for the pathogenesis of AD, which results from a mutation in the Aβ precursor protein (AβPP) that results in the accumulation of Aβ. Recent data suggest that the molecular chaperon suppresses protein misfolding and aggregation, and hence could be a therapeutic target for protein-misfolding brain disorders.

Pro-inflammatory cytokines such as tumor necrosis factor (TNF), interleukin (IL)-1, and IL-6, produced during the activation of innate immunity cells in peripheral tissues, are able to modulate the activity of CNS neuronal circuits through specific receptors expressed by neurons of the hypothalamus and other regions of the brain. Regulation of mitochondrial dynamics is essential for CNS health maintenance and leading to the induction of IL-10 and reduction of TNF-α secretion, increased cell viability and diminished cell injury in addition to

reduced oxidative stress. Mitochondria's position in astrocytes influences intracellular calcium level by the transferring between mitochondrial reticulum and endoplasmic reticulum. Remarkably, several neurodegenerative diseases correlate with detrimental calcium homeostasis. Mitochondria play an essential role in pathophysiology of neuropathic pain (NP). Recent research illustrates that mitochondria within the spinal dorsal horn (SDH), are sensitive to NP, and targeted mitochondrial Drp1 overexpression attenuates pain hypersensitivity. Drp1 offers a novel therapeutic target for pain treatment.

S16.1

Role of a selenoprotein in neuroprotection: Application to PD after intranasal administration

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Oxidative stress is central to the pathogenesis of different diseases affecting the central nervous system, but therapeutic strategies targeting this pathological process have been difficult to design. We have previously demonstrated that selenoprotein T (SELENOT), a new thioredoxin-like protein of the ER, is essential for embryonic development and dopaminergic neuron survival and function. In fact, analysis of human brain samples showed that SELENOT is highly expressed in the striatum of Parkinson disease (PD) patients compared to controls. In an animal model of PD, targeted SELENOT gene disruption in the brain provoked rapid and severe parkinsonian-like motor deficits. Based on these findings, we designed a 10-amino acid peptide named PSELT as a potential mimic of SELENOT active site to test its activity in PD and other nerve injury animal models. PSELT proved to be efficient in protecting dopaminergic neurons *in vitro* and *in vivo* and could improve motor skills in animal models of PD. Additionally, in a model of nerve injury exemplified using the facial nerve transection model in rat, we showed that PSELT improves motor recovery of the mystacial pad vibrissae, increases the electrical activity of the motor units of mystacial pad muscles and enhances axonal elongation and myelination of newly formed axons after injury. These results uncover the role of SELENOT as a neuroprotective enzyme and indicate that PSELT is a new therapeutic candidate for treatment of diseases affecting the nervous system.

S16.2

MicroRNAs as Potential Orchestrators in Alzheimer's related inflammatory Pathology: An experience from Egypt

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Alzheimer's (AD) is a deleterious multifactor neurodegenerative disorder and neuroinflammation is a characteristic hallmark of AD throughout its progression. Controlling triggers that unfold AD pathologies remain unclear, which hinder earlier diagnosis and successful therapy. More than 70% of experimentally detected microRNAs (miRNAs) are expressed in the brain, where they regulate signaling pathways, synaptic plasticity, microglial behavior, and neurite outgrowth. Increasing evidence suggest that miRNAs dysregulations are pivotal contributors in AD through deregulating diverse pathways implicated in AD pathogenesis. However, there is obvious scarcity in miRNAs data originating from low- and middle-income countries.

We explored the diagnostic and regulatory values of serum miR-34a, miR-29b and miR-181c in Egyptian AD patients as potential less invasive diagnostic AD markers. We utilized bioinformatics tools for target gene prediction. MicroRNAs levels were quantified in AD patients and healthy controls, together with the levels of amyloid Beta 42 (Aβ42), phosphorylated Tau (p-Tau) and TNF- α levels as distinctive AD markers and targets of the measured miRNAs. Sera miR-34a, miR-29b and miR-181c were significantly downregulated and associated with cognitive decline in AD patients. Gene ontology showed amyloid binding, inflammation signaling, and phosphorylation as major affected functions. Aβ42, pTau and TNF-α levels were significantly increased in AD patients. ROC analysis showed that combining miRNAs panel with Aβ42, TNF-α and pTau levels remarkably increased their diagnostic power (AUC = 0.97, 95 % C·I. 0.94–1.00 at $p < 0.001$).The study highlights the promising diagnostic potential of miRNAs in AD and spots miRNAs importance for deeper understanding of AD progression.

S16.3

Analgesic effects of the relaxin family peptides in inflammatory pain.

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Affecting around 10% of world population, chronic pain and its related emotional comorbidities are major health issues. Pathways and modulation of pain are well documented in the spinal cord, but the implication of neuropeptides in this modulation remains poorly described in the brain. Relaxin-3 neuropeptide displays antidepressant and anxiolytic effects, and our preliminary results indicate an analgesic role in rat and mouse.

Relaxin-3 is expressed by nucleus incertus (NI) neurons that project to different cortical (e.g. anterior cingulate cortex (ACC)) and subcortical (e.g. amygdala) areas of the pain matrix.

Because of the prominent expression of the relaxin-3 G protein-coupled receptor (RXFP3) in those areas, we aim at studying the pain modulatory effects of relaxin-3 by using pharmacological, behavioral and anatomical approaches in a mouse model of persistent inflammatory pain obtained by the injection of Complete Freud's Adjuvant in the hind paw.

Acute intra-amygdalar injection of RXFP3 agonists (A2 or A5) alleviates both mechanical and thermal pain, while intra-ACC injection has an effect only on mechanical sensitization. The effect of AAV-mediated chronic release of another RXFP3 agonist (I5/R3) has been also tested in the ACC and amygdala. Antegrade tracing experiments have been performed using AAV-DIO-eGFP injection in NI. A whole-brain mapping of eGFP-labelled RLN3 neurons was done to estimate the density of projections from NI in physiological and pain conditions.

RXFP3 mRNA expression was assessed in somatostatin-expressing interneurons both in the ACC and amygdala by using multiplex fluorescent in-situ hybridization (RNAscope). Relaxin-3 innervation of somatostatin interneurons was studied with an in-house automated routine for quantitative 3D immunolabelling.

Our data establish the organization of relaxin-3/RXFP3 microcircuits and highlight a novel role for this peptide family and suggest their therapeutic potential in persistent pain conditions.

S16.4

Implication of the pleiotropic APE1/Ref-1 Redox activity in pain sensitization mechanism

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Pain condition is complex and multifactorial involving disruption of different cellular signaling pathways. An interesting, multifunctional protein called Apurinic/Apyrimidinic Endonuclease 1/Redox Effector- 1 (APE1/Ref-1) has been reported to play a key role in many pathological conditions associated with inflammation including those in CNS. We investigated the possible implication of APE1/Ref-1 expression level upon induction of inflammatory pain condition using formalin injection in experimental rats. To understand the role of APE1 we co-administered some groups with a selective chemical inhibitor of the redox activity (E3330) versus nutraceutical compounds like Curcumin or Spirulina in other groups.

Behavioral effects and pain sensitization were followed up in the different experimental groups in a timely manner. The results confirmed the protective effects of these compounds in inflammatory conditions. APE1 level was reduced in the spinal cord tissues in response to formalin induction, while co-administration of either the selective redox activity inhibitor or the nutraceuticals alleviated this inhibition significantly. Different biomarkers (redox and proinflammatory markers) were also analyzed to investigate the mechanistic process of healing/protection.

In conclusion, the results indicated that APE1 plays a critical role in formalin-induced pain condition and therefore is a promising therapeutic target that needs further investigations in CNS disorders. The special focus on the effects of nutraceuticals in controlling inflammatory signaling pathways along with the modulation of key cellular effector proteins like APE1 draws attention to their potential efficiency as possible protective/therapeutic agents in the future.

S16.5

Efficacy and pharmacodynamic profile of *Brassicaceae* constituents in the management of chronic pain

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Brassicaceae are natural sources of compounds endowed of anti-inflammatory, antioxidants and neuroprotective effects. The interest in *Brassicaceae* began with the evidence that their peculiar constituents, glucosinolates (GLs) and the hydrolysis-derived isothiocyanates (ITCs), can modulate both the inflammatory response (NF-kB-pathway) and oxidative stress (Nrf2/ARE-pathway), largely involved in chronic pain pathogenesis. In this scenario, our preclinical research proved the efficacy of GLs and ITCs against different chronic musculoskeletal, neuropathic and visceral pain conditions. In particular, we demonstrated that ITCs, by the slow-H_2S release *in vivo*, can modulate the activity of a subtype of K_V7 potassium channels involved in both somatic and visceral pain transmission, providing a further incentive to their use in pain management. We observed that GLs-enriched preparations from plants as *Brassica oleracea*, *Eruca sativa* and *Camelina sativa* are effective in the symptomatic relief of pain, without developing tolerance after repeated administrations. Moreover, the employment of *Brassicaceae*-based products can counteract chronic pain establishment by protecting the nervous system from inflammatory insult, like that caused by colitis. *Brassicaceae* constituents are also able to modulate the activity and the expression of several targets involved in pain regulation, like opioid and proliferator- activated receptor alpha (PPAR α) receptors, as in the case of *Camelina sativa*, an ancient oilcrop which is attracting renewed attention for its nutraceutical potential. In conclusion, the efficacy and versatility against different type of pain, the good bioavailability and safety,

together with the variety of formulations available, confer to *Brassicacea*e a high degree of clinical translatability in the pain therapy.

S17

From neuronal plasticity to glia protection: mapping the path of resilience and vulnerability to stress

CHAIR: Marta Valenza[1], Carla Nasca[2]

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This symposium will discuss i) novel evidence of central and peripheral inflammation (cytokine signaling, insulin resistance, mitochondrial dysfunction) in response to acute and chronic stress using cross-species models; ii) the cross-talk between glial cells and neurons regulating stress neuroplasticity and iii) computational approaches to integrated system-levelstrategies for identifying and more effectively treating subtypes of stress-related depressive and cognitive disorders. New data will be presented and discussed as described below. Barbara Di Benedetto (University of Regensburg, Germany) will discuss specific astroglia signatures in social and emotional dysfunctions. Benedetta Bigio (New York University, USA) will present new data on the role of neuronal and glial exosomes in stress-related phenotypesof depressive and cognitive disorders. Roberta Facchinetti (Sapienza University of Rome, Italy) will present recent preclinical findings showing the differential contribution of astrocytes andmicroglia, as well as neuroinflammation, in the adaptive and maladaptive response to acute inescapable stress, dwelling on a possible treatment strategy. Laura Musazzi (University of Milan, Italy) will discuss in vivo data on the differential changes in microglial morphology andboth central and peripheral inflammation in resilient and vulnerable subjects after chronic stress. Prof. Carla Nasca (New York University, USA, chair and presenter) will present new preclinical and clinical evidence on the emerging role of mitochondria as regulators of epigenetic programming of neuroplasticity to stress.

S17.1

Molecular and morphological signatures of astroglial responses to socio-emotional dysfunctions

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Socio-emotional dysfunctions are debilitating neuropsychiatric (NP) disorders with a huge economic burden worldwide. However, disease trajectories are still not completely

understood and treatments not fully efficacious. An astrocyte pathology has been long aknoweledged for its contribution to the development of NP disorders. Clinical and pre-clinical studies show alterations in astrocyte cell number, morphology and molecular makeup in different affected brain regions.
Astrocytes regulate shape and functions of the synaptic compartment through modulatory membrane-bound proteins or released factors. Thereby, they support nerve cells in the acquisition and storage of information through learning processes accompanied by synaptic remodelling. An imbalanced astrocyte activity can therefore negatively affect synaptic changes, leading to the onset of socio-emotional dysfunctions.
The peculiar position of astrocytes between synaptic and vascular compartments further allows them to form a functional unit that "senses" the brain state and secrete factors in the bloodstream as a reflection of this state. Such factors may serve as biomarkers of distinct cellular (dys)functions and help to improve diagnostic/treatment options tailored to the needs of individual patients.
During development and in adulthood, synaptic phagocytosis (pruning) is pivotal to refine neuronal networks. Astrocyte-dependent pruning, mediated by the membrane-bound protein MEGF10, regulates synapse elimination and its altered activity may result in imbalanced synaptic remodelling and the onset of NP disorders.
We examined MEGF10 expression and localization to evaluate its impact on pruning and neuronal network refinement in socio-emotional dysfunctions and its potential as a novel target for the development of more efficacious treatment strategies for NP disorders.

S17.2

Computational approaches and exosomes to identify modifiable targets for stress-related disorders

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Mood and cognitive disorders are highly prevalent diseases worldwide. At present, objective tools for detecting these disorders and monitoring treatment responses are not available. Our

prior work showed decreased levels of the pivotal mitochondrial metabolite acetylcarnitine (LAC) in patients suffering from depression, and that the deficiency of LAC is accompanied by a brain metabolic dysfunction known as insulin resistance (IR) as assessed by measures of key insulin markers in discrete exosomes enriched for proteins highly expressed in the brain. Here, we present new data showing a role of the epigenetic modulator of hippocampal glutamatergic function LAC in cognitive regulation with important sex differences in free carnitine (the main derivative of LAC). Our new data showed decreased levels of LAC in subjects with cognitive impairments (CI) as compared to age- and sex-matched cognitively healthy controls, and sex differences in free carnitine levels in relation to the severity of cognitive dysfunction as assessed by using the Mini Mental Status Exam (MMSE). Using computational approaches, we also found that the integration of peripheral measures of mitochondrial metabolism with CSF measures of amyloid-beta 42 and total Tau meaningfully improves diagnostic accuracy. The current findings of sex differences in mitochondrial metabolism in relation to the severity of cognitive dysfunction point to new mechanistic targets of cognitive regulation.

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S17.3

Molecular changes of glia and neurons in the maladaptive response to acute stress are prevented by a single administration of ketamine in a rodent model of PTSD

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Exposure to stress can be differently perceived by individuals depending on their level of stress resilience or vulnerability. Vulnerability to stress increases the risk of developing

several neuropsychiatric disorders, including post-traumatic stress disorder. Thus, exploring the neurobiology of the resilient and vulnerable response to acute stress is critical for the treatment and prevention of stress-related disorders and represents a currently unmet need. Using a model of acute inescapable footshock stress, we demonstrated the selective presence of anhedonic behavior, glial reactivity, and neuronal changes in the prefrontal cortex of vulnerable but not resilient rats, both classified according to their anhedonic-like behavior. Resilient rats instead showed a neurotrophic response, characterized by increased protein expression of brain-derived neurotrophic factor (BDNF) and microtubule-associated protein (MAP)2. Considering its anti-inflammatory and neuroprotective properties, we studied the effect of a single subanesthetic i.p. administration of ketamine (10 mg/kg) on the observed maladaptive changes. Ketamine selectively blocked the excessive release of astrocytic S100B, microglial reactivity, activation of NF-kB, and increased expression of interleukin-18 and tumor necrosis factor-α found in vulnerable animals, together with restoring the elevated protein levels of astrocytic connexin 43. At the neuronal level, ketamine counteracted the decreased expression of MAP2 and the increased levels of glial-derived neurotrophic factor (GDNF), selectively detected in susceptible rats. Collectively, these results suggest glial reactivity, alteration of brain factors, and neuronal damage as critical factors characterizing vulnerability to acute traumatic stress and propose ketamine as a pro-resilience agent able to potentially protect against the development of stress-induced psychiatric disorders.

S17.4

Mechanisms of resilience and vulnerability to chronic mild stress in rats: a role for inflammation?

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Stress is a physiological response orchestrated by the brain. However, when stress is overwhelming or prolonged, some individuals may fail in activating coping strategies leading to maladaptive consequences and higher pathological risk. Understanding the mechanisms underlying the trajectories of stress vulnerability and resilience would be extremely important to develop novel therapeutic approaches for the treatment of stress-related diseases, including depression.
Neuroinflammation has been reported to contribute to the maladaptive consequences of stress affecting neuroplasticity. Microglia, being the immune cells in the central nervous system, play crucial roles in neuroinflammation. Nevertheless, little is known about the role of microglial morphological changes in the response to stress.

In this study, we used high-throughput microscopy and three-dimensional image analysis to investigate brain area-specific changes in microglia morphology and measured changes in the levels of cytokines in vulnerability and resilience to chronic stress.
We applied the chronic mild stress animal model of depression on rats and deemed animals vulnerable or resilient according to the anhedonic-like phenotype measured by the sucrose preference test. After sacrifice and brain collection, we performed immunohistochemistry and deep microscope acquisition on hippocampal and prefrontal cortex coronal sections. We found that in animals resilient to chronic stress microglia cells were more ramified than in vulnerable ones, suggesting an active inflammatory state associated to stress vulnerability. We also found brain-area specific changes in the pattern of inflammatory and antinflammatory cytokines. Overall, our study supports an involvement of neuroinflammation and microglia remodeling in vulnerability and resiliency to stress.

S17.5

Epigenetic mechanisms of neuroplasticity to stress: emerging role of mitochondria

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Growing evidence suggest a key role of the pivotal mitochondrial metabolite L-acetylcarnitine (LAC) as a novel epigenetic modulator of neuroplasticity and a promising therapeutic target for clinical phenotypes of depression associated with childhood trauma. In rodent models of chronic stress, administration of LAC leads to a rapid and persistent antidepressant-like response by increasing a chronic stress-induced suppression of acetylation of histone H3 lysine K27 (H3K27ac) and the related expression of key genes for neuronal plasticity, such as the metabotropic glutamate receptor-2 (mGlu2) in ventral dentate gyrus (vDG) glutamatergic neurons. We also showed that mGlu2 receptors are part of a glial-neuronal network involving an xCT-driven release of glial glutamate that stimulates activation of mGlu2 receptors, which, in turn, inhibits neuronal glutamate release to regulate resilience to chronic stress. Furthermore, modulating mitochondrial metabolism of LAC is predictive of changes in other important aspects of human physiology involved in mood and cognitive disorders, such as central and peripheral insulin resistance (IR). Ongoing analyses of the molecular cargo of neuronal and glial exosomes will help us to characterize the phenotypes of mitochondrial dysfunction. Further understanding of the cellular and molecular bases of mitochondrial metabolism may reveal surprising insights in a complex network of biological factors contributing to the risk for stress-related diseases, ultimately leading to personalized medicine strategies.

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S18

New Perspectives in Mechanisms of Neurodegeneration

CHAIR: Alexia Polissidis

American College of Greece; Collaborating Researcher, Biomedical Research Foundation Academy of Athens

By 2030, 1 in 6 people in the world will be aged 60 years or over. As aging is the greatest risk factor for neurodegenerative diseases, the mounting burden of these currently incurable diseases needs to be addressed. Despite the trials and tribulations associated with studying the enigmatic processes of neurodegeneration, we are closer than ever before to unraveling its mysteries. In this symposium, we will present and discuss the most advanced science behind neurodegeneration including the role of adaptive immunity, gene expression regulation, RNA metabolism, and how these discoveries are spurring novel therapeutic strategies.

S18.1

Two New ALS Targets (and one new Drug)

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Mutations in the ataxin-2 gene (ATXN2) cause the neurodegenerative disorders amyotrophic lateral sclerosis (ALS) and spinocerebellar ataxia type 2 (SCA2). A therapeutic strategy using antisense oligonucleotides targeting ATXN2 has entered clinical trial in humans. Additional ways to decrease ataxin-2 levels could lead to cheaper or less invasive therapies and elucidate how ataxin-2 is normally regulated. We performed two genome-wide screens in human cells to identify genes that regulate ataxin-2 levels. In one screen, we identified *RTN4R*, the gene encoding the RTN4/NoGo-Receptor, as a potent modifier of ataxin-2 levels. *RTN4R* knockdown, or treatment with a peptide inhibitor, is sufficient to lower ataxin-2 protein levels in mouse and human neurons in vitro, and *Rtn4*r knockout mice have reduced ataxin-2 levels *in vivo*. We provide evidence that ataxin-2 shares a role with the RTN4/NoGo-Receptor in limiting axonal regeneration. Reduction of either protein increases axonal regrowth following axotomy. In another screen, we identified genes encoding components of the lysosomal

vacuolar ATPase (v-ATPase) as modifiers of endogenous ataxin-2 protein levels. We show that multiple FDA-approved small molecule v-ATPase inhibitors lower ataxin-2 protein levels in mouse and human neurons, and oral administration of at least one of these drugs-etidronate-is sufficient to decrease ataxin-2 in the brains of mice. Together, we propose RTN4/NoGo-Receptor and v-ATPase as drug targets for ALS and SCA2 and demonstrate the value of unbiased screens in identifying genetic-and potentially druggable-modifiers of human disease proteins.

S18.2

Unraveling the Complex Role of Protein Aggregation in Parkinson's Disease; From mechanisms to diagnostics and therapeutic strategies

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It has been more than 100 years since Lewy bodies (LBs) were first discovered in the brain of Parkinson's disease patients and more than 20 years since alpha-synuclein (α-syn) aggregates were identified as one of the main components of LBs. However, several fundamental questions regarding how LBs are formed, their composition, and whether they protect against or cause neurodegeneration in Parkinson's disease (PD) and other synucleinopathies remain unanswered. Recent application of advanced electron microscopy, mass spectrometry and imaging technologies in combination with access to novel antibodies has enabled major advances towards deconstructing the complexity of LBs and alpha-synuclein pathology in the brain and reverse engineering LB formation in neurons and rodent models. These studies show that the process of LB formation involves a complex interplay between α-syn fibrillization, posttranslational modifications, and interactions between α-syn aggregates and proteins, lipids, and membranous organelles. Furthermore, they provide strong evidence linking the process of LB formation, rather than merely α-syn fibril formation, as one of the major drivers of neurodegeneration through disruption of cellular functions and proteostasis, and inducing mitochondria damage and deficits, and synaptic dysfunctions.

Relying on recent insights into the 1) clinical heterogeneity of PD; 2) the biochemical and ultrastructural properties of LBs in the brain; 3) the heterogeneity of alpha-synuclein pathology and co-occurrence of other co-pathologies in PD and aging brains, I will present working models and hypotheses that could explain the relationship, or lack of, between alpha-synuclein pathology, and neurodegeneration in sporadic and some genetic forms of PD.

I will then present evidence that 1) supports important roles for the processes of alpha-synuclein misfolding, aggregation, and LB formation in the development and progression of sporadic and some genetic forms of PD; 2) shows how these processes could contribute to neuronal dysfunction and degeneration through a combination of both loss and gain of toxic

mechanisms; and 3) demonstrate that targeting the native state of alpha-synuclein and/or alpha-synuclein pathology formation and spreading represents a viable strategy for developing disease-modifying therapies to treat PD. I will close by emphasizing the need for combination therapies that account for the pathological and clinical heterogeneity of PD and other synucleinopathies.

S18.3

The Impact of Melatonin on Diurnal Variation of Extracellular Dopamine in CBA/CaJ and C57BL/6 Mice: A Comparative Study

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Melatonin, an indolamine, is derived from the precursor tryptophan through a series of enzymatic steps mediated by tryptophan 5-hydroxylase, L-amino acid decarboxylase, hydroxyindole-0methyltransferase and arylalkylamine N-acetyltransferase. In a commonly used strain of C57BL/6J mice, the genes for both of these enzymes are truncated, resulting in a lack of circadian melatonin rhythmicity. By introducing these alleles, a C57BL/6J congenic line known as CBA/CaJ was created, which regained the ability to synthesize melatonin. It has been shown that extracellular striatal dopamine (DA) levels fluctuate during the day, most likely as a result of changes in the cholinergic neurons' circadian rhythm-dependent activity, which itself would be controlled by melatonin's rhythmicity. As diurnal changes in DA have been shown to alter synaptic connectivity and animal behavior, understanding this modulation has consequences for diagnostics and treatment of neurodegenerative and psychiatric disorders. Here, we investigated the effect of MLT on evoked DA release using fast scan cyclic voltammetry (FSCV) in acute striatal slices from CBA/CaJ and C57BL/6J mice. Slices were prepared twice during the light/dark cycle, at the nadir and peak of the MLT levels. Our results demonstrate that during the dark cycle, when MLT concentration is highest, DA release decreases only in CBA and not in C57BL6 mice. Furthermore, physiological concentrations on exogenous MLT applied to the slice inhibit DA release in both strains of animals with the same potency, confirming the presence of melatonin receptors. Our findings further support the notion that melatonin receptor activation plays an important physiological function in modulating striatal DA release and establish dose- and time- dependent kinetics of the release inhibition and recovery. Future work will be aimed at elucidating the cell type and receptors responsible for the effect of MLT.

S18.4

Drosophila Melanogaster as A Model System for Drug Discovery in Neurodegenerative Disorders

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Aging is a complex phenomenon caused by the time-dependent loss of cellular homeostasis and consequently of physiological functions. This process is affected by both genetic and environmental factors. The balanced functionality of cellular antioxidant and proteostatic modules is central to genome, proteome and mitochondrial stability. The antioxidant response system comprising (among others) the ubiquitously expressed NFE2-related transcription factor 2 (NRF2) and its redox-sensitive cytoplasmic inhibitor Kelch-like ECH-associated protein 1 (KEAP1) defends tissues against oxidative stress, thereby protecting against pathologies that relate to cellular biomolecules damage. **Aim:** To reveal in higher metazoans the NRF2/KEAP1 regulatory function during the different phases of life and in age-related diseases. Methods: Studies were performed in a range of transgenic Drosophila flies. **Results:** Our studies have revealed the dose-, tissue- and disease-dependent activity of the NRF2/KEAP1 regulatory network. Specifically, NRF2 is part of a circuit that ensures functional wiring of proteostatic and mitostatic modules and consequently organismal survival during stress; notably, prolonged NRF2 hyperactivation increases stress tolerance at the cost of aging acceleration due to metabolic deregulation. Interestingly, we found a cytoprotective role of NRF2 in various age-related degenerative diseases. These results parallel an extensive screening program for the identification of natural products (e.g., extracts or small molecules) from various sources of the biosphere that can be used in a translational intervention as NRF2 activators. **Conclusions:** The understanding of the NRF2/KEAP1 regulatory network function at a whole organism level will aid the development of future clinical interventions targeting this pathway.

S19

New Insights into Activated Kinases, Multiple Sclerosis and Receptors Mechanisms

CHAIR: Lamia Bouslama-Oueghlani (FR)

The symposium titled "New Insights into Activated Kinases, Multiple Sclerosis, and Receptors Mechanisms" brings together groundbreaking research findings from four distinct presentations. These four presentations collectively broaden our understanding of activated kinases, multiple sclerosis, and receptor mechanisms. They shed light on novel regulatory pathways in myelination, viral associations in neuroimmunological diseases, and the molecular interactions between organic polysulfides and the TRPA1 receptor. These insights

may have significant implications for future research and potential therapeutic strategies in these complex neurological conditions.

Lucas Baudouin et al. delve into the role of PAK1 (P21 Activated Kinase 1) in oligodendrocytes (OLs) and its impact on myelin formation. They find that PAK1's inhibition leads to actin disassembly, a crucial step in myelination, shedding light on a novel regulatory mechanism in OLs.

Rafika Ben Laamari et al. explore the intricate involvement of viral infections, particularly herpesviruses, in neuroimmunological diseases like multiple sclerosis (MS) and neuro-Behçet (NB). Their study uncovers the presence of herpesviruses in cerebrospinal fluid and highlights variations in viral prevalence between NB and MS patients, raising questions about the role of viral infections in these conditions.

Balázs Nemes et al. investigate the binding sites of organic polysulfides on the human TRPA1 receptor, revealing the critical role of cysteine residues in the receptor's activation. This study provides insights into the mechanism of action of organic polysulfides and their interaction with TRPA1, potentially paving the way for therapeutic applications.

Rafika Ben Laamari et al. (different from the previous presentation) continue their exploration of herpesvirus infections and their correlation with T CD8+ effector cells in patients with MS and NB. They identify the presence of multiple herpesviruses in cerebrospinal fluid and highlight differences in viral prevalence between NB and MS patients. Moreover, theirfindings suggest a link between herpesvirus infections and T CD8+ effector cell populations.

S19.1

PAK1 inactivation triggers myelin formation through actin disassembly in oligodendrocytes

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In the central nervous system (CNS), myelin formation by oligodendrocytes (OL) relies on actin dynamics. Actin polymerization supports the ensheathment step when OL processes contact and surround selected axons. A drastic deconstruction of actin cytoskeleton is then required to enable the wrapping phase and the formation of multilayered myelin membrane sheaths. Willing to decipher the mechanisms controlling myelin wrapping, we studied PAK1 (P21 Activated Kinase 1), a kinase protein whose inhibition is known to trigger actin depolymerization outside the CNS. Herein, we show that PAK1 is increasingly expressed in

mature myelinating OLs, while its kinase activity is greatly inhibited. *In vivo*, PAK1 conditional deletion in OLs leads to a thickening of myelin sheaths. Using *in vitro* and *ex vivo* models, we provide compelling evidence demonstrating that inhibition of PAK1 kinase activity in OLs is crucial for myelination through its regulation of actin cytoskeleton. Indeed, preventing PAK1 inhibition in mature OLs maintains actin in a polymerized state, and consequently restrains myelin expansion. Conversely, strengthening PAK1 inhibition in mature OLs enhances actin depolymerization and increases myelin expansion. These results stress the presence of an endogenous inhibitor of PAK1 in OLs. We therefore investigated the involvement of an attractive candidate known to inhibit PAK1 outside the CNS through direct binding, but whose role in OLs has not yet been studied. Overall, this study presents PAK1 and its inhibitor as a molecular duo regulating OL myelination through actin disassembly.

S19.2

The Fine Tuning of Infiltrated T Cells in Multiple Sclerosis.

Rafika Ben Laamari[1], Olfa Maghrebi[1], Zakaria Saied[2], Samia Ben Sassi[2], Mohamed-Ridha Barbouche and Meriam Belghith[1]

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Neuroimmunological diseases are known as multifactorial diseases including genetic, immunological and environmental factors. Viral infection seems to play a major role in the onset of these diseases. In the multiple sclerosis (MS) model, the presence of immunoglobulins in the cerebrospinal fluid (CSF) demonstrates that a viral infection could be responsible for the breakdown of tolerance in patients. In our laboratory, we are interested in the study of two neuroinflammatory diseases: neuro-Behçet (NB) and MS.

The main objectives of this study are to analyze the presence of herpesviruses in the CSF of patients with NB and MS and to explore a correlation between these infections and TCD8+effector populations.

This study included blood and CSF samples from 32 MS patients and 27 NB patients from Mongi Ben Hamida National Institute of Neurology.

For the molecular study, herpesviruses (except HHV-8) screening was established by multiplex PCR and cytokines (IFN-γ, IFN-α, granzyme and perforine) quantification was assessed by qRT-PCR. For the cellular study, the analysis of CD4 and CD8 T lymphocytes was performed by flow cytometry.

First, we identified in the CSF of the two studied groups, the presence of the following herpesviruses: HSV-1, HSV-2, EBV, HHV-6 and VZV. The most striking finding is the higher presence of EBV in patients suffering from NB (59.26%) as compared to MS (28.12%).

Otherwise, we confirmed by flow cytometry the high infiltration of CD4+ and CD8+ T populations in the CSF of the two groups of patients, while discovering that the majority of

IFN-γ secreting population corresponds to the CD8+ population. In addition, quantification of the antiviral cytokine IFN-α and IFN-γ were performed. We obtained no significant difference in the expression of these two cytokines between the two groups of patients studied. For the cytotoxic cytokines granzyme and perforine response, results are still in progress.
In conclusion we demonstrate for the first time the presence of EBV infection in more than half of NB patients. We also found an IFN-γ secreting CD8 T population in the two patient groups. An analysis with a larger cohort would allow us to realize the existence of a possible correlation between these parameters.

S19.3

Determination of the binding sites of organic polysulfides on human TRPA1 by mutant variants of the receptor

Balázs Nemes[1], Szabolcs László[1,2], Balázs Zoltán Zsidó[1], Csaba Hetényi[1], Ádám Fehér[3], Ferenc Papp[3], Zoltán Varga[3], Éva Szőke[1], Zoltán Sándor[1] Erika Pintér[1]

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[3]Department of Biophysics and Cell Biology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary

Earlier data have established that endogenous inorganic polysulfides have significant biological actions activating the Transient Receptor Potential Ankyrin 1 (TRPA1) receptor. Organic polysulfides are much more stable molecules with TRPA1 agonist effects The aim of the present study was to investigate the mechanism of action of organic polysulfides by identification of their binding sites on the receptor. Since polysulfides can readily interact with the thiol side chain of the cysteine residues of the protein, several cysteine residues were replaced by alanine or serine via site-directed mutagenesis. TRPA1 mutant variants decreased or lost activating effect of the polysulfides, but their other functions, such as the effects of non-electrophilic agonists and antagonists remained intact. The binding properties of the mutant receptors were also analyzed by in silico molecular docking. Functional changes were tested by in vitro methods: calcium sensitive fluorescent flow cytometry, whole-cell patch-clamp and radioactive calcium-45 liquid scintillation counting. Our results indicate that cysteines forming the conventional binding site of electrophilic agonists. Although C621, C641 and C665 also bind the organic polysulfides, C621 plays the key role. However, only their combined mutation caused complete inhibition of the receptor activation. Our study provided clear evidence that organic polysulfides activate the TRPA1 exclusively by the reactive cystein residues.
Funded by The Hungarian National Brain Research Program 3.0 (NAP 3.0)

S19.4

Study of the Correlation between Herpesvirus Infection and T CD8+ Effector Cells in Patients with Multiple Sclerosis and Neuro-Behçet's Disease

Rafika Ben Laamari[1], Olfa Maghrebi[1], Zakaria Saied[2], Samia Ben Sassi[2], Mohamed-Ridha Barbouche and Meriam Belghith[1]

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Background: Neuroimmunological diseases are known as multifactorial diseases including genetic, immunological and environmental factors. Viral infection seems to play a major role in the onset of these diseases. In the multiple sclerosis (MS) model, the presence of immunoglobulins in the cerebrospinal fluid (CSF) demonstrates that a viral infection could be responsible for the breakdown of tolerance in patients. In our laboratory, we are interested in the study of two neuroinflammatory diseases: neuro-Behçet (NB) andMS.
The main objectives of this study are to analyze the presence of herpesviruses in the CSF of patients with NB and MS and to explore a correlation between these infections and TCD8+effector populations.

Material and methods: This study included blood and CSF samples from 32 MS patients and 27 NB patients from Mongi Ben Hamida National Institute of Neurology.
For the molecular study, herpesviruses (except HHV-8) screening was established by multiplex PCR and cytokines (IFN-γ, IFN-α, granzyme and perforine) quantification was assessed by qRT-PCR. For the cellular study, the analysis of CD4 and CD8 T lymphocytes was performed by flow cytometry.

Results and conclusion: First, we identified in the CSF of the two studied groups, the presence of the following herpesviruses: HSV-1, HSV-2, EBV, HHV-6 and VZV. The most striking finding is the higher presence of EBV in patients suffering from NB (59.26%) as compared to MS (28.12%).
Otherwise, we confirmed by flow cytometry the high infiltration of CD4+ and CD8+ T populations in the CSF of the two groups of patients, while discovering that the majority of IFN-γ secreting population corresponds to the CD8+ population. In addition, quantification of the antiviral cytokine IFN-α and IFN-γ were performed. We obtained no significant difference in the expression of these two cytokines between the two groups of patients studied. For the cytotoxic cytokines granzyme and perforine response, results are still in progress.
In conclusion we demonstrate for the first time the presence of EBV infection in more than half of NB patients. We also found an IFN-γ secreting CD8 T population in the two patient groups. An analysis with a larger cohort would allow us to realize the existence of a possible correlation between these parameters.

S20
Novel approaches in preclinical neuroscience
CHAIR: Christina Dalla (GR) and Olfa Masmoudi-Kouki (TN)

This symposium, " Novel approaches in preclinical neuroscience " showcases groundbreaking research spanning multiple dimensions of neuroscience. The talks within this symposium delve into diverse aspects of the field, providing valuable insights into different facets of brain function, neurological diseases, and therapeutic approaches.
- "Sex as a Biological Variable in Preclinical Neuropsychopharmacology" by Christina Dalla
This presentation focuses on the integration of sex and gender into neuropsychopharmacology research, emphasizing its relevance for understanding sex-related differences in neuropsychiatric disorders and treatment responses. It highlights the importance of proper study design to detect such differences and discusses recent developments in the field.
"Gene Regulation Networks in Neural Development and Cancer Progression: Novel Therapeutic Targets in Brain Tumors and Diseases" by Dimitrios Gkikas, Valeria Kaltezioti, Dimitris Stellas, Alexia Polissidis, Panagiota Milioti, and Panagiotis K. Politis
This talk unveils promising insights into glioblastoma treatment by exploring the orphan nuclear receptor NR5A2/LRH1 as a potential drug target. Clinical data analysis and experimental evidence support the role of NR5A2 in inhibiting cancer cell growth, presenting new therapeutic possibilities for nervous system tumors.
- "Cytoprotective and Neurotrophic Effects of OctaDecaNeuropeptide (ODN) in In Vitro and In Vivo Models of Neurodegenerative Diseases" by Yosra Hamdi, Tasnim Chagrani, Sada Mashadani, Ikram Ghouili, Jérôme Leprince, Taoufik Ghrairi, David Vaudry, Marie-Christine Tonon, Gérard Lizard, and Olfa Masmoudi-Kouki
This talk delves into the therapeutic potential of OctaDecaNeuropeptide (ODN) in neurodegenerative diseases. ODN's role in protecting neurons and glial cells from neurotoxicity, along with its antiapoptotic and neurotrophic properties, offers promising insights for treating cerebral injuries involving oxidative stress and neurodegeneration.

S20.1
Sex as a biological variable in preclinical neuropsychopharmacology

Christina Dalla

Dep. of Pharmacology, Medical School, National and Kapodistrian University of Athens

Recent guidelines, policies and gender equality plans in the European Commission and worldwide are promoting the integration of sex and gender in research. This is of particular

importance for neuroscience and psychopharmacology, as many neuropsychiatric disorders are characterized by sex differences in prevalence, symptomatology and treatment response. For example, depression and anxiety disorders are overall more prevalent in women than in men and sex differences exist in their pathophysiology and treatment. Also, it is known that there are substantial sex differences in pharmacokinetics and pharmacodynamics of several psychotropic drugs, including antidepressants. Therefore, both animal and human studies need to be properly designed and powered, in order to detect sex and/or gender differences. Recent advances in the field of neuropsychopharmacology facilitates research in males and females. An educational video series (https://www.preclinicaldataforum.org/addressing-sex-as-a-biological-variable-training/) that provides the practical knowledge necessary for researchers to incorporate sex as a biological variable into research has been developed through a grant from the National Institute of General Medicines.
In this respect, our group in the National and Kapodistrian University of Athens has thoroughly studied sex differences in models of depression, stress response and antidepressant activity. Moreover, we have investigated the behavioral and neurochemical effects of estrogen depletion by aromatase inhibition in both male and female rats. Currently, we are studying sex differences in the estrogen membrane GPER1 receptor in the brain, which could serve as a potential target for rapid-acting drugs. Overall, our studies highlight the importance of studying sex differences and aim to gender-based neuropsychopharmacological treatments.

This research has been supported by the Special account for Research Grants of the National and Kapodistrian University of Athens, Greece and the Hellenic Foundation for Research and Innovation (HFRI-FM17-1676).

S20.2

Gene regulation networks in neural development and cancer progression: novel therapeutic targets in brain tumors and diseases

Dimitrios Gkikas[1], Valeria Kaltezioti[1], Dimitris Stellas[2], Alexia Polissidis[3], Panagiota Milioti[1], and Panagiotis K. Politis[1]

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[3]*Centre for Clinical, Experimental Surgery & Translational Research, Biomedical Research Foundation of the Academy of Athens, 11527 Athens, Greece*

Glioblastomas are nervous system tumors that originate from astrocytes and neural stem or progenitor cells. They are characterized by rapid progression and poor survival rates. Despite recent advances in the provided therapy, the average survival time remains extremely low, between 12 and 15 months. These clinical observations underscore the need for novel

therapeutic insights and pharmacological targets. In this study, we show that the orphan nuclear receptor NR5A2/LRH1 is a negative regulator of cancer cell growth and a possible drug target for tumors of the nervous system. In particular, by meta-analyzing clinical data from the TCGA and Oncomine databases, we find that high expression levels of NR5A2 are associated with a favorable prognosis in patients with glioblastoma tumors. In addition, we experimentally show that two well-established pharmacological agonists of NR5A2, DLPC and DUPC, are able to inhibit proliferation of neural stem cells and glioblastoma cells through NR5A2 activation. Most importantly, treatment with DLPC inhibits glioblastoma tumor growth in vivo in heterotopic and orthotopic xenograft mouse models. These data render NR5A2 a potential pharmacological target for the treatment of nervous tissue-related tumors.

This work is supported by the Hellenic Foundation for Research and Innovation (H.F.R.I.) under the "First Call for H.F.R.I. Research Projects to support Faculty members and Researchers and the procurement of high-cost research equipment grant" (Project Number: 1782).

S20.3

Cytoprotective and neurotrophic effects of OctaDecaNeuropeptide (ODN) in in vitro and in vivo models of neurodegenerative diseases

Yosra Hamdi[1], Tasnim Chagrani[1], Sada Mashadani[1], Ikram Ghouili[1], Jérôme Leprince[2], Taoufik Ghrairi[1], David Vaudry[3], Marie-Christine Tonon[2], Gérard Lizard[4] and Olfa Masmoudi-Kouki[1]

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[3]Normandy University, Regional Platform for Cell Imaging of Normandy (PRIMACEN), Institute for Research and Innovation in Biomedicine (IRIB)/ Genetics and Pathophysiology of Neurodevelopmental Disorders' Team INSERM U 1245, Rouen, France
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Octadecaneuropeptide (ODN) and its precursor diazepam-binding inhibitor (DBI) are peptides belonging to the family of endozepines, which are exclusively produced by astroglial cells in the central nervous system of mammals. There is now compelling evidence that the gliopeptide ODN protects cultured neurons and astrocytes from apoptotic cell death induced by various neurotoxic agents. ODN, at very low concentrations (in the subpicomolar range), has been shown to rescue neurons and glial cells from neurotoxicity induced by several substances such as H2O2, 6-OHDA and MPTP. ODN also exerts a strong protective effect against oxidative stress-induced apoptosis on cultured neurons and astrocytes. ODN acts by preventing *i*) the accumulation and overproduction of intracellular reactive oxygen species (ROS), *ii*) the depletion of glutathione (GSH) levels, and *iii*) the decrease of the expression and activity of the antioxidant enzymes provoked by oxidative stress. *In vivo*, ODN prevents

degeneration of nigrostriatal DA neurons in a mouse model of Parkinson's disease,through mechanisms involving downregulation of neuroinflammatory, oxidative and apoptotic processes. The gliopeptide ODN exerts its cytoprotective effects by activation of ODN metabotropic receptor positively coupled to PKA, PKC and MAPK/ERK transduction pathway, which ultimately reduces the pro-apoptotic gene Bax and stimulates Bcl-2 expressions, and inhibits the mitochondrial apoptotic pathway. The antiapoptotic and neurotrophic properties of ODN, including its antioxidant, antiapoptotic, and neurotrophic actions, suggesting that ODN derivatives could potentially be useful for treatment of cerebral injuries involving oxidative stress and neurodegeneration. *This work was supported by a France–Tunisia CMCU-Campus France/PHC Utique 20G0826/44306YD exchange program.*

S20.4

Cytoprotective and neurotrophic effects of OctaDecaNeuropeptide (ODN) in in vitro and in vivo models of neurodegenerative diseases

Yosra Hamdi1, Tasnim Chagrani1, Sada Mashadani1, Ikram Ghouili1, Jérôme Leprince2, Taoufik Ghrairi1, David Vaudry3, Marie-Christine Tonon2, Gérard Lizard4 and Olfa Masmoudi-Kouki1

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4University Bourgogne Franche-Comté, Team 'Biochemistry of the Peroxisome, Inflammation and Lipid Metabolism' EA7270 / Inserm, 21000 Dijon, France

Octadecaneuropeptide (ODN) and its precursor diazepam-binding inhibitor (DBI) are peptides belonging to the family of endozepines, which are exclusively produced by astroglial cells in the central nervous system of mammals. There is now compelling evidence that the gliopeptide ODN protects cultured neurons and astrocytes from apoptotic cell death induced by various neurotoxic agents. ODN, at very low concentrations (in the subpicomolar range), has been shown to rescue neurons and glial cells from neurotoxicity induced by several substances such as H2O2, 6-OHDA and MPTP. ODN also exerts a strong protective effect against oxidative stress-induced apoptosis on cultured neurons and astrocytes. ODN acts by preventing i) the accumulation and overproduction of intracellular reactive oxygen species (ROS), ii) the depletion of glutathione (GSH) levels, and iii) the decrease of the expression and activity of the antioxidant enzymes provoked by oxidative stress. In vivo, ODN prevents degeneration of nigrostriatal DA neurons in a mouse model of Parkinson's disease, through mechanisms involving downregulation of neuroinflammatory, oxidative and apoptotic processes. The gliopeptide ODN exerts its cytoprotective effects by activation of ODN

metabotropic receptor positively coupled to PKA, PKC and MAPK/ERK transduction pathway, which ultimately reduces the pro-apoptotic gene Bax and stimulates Bcl-2 expressions, and inhibits the mitochondrial apoptotic pathway. The antiapoptotic and neurotrophic properties of ODN, including its antioxidant, antiapoptotic, and neurotrophic actions, suggesting that ODN derivatives could potentially be useful for treatment of cerebral injuries involving oxidative stress and neurodegeneration. This work was supported by a France–Tunisia CMCU-Campus France/PHC Utique 20G0826/44306YD exchange program.
Key words: ODN, neuroprotection, glioprotection, oxidative stress, apoptosis

S20.5

Involvement of gut microbiota and epigenetic factors in food addiction
Rafael Madonado
University Pompeu Fabra, Barcelona, Spain

Food addiction is characterized by a loss of behavioral control over food intake and is associated with obesity and other eating disorders. The mechanisms underlying this behavioral disorder are largely unknown. We have investigated the changes in miRNA expression promoted by food addiction in animals and humans and their involvement in the mechanisms underlying the behavioral hallmarks of this disorder. We found sharp similitudes between miRNA signatures in the medial prefrontal cortex (mPFC) of our animal cohort and circulating miRNA levels in our human cohort, which allowed us to identify several miRNAs of potential interest in the development of this disorder. In addition, we used the YFAS 2.0 criteria to classify extreme food addiction mouse and human subpopulations to identify gut microbiota signatures associated with vulnerability to this disorder. Interestingly, our animal and human cohorts showed sharp similitudes in the gut microbiota signatures. We believe the elucidation of these epigenetic and microbiota mechanisms will lead to advances toward identifying innovative biomarkers and possible future interventions for food addiction and related disorders.

Key words: ODN, neuroprotection, glioprotection, oxidative stress, apoptosis

S21

Fighting neurological diseases from the intestine: impact of enteric microbiota, immune and nervous system on the gut-brain axis.

CHAIR: Seguella Luisa[1], Lucarini Elena[2]

[1]*Department of Physiology and Pharmacology "V. Erspamer", Sapienza University of Rome*
[2]*Department of Neurosciences, Psychology, Drug Research and Child Health (NEUROFARBA), University of Florence*

One of the most recent transformative developments in neuroscience is the realization that many neurodegenerative and neuropsychiatric diseases normally attributed to neural circuits

dysfunction in the brain involve abnormal interaction with the intestine through the so-called gut-brain axis: a direct route by which the intestine quickly conveys sensory cues to the brain. A key relay station along the gut-brain axis is the enteric nervous system (ENS). This is a complex neural network throughout the gastrointestinal tract that provides local control over essential gastrointestinal functions through 'brain-like' neural circuitry composed of neurons and glia. Active signaling mechanisms between the central and enteric nervous systems, modulate not only gastrointestinal activity, but also control mucosal and systemic immune responses, the energy balance and glucose homeostasis, and, in certain circumstances, function to drive neuroinflammatory processes along the gut-brain axis that lead to long-term dysfunctions in the brain. These latter were also associated with an imbalance of gut dysbiosis, raising the possibility to target the microbiota-gut-brain axis as a strategy to influence the course of brain diseases, such as Alzheimer's or Parkinson's disease. The intestinal microbiota is the largest symbiotic ecosystem associated with the host, including bacteria, viruses, and fungi, that was proven to play an important role in maintaining local and systemic homeostasis. The bidirectional communication between the nervous system and the intestinal microbiota occurs along various pathways and is highly integrated and regulated by either neuronal or non-neuronal factors, namely neuron-glia networks, neuro-immune interactions, hypothalamus-pituitary axis, emotional inputs, autonomic responses, endocrine regulation, and gut microbiota metabolism.

The neuroimmunological *"priming"* of gut-brain dysfunctions seems to arise from the exposure of the ENS to peculiar outer (microbiota, metabolites, and nutrients) and inner (immune cells and stromal cells) intestinal factors. Although the mechanisms responsible for several gut-originating neurodegenerative/neuropsychiatric diseases are still largely unknown, alterations in the gut microenvironment might represent early "prompting conditions" that later develop in symptomatologic emergence and might represent druggable targets for a successful and early therapeutical approach.

In this symposium, we discuss the novel insight into the role of the microbiota-gut-brain axis in the development of peripheral and central nervous systems disorders and the most innovative therapeutical strategies to protect from neurological diseases by preserving gut health.

Keywords: Enteric Nervous System (ENS); Microbiota; Gut–Brain Axis; Neuroimmune Interaction; Parkinson's Disease.

S21.1

Intestinal epithelial barrier at the crossroads between the microbiota-gut-brain axis and neurodegenerative disorders

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The intestinal barrier, which primarily consists of a mucus layer, an epithelial barrier, and a gut vascular barrier, has a crucial role in health and disease by facilitating nutrient absorption and preventing the entry of pathogens. The intestinal barrier is in close contact with gut microbiota on its luminal side and with enteric neurons and glial cells on its tissue side. Over the last years, increasing body of evidence suggest that neurological, neurodevelopmental, and psychiatric disorders, including mild cognitive impairment, Parkinson's disease, Alzheimer's disease, multiple sclerosis, autism spectrum disorder, and depression, have been associated with morphological and functional changes in the intestinal epithelial barrier, some of which could be related to disease severity. On the basis of this evidence, it is providedan overview of existing knowledge on the role of the intestinal barrier, including its mucus layer, epithelial barrier, and gut vascular barrier, in health and brain disease, as well as the mechanisms that possibly link gut barrier dysfunction and CNS disorders and the potential impact that evaluating enteric barriers in brain disorders could have on clinical practice, in terms of novel diagnostic and therapeutic strategies, in the near future.

S21.2

Gut microbiota alterations affect glioma growth and innate immune cells

Maria Rosito[1], Francesco Marrocco[1], Fabrizio Antonangeli[2] Ottavia Giampaoli[3], Silvia Di Angelantonio[1], Flavia Trettell[1], Alfredo Miccheli[3], Giuseppina D'Alessandro[1*], Cristina Limatola[1*]

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Glioma is a CNS tumor with few therapeutic options. Recently, the host microbiota has been implicated in immune modulation of various tumors and in glioma growth and progression, but the specific metabolites involved in this modulation have not been identified. Here, we investigated the effect of gut microbiota alteration in a syngeneic (GL261) mouse model of

glioma by treating mice with two antibiotics (ABX) and evaluating the effects on tumor, microbiota, natural killer (NK) cell and microglial. We report that antibiotic treatment (i) altered the gut microbiota at the family level and the gut and brain metabolomic profiles; (ii) reduced cytotoxic NK cell subsets; ii) modeled the tumor microenvironment toward a pro-angiogenic phenotype in which microglia and glioma cells are actively involved; iii) increased glioma stemness; iv) induced transdifferentiation of glioma cells into endothelial progenitor cells, thereby increasing vasculogenesis. All these findings could contribute to the increased growth of intracranial gliomas observed after ABX treatment, and we proposed glycine as a putative modulator of these activities, shaping the brain microenvironment.

S21.3

Can probiotics modulate gut inflammation and induce gut-brain axis remodelling?

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Gut-brain axis and inflammation are two hot topics in Parkinson's disease (PD), and molecular links are sought between gut inflammation, PD and inflammatory bowel disease (IBD) such as Crohn's disease (CD). There is now strong epidemiological and genetical evidence linking PD to IBD diseases and we recently demonstrated that the neuronal protein alpha-synuclein, which is critically involved in PD pathophysiology, is upregulated in inflamed segments of Crohn's colon. We have also shown that the microtubule associated protein tau, another neuronal protein critically involved in neurodegenerative disorders, is upregulated in the enteric nervous system (ENS) of CD but not ulcerative colitis patients. Enteric glial reactivity, observed through the expression of the glial marker GFAP is also increased in PD gut as well as in inflamed area of IBD patients along with pro-inflammatory cytokines. Our last work is demonstrating that treatment of a murine model of colitis with the probiotic *Propionibacterium Freudenreichii,* not only improve gut functions but also correct glial GFAP and neuronal Tau expression.

Our findings, which provide the first characterization of alpha-synuclein and tau expression in CD, suggest that the key proteins involved in neurodegenerative disorders are linked to glial reactivity and might also play a role in CD. This reactivity can be controlled by probiotic supplementation.

S21.4

Gut-brain communication in bipolar disorder

Grace Bukowski-Thall[1], Frederike Fellendorf[2], Melanie Lenger[2], Tobias Madl[3], Christine Moissl-Eichinger[4], Eva Reininghaus[2], Aitak Farzi[1]

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Bipolar disorder (BD) is a chronic mood disorder characterized by recurrent episodes of depression and (hypo-) mania. The exact biological mechanisms underlying BD are unclear; however, the gut microbiome may be an avenue through which environmental factors or immuno-inflammatory responses influence BD pathogenesis. In order to proof a potential causal involvement of the gut microbiota, fecal microbiota transplantation (FMT) is a powerful translational tool for researching psychiatric disorders and there is evidence that mood disorder symptoms are transferable from humans to mice via FMT.
In this study, we investigated the impact of FMT from a human donor in a mixed bipolar episode and a healthy, weight and age matched control to C57BL/6 mice. A battery of behavioral tests assessing anxiety- and depression-like behaviors were initiated 1 week after FMT. Key messenger molecules involved in gut-brain communication including gut microbiome composition, and fecal and brain metabolites were assessed in recipient mice after FMT.
Here we demonstrate that recipient mice of microbiota of bipolar patients displayed a decreased abundance of *Akkermansia muciniphila*. Changes in gut microbiome composition were associated with decreased fecal short chain fatty acids levels and related gut hormone expression in the bipolar microbiota recipient group. Furthermore, FMT from bipolar patients induced increased anxiety-like behavior and decreased sociability, while no changeswere observed in other tests. FMT from bipolar patients induced pronounced changes in thebrain metabolome, with decreased glycine being the most prominent metabolite affected.
These findings implicate a potential involvement of gut-brain signaling in psychiatric disorders.

S20.5
Involvement of gut microbiota and epigenetic factors in food addiction

Rafael Madonado

University Pompeu Fabra, Barcelona, Spain

Food addiction is characterized by a loss of behavioral control over food intake and is associated with obesity and other eating disorders. The mechanisms underlying this behavioral disorder are largely unknown. We have investigated the changes in miRNA expression promoted by food addiction in animals and humans and their involvement in the mechanisms underlying the behavioral hallmarks of this disorder. We found sharp similitudes between miRNA signatures in the medial prefrontal cortex (mPFC) of our animal cohort and

circulating miRNA levels in our human cohort, which allowed us to identify several miRNAs of potential interest in the development of this disorder. In addition, we used the YFAS 2.0 criteria to classify extreme food addiction mouse and human subpopulations to identify gut microbiota signatures associated with vulnerability to this disorder. Interestingly, our animal and human cohorts showed sharp similitudes in the gut microbiota signatures. We believe the elucidation of these epigenetic and microbiota mechanisms will lead to advances toward identifying innovative biomarkers and possible future interventions for food addiction and related disorders.

S21.5

Early life adversity disrupts enteric glial genes and functions

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Adverse early life events such as maternal neglect or abuse increase susceptibility to developing irritable bowel syndrome in males and females, respectively. The specific cell types and enteric nervous system mechanisms contributing to these effects remain unknown. Here, we tested the hypothesis that early life stress induces genomic and function alterations in enteric glia, which contribute to abnormal intestinal function.

Glial-specific transcriptional signatures were studied in *Sox10^{CreERT2};RiboTag* mice using the neonatal-maternal separation (NMS) model of early life stress. Myenteric glial RNA-seq data were analyzed by STAR and DESeq2. Integrative physiological consequences were assessed by measuring visceral hypersensitivity and motility. Cellular physiological responses were studied using calcium imaging in *Wnt1$^{Cre;GCaMP5g\text{-}tdT}$/Gfap^{hM3Dq}* mice.

More than 600 genes are differentially expressed between male and female enteric glia in non-stressed animals (FDR<0.1). Interestingly, the gene expression patterns of male glia become more like those from females following NMS. This remodeling of molecular architecture is associated with a higher excitability of glia, demonstrated by a smaller calcium response after glial stimulation ($p<0.001$) in both sexes and an increased activation frequency ($p<0.001$) in females. Finally, males exhibit visceral hypersensitivity after NMS ($p<0.01$), and slower intestinal transit ($p<0.05$), which may be linked to glial alterations.

Together, these data show that early life adversity shifts the molecular architecture of enteric glia in a sex-specific manner, with consequences on glial function. Glial sex-specific remodeling is associated with physiological consequences on intestinal motility and visceral hypersensitivity.

S22

The role of nitric oxide signaling in brain pathologies. Therapeutic implications and their limits.

CHAIR: Joanna M. Wierońska

Maj Institute of Pharmacology Polish Academy of Sciences, Krakow, Poland, Head of the Laboratory of Neurobiology of Psychiatric Disorders

The symposium titled "The Role of Nitric Oxide Signaling in Brain Pathologies: Therapeutic Implications and Their Limits" brings together five esteemed researchers in the field, shedding light on various aspects of nitric oxide signaling and its impact on brain pathologies. Each speaker offers unique insights into this critical area of study.

Vicente Felipo et al. delve into the differential role of nitric oxide signaling in acute and chronic hyperammonemia, highlighting its profound implications in conditions such as acute liver failure and liver cirrhosis. They elucidate the glutamate-NO-cGMP pathway's involvement in ammonia-induced death and propose potential interventions to mitigate its effects.

Nikolaos Pitsikas et al. explore the potential therapeutic use of nitric oxide (NO) donors in the treatment of anxiety disorders. They discuss the limitations of current medications and present evidence suggesting that targeting the nitrergic system, with compounds like sodium nitroprusside and molsidomine, could offer promising alternatives for anxiety treatment.

Joanna M Wierońska et al. investigate the role of nitric oxide-dependent pathways in the procognitive activity of metabotropic glutamate receptors ligands. Their research unveils the synergistic effects of mGlu receptor activators and NO releasers in mitigating cognitive deficits induced by MK-801. However, they also caution against potential deficits related to eNOS activity with prolonged use of these compounds.

Tounsi Fella et al. examine the impact of Thiamethoxam, a neonicotinoid pesticide, on oxidative stress levels in the hypothalamic-pituitary axis. They report disruptions in the antioxidant defense system and oxidative stress markers, shedding light on potential effects on neuronal function and signaling pathways.

Paulina Bastian et al. explore the use of 2-methoxyestradiol (2-ME) in glioblastoma treatment, a highly malignant form of brain tumor. Their study reveals that 2-ME induces nitro-oxidative stress and modulates heat shock proteins in glioma cells, suggesting its potential as a therapeutic candidate for this challenging condition.

In summary, these presentations collectively emphasize the multifaceted role of nitric oxide signaling in brain pathologies and its therapeutic potential. While offering promising avenues for treatment, they also caution against potential limitations and side effects, highlighting the need for further research in this complex field.

S22.1

Differential role of nitric oxide signaling in the deleterious effects of acute and chronic hyperammonemia

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Acute hyperammonemia, as occurs for example in acute liver failure, may lead to rapid death, while chronic moderate hyperammonemia, as occurs for example in patients with liver cirrhosis, results in cognitive and motor impairment, resulting in hepatic encephalopathy, which affects several million people, reducing their quality of life and life span.
In acute hyperammonemia, excessive activation of NMDA receptors increases activation of nitric oxide synthase, increasing nitric oxide (NO), which activates guanylate cyclase, leading to increased cyclic GMP (cGMP). Enhanced activation of this glutamate-NO-cGMP pathway plays a key role in ammonia-induced death. Ammonia-induced death of mice and rats may be prevented by blocking the NMDA receptor with selective antagonists or by inhibiting nitric oxide synthase with selective inhibitors such as nitroarginine.
In contrast, in chronic moderate hyperammonemia, to prevent death induced by excessive activation of this pathway, there is an adaptive process by which enhanced activation of NMDA receptors enhances activation of CaMKII, which phosphorylates neuronal nitric oxide synthase, reducing its activity. So that, the formation of nitric oxide and the function of the glutamate-NO-cGMP pathway are reduced in chronic hyperammonemia. Proper function of this pathway is necessary for some forms of learning and memory. Reduced function of the pathway is responsible for impairment of cognitive function in chronic hyperammonemia and hepatic encephalopathy. Learning ability may be restored in hyperammonemic rats by treatments that restore the function of the glutamate-NO-cGMP pathway and cGMP levels, for example with inhibitors of phosphodiesterase 5, antagonists or modulators of GABAA receptors or anti-inflammatories.

S22.2

Nitric oxide (NO) donors. Potential candidates for the treatment of anxiety disorders?

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Anxiety-related disorders are a common public health issues. Current medication for anxiety disorders involves the GABA-ergic or the serotonergic transmission. Different forms of anxiety, however, are resistant to treatment with GABA-ergic or serotonergic agents and the use of these compounds is associated with severe side effects. Thus, there is urgent need not only for fresh medications but also alternative targets. The nitrergic system has emerged as a promising target since several lines of evidence suggest that nitric oxide (NO), an intra- and

inter-cellular messenger in the brain, is implicated in anxiety. Therefore, compounds that targeting NO might be beneficial. Nonetheless, little and contradictory information is available concerning the effects of NO donors in anxiety. The present research was designed to further explore this issue in the rat. To this end, the therapeutic potential of the NO donors, sodium nitroprusside (SNP) and molsidomine was assessed in behavioural models of generalized anxiety disorder (GAD), social phobia, obsessive-compulsive disorder (OCD), and post-traumatic stress disorder. Results obtained suggest that NO donors are efficacious in attenuating abnormal behaviours revealed in animal models resembling different forms of anxiety. The effects expressed by SNP and molsidomine in the different procedures evaluating anxiety were dose, time and treatment schedule-dependent. Overall, the present findings propose a potential therapeutic role for NO donors for the treatment of some behaviours that may have translational relevance in anxiety. In this context, it is important to take into account, however, the narrow therapeutic window of NO-related compounds.

S22.3

The role of nitric oxide dependent pathways in the procognitive activity of metabotropic glutamate receptors ligands.

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Metabotropic glutamate (mGlu) receptors are well recognized as putative targets for novel antipsychotic drugs. Among different subtypes $mGlu_2$ and $mGlu_5$ seem to be especially interesting. The role of NO-related pathways in their procognitive activity is poorly investigated, thus we focused the attention on this aspect.
At first stage of the study the effect of simultaneous administration of $mGlu_2$ and $mGlu_5$ activators (LY487379 and CDPPB) with NO releasers (spermineNONOate and DETANONOate) was investigated on MK-801-induced cognitive deficits in the novel object recognition test. The compounds were administered at the combinations of subactive, intermediate and top doses and the synergistic effect of subactive and intermediate, but not top doses was observed. In the second part of the studies the level of l-arginine (substrate for NO production), endothelial NO synthase expression, and cGMP production were measured in the frontal cortices or hippocampi of MK-801-treated mice alone and after LY487379 or CDPPB administration. Our results indicate that the administration of MK-801 induced decrease in l-arginine level which was reversed by the administration of mGlu receptor activators. Slight increase in cGMP production was observed and the effect was further intensified by the compounds. MK-801 impaired eNOS function (the number of eNOS monomers was significantly higher) and the drugs further enhanced this effect.

Reasuming, despite clear antipsychotic-like activity of CDPPB or LY487379 observed in animal models, their use in humans should be considered with caution as their prolonged administration may enhance deficits related to eNOS activity, thus in consequence the benefit/loss ratio of their use is questionable.

The study was supported by the grant no 2019/33/B/NZ7/02699 (OPUS) from National Science Center, Poland.

S22.4

The impact of Thiamethoxam on oxidative stress level in hypothalamic pituitary axis in Wistar rat

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Neonicotinoid pesticides, a class of chemicals, are considered to have the potential to cause adverse effects on biological systems and pesticide-induced oxidative stress has also been investigated in toxicology as a possible mechanism of toxicity.

In this context, our work consists in studying the effect of exposure to Thiamethoxam, an insecticide from the neonicotinoid family on markers of oxidative stress in rats, For this, 24 adult male rats of the *Wistar* strain were divided into four groups: controls-group (1 ml/day of water), and three other groups treated by gavage daily for 10 weeks with TMX at different doses: ADJ-group (Acceptable Daily Intake) : 0.026 mg/kg, NOAEL-group (No Observable Adverse Effect Level) : 2.6 mg/kg and NOAELx2-group : 5.2 mg/kg. At the end of the treatment, pro-oxidative factors such as nitric oxide (NO) and Malondialdehyde (MDA) and the anti-oxidative factor Gluthathion reductase (GSH) were measured on hpothalamic and pituitary extracts.

The results revealed a significant increase in body weight in NOAEL and NOAELx2 rats, and of food consumption and water ingestion in ADI, NOAEL and NOAELx2 compared to the control. Moreover, an alteration of the antioxidant defense system characterized by a decrease in reduced glutathione (GSH) at the pituitary-hypothalamic axis, and a significant increase in markers of oxidative stress, malondialdehyde (MDA) and nitric oxide (NO) only in hypothalamic region.

These observations are in favor of a disruption of the hypothalamic-pituitary axis function via subtle changes of the signaling pathways subsequently on the neuronal function in a direct or indirect way, by several phenomena such as neuro-inflammation, angiogenesis and apoptosis.

S22.5

2-methoxyestradiol – mediated control of nNOS and Heat Shock Proteins affects DNA in glioblastoma cells

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Over fifty percent of all primary intracranial neoplasms are gliomas, making them the most common primary tumors of the central nervous system (CNS). Glioblastoma (GBM) is the most frequent type of malignant glioma, and it is frequently incurable. GBM is distinguished by the presence of hypoxic regions accompanied by angiogenesis enhancement. 2-Methoxyestradiol (2-ME) is an antiangiogenic and antiproliferative substance with a long history of use. In recent clinical trials, 2-ME, also known as Panzem, was evaluated for breast, ovarian, prostate, and multiple myeloma cancers. In the presented study, with pharmacological and physiological concentrations of 2-ME, the SW1088 grade III glioma cell line was treated. Using flow cytometry, the induction of apoptosis and necrosis, oxidative stress, cell cycle arrest, and mitochondrial membrane potential were determined. Using confocal microscopy, DNA damage was detected. Nitric oxide synthase and heat shock proteins were quantified utilizing the Western blot technique. Here, it is demonstrated for the first time that 2-ME induces nitro-oxidative stress and modulates heat shock proteins (HSPs) in the SW1088 grade III glioma cell line. Important GBM therapeutic strategies should target both cell proliferation and angiogenesis, and due to the aforementioned, 2-ME appears to be an ideal candidate for GBM treatment.

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S23

Novel insights into alpha-synuclein pathology and toxicity in neurodegenerative diseases

CHAIR: Arianna Bellucci

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The deposition of insoluble aggregates composed of fibrillary alpha-synuclein in neuronal and/or glial cells is a key neuropathological hallmark of several neurodegenerative disorders such as Parkinson's disease, Lewy body dementia or multiple system atrophy, that for this reason are defined as synucleinopathies.
Alpha-synuclein is a protein mainly expressed in neuronal terminals, that in physiological conditions affects neurotransmitter release by modulating synaptic vesicles and numerous synaptic proteins. However, it also associates with mitochondria and modulates endoplasmic reticulum, Golgi and lysosomal homeostasis.
Studies in the post-mortem brain of patients and in experimental models support that alpha-synuclein aggregates play a causative role in the onset of neuronal loss in synucleinopathies. Yet, it is not clear whether the main trigger for neurodegeneration in such disorders is the toxicity exerted by alpha-synuclein aggregates or the defeat in alpha-synuclein physiological function arising from their formation.
This symposium will highlight how post-translational modifications can modulate the physiological and pathological function of alpha-synuclein and how dopamine dyshomeostasis can elicit alpha-synuclein neuronal accumulation by hampering its clearance. Moreover, it will delineate the critical interplay between alpha-synuclein and protein degradation systems in health and disease and clarify how the pathological accumulation of alpha-synuclein microaggregates at synaptic terminals may initiate a retrograde deafferentation that progressively flows into neuronal loss. Finally, we will present key findings supporting that the clearing of synaptic alpha-synuclein microaggregates may halt pathology spreading, neurodegeneration and neuroinflammation in synucleinopathies.

S23.1

Dopamine metabolites initiate αSynuclein-mediated impaired proteostasis and degeneration in neuronal projections

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Dopamine dyshomeostasis has been acknowledged among the determinants of nigrostriatal neuron degeneration in Parkinson's disease (PD). Several studies in experimental models and postmortem PD patients underlined increasing levels of the dopamine metabolite 3,4-dihydroxyphenylacetaldehyde (DOPAL), which is highly reactive towards proteins. DOPAL has been shown to covalently modify the presynaptic protein αSynuclein (αSyn), whose

misfolding and aggregation represent a major trait of PD pathology, triggering αSyn oligomerization in dopaminergic neurons. Here, we demonstrated that DOPAL elicits αSyn accumulation and hampers αSyn clearance in primary neurons. DOPAL-induced αSyn buildup lessens neuronal resilience, compromises synaptic integrity, and overwhelms protein quality control pathways in neurites. The progressive decline of neuronal homeostasis further leads to dopaminergic neuron loss and motor impairment, as showed in in vivo models. Finally, we developed a specific antibody which detected increased DOPAL-modified αSyn in human striatal tissues from idiopathic PD patients, corroborating the translational relevance of αSyn-DOPAL interplay in PD neurodegeneration.

S23.2

Alpha-synuclein interplay with protein degradation systems

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Regulation of alpha-synuclein (AS) levels is critical for the pathogenesis of Parkinson's Disease (PD) and other synucleinopathies. Such levels are in part regulated by protein degradation systems. In particular, evidence suggests that, depending on the particular AS species and cellular context, the proteasomal or the Autophagic Lysosomal Pathway (ALP) may be predominantly involved in the degradation of intracellular AS. Our work has focused particularly on the role of the AL pathway of Chaperone Mediated Autophagy (CMA) in AS degradation. We have shown that AS is degraded by this system in various cell culture models, and that in vivo Adeno-Associated Virus (AAV)-mediated downregulation of Lamp2a, the transmembrane protein which is the rate-limiting step of the pathway, leads to nigral accumulation of endogenous AS, including aberrant species. Conversely, AAV-mediated overexpression of Lamp2a and consequent CMA induction leads to amelioration in a rat model of synucleinopathy induced by AS overexpression in the nigrostriatal axis. More recent work from our group has shown that: a) AAV-mediated overexpression of Lamp2a in the anterior olfactory nucleus leads to amelioration of incipient and established synucleinopathy in a rat transgenic model of overexpressed AS, b) AAV-mediated Lamp2a downregulation leads to selective neurodegeneration of nigral versus hippocampal neurons, and c) AS is not essential for nigrostriatal degeneration following AAV-mediated Lamp2adownregulation. These findings underscore the importance of the CMA pathway in the context of neurodegenerative synucleinopathies and suggest that strategies to promote its activity may be therapeutically beneficial.

S23.3

Magnetothermal nanoparticle technology alleviates parkinsonian-like symptoms in mice

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Deep brain stimulation (DBS) has long been used to alleviate symptoms in patients suffering from psychiatric and neurological disorders. The application of DBS to modulate neural circuits is, however, afflicted by its mechanical invasiveness and the use of chronically implanted leads. Here, we further characterized a wireless alternative to DBS, called magnetothermal DBS, in freely moving mice. Magnetothermal DBS exploits hysteretic heating of magnetic nanoparticles in the presence of an alternating magnetic field. Therefore, we heatsensitized neurons by expressing the cation channel TRPV1 in the subthalamic nucleus (STN) first in naïve and then in parkinsonian mice. We found that the delivery of magnetic nanoparticles to the STN allows remote modulation of motor behavior in mice exposed to an alternating magnetic field. Moreover, mDBS of the STN reversed the motor deficits in a mild and severe parkinsonian model. Immunohistochemical analysis revealed increased neural activity in several motor regions, suggesting a circuit-wide effect of STN mDBS. Our results indicate that mDBS is able to activate deep-brain circuits therapeutically without the need for surgical implants and connectors.

S23.4

Synaptic alpha-synuclein microaggregates in synucleinopathies: engine of neurodegeneration and key therapeutic targets

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Synaptic α-synuclein micro-aggregation constitutes a discerning facet of synucleinopathies such as Parkinson's disease (PD). As α-synuclein physiologically modulates several synaptic proteins and synaptic vesicle homeostasis, its pathological deposition at nerve terminals severely affects neuronal function and resilience, initiating a retrograde synapse-to-cell body degeneration.
Consistently, we found that several synaptic proteins can be detected in α-synuclein aggregates or can be progressively redistributed following α-synuclein pathological deposition, thus affecting synaptic function. Among them, the phosphoprotein synapsin III (Syn III), a key interactor of α-synuclein in the modulation of dopamine release, is another key component of α-synuclein insoluble fibrils extracted from post-mortem PD brains. Notably, Syn III knock-out mice do not develop α-synuclein fibrillary aggregates, synaptic derangement and dopaminergic neuron degeneration following the injection of adeno-associated viral vectors (AAV) overexpressing human wild type α-synuclein in the substantia nigra, supporting that Syn III controls α-synuclein deposition. Moreover, AAV-based Syn III gene silencing in an α-synuclein transgenic mice at a pathological stage with marked α-synuclein fibrillary aggregation, severe synaptic damage and dysfunction, reduced α-synuclein aggregates, restored dopamine release and prevented the onset of striatal dopaminergic terminal deafferentation and motor deficits. Finally, small molecules disrupting the pathological α-synuclein/Syn III interaction, can reduce α-synuclein synaptic microaggregates and protect dopaminergic neurons from neurodegeneration in mice transgenic for human α-synuclein.
These data support that synaptic α-synuclein microaggregates are the main engine of neuronal degeneration in PD and other synucleinopathies and that Syn III, along with other synaptic proteins, may constitute a suitable therapeutic target for these neurodegenerative disorders.

S25

Non-neuronal cells as guardians of CNS homeostasis: relevance in brain development and diseases

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Non-neuronal cells of the CNS comprehend neural stem cells (NSCs), glia, pericytes, endothelial and ependymal cells. NSCs have the potential to give rise to progeny cells that grow and differentiate into neurons and glia but are also immunomodulatory cells. Glial cells are parenchymal cells that include microglia, astrocytes, oligodendrocytes, and oligodendrocyte progenitors (NG2 glia). In the past, such diverse cellular phenotypes were

mainly regarded as supportive cells for neurons. More recently, additional and important functions for non-neuronal cells have been demonstrated, including involvement in neurotransmission, regulation of synaptic connectivity and pruning, support of myelination and brain development, shaping of the blood-brain barrier, defense of the brain against any kind of insult, buffering of pH and ion concentrations, and release of molecules that act as neuromodulators, trophic factors, and hormones. The recognition of their crucial role in maintaining brain homeostasis supports the idea that non-neuronal cells, when dysfunctional, may contribute to neuronal damage and be involved in many brain pathologies, spanning from neurodevelopmental to neurodegenerative and neuropsychiatric disorders. In early stages of disease, that precede the occurrence of neuronal damage, non-neuronal cells may respond to potential noxae by changing their morphology and/or gaining/losing/modulating one (or more) of their functions. Such a scenario is as fascinating as complex to be understood. Unveiling the mechanisms by which these neural cells regulate CNS homeostasis during brain development and lose their homeostatic function under pathological conditions could be relevant for the discovery of novel therapeutic targets for the treatment of several undertreated brain diseases. To this end, the proposed symposium gathers early/mid-career and established researchers, well-recognized in their field and coming from three different countries, to discuss novel data about the contribution of non-neuronal cells (microglia, astrocytes, NG2 glia, oligodendrocytes, NSCs and their progeny) to neurodevelopment, neurodegeneration, psychiatric disorders, and neuro-oncology. Thanks to the scientific discussion resulting from each presentation, future research studies on this under-explored topic will be stimulated, eventually fostering international networking and collaboration among researchers working in different neuroscience fields.

S25.1

The role of astrocytes in mediating oligodendrocyte maturation and function: evidence with co-ultramicronized palmitoylethanolamide/luteolin in models of beta-amyloid toxicity

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The importance of astrocytes to the proper functioning of the brain is now well established. One of their less explored activities is their role in myelination, which requires good cooperation between astrocytes and oligodendrocytes. White matter alterations have been observed in many neurodegenerative diseases, including Alzheimer's disease (AD), in which some brain imaging studies have linked myelin defects to beta-amyloid (Aβ) deposition as a

possible etiologic factor [*1*]. However, Aβ has been shown to stimulate the maturation of oligodendrocyte precursor cells (OPCs) into myelinating oligodendrocytes in vitro [*2*], but it may also induce astrogliosis both in vitro and in vivo. Given the role of astrocytes in myelination and their known susceptibility to the toxic effects of Aβ, we therefore hypothesized that Aβ might indirectly induce myelin damage by affecting astrocytes. Our recent in vitro data support this hypothesis [*3*]. In addition, we tested a possible preventive approach against Aβ toxicity by testing a compound (co-ultra PEA/Lut) containing palmitoylethanolamide, known to modulate astrocyte reactivity, and the flavonoid luteolin, which has antioxidant properties [*1*]. Our data show that co-ultra PEA/Lut prevents Aβ-induced changes and that some of its effects are mediated by the peroxisome proliferator-activated receptor (PPAR) α.
Overall, our results support the idea that maintaining astrocyte health and function is critical to halt neurodegeneration. Furthermore, considering that co-ultra PEALut is already approved as a dietary supplement for humans, our results open new possibilities for the treatment of diseases characterized by altered myelination, such as AD.

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2. Quintela-Lopez T et al., Cell Death & Disease 2019;10(6):445. doi: 10.1038/s41419-019-1636-8.
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S25.2

The Alzheimer's disease risk gene INPPP5D modulates synaptic pruning by microglia in the developing hippocampus

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Microglia, the innate immune cells of the central nervous system, actively participate in brain development and homeostasis, supporting neuronal maturation and refining synaptic connections. Microglia are also centrally implicated in brain diseases, playing important roles in pathological synaptic pruning and in the clearance of toxic protein aggregates.
A growing body of evidence, based on recent Genome-wide Association Studies (GWAS), shows that multiple genetic variants associated with increased risk to develop neurodegenerative diseases involve transcripts largely restricted to microglia within the CNS, suggesting that microglial dysfunction underlies susceptibility to neurodegeneration.
Using microglia conditional KO mouse models, we show that the Alzheimer's risk gene INPP5D regulates microglial function altering the phagocytic capacity and synaptic pruning. Of note, we report that its specific loss of function in microglia at early postnatal stages is sufficient to have long lasting effects on learning and memory in adulthood. Our findings suggest that risk genes associated with neurodegeneration may modulate microglia-mediated brain maturation and thus provide vulnerability for diseases later in life.

S25.3

Multifaceted non-neuronal dysfunction as a novel pharmacological target in neurodevelopmental and neuropsychiatric disorders

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Drug discovery failures have marked the last decade of research in the field of neurodegenerative and neuropsychiatric disorders with high medical need. Such failures may, at least in part, depend on a rather consolidated approach where neuronal cells are regarded as privileged targets of drug intervention. The dominant neuron-centric paradigm in neuroscience has indeed tailored research activities and drug development pipelines primarily towards neuronal dysfunction, while the role and therapeutic potential of "non-neuronal components" of the nervous system have been largely overlooked. In the clinical setting the stage when neuronal cells are damaged or dysfunctional usually corresponds to a symptomatic phase of the disease. At that stage the room for therapeutic intervention is reduced as demonstrated by the limited efficacy of currently approved CNS drugs. Preclinical and prodromal stages of neurological diseases represent the window of opportunity for future development of preventive and disease-modifying therapies. For these reasons, we are currently pursuing the identification of early signatures in glia and non-neuronal cells, including neural stem/progenitor cells, that may represent commonalities among a wide range of disorders. In particular we actively pursue the possibility that several CNS disorders may represent conditions where disfunctional non neuronal cells may result in a loss of homeostasis that later on may impact on neuronal cells and their function. In particular we will provide several examples of key disorders (i.e. Alzheimer's disease, major depressive disorder, Down syndrome) where a better understanding of early non neuronal cell disfunction(s) can unravel targets for novel therapeutic interventions.

S25.4

TIMP1 mediates astrocyte-dependent local immunosuppression in brain metastasis

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Immunotherapies against brain metastases have shown clinical benefits mainly when applied to locally asymptomatic patients. It is currently unclear why responses to this therapy drop in symptomatic brain metastases since the use of corticoids is not consistently involved. Our study demonstrates that dissecting the heterogeneity within the brain microenvironment to cell type specific subpopulations defined functionally, offers the possibility to develop novel therapeutic vulnerabilities in brain metastasis patients. We report here that a subpopulation within STAT3+ brain metastasis-associated astrocytes is responsible to block the anti-tumor activity of infiltrating CD8+ T cells. The underlying molecular crosstalk involving astrocyte-secreted TIMP1 signaling on CD63+ CD8+ T cells demonstrates the strong immunomodulatory role of astrocytes in the context of brain metastases. By using genetic and pharmacologic approaches applied not only to mouse models but also to alive human brain metastases we conclude that a combined immunotherapy blocking this local immunosuppressive hub could benefit patients with symptomatic brain metastases. Furthermore, the detection of TIMP1 in the CSF provides a biomarker to select patients for this therapeutic approach. Our findings uncover the importance of dissecting the heterogeneity within the metastasis associated-microenvironment at the functional level to improve the efficacy of organ-specific therapies in brain tumors.

S26

Dissecting the complexity of neurodevelopmental disorders: from pathophysiology to novel therapeutic approaches.

CHAIR: Antonia Manduca[1], Anna Maria Tartaglione[2]

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Neurodevelopmental disorders (NDDs) are complex and heterogeneous conditions affecting brain development and function. Both genetic and environmental risk factors play key role in the etiopathogenesis of NDDs: thus, exploiting their molecular and functional underpinning is important not only for understanding the molecular mechanisms underlying brain development, but also to decipher how genetic factors and environmental stressors affect brain maturation and functioning relevant to major NDDs. In face of the substantial individual burden and the societal costs these conditions incur on public health care, it becomes urgent to mitigate/prevent the risk and severity of NDDs.

In this symposium, four young neuroscientists will present their innovative research aimed to discover novel biological markers and therapeutic targets for major NDDs including early-onset schizophrenia, autism spectrum disorder (ASD) and its comorbidities such as Fragile X syndrome and Rett syndrome. Our speakers come from academia and public health research

institutes and offer a multidisciplinary approach and vision of the complexity of treating developmental brain disorders. By their research, they are contributing to a significant progress in determining the mechanisms whereby genes and environment impact brain development, suggesting hints for new therapeutic strategies.

We believe that this symposium has several strengths that will make it an appropriate choice for the Mediterranean Neuroscience Society meeting. The topic is of interest to MNS members, and the talks include multidisciplinary cutting-edge approaches, ranging from behavioral to molecular and in vivo electrophysiological techniques. Furthermore, the talks will provide converging data from animals and humans, which reflects some of the diversity of our membership. Finally, the proposed speaker list includes scientists from different institutions over different Countries, within and outside the Mediterranean area, to offer new insights on the pathogenesis and treatment of NDDs.

S26.1

Disruption of cholesterol homeostasis in Rett syndrome: a new role for BET proteins

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Rett syndrome (RTT) is a devastating neurodevelopmental disorder that primarily affects females, most of whom have mutations in the *Mecp2* gene. The typical clinical picture is characterized by neurological regression, loss of acquired cognitive, social, and motor skills, and the onset of autistic behavior. It is becoming increasingly clear that RTT represents a neurological disease with important metabolic components. For instance, significant disturbances in cholesterol homeostasis have been observed in the brain and peripheral tissues of RTT mouse models and patients (1,2). Recent findings demonstrated that Bromodomain and Extra-Terminal domain (BET) proteins are epigenetic factors strongly involved in the regulation of cholesterol metabolism (3). In this context, data from our laboratory revealed that pharmacological inhibition of BET proteins effectively counteracts the abnormalities in cholesterol homeostasis found in cultured fibroblasts derived from RTT patients. Taken together, this evidence suggests that RTT physiopathology is characterized by cholesterol alterations and that BET blockade may represent a novel therapeutic avenue.

1) Buchovecky et al. Nat Genet. 2013 Sep;45(9):1013-20. doi: 10.1038/ng.2714.
2) Segatto et al. PLoS One. 2014 Aug 12;9(8):e104834. doi: 10.1371/journal.pone.0104834
3) Tonini et al. Int J Mol Sci. 2020 Feb 14;21(4):1297. doi: 10.3390/ijms21041297.

S26.2

THC exposure during adolescence increases impulsivity-like behavior in adulthood in a WIN 55,212-2 self-administration mouse model

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Cannabis addiction is a chronically relapsing disorder lacking effective treatment. Regular cannabis consumption typically begins during adolescence and this early cannabinoid exposure may increase the risk for drug addiction in adulthood. This study investigates the development of cannabis addiction in adult mice after adolescent exposure to the main psychoactive component of cannabis, Δ^9-tetrahydrocannabinol (THC). Adolescent male mice were exposed to 5 mg/kg of THC from postnatal days 37 to 57. Operant self-administration sessions of WIN 55,212-2 (12.5 µg/kg/infusion) were conducted for 10 days. Mice were tested for three addiction-like criteria (persistence of response, motivation, and compulsivity), two parameters related with craving (resistance to extinction and drug-seeking behavior), and two phenotypic vulnerability traits related to addiction (impulsivity and reward sensitivity). Additionally, qPCRs were performed to detect differentially expressed genes in medial prefrontal cortex (mPFC), nucleus accumbens (NAc), dorsal striatum and hippocampus (HPC) of addicted and non-addicted mice. Adolescent THC exposure did not modify the reinforcement of WIN 55,212-2 nor the development of cannabis addiction. Inversely, THC pre-exposed mice displayed an impulsive-like behavior in adulthood, which was more pronounced in the subgroup of mice that developed the addiction criteria. Moreover, a downregulated *drd2* and *adora2a* gene expression in NAc and HPC was revealed in THC pre-exposed mice, as well as a downregulation of *drd2* expression in mPFC of vehicle pre-treated mice that developed addiction. These findings suggest that adolescent THC exposure may promote impulsivity-like behavior in adulthood, associated with downregulated *drd2* and *adora2a* expression in NAc and HPC.
Keywords: Cannabis addiction, adolescence, WIN 55,212-2 self-administration mouse model, THC, impulsivity, *adora2a*, *drd2*.

S26.3

Role of the endocannabinoid system in the pathophysiology and treatment of schizophrenia: the emerging potential of preventive approach

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Despite robust support for neurodevelopmental nature of schizophrenia in recent research, the role of distinct sensitive periods in brain maturational processes of young individuals is still not properly reflected in currently available therapeutical approaches. Further fuelled by worldwide alarming rise of cannabis use among adolescents, a specifically sensitive demographic group, and strong evidence in favor of the involvement of the endocannabinoid system in the pathophysiology of schizophrenia [1], my work focused on its potential role as a novel preventive treatment as well as a diagnostic tool.
Using two neurodevelopmental models mimicking schizophrenia symptomatology, pharmacological interventions in critically sensitive periods and battery of behavioral, epigenetic, molecular, imaging, and in-situ modelling methods, my colleagues and I described long-lasting effects of both pre/perinatal and peripubertal interventions on endocannabinoidome and its cross-talk with the dopaminergic system.
My talk will summarize these results that highlighted the importance of commonly underrepresented detection of alterations in the brain developmental trajectories with specific focus on critically responsive developmental windows, in order to introduce our recent pilot study that characterizes long-lasting effects of endocannabinoidome alteration by repeated THC exposure during adolescent age on adult behavior and brain structure of exposed mice using longitudinal imaging with nuclear magnetic resonance spanning from PND28 to late adulthood.

[1]Stark, et al. "Phytocannabinoids and schizophrenia: Focus on adolescence as a critical window of enhanced vulnerability and opportunity for treatment." Pharmacological research vol. 174 (2021): 105938. doi:10.1016/j.phrs.2021.105938

S26.4

Exploring the role of endogenous retroviruses in Autism Spectrum Disorder: evidence from preclinical models.

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Endogenous retroviruses (ERVs) are genetic elements, relics of ancestral retroviral infection to germline cells; they comprise about 8% of the genome in humans and over 10% in mice. During co-evolution with the host, most ERVs were silenced by cellular machinery, while their activation has been associated with several neurological and psychiatric disorders including autism spectrum disorder (ASD). Our central hypothesis is that ERVs could act as a bridge between environmental insults during critical windows of brain development and the cascade of pathophysiological events underlying the derailed neurodevelopment, including epigenetic changes and immune dysregulation. We found that the inbred mouse strain BTBR T^{+} $Itpr3^{tf}$/J (BTBR), considered a model of idiopathic autism, and valproic acid (VPA)-induced mouse model of ASD, showed higher expression levels of ERVs from intrauterine life up to adulthood

compared to relative controls[1-2]. The aberrant expression of some ERV families positively correlated with expression levels of pro-inflammatory cytokines and TLR-3 and TLR-4 in embryos and brain tissues, supporting the interplay between ERVs and the immune response. Interestingly, in mice prenatally exposed to VPA, the increased expression of ERVs and behavioral alterations were inherited across generations via maternal lineage[2]. More recently, we also found deregulated expression of some ERVs and ERV-related genes in the maternal immune activation model of ASD, demonstrating tissue (blood *vs* brain) and brain region (prefrontal cortex *vs* hippocampus) specificity of ERV activity[3].
Further investigations are ongoing to verify whether pharmacological modulation of transcriptional activity of ERVs could prevent behavioral alterations in the aforementioned ASD animal models.

[1]Cipriani et al., Scientific Reports, 2018, PMID: 29330412
[2]Tartaglione et al., Molecular Neurobiology, 2019, PMID: 30194517
[3]Cipriani & Tartaglione et al., International Journal of Molecular Sciences, 2022, PMID:36430402

S27
Therapeutic Use of Cannabinoids in Neurodegenerative Disorders

CHAIR: Alessia Ligresti[1], Eva De Lago[2]

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[2]UCM (Spain)

Since its discovery, considerable progresses have been achieved in understanding the role of the endocannabinoid system in the modulation of several progressive neurodegenerative diseases. Endocannabinoids modulate neuronal, glial and endothelial cell function and exert neuromodulatory, anti-excitotoxic, anti-inflammatory and vasodilatory effects. Therefore, endocannabinoid system and its pharmacological modulation is a promising field for the therapeutic intervention at a wide spectrum of neurological diseases such as Parkinson's disease, Alzheimer's disease, Huntington's chorea, multiple sclerosis, amyotrophic lateral sclerosis and epilepsy. The purpose of this symposium is to give a wide overview on the therapeutic application of the endocannabinoid system in such neurodegenerative diseases from different fields (biochemistry, medicinal chemistry, pharmacology, pre-clinical/clinical).

S27.1
Neuropharmacodynamic effects of CB2 activation on cognitive networks: new insights from a chemical perspective

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Endocannabinoid system is a widely investigated neuromodulatory system involved in multiple different pathologies such as cancer, inflammation, and psychiatric diseases. Particularly, CB2 receptor has gained increased attention for its crucial role in modulating neuroinflammation in several neurodegenerative diseases. Here we present the rational design of pyrrole-based analogues, which led to a potent and pharmacokinetically suitable CB2 full agonist particularly effective in improving cognitive functions in a scopolamine-induced amnesia murine model. We further investigated the interconnection between CB2 activation and neurotransmission in this experimental paradigm via a MALDI imaging analysis on mice brains. The lead compound was able to revert, in a CB2-mediated way, the effect of scopolamine on different neurotransmitters tone, such as acetylcholine, serotonin and GABA, shedding light on important networks not fully explored, so far.

S27.2

Cannabinoid modulation of microglial function in the context of neuroinflammation

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Neuroinflammation is a common feature in various neurodegenerative conditions, including Alzheimer's disease (AD). However, the exact role of neuroinflammation in the progression of AD remains a subject of debate. We have recently reported that 5xFAD mice lacking the endocannabinoid-degrading enzyme fatty acid amide hydrolase (FAAH) exhibit an intensified inflammatory phenotype, including increased microglial activation, heightened phagocytosis, elevated expression of pro-inflammatory cytokines, enhanced glial receptor activity, and overactivation of the complement pathway. Strikingly, this heightened inflammation is paradoxically associated with several neuroprotective effects.

To gain a deeper understanding of the role of microglial cells in this context, we conducted a time-course analysis using in vivo multiphoton microscopy in 5xFAD/Cx3cr1$^{+/GFP}$ and 5xFAD/FAAH$^{-/-}$/Cx3cr1$^{+/GFP}$ mice. They were exposed to PLX5622, a CSF1R antagonist, for 28 days, resulting in the pharmacological ablation of microglia. Images were captured weekly, and the mice were switched to a control diet for an additional 7 days to allow microglia to repopulate. In addition, we conducted molecular analyses (mRNA and protein) in 5xFAD/Cx3cr1$^{+/GFP}$ and 5xFAD/FAAH$^{-/-}$/Cx3cr1$^{+/GFP}$ mice. Intravital multiphoton microscopy data demonstrated that brain microglia nearly disappeared within just one week of exposure to PLX5622, and discontinuation of the treatment led to a rapid repopulation of microglial cells, with significant differences associated to FAAH deletion. We also identified several molecular changes associated with FAAH deletion and microglia ablation, particularly related to the NLRP3 inflammasome and the CSF1 system. These findings suggest that the genetic inactivation of FAAH enzyme could result in a distinct microglial activity profile in the context of AD.

S27.3

Preclinical development of cannabinoid-based therapies in pathologies related to TDP-43 dysregulation: Amyotrophic lateral sclerosis and frontotemporal dementia.

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The neuroprotective potential of cannabinoids has been extensively investigated at the preclinical level in the most frequent neurodegenerative disorders such as Alzheimer's or Parkinson's diseases. Recently, similar studies have been initiated in experimental models of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). Both diseases are neurodegenerative disorders considered to belong to a common disease spectrum regarding their clinics, genetics, and neuropathology. A noteworthy common factor is the involvement of TAR DNA binding protein, TDP-43, in their pathogenesis. Approximately 65% of FTD cases and 95% of ALS patients exhibit aggregates of the TDP-43 protein. Modulating the endocannabinoid system has been proposed as a potential therapeutic option for TDP-43-related disorders. Of particular interest is the CB_2 receptor in ALS since the pharmacological activation preserves motor neurons and reduces glial reactivity in experimental models of ALS. Conversely, the inactivation of the CB_2 receptor significantly accelerates the neurological decline in TDP-43 transgenic mice. Furthermore, the treatment with several endocannabinoid-acting compounds (e.g., pharmacological inactivation of FAAH or selective activation of CB_1 and CB_2 receptors) delayed the progression of the pathological phenotype in an FTD-TDP-43 mouse model. These treatments also were effective in improving cognitive, emotional, and social behavior deterioration, preserving pyramidal neurons of the medial prefrontal cortex and the hippocampus, and reducing glial reactivity in both structures, which situates the elevation of the endocannabinoid tone as a promising therapy against TDP-43-induced neuropathology in FTD and ALS. Consequently, valuable information is being accumulated to support the development of cannabinoid-based therapies for these two conditions.

S27.4

Controlling and Visualizing Lipid Signaling in the Brain

Mario van der Stelt

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Signaling lipids, such as the endocannabinoids, play an important role in the brain. They regulate synaptic transmission and control various neurophysiological processes, including

pain sensation, neuroinflammation, stress and anxiety. Unlike classical neurotransmitters, lipid messengers are produced on demand and degraded by metabolic enzymes to control their lifespan and signaling actions. Chemical biology approaches have become one of the main driving forces to study and unravel the physiological role of lipid messengers in the brain. In this presentation, I will discuss our program to study lipid metabolism in the brain of multiple sclerosis patients and neuropathic pain in preclinical models using chemical probes.

Punt JM, van der Vliet D, van der Stelt M. Chemical Probes to Control and Visualize Lipid Metabolism in the Brain. *Acc Chem Res*. **2022**;55(22):3205-3217.

S28

Chemical and Molecular Tools to Understand the Brain in Health and Disease

CHAIR: Ismail Ahmed[1], Hilal Lashuel[2]

[1]*Neuroscience Institute, New York University School of Medicine*
[2]*Swiss Federal Institute of Technology Lausanne*
[*]*Co-organizer*

Description: Our ability to understand biological processes and how they regulate our health and behavior or contribute to disease development requires the development of experimental approaches and tools that allow for perturbing, manipulating, and monitoring these processes with spatial and temporal resolution. Recent advances in optogenetics, protein chemical synthesis, super-resolution microscopy, and the increasing availability of novel chemical tools and probes are paving the way for achieving this goal.

The design and utility of novel chemical and molecular methods and tools have become indispensable in modern-day neuroscience research. They have enabled unprecedented activation and inhibition of neuronal activity in both brain slices and behaving animals. Additionally, over the past two decades, optical methods and tools from chemistry and genetics have enabled the monitoring of activity in large numbers of neurons in both physiological and pathological states. This ability to sense and alter endogenous neural signaling is crucial for discovering mechanisms underlying neural circuit function/dysfunction and animal behavior.

Recent advances in chemical biology have led to the development of highly specific and sensitive molecular probes for studying cellular changes in neural activity and neuromodulator/neuropeptide release. This session will highlight new approaches for observing and manipulating neurochemical and electrical signaling in the brain and new chemical approaches to decipher and leverage the protein post-translational modification code to develop novel biomarkers and therapies for neurodegenerative diseases.

Appeal: The techniques described here are broadly applicable across multiple subfields in neuroscience – including molecular, cellular, systems, circuits, and neuropathologies. We also highlight different types of signaling (voltage, calcium, neuromodulators, neuropeptides) to

ensure that the session is not too focused on only one technique. Finally, we also aim to showcase how chemical biology approaches have been successfully applied to dissect and reconstruct the complexity of the molecular mechanisms underpinning the pathogenesis of neurodegenerative diseases and uncover novel therapeutic targets for disease-modifying strategies.

Clinical Relevance: Diseases of the nervous system are accompanied by alterations in neural excitability, signaling, and connectivity. Applying new molecular probes in translational models could be a critical advantage for clinicians and clinician-scientists studying mechanisms of disease and to evaluate or validate novel targets and therapies. All the speakers work on interdisciplinary projects at the interfaces of neurobiology, chemistry, and CNS disorders. The talks aim to showcase the power of novel chemical tools and approaches for studying normal and diseased brain states with the aim of encouraging cross-collaborations and discussions between basic and translational neuroscientists, engineers, and clinician scientists.

S28.1

Optopharmacological tools for precise spatio-temporal control of oxytocin signaling in the central nervous system and periphery

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Oxytocin is a neuropeptide critical for maternal physiology and social behavior, and is thought to be dysregulated in several neuropsychiatric disorders. Despite the biological and neurocognitive importance of oxytocin signaling, methods are lacking to activate oxytocin receptors with high spatiotemporal precision in the brain and periphery in mammalian tissues. Here we developed and validated caged analogs of oxytocin which are functionally inert until cage release is triggered by ultraviolet light. We examined how focal versus global oxytocin application affected Ca2+ wave propagation in mouse mammary tissue. We validated the application of caged oxytocin in the hippocampus and auditory cortex with electrophysiological recordings in vitro, and demonstrated that oxytocin uncaging can accelerate onset of mouse maternal behavior in vivo. Together, these results demonstrate that optopharmacological control of caged peptides is a robust tool for modulating neuropeptide signaling throughout the brain and body.

S28.2
The imbalance between pro-epileptogenic and protective cytokines in human epilepsies

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Human drug-resistant epilepsy is a daunting issue in clinical practice and its prevalence continues to be reported at around 30% among epileptic patients.
Low-grade brain tumors and malformations of cortical development (as TSC and FCD) are frequent conditions that lead patients to epilepsy surgery.
A partially unexploited pathophysiological mechanism that could be an additional therapeutic target in this disorders is inflammation. Indeed, in the aforementioned conditions there is evidence of a sustained inflammatory response with a pivotal involvement of the pro-inflammatory cytokine IL-1β. While the neuropathological role of pro-inflammatory pathways is well described, anti-inflammatory mediators are less studied.

Human gangliogliomas (GG) represent developmental low-grade brain tumors and are a well-recognized cause of intractable focal epilepsy in children and young adults.

Here, we aimed to define a potential effect of IL-1β and the protective IL-10 on GABAergic neurotransmission in epilepsies.
With transcriptomics, we described an upregulation of the mRNAs linked to IL-10 axis which was present in TSC and GG, but was more prominent in these latter. This observation was confirmed by electrophysiology experiments using membrane microtransplantation from GG and TSC samples in *Xenopus* oocytes. We found a IL-10 induced time- and dose- dependent GABA current increase in GG and only a tendency in TSC. Interestingly, IL-1β prevented the IL-10 induced GABA current modulation.

These results suggest that: the hyper-production of pro-inflammatory cytokines could act by preventing the beneficial effects of anti-inflammatory mediators and that modulating the equilibrium between mediators that promote or suppress inflammation may be a promising therapeutic opportunity.

S28.3
Developmental dynamics of bottom-up and top-down input integration onto L1 interneurons in the sensory cortex

Leena Ali Ibrahim

Harvard Medical School, MA, USA

Higher order projections to sensory cortical areas converge on layer 1 (L1), the primary site for integration of top-down information via the apical dendrites of pyramidal neurons and L1 GABAergic interneurons. I will discuss our recent study that investigated the contribution of early thalamic inputs onto L1 interneurons for the establishment of top-down connectivity in the primary visual cortex. We found that bottom-up thalamic inputs predominate during L1 development and preferentially target neurogliaform cells. Interestingly, these projections were found to be critical for the subsequent strengthening of top-down inputs from the anterior cingulate cortex onto L1 neurogliaform cells.
Sensory deprivation or selective removal of thalamic afferents blocked this phenomenon. While early activation of the anterior cingulate cortex resulted in a premature strengthening of these
top-down afferents, this was dependent on thalamic inputs. We are currently investigating how the balance between bottom-up and top-down signaling onto L1 interneurons is disrupted in neuropsychiatric disorders such as autism and schizophrenia.

S28.4
Insights into Parkinson's with Potassium Channels at the Forefront

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Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder with early prominent death of dopaminergic neurons in the substantia nigra pars compacta. Under pathological conditions, the presynaptic protein alpha-synuclein (α-Syn) misfolds, aggregates, and accumulates in the form of cytosolic inclusions known as the Lewy bodies and Lewy neurites, which are the defining hallmarks of PD. Together, these observations point to α-Syn as a central player in PD onset and explain why it has emerged as one of the primary targets for the development of diagnostics and therapies for PD. Previous studies have shown that extracellular α-syn aggregates are toxic and bind to cell surface receptors such as ion channels on neurons and/or microglia, leading to chronic neuroinflammation and neuronal damage. Accordingly, we hypothesize that specific ligands with known high affinity to integrins, metalloproteases, and ionic channels, such as active biomolecules from scorpion venom, could have a therapeutic effect on PD. To test this model, we employed a neuronal model that recapitulates the process of pathology formation (e.g., Lewy bodies, and Lewy neurite) and shows α-Syn-aggregation linked neuronal dysfunction and degeneration. Using this model, we identified and validated venom-derived active biomolecules that exert marked inhibition of α-Syn pathology formation and protect against α-Syn-induced toxicity. Our findings suggest that targeting potassium ion channels offer new and exciting opportunities for treating Parkinson’s disease.

S28.5

Post-translational Modifications in Parkinson’s disease and Synucleinopathies: From mechanisms to novel targets and therapeutic opportunities.

Hilal A. Lashuel

Institute of Bioengineering, School of Life Sciences, École Polytechnique Fédérale de Lausanne

The misfolding and aggregation of the presynaptic protein alpha-synuclein (aSyn) play central roles in the development and progression of Parkinson’s disease (PD) and several other neurodegenerative diseases, collectively referred to as Synuclienopathies. However, what triggers aSyn aggregation in the first place remains a mystery, and our knowledge about the molecular determinants of aSyn pathology and how it spreads in the brain remains incomplete. Although aSyn in pathological aggregates is subjected to extensive post-translational modifications (PTMs), whether these PTMs represent makers or drivers of pathology formation was not clear.

In this lecture, I will present work from our group that illustrates how using integrative chemical biology approaches and novel neuronal models of pathology formation enabled addressing this knowledge gap, deciphering the aSyn PTM code, and uncovering new therapeutic opportunities for the treatment of PD. Collectively, our work shows that targeting PTMs presents unique opportunities to 1) stabilize the native state of aSyn; 2) lower aSyn protein levels, or 3) neutralize the activity of pathogenic aSyn species and prevent their propagation in the brain. I will close by discussing the implications of our findings for ongoing efforts to develop aSyn targeting therapies and biomarkers.

S29

Clinical, behavioral and neurodevelopmental effects of stress life span: can we identify biomarkers of vulnerability?

CHAIR: Annamaria Cattaneo[1]

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It is well known that different forms stress acting on different temporal windows, can have a detrimental effect on both mental and physical health.
Even though we understand that there is an association between these exposures and an increased risk at later life to develop mental and metabolic health problems, the biological underpinnings are multifaceted, complex, and not yet fully understood. We currently lack i) early biomarkers to detect populations or individuals at risk, ii) the (neurobiological) mechanisms underlying the programming effects of adversity, iii) and effective interventions to protect exposed individuals from the detrimental effects of stress during the entire life span.
In this session, we will discuss, from both clinical and preclinical perspectives, the role of possible markers related to (neuro)inflammation, microbiota, epigenetics, and nutrition in this context.
This session will bring together speakers from different regions, and a good balance in gender and seniority. We will discuss in human studies the role of inflammation in the vulnerability for depression development and in the efficacy of treatments, both in adulthood and in adolescence.
This will be followed by presenting the importance of the microbiome as possible biological substrate for stress induced increased risk for later life psychopathology. Moreover, we will also discuss breast milk composition as a potential mediator in the intergenerational transmission of the effects of early-life adversity to the offspring's neurodevelopment and potential nutritional interventions to protect against the long-term impact of early-life adversity. Finally, we will discuss the importance of monitor key genes associated with the development of several psychopathology, including stress related disorders, as biomarkers able to predict the onset or the course of the illness.
Overall, this symposium will present clinically relevant research that combines innovative tools in rodents with findings from human studies to provide transformative frameworks on

how we may be able to better understand, treat and prevent the detrimental programming by adversities on health.

S29.1

Inflammatory biomarkers for an early screening of vulnerability and for a personalized intervention

Annamaria Cattaneo[1,2]

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It is well accepted that early life stress affects the brain developmental trajectories leading to an enhanced vulnerability for stress-related psychiatric disorders later in life. However, even though we understand that there is a clear association between these exposures and an increased risk at later life to develop mental problems, the biological underpinnings are multifaceted, complex, and not yet fully understood. We currently lack early biomarkers to detect individuals at risk, ii) the mechanisms underlying the programming effects of adversity, iii) and biomarkers that can predict and monitor the efficacy of interventions.
In this talk I will discuss from both clinical and preclinical perspectives, the role of inflammation as biological system that could be involved in the vulnerability, pathophysiology and treatment of mental disorders, with particular focus to depression.
I will also show preclinical data, where for example we have demonstrated that an exposure to prenatal stress is leading to a pro-inflammatory status in the brain in the offspring with adolescence as the temporal window where such alterations are most pronounced.
I will also discuss the importance of monitor key genes associated with inflammation as possible biomarkers that can predict and monitor the efficacy of pharmacological interventions. I will show data from cohorts where we showed that the baseline levels of several pro-inflammatory mediators can predict the treatment response, and where we performed RNAseq analyses to identify not only biomarkers but also peripheral mechanisms underlying the efficacy of pharmacological interventions.
Overall, this talk will present clinically relevant research that combines innovative tools in rodents with findings from human studies to provide transformative frameworks on how we may be able to better understand, treat and prevent the detrimental programming by adversities on health.

S29.2

Impairment of social behavior is associated with a different transcriptomic profile of the Habenula in vulnerable and resilient rats exposed to prenatal stress

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Preclinical studies showed that exposure to prenatal stress (PNS) can produce different behavioral alterations, although not all the exposed animals show a vulnerable phenotype. Recent studies pinpointed the habenula as a potential key brain region in mediating the mechanisms underlying vulnerability and resilience to stress [1]. Thus, the aim of this study was to better dissect the biology underlying the connection between stress early in life and social impairment in the habenula.
Sprague Dawley pregnant rats underwent a PNS paradigm during the last week of gestation. After birth, male offspring were left undisturbed until early adulthood (PND68) when sociability was evaluated. One week later, animals were sacrificed and RNA-Sequencing performed on the habenula.
A reduced sociability was observed in PNS males animals, as shown by a reduction in the social interaction ratio (SI ratio). Vulnerable (VULN) rats show a reduced SI ratio compared with resilient (RES) animals (VULN: 45% ± 34; RES: 87%± 7; $p < 0.0001$). Then, we focused on the genes differentially expressed in VULN and RES rats (q-value < 0.1, FC ± |1.2|), and we observed the down-regulation of several inflammatory-related pathways in RES, such as the CXCR4 ($p < 0.001$, z-score -2.33), the IL-3 ($p<0.001$, z-score -1.63), the IL-8 ($p<0.05$, z-score -1.63) and the IL-6 signaling pathways ($p<0.01$, z-score -1.34).
Overall, exposure to PNS produced an impairment of sociability in adult male rats. RES animals showed a significant down-regulation of several inflammatory-related pathways in the habenula, which may represent the resilience mechanisms following stress exposure during gestation.

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S29.3

From maternal psychopathology to child neurodevelopment: the role of early-life nutrition, mechanisms and promising targets for intervention

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Background: Maternal stress in the postpartum period affects her new-born child who is at increased risk to develop a wide range of disorders. The mechanisms underlying transmission of maternal stress to the child remain elusive. One of the suggested mechanisms is stress-induced changes in human milk (HM) composition.

Methods: This cohort study investigates whether maternal stress influences the composition of HM and subsequently infant neurodevelopment. HM composition was compared between two groups of lactating women: 1) a high stress (HS) group, women whose child was hospitalized for a minimum of 2 days and 2) a control (CTL) group which consisted of women who gave birth to a healthy child. HM was collected three times a day at postpartum days 10, 17 and 24. Perceived stress was measured using validated questionnaires, while biological stress was measures via cortisol concentrations.

Results: HM of women in the HS group had lower absolute concentrations of fatty acids (p=0.013) and polyunsaturated fatty acids (PUFAs) (p=0.031), while concentrations of amino acids where higher (p=0.028). Moreover, women in the HS group had a different compositions of the HM microbiome, metabolome and oligosaccharides. The stress induced changes in HM fatty acid and PUFA concentrations significantly mediated (45-49%) the association between maternal stress and infant temperament at three 3 months of age.

Conclusion: The findings of this study highlight the importance of the maternal psychological state in the postpartum period and indicate a possible route of transmission of maternal stress signals to the infant.

S29.4
Impact of stress on mental health: epigenetic biomarkers

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Epigenetic changes brought on by stress play a significant role in long-term biological pathways leading to stress-related psychiatric disorders, reflecting both individual genetic predisposition and environmental influences. Salivary samples of young university students assessed for stress levels by Perceived Stress Scale (PSS) and for an innate personality trait, the Highly Sensitive Person (HSP) test, were collected to obtain genomic DNA for the study of DNA methylation, SNPs and VNTRs and exosomal miRNAs for the study of target miRNAs expression and thus analyze the genetic and epigenetic regulation of key genes, namely Oxytocin receptor (OXTR), Dopamine transporter (DAT), Serotonin Transporter (SERT).
We observed that high-sensitive individuals have different levels of DNA methylation when compared to low-sensitive and medium-sensitive individuals at specific CpG sites at OXTR

(hypermethylation) and DAT (hypomethylation) genes. Moreover, in high-sensitive

individuals with higher PSS scores, OXTR CpG sites resulted to be even more hypermethylated and the expression of target miRNAs over-expressed when compared with high-sensitive subjects less stressed. No association between gene SNPs and/or VNTRs and HSP scores have been observed.
The reported epigenetic regulation of key genes known to be relevant in mental health might be suggested as possible biomarkers in highly sensitive persons, in particular under stressful condition, that could make them more likely to develop a mental illness.

S30

Precipitants of brain (mal)plasticity and pathology in the new era of precision medicine

CHAIR: Ioannis Sotiropoulos[1,2]

[1]*Researcher C- Group leader, Institute of Biosciences & Applications, NCSR Demokritos, Greece*
[2]*ICVS Institute, Portugal*

In the new era of precision medicine, there is an urgent need to understand the interaction between different precipitants of brain (mal)plasticity and how they contribute to the onset of complex brain pathologies, e.g., Alzheimer's disease and major depression. This symposium will gather basic and clinical researchers (4 female and 1 male) from both academia and industry in Europe, USA, and Canada. They will discuss experimental and clinical findings related to the interplay of different biological and environmental precipitants of disease such as aging, chronic stress, sex, and their impact on cognitive and mood status as well as axonal and synaptic function, brain connectivity, and inflammatory and neuroplastic pathways related to Alzheimer's disease, major depression, and stroke.

S30.1

The expected and the unexpected: neuroprotective effects of estrogens for stroke diverge dependent on reproductive age

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Stroke is a leading cause of long-term disability and dementia. Older women sustain more severe strokes than men and are more likely to develop cognitive impairment. Our studies show that young female rats (5-6 months) have smaller stroke-induced infarction as compared to reproductively senescent females (10-12 months). Estrogen treatment to ovariectomized (OVX) young females improves stroke outcomes but is paradoxically neurotoxic to middle-aged female rats. To better understand how reproductive senescence contributes to stroke severity, our recent studies have focused on the gut microbiome and

metabolites. We noted significant gut dysbiosis in reproductive senescent females constitutively and after stroke as indicated by an alterations in the major phyla, reduced alpha diversity, and significant shifts in beta diversity. Relative to OVX+E young females, middle-aged OVX+E females had lower basal levels of the neuroprotective gut metabolites butyrate, and elevated levels of the endotoxin after stroke. These data provide the first evidence that microbial gut communities and metabolites are altered by reproductive senescence and E2 treatment and may underlies the anomalous effects of estrogen on stroke. While it is not known how these microbial communities diverge with reproductive age since diet is similar is both groups, the aging ovary itself may be the locus of metabolic changes. Thus, while OVX in young females impairs stroke outcomes, our recent work shows that removal of ovaries in middle-aged females reduces specific cohorts of immune cells and improves stroke outcomes compared to gonadally-intact females. These studies underscore the complex role of ovarian hormones and stroke recovery.

Supported by NIH NS074895 and AG042189

S30.2

The stressed brain: a gate along the path from depression to Alzheimer's disease

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Chronic stress and high levels of the stress hormone, glucocorticoids (GC), are implicated in susceptibility to brain pathologies such as depression and Alzheimer's disease (AD), as they promote neural plasticity damage and glial reactivity, which can lead to dendritic/synaptic loss, reduced neurogenesis, mood deficits, and impaired cognition. Moreover, depression is implicated in the development of AD with chronic stress being a potential link between both disorders via common neurobiological underpinnings. Hereby, I will present and discuss the clinical and preclinical evidence related to the detrimental effect of chronic stress as a precipitator of AD through the activation of pathological mechanisms leading to the accumulation of amyloid β (Aβ) and Tau protein as well as various downstream cellular cascades related to both neuroplasticity and neuropathology. Given that the modern lifestyle increasingly exposes individuals to high stress loads, it is clear that understanding the mechanistic link(s) between chronic stress, depression and AD pathogenesis may facilitate the treatment of AD and other stress-related disorders.

S30.3
Sex Differences in Negative Cognitive Bias

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Females are twice more likely to develop major depressive disorder (MDD) compared to males. Negative cognitive bias, a cognitive symptom of MDD, is the increased perception of ambiguous situations as negative and predicts future depressive episodes. Cognitive bias involves pattern separation, which relies on adult hippocampal neurogenesis, connectivity between the hippocampus and amygdala, and is impaired by inflammatory signalling via IL-1β. We examined sex differences in the neural and molecular underpinnings of negative cognitive bias after chronic unpredictable stress (CUS). CUS exposure increased negative cognitive bias, regardless of sex. However, CUS increased IL-1β and TNFα in the basolateral amygdala (BLA) of females but not in males. These data indicate that neuroinflammation in the BLA has an important role in modulating negative cognitive bias in females, but not in males. CUS decreased neurogenesis in the ventral dentate gyrus of both sexes, and increased activation of new neurons in the dorsal dentate gyrus of males but not females. Positive correlations between negative cognitive bias and neurogenesis in males but not in females were seen. Although there were no significant sex differences in negative cognitive bias, we saw profound sex differences in possible mechanisms. Our results suggest that inflammation in the BLA drives stress-induced negative cognitive bias in females, whereas hippocampal neurogenesis drives stress-induced negative cognitive bias in males. These results highlight that sex is a necessary factor in understanding the mechanisms of negative cognitive bias.

S30.4
Oligodendroglial Support of Axonal Function in Health and Disease

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Oligodendroglia, the myelinating cells of the central nervous system, are essential for neuronal impulse propagation via saltatory conduction. The importance of these cells for brain development and homeostasis is exemplified by diseases of dysmyelination such as leukodystrophies and by diseases of myelin breakdown such as multiple sclerosis. But are oligodendroglia just electrical insulators? Evidence suggests that myelinating oligodendroglia are glycolytic cells that can release glycolytic end products to support axonal function. Moreover, oligodendroglia increase their glycolytic output in order to match increased metabolic demands of rapidly firing axons. But how is oligodendroglial support of axonal

function regulated? Oligodendroglia have proven essential for axonal integrity and neuronal survival even in the presence of normally-appearing myelin. Moreover, white matter abnormalities precede wide spread neurodegeneration in diseases such as Alzheimer's disease. Are modalities aimed at increasing oligodendroglial glycolysis and thereby trophic support of axonal function a viable avenue for the development of novel therapies for neurogenerative diseases?

S31

Preclinical study of the mechanism of action of psychedelics
CHAIRS: Nasser Haddjeri (FR), Philippe De Deurwaerdère (FR)

Psychedelic substances have reemerged as a subject of intense research interest, holding significant promise in the fields of neuroscience and mental health. This symposium, "Psychedelics in Focus: Mechanisms and Therapeutic Potential," offers a comprehensive exploration of the latest advancements in understanding the psychopharmacological effects and therapeutic applications of psychedelics. With a focus on substances such as LSD and 5-MeO-DMT, our esteemed panel of experts delves into the intricate mechanisms underlying these compounds' rapid and transformative actions.The first talk by Romain Hacquet, Lionel Mouledous, and Bruno Guiard examines how the context of administration influences the psychopharmacological profile of 5-MeO-DMT. By investigating the impact of setting on therapeutic responses, this research provides invaluable insights into the temporal dynamics of these compounds. Amel Bouloufa, Sarah Delcourte, Renaud Rovera, Ouria Dkhissi-Benyahya, and Nasser Haddjeri take the stage in the second talk to unveil the rapid antidepressant effects of LSD through 5-HT2B receptor activation. This revelation opens new avenues for understanding the neural mechanisms underpinning the therapeutic potential of psychedelics. In the third talk, Jasmine Jade Butler, Margherita Virgili, and Philippe De Deurwaerdère delve into the complex interactions between neurotransmitters when exposed to the non-selective 5-HT2A receptor agonist TCB-2. Their work unravels the intricate web of neurotransmitter systems modulated by psychedelics, offering a fresh perspective on their pharmacology. The symposium concludes with a presentation by Carolina Giulia Ferroni, Stefano Comai, Flavia Valtorta, and Danilo De Gregorio, focusing on LSD's potential in addressing Alcohol Use Disorder (AUD). Through a translational approach, they explore how LSD affects alcohol consumption, behavior, and dopaminergic systems, shedding light on novel approaches to AUD treatment. Collectively, these talks provide a profound understanding of the mechanisms and therapeutic potential of psychedelics, offering a glimpse into the exciting future of these compounds in neuroscience and psychiatry. This symposium is a testament to the resurgence of interest in psychedelics and their transformative potential in the quest for effective treatments for mental health disorders.

S31.1

Influence of the context of administration in the psychopharmacological profile of the psychedelic 5-MeO-DMT

Romain Hacquet, Lionel Mouledous, Bruno Guiard

Centre de Recherches sur la Cognition Animale, Centre de Biologie Intégrative, CNRS UMR 5169, Université Paul Sabatier, Toulouse (France)

Psychedelics like psilocybin display rapid efficacy on anxio-depressive symptoms. Other psychedelics, with a shorter half-life (DMT, 5-MeO-DMT), have also shown positive preliminary outcomes in depression. However, the influence of the context on the trajectory of the therapeutic response is still poorly documented. Here, we have implemented studies aimed at evaluating the psychopharmacological profile of 5- MeO-DMT in contexts previously validated in mice as pleasant (positive setting) or, on the contrary, aversive (negative setting). Male mice received a single injection of 5-MeO-DMT and different delays were tested post-administration. The most effective dose of 5-MeO-DMT was also tested in the corticosterone (CORT) mouse model of depression while behavioral tests recapitulating core symptoms of depression were applied.

In healthy mice, 5-MeO-DMT showed an antidepressant- and anxiolytic-like action at the dose of 0.5 mg/kg 24h after its administration whereas the effects with higher doses (5 or 10 mg/kg) were less pronounced or completely blunted. The beneficial effect of 5-MeO-DMT (0.5 mg/kg) was no longer detected one week after its administration. In CORT exposed mice, the acute dose of 0.5 mg/kg produced antidepressant-like effects 24h after administration when given in a neutral or positive setting. However, such a beneficial effect was completely hindered in a negative setting.

To precise the neurobiological mechanisms underlying the influence of setting on the rapid and transient activity of 5-MeO-DMT, we will quantify cortical markers of pre- and post-synaptic density (i.e., SV2A and PSD95, respectively) and test them to highlight putative correlations with mice behavioral performances.

S31.2

The prototypical hallucinogen LSD produces rapid antidepressant effects via 5-HT2B receptor activation.

Amel Bouloufa[1], Sarah Delcourte[1], Renaud Rovera[1], Ouria Dkhissi-Benyahya[1] and Nasser Haddjeri[1]

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Major depression is predicted to become a leading cause of disability by the year 2030, yet current strategies still remain inadequate, therefore more rapid, safe and efficacious medications are urgently needed. Recent clinical trials show that serotonergic psychedelics, including the prototypical hallucinogen lysergic acid diethylamide (LSD), possess a great promise for treating psychiatric disorders, including treatment-resistant depression.

LSD is a potent 5-HT receptors agonist presenting high affinity for most of all 5-HT subtypes and is regularly used as a pharmacological tool to describe 5-HT1A and 5-HT2A mediations [1]. Besides, the crystal structure of LSD in complex with the human 5-HT2B receptor has been also described [2].

Using in vivo electrophysiological, functional and behavioral paradigms, our aim was to examine possible involvement of the 5-HT2B receptors in the action of LSD on both the 5-HT neurotransmission and on the anxio-depressive-like phenotype in rodent.

Hence, our data shed light on contribution of 5-HT2B receptor in the antidepressant effect of LSD and propose new neural mechanisms underlying the therapeutic effects of psychedelics.

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S31.3

The 5-HT2A receptor agonist TCB-2 disrupts the correlative links between numerous classical neurotransmitters in the mouse brain

Jasmine Jade Butler[1], Margherita Virgili[1], Philippe De Deurwaerdère[1]

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The mechanism of action of classical psychedelics is still unknown despite evidence that they modulate the activity of neurotransmitter systems across the brain. In mice, we studied the effect of the non-selective 5-HT2A receptor (5-HT2AR) agonist TCB-2 (0.3, 3, and 10mg/kg) and the combination TCB-2 (3 mg/kg)/MDL100,907 (5-HT2AR antagonist; 0.2 mg/kg) on tissue content of neurotransmitters [noradrenaline (NA), dopamine (DA), serotonin (5-HT) with some metabolites, GABA, glutamate] measured by HPLC in 30 brain regions belonging to various neurobiological networks.

TCB-2 decreased the 5-HT turnover (usually an increase in 5-HT) in all brain regions. It decreased the ratio 3-methoxytyramine/DA in the striatum, and enhanced markers of the DA system in a few cortices (cingulate, somatosensorial, auditory) or NA in the cingulate cortex and the ventral hippocampus. The decrease in 5-HT turnover induced by TCB-2 was insensitive to MDL100,907 in general, acknowledging that MDL100,907 prevented TCB-2-induced head

twitched. However, MDL100,907 blocked the increase in 5-HT levels in a few cortices (cingulate and auditory) and the ventral hippocampus. It also blocked some DA and NA effects notably in the cingulate cortex. TCB-2 alone or combined with MDL-100,907 did not alter amino acid tissue contents, but dramatically decreased the correlations of isolated neurotransmitter contents across the brain (MDL100,907 also did), an effect partially counteracted by MDL100907 for 5-HT, glutamate, and GABA. Irrespective of its questionable action beyond 5-HT2AR, the data indicate that TCB-2 dramatically alters the activity of 5-HT neurons in the brain, and disrupts the correlative links between brain regions for all neurotransmitters.

S31.4

Impact of lysergic acid diethylamide (LSD) in alcohol use disorder (AUD)

Carolina Giulia Ferroni, Stefano Comai, Flavia Valtorta , Danilo De Gregorio

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Alcohol use disorder (AUD) is a major problem that causes significant health and social problem. Pharmacological treatments for AUD are limited in their effectiveness, and new drugs are required. Recently, the potential use of hallucinogens as novel therapies in treating mental diseases has come to the forefront in psychiatry. For instance, lysergic acid diethylamide (LSD) is a hallucinogen acting as partial agonist of 5-HT2A receptors and exerts its mechanism of action through the modulation of the dopaminergic system in the ventral tegmental area (VTA) and the glutamatergic transmission in the medial prefrontal cortex (mPFC). For instance, VTA plays a pivotal role in mediating the neurophysiology of AUD. However, the mechanism of action and pre-clinical data about the effectiveness of hallucinogen-based therapies for AUD remain limited. This translational study aims at determining whether the LSD can reduce alcohol consumption in an animal model of AUD and its mechanism of action. To do so, we will employ a mouse model of self-ethanol administration with a paradigm DID (Drinking in the dark) to mimic binge-like drinking in humans.

In particular, C57BL6/J 8-week-old male mice will undergo 6 cycles of DID. Each cycle consists in: one experimental group (AUD mice) in which the water bottles will be removed from all cages and replaced with bottles containing 20% ethanol solution for 2 hours per day, for 4 consecutive days; another group of mice (control, CTL) in which the water bottles will be not replaced with ethanol. After 6 cycles of DID, mice will receive a single intraperitoneal injection of vehicle or LSD (150 µg/kg). Immediately after, animals will undergo alcohol consumption assessment with the 40 days two-bottle choice test. Twenty-four hours from the last drinking session, locomotion was assessed employing the open field test (OFT) and the rotarod test. Finally, *in vivo* single unit extracellular recordings of VTA DA neurons will be performed.

Our preliminary results show that AUD mice did not show difference in locomotion during the OFT, compared to CTL ($p=0.012$). However, AUD mice displayed decreased latency to fall ($p<0.01$) in the rotarod test. These effects were coupled to an increased DA VTA firing rate activity ($p<0.05$) in AUD mice compared to CTL. We will then investigate if LSD will be able to modulate alcohol intake as well as the locomotor activity and DA VTA firing in AUD mice. This work will broaden our understanding of the effects of hallucinogen on AUD.

S32
Neurobiology of alcohol and opiates use disorders

CHAIR: Sami Ben Hamida[1]

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Addiction is a brain disease that affects multiple brain circuits, including those responsible for reward/aversion, motivation, learning and memory, and inhibitory control. Adolescence is a critical period of brain development and exposure to drugs during this time can increasethe risk of developing addiction. The vulnerability to addiction varies depending on genetic makeup, age of exposure to drugs, and environmental influences. Over time, prolonged drug exposure alters brain function, compromising an individual's ability to choose and leading to compulsive drug seeking and use that is beyond their control.

The basal ganglia are affected by changes in dopamine and opioid peptides during the binge/intoxication stage of addiction, leading to rewarding drug effects and the development of drug-seeking habits. During the withdrawal/negative affect stage, different brain structures, including some newly identified, may be involved in the increases in negative emotions and stress-like responses. A deeper understanding of the complex stagesand states of addiction is crucial in addressing alcohol and drug abuse, especially in adolescence when the brain is still developing.

Molecular genetics have identified transduction and transcription factors that play a role in the development and maintenance of addiction and may mediate initial vulnerability, maintenance, and relapse. This symposium will present recent advances in research on neurobehavioural and neuronal circuiteries determinants of vulnerability to alcohol and drug use disorders.

S32.1
Effectiveness of psychedelics on alcohol use disorders

Jérôme Jeanblanc[1], Fahd Hilal[1], Romain Bordy, Grégory Fouquet[1], Virginie Jeanblanc[1], Chloé Deschamps[1], Olivier Pierrefiche[1], Mickael Naassila[1]

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Psychedelic are very promising therapy in alcohol use disorder (AUD) but the underlying brain mechanisms are still not well understood. Despite the initiation of several clinical trials for psychiatric disorders, unexpectedly little preclinical research has been conducted so far using psychedelics. Here, we used two relevant animal models of alcohol use disorders in rats to better understand their behavioral effects and their brain targets. We previously demonstrated that psilocybin reduced alcohol relapse after abstinence in the post-dependent state model of AUD possibly through rescuing mGluR2 expression in the nucleus accumbens (Meinhardt 2019). Now we are providing new unpublished results showing the effectiveness of psilocybin injected either i.p. or directly into brain structures to reduce alcohol self-administration and the blockade of its effect after the injection of a 5-HT_{2A}R antagonist directly into the brain. We also show that this effect may be mediated, at least in part, through increased expression of dopamine receptors. Finally, we also tested the effects of other psychedelics and psychedelic-like such as LSD and ketamine. To the best of our knowledge, we are the first to demonstrate the effectiveness of psychedelics directly administered into the brain and our results bring new important perspectives in terms of the mechanisms of action of psychedelics as AUD treatments. Several clinical trials on psychedelics in AUD will be launched soon in France.

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S32.2

The GABA transporter GAT-3 and GABAergic transmission in the CeA : a common role in alcohol and drug use disorder ?

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We recently identified that impaired GABAergic transmission, due to decreased expression of the GABA transporter GAT-3, within central amygdala (CeA) was causal for alcohol choice behavior and translated to humans. Whether this mechanism also operates for other drugs, including opioids and stimulants is currently unknown.

Our main objective was therefore to investigate whether experimentally impairing the function of GAT-3 in the CeA would promote addiction-like behaviors in rat models of cocaine

and oxycodone addiction. Using intravenous self-administration, we first trained Wistar rats to self-administer cocaine under an extended access of 6 hours (Long Access, LgA), a regimen that promotes escalation of drug intake and increased motivation to obtain cocaine. We found that GAT-3 expression was robustly decreased in the CeA of animals that escalated their cocaine intake compared to animals with stable intake (Short Access, ShA). We then investigated the functional role of GAT-3 in both male and female Wistar rats, using CeA injections of an AAV-shRNAi targeting GAT-3, or a scrambled control vector. GAT-3 KD in the CeA potently promoted escalation of cocaine intake and increased motivation for cocaine and cocaine craving, irrespective of sex. In marked contrast, we found that GAT-3 KD didn't affect oxycodone-related behaviors in a preclinical model of opioid use disorder.

All together, these results provide evidence that the GABA transporter GAT-3 may also play a role in cocaine-related behaviors and indicate that rescuing impaired GABA clearance due to suppressed GAT-3 expression might be a successful therapeutic mechanism in cocaine use disorder.

S32.3

Implication of opiate responsive neuronal circuitries in aversive/depressive states.

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The mu opioid receptor (MOR) is central to hedonic balance, and produces euphoria by engaging reward circuits. MOR signaling may also influence aversion centers, and notably the habenula (Hb), where the receptor is highly dense. Our previous data suggest that the inhibitory activity of MOR in the Hb may limit aversive states. To investigate this hypothesis, we here tested whether neurons expressing MOR in the Hb (Hb-MOR neurons) promote negative affect. Using Oprm1-Cre knock-in mice, we combined tracing and optogenetics with behavioral testing to investigate consequences of Hb-MOR neuron stimulation in approach/avoidance (real-time place preference), anxiety-related responses (open field, elevated plus maze and marble burying) and despair-like behavior (tail suspension). Opto-stimulation of Hb-MOR neurons elicited avoidance behavior, demonstrating that these neurons promote aversive states. Anterograde tracing showed that, in addition to the interpeduncular nucleus (IPN), Hb-MOR neurons project to the dorsal raphe nucleus (DRN). Opto-stimulation of Hb-MOR/IPN terminals triggered avoidance and despair-like responses with no anxiety-related effect, whereas light-activation of Hb-MOR/DRN terminals increased levels of anxiety with no effect on other behaviors, revealing two dissociable pathways controlling negative affect.

S32.4
mPFC and alcohol related-behaviors

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The medial prefrontal cortex (mPFC) plays a critical role in addiction-related cognitive and emotional processes, reward processing, decision-making, and impulse control. GABAergic interneurons within the mPFC modulate the activity of pyramidal neurons and their output to brain areas implicated in alcohol addiction. However, the precise mechanisms through which mPFC neurons encode real-time alcohol-seeking behaviors remain largely unknown. In this study, we selectively targeted specific cell populations in the mPFC to investigate the causal relationship between mPFC activity and alcohol-related behaviors. We used single-cell calcium imaging and chemogenetic methods in rats to observe and track neuronal activity in the mPFC during alcohol-related behaviors. Our findings revealed distinct and dynamic ON and OFF neural ensembles within the mPFC that exhibited differential activity patterns to encode real-time alcohol-related behavioral information. These ensembles demonstrated specific tuning towards compulsive alcohol seeking and taking, pointing to their potential role in the development of alcohol use disorders (AUD). Notably, dysfunctions in mPFC neural activity were associated with altered alcohol seeking and reduced alcohol intake, highlighting the significance of mPFC neural ensembles in driving alcohol-related behaviors. Furthermore, this study provides a comprehensive understanding of the dynamic changes in neuronal activity within the mPFC associated with impaired cognitive flexibility in decision-making in rats with a history of alcohol intake.
Elucidating these mechanisms contributes to the broader knowledge of alcohol addiction-related neural circuitry and may have consequences for our comprehension of AUD.

S32.5
A reverse translational approach to evaluate individual variability in treatment response in alcoholism.

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Due to the large heterogeneity of alcohol use disorders (AUD), treatments efficacy varies between patient subgroups and many promising targets failed clinical expectations. Using a reverse translational we verified that preclinical models of heterogeneous AUD-like behavior would predict the efficacy of approved an AUD medication (Naltrexone) and the lack of efficacy of a drug that failed clinical trials (Memantine). Innate exploratory activity, anxiety

and pain sensitivity were initially screened in forty NIH heterogeneous-stock (HS) rats (sex balanced), then subjected to multiple alcohol seeking behavioral screening (motivation under progressive ratio contingency, quinine adulterated alcohol intake, and cued relapse) to allocate them into three clusters: AUD-cluster-2 scored the lowest in every behavior (AUD resilience-like); AUD-cluster-1 and 3 showed similar alcohol intake and cued relapse and were differentiated by higher motivation in AUD-cluster-1 and higher quinine resistance in AUD-cluster-3 representing two different AUD-like profiles. Both doses of Naltrexone (0, 0.3 and 1.0 mg/kg) reduced alcohol self-administration in AUD-Clusters-1 and 3, with the lowest dose being selective for alcohol as the highest also reduced saccharin self-administration. Conversely, the highest dose of memantine (0, 6, 12, 25 mg/kg) reduced both alcohol and saccharin self-administration in all AUD-clusters, showing lack of selectivity and confirming our hypothesis. Naltrexone effect size inversely correlated with anxiety, thus we applied k-mean to divide rats into naltrexone-responder and non-responder subjects and demonstrated that naltrexone-responder showed higher innate anxiety than non-responder. Our results demonstrated that models of individual variability can predict treatment efficacyand allow to spot and predict drug non-responder subjects.

S33

"EpiEpiNetwork MNS Symposium: Next steps on epilepsy research: from brain dysfunction and immunity to comorbidities"

CHAIR: Sandra H Vaz[1], Tatiana P. Morais[1,2]

[1]Instituto de Medicina Molecular João Lobo Antunes[1] and Faculdade de Medicina da Universidade de Lisboa
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Epilepsy refers to a set of signs and symptoms having in common repeated unprovoked seizures that may manifest in several ways, with a broad range of different etiologies and resulting from different triggers. Additionally to the seizures, epileptic patients may present several comorbidities that have a profound impact in their life. Available treatments fail in more than 30% of the patients and have been directed towards control of seizures, with little understanding of the underlying causes of the different forms of epilepsy and of the mechanisms underlying epileptogenesis and the development of comorbidities. Thus, there is a need of not only to find new drugs with better efficacy and with fewer side effects, but also to clarify risk factors, i.e. genetic risk factors, and to identify strategies to prevent epileptogenesis, as well as, to treat or decrease associated comorbidities. All this knowledge on epilepsy and theirs comorbidities will provide the neuronal network with the tools necessary to restore its physiological balance.

Thus, this symposium will bring together the work of three partners of the European Epileptogenesis and Epilepsy Network (EpiEpiNet), and it will cover the most recent advances

in the immune system, genetic mutations or imbalance between inhibition and excitation in epilepsy that ultimately may lead to the development of comorbidities.

S33.1

GABAergic neurotransmission: a common hallmark of neurodevelopmental impairment

Gabriele Ruffolo[1,2], Veronica Alfano [2], Alessia Romagnolo[3], James D. Mills[3,4,5], Pierangelo Cifelli[6], Alessandro Gaeta[1],, Eleonora Aronica[3,7] & Eleonora Palma[1,2]

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Alterations of GABAergic neurotransmission are fundamental pathogenic factors of several disorders characterized by high incidence of epileptic seizures. In particular, chloride homeostasis possesses a pivotal role in the aberrant GABA-mediated inhibition and the main cation-chloride cotransporters (NKCC1 and KCC2) are currently under the spotlight of physiological and pharmacological investigation as potential candidates for the development of new drugs.

This dysregulation of chloride homeostasis and GABAergic neurotransmission acquires an even greater importance in all the diseases that can impair the normal development of the nervous system. Interestingly, neurodevelopmental disorders such as Tuberous Sclerosis Complex (TSC), Focal Cortical Dysplasia and Rett syndrome are all characterized by a certain degree of alteration of GABA-mediated neurotransmission, which maintains features typical of an immature brain.

This disruption of inhibitory function has widespread consequences since it is indeed correlated with the intrinsic excitability that characterizes the aforementioned disorders, in which epileptic seizures are extremely common, but recent evidence allows to infer that it can have a role also in the development of cognitive impairment and other comorbidities.

Hence, this discussion will focus on the electrophysiological basis of GABAergic dysfunction in neurodevelopmental disorders and the strategies that have been used, in a basic research setting, to restore a physiological inhibitory neurotransmission. These could represent a potent link between the bench and the bedside, since it was demonstrated that the recovery

of GABAergic neurotransmission ameliorates both epileptic seizures and cognitive impairment.

S33.2

GABAergic modulation by immune cells and effects on memory

Stefano Garofalo, Germana Cocozza, Alessandro Mormino, Giovanni Bernardini, Eleonora Russo, Donald Ielpo, Diego Andolina, Rossella Ventura, Katiuscia Martinello, Massimiliano Renzi, Sergio Fucile, Mattia Laffranchi, Eva Piano Mortari, Rita Carsetti, Giuseppe Sciumè, Silvano Sozzani, Angela Santoni, Marie-Eve Tremblay, Richard M. Ransohoff & Cristina Limatola

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The mechanisms of communication between the brain and the immune cells are still largely unclear. We have recently characterized populations of resident natural killer (NK) cells and innate lymphoid cells (ILC)1in the meningeal dura layer of mice. We described that ILC1/NK cell-derived interferon-γ and acetylcholine can contribute to the modulation of brain homeostatic functions, shaping synaptic neuronal transmission and neurotransmitter levels with effects on mice behavior. In particular we described that interferon-γ produced by these cell populations plays a role in the formation of non-spatial memory, tuning the frequency of GABAergic neurotransmission on cortical pyramidal neurons. We also described that NK cells produce acetylcholine, which mediates the modulation of brain circuitries that regulate anxiety-like behavior in mice. Altogether, these findings disclose new mechanisms of immune-to-brain communication that modulate brain functions under physiological conditions.

S33.3

Early postnatal transplantation of human stem cell-derived GABAergic interneurons alters the adult epileptic phenotype of *Cntnap2* knock-out mice

Ana Gonzalez-Ramos[1], Fredrik Berglind[2], Kerstin Laurin[2], Diana Hatamian[2], Mohanad Hayatleh[2], Anja Vombergar[3], Marco Ledri[3], Merab Kokaia[1], and My Andersson[2]

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Refractory epilepsy during childhood has severe detrimental effects on brain development. Moreover, early-onset of epilepsy has been associated with other neurodevelopmental disorders such as autism, which at the same time seem to share underpinning mechanisms of the pathology as alterations in the excitatory and inhibitory balance of neuronal networks. Several genes have been linked to those disorders, among them *contactin-associated protein-like 2* (*CNTNAP2*) has generated interest by being associated with cortical dysplasia, refractory focal epilepsy, and autism spectrum disorders. Here we have investigated the development and characteristics of the abnormal electroencephalogram (EEG) in the *Cntnap2* knock-out (KO) mouse model. We have identified the hippocampus as a potential origin of the spontaneous recurrent seizures developing after six months of age, and an association between an increase in interictal epileptiform discharges (IEDs) and seizures. Moreover, *Cntnap2* KO mice showed impaired long-term memory after seizure onset. Further, we explored an inhibitory cell-based replacement therapy targeting the focus of the pathological EEG. Human stem cell-derived interneurons (hdINs) were transplanted to the dorsal hippocampus at postnatal day 2 *Cntnap2* KO mice and behavioral tests were performed at 4- and 7-months of age, followed by two weeks of continuous video-EEG monitoring. The hdINs survived up to nine months post-transplantation, with hdINs dispersed along both ipsi- and contralateral to the transplanted hippocampus. Unexpectedly, hdIN-transplanted animals exhibited an increased number of IEDs and seizures compared to the sham-transplanted group, suggesting that hdINs do not prevent the development of epilepsy in this model, as hypothesized, but rather enhance it.

S33.4

Cognitive comorbidities of absence seizures

Mariana Neuparth-Sottomayor[1,2], Carolina C. Pina[1,2], Tatiana P. Morais[3,4], Miguel Farinha-Ferreira[1,2], Daniela Sofia Abreu[1,2], Filipa Solano[1,2], Francisco Mouro[1,2], Mark Good[3], Ana Maria Sebastião[1,2], Giuseppe Di Giovanni[4,5], Vincenzo Crunelli[4], Sandra H. Vaz[1,2]

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Typical absence seizures (ASs) of 3-4 Hz thalamocortical spike-wave discharges, are the hallmark of Childhood Absence Epilepsy (CAE). In recent studies in CAE cohorts, 60% of patients show psychiatric comorbidities, including attention, cognitive, memory and mood impairments. Similar cognition and memory deficits have been reported in different, but not all, genetic animal models of ASs. Since cognitive alteration may be subtle, not easily detected and task-specific, their presence may be confounded by an anxiety-like phenotype. Using ASs animal models, the Genetic Absence Epilepsy Rats from Strasbourg (GAERS), their inbred strain of Non-Epileptic Control (NEC) strain (that lack ASs) and normal outbred Wistar rats,

and STARGAZER (STG) mice and respective controls, we aimed to assess behaviour comorbidities in both models. GAERS did not exhibit impaired locomotor activity neither anxiety-like behaviour. In contrast, GAERS show decreased spontaneous alternation in the Y-maze, spatial working memory and cross-modal object recognition compared to both NEC and Wistar rats. Notably, GAERS preferentially used egocentric strategies to perform spatial memory tasks. Moreover, STG mice did not exhibit increased anxiety but had deficits in spatial reference memory, compared to wildtype mice. In summary, these results provide solid evidence of memory deficits in GAERS rats and STG mice, which do not depend on an anxiety phenotype. Moreover, the presence of differences between NEC and Wistar rats stresses the need of using both outbred and inbred control rats in behavioural studies of inbred models of ASs.

S33.5

Absence Seizures Comorbidities and Their Pharmacological Modulation

Tatina P Morais[1,2], Daniel Cassar[1], Mnauela Radic[1], Mariana Sottomayor[3,4], Sandra H Vaz[3,4], Vincenzo Crunelli[2], Giuseppe Di Giovanni [1,2,] *

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Absence epilepsy, a common form of childhood epilepsy, is characterized by brief episodes of altered consciousness and generalized spike-and-wave discharges on electroencephalography. In childhood/juvenile absence epilepsy, seizures are commonly accompanied by neuropsychiatric comorbidities, including cognitive, memory and mood impairments. This presentation aims to delve into the understanding of the comorbidities associated with absence seizures, specifically in Genetic Absence Epilepsy Rats from Strasbourg (GAERS) and explore the pharmacological modulation of these comorbidities.
The focus of this talk will revolve around the involvement of various neurotransmitter systems and their receptors in the pathophysiology of absence seizures. Specifically, we will discuss the role of serotonin 2A and 2C receptors, known to influence neuronal excitability, in the modulation of absence seizures. Furthermore, the involvement of cannabinoid receptors, which have shown promise in modulating seizure activity, will be explored.
In addition to elucidating the underlying mechanisms, we will discuss the pharmacological interventions employed for managing absence seizures and their associated comorbidities. This includes a comprehensive review of current antiepileptic medications that target specific neurotransmitter systems and their receptors. The presentation will highlight the efficacy,

limitations, and potential side effects of these medications in the management of absence seizures and associated comorbidities.
Through this talk, we aim to provide a comprehensive overview of the neurobiological underpinnings of absence seizures and their comorbidities, while emphasizing the potential of pharmacological modulation. The knowledge presented in this talk will contribute to the development of more targeted therapeutic interventions for individuals with absence seizures, ultimately improving their quality of life.

S34
Regulation of Cognitive Control from Rodents to Primates and Humans

CHAIR: Radwa Khalil[1]

[1]*School of Business, Social and Decision Sciences, Constructor University, Bremen, Germany*

Cognitive control or executive functions (EFs) plays an essential role in our daily life as it makes it possible to mentally re-construct ideas and perceive the world around us, control our actions, face novel, unexpected and uncertain challenges, avoid impulses and remain focused. The general characteristics of EFs comprise inhibitory control (including attention), working memory, and cognitive flexibility. The latter is a crucial feature of creatively thinking, considering views or problems from distinctive perspectives, and quickly and flexibly adapting to changing circumstances). These functions greatly influence our daily decisions, reasoning, planning, problem-solving, and creative performances. Therefore, a better understanding of EFs and its regulation is crucial to improving the quality of life. This can be achieved by advancing our knowledge of brain structures that underlie EFs and their role in healthy and pathological conditions. This symposium will shed light on some of the most fundamental EFs, specifically inhibitory control, and attention. The possibility that EFs (namely, attention and impulsivity) are impaired in pathological conditions will be illustrated in a rodent model of pain sensitization. We will then highlight the neuroanatomical basis of decision-making in rodents and primates. We will discuss how EFs shapes decision-making and creative thinking in non-human and human primates. Altogether, the commonalities and similarities between EFs and their regulation will be discussed in the context of decision-making, creative thinking, and pain sensation in three experimental models: rodents, monkeys, and humans.

S34.1
Combining external and internal signals for attentional selection : from simple visual displays to active behavior in complex virtual environments

Emiliano Macaluso

Université Claude Bernard Lyon 1, Centre de Recherche en Neurosciences de Lyon, Bron, France

Cognitive control provides us with the ability to handle the vast amount of information that characterize any everyday-life situation. Attention is one of the mechanisms that allows selecting relevant signals to guide behavior. Albeit the underlying brain substrates have been extensively studied in humans and animal models, most of the past research made use of simple and stereotyped paradigms that fail to capture the complexity of real-world situations. Here I will present a series of studies that sought to bridge this gap by using a large variety of stimuli and tasks, ranging from the discrimination of simple visual shapes to active exploration of large virtual environments. In the "priority maps" framework, these studies investigated how signals arising in the external world are combined with internal information related to goals and prior knowledge. Using behavioral measures (eye-tracking) and functional neuroimaging in humans, as well as pharmacology in non-human primates, the resultsconfirm the central role of fronto-parietal control networks but also indicate that the allocation of attention resources follows different constraints in stereotyped versus naturalistic contexts. Moreover the use of rich and meaningful stimulus material highlighted the engagement of regions outside the classical attention networks, including the medial temporal cortex and the precuneus. These findings call into question traditional models of attention control which overemphasize the role of goal-directed signals and underestimate the impact of internal knowledge for the allocation of processing resources.

S34.2

Unravelling the contribution of the mediodorsal thalamus in reward-guided decision making: insights from rodents and primates' studies

Zakaria Ouhaz

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Distributed brain networks govern adaptive decision-making, new learning, and rapid updating of information. Cognitive flexibility, attributed to the frontal cortex, is vital for navigating the complexities of everyday life. The mediodorsal thalamus (MD), interconnected to the frontal cortex, may influence cognitive flexibility. During my presentation, I will focus on three aspects: Perceptual attentional set-shifting, the dissociable contributions of MD subnuclei in cognition, and the corticocortical and thalamocortical changes in functional connectivity and white matter structural integrity after reward-guided learning of visuospatial discriminations.

I will show evidence supporting that the transfer of information via the MD is critical when rapid within-trial updates in established choice response strategies are required after a rule change.

Then, I will demonstrate selective dissociable roles for the two adjacent nuclei of the primate MD, namely MDpc, as part of a frontal cortical network, and the MDmc, as part of a frontal-temporal cortical network, in learning, memory, and the cognitive control of

behavioural choices after changes in reward value. The functional cognitive deficits produced after differing MD damage show that the different subdivisions of the MD thalamus support distributed neural networks to rapidly and fluidly incorporate task-relevant information to optimise the animals' ability to receive rewards.

This presentation will also provide novel insight by showing that specific corticocortical and thalamocortical functional connectivity are important in reward-guided learning in the normal brain and identifying brain structures important for memory capabilities after injury.

S34.3

Neuroinflammatory Mechanisms of Pain Hypersensitization in a Mouse Model of Attention-Deficit/Hyperactivity Disorder (ADHD)

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Attention-deficit/hyperactivity disorder (ADHD) is a complex neurodevelopmental disorder characterized by symptoms of inattention, hyperactivity, and impulsivity. It is one of the most common childhood disorders, with 8,4% of children diagnosed worldwide (APA, 2021). Clinical evidence suggests that pain hypersensitivity develops in subjects with ADHD. However, the mechanisms and neural circuits involved in these interactions remain unknown. We previously validated a mouse model of ADHD obtained by neonatal 6-hydroxydopamine (6-OHDA) intracerebroventricular injection. Here, we show that 6-OHDA mice exhibited a marked sensitization to thermal and mechanical stimuli, suggesting that ADHD conditions increase nociception. In addition, sensitization to pathological inflammatory pain is amplified in 6-OHDA mice as compared to shams. Moreover, by combining in vivo electrophysiology, optogenetics, and behavioral analyses, we demonstrated that the anterior cingulate cortex (ACC) hyperactivity alters the 'ACC – posterior insula' circuit, and triggers changes in spinal networks that underlie pain sensitization. We make the hypothesis that neuroinflammation is a major factor triggering ACC hyperactivity and the comorbidity between ADHD and pain. By using multiple techniques such as immunofluorescence staining and RT-qPCR, we demonstrated microglial and astrocytic activation and identified markers of inflammation and oxidative stress in different brain regions. Through high-throughput and unbiased phosphoproteomic assays, we also demonstrated changes in kinase activity under ADHD conditions. The identification of shared mechanisms, engaging overlapping neuronal circuits and inflammation, and underlying both disorders, is key to better treatments.

S34.4

The imprint of Inhibitory Control on Creative Thinking

Radwa Khalil

School of Business, Social and Decision Sciences, Constructor University, Bremen, Germany

Inhibitory control (IC)—suppressing extraneous or distracting information—is crucial to expressing creativity. IC enables us to filter out irrelevant or prepotent responses and suppress habitual reflexes, allowing us to expand and generate a broader range of innovative ideas. By suppressing habitual reflexes, we can generate a broader range of ideas. Consequently, IC allows us to produce more ideas by inhibiting dominant or traditional responses, reducing our rigid thinking, and exploring more options. Thinking creatively requires cognitive flexibility, which refers to switching mental sets and approaching problems from multiple perspectives linked to IC. For instance, this flexibility permits solving problems creatively and connecting seemingly unconnected ideas, while IC prevents fixation, which hinders creativity. Creative thinking typically includes selectively ignoring unimportant or distracting cues. This fixation occurs when individuals become fixated on one concept or solution, but IC constraints focus and break inflexible cognitive habits, allowing individuals to think more creatively by avoiding distractions. Therefore, in this talk, I will shed light on the current state of the art on how developing and strengthening IC can enhance creative thinking and problem-solving skills in various creative domains.

S34.5

Evidence for two sources of EEG theta-band activity during proactive action control: midfrontal and right lateral-prefrontal.

Ilona Kotlewska, Bartłomiej Panek, Dariusz Asanowicz

Institute of Psychology, Jagiellonian University, Krakow, Poland

Proactive control refers to the ability of deploying top-down regulations ahead of time, aimed at strategic guiding goal-directed actions and overcoming reflexive, impulsive, or habitual conflicting behavioral tendencies. It is hypothesized that action control is mechanistically implemented via theta-band (3-8 Hz) oscillatory activity, which functionally connects the medial frontal cortex (MFC) with task-relevant sensory and motor areas. Here, we investigated the oscillatory EEG activity underlying proactive implementations of control, and their modulatory effects on online processing of behavioral conflict. In two EEG experiments, human participants (N 59) performed the flanker task, in which conflict stems from simultaneous activation of two competing response programs entailed by target and flanker stimuli. To involve proactive control, trials with response conflict were signaled by explicit predictive cues. Analysis of pre-target activity showed that predictive cueing triggered a burst

of theta power localized in the right dorsal and ventral lateral prefrontal cortices, along with increased theta power in the MFC. Analysis of source-level inter-regional phase coherence showed that these lateral and midfrontal areas were functionally connected during the implementation of proactive control. Secondly, analysis of post-target activity showed that predictive cueing reduced modulations of conflict-related local midfrontal theta power and inter-regional theta phase synchrony during online conflict processing. The latter effects were associated with smaller behavioral conflict costs, indicating that proactive pre-activation of executive control led to better performance and smaller demands for the executive system. The results will be discussed in light of the current theoretical accounts of neural mechanisms of action control.

S35
Molecular targets in alcoholism and associated neuropsychiatric disorders.

CHAIR: Mohamed Kabbaj[1]

[1]*Florida State University Florida, USA*

Alcohol is the most abused substance in the world, and so far there are no effective treatments for alcoholism. In this symposium, the presenters will describe some of the molecular mechanisms behind targeted therapies for alcoholism and other associated neuropsychiatric disorders. Specifically, the four speakers will highlight the potential therapeutic benefits of targeting epigenetic mechanisms (i.e.: specific isoforms of histone deacetylases) in excessive alcohol consumption, the potential use of ketamine for the treatment of alcoholism and the role of the of the medium spiny neurons of the nucleus accumbens in mediating the addictive effects of ketamine, the complex role played by glutamate metabotropic receptors (mGlu) in neurotoxicity and alcoholism, and the role of early life developmental periods and potential molecular targets that lead to increased vulnerability to alcoholism.

S35.1
Ketamine effects on alcohol drinking in rats

Sarah Jennings, Samantha Saland, Mohamed Kabbaj

Florida State University

In 2016, the World Health Organization reported that more that 283 million people aged 15 and older experienced Alcohol Use Disorder (AUD). Since the pharmacological treatments for this condition have limited efficacy, there have been recent studies suggesting that psychomimetic drugs, such as ketamine, may have beneficial effects for AUD treatment. Some recent clinical trials have shown promising effects of ketamine for the treatment of AUD and AUD with comorbid depression. In this communication, we will share some of our recent findings on the effects of ketamine, infused repeatedly and through different routes, on

alcohol drinking and alcohol preference in Long Evans male and female rats. We will also briefly discuss some of the potential mechanisms that may underlie ketamine effects on alcohol drinking.

This work is supported by an NIH/NIDA grant R01DA043461 to Mohamed Kabbaj

S35.2

Targeting epigenetic mechanisms to treat alcohol use disorder: insights from animal models

Jérôme Jeanblanc[1], Fahd Hilal[1], Romain Bordy[2], Grégory Fouquet[1], Virginie Jeanblanc[1], Chloé Deschamps[1], Olivier Pierrefiche[1], Mickael Naassila[1]

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Psychedelic are very promising therapy in alcohol use disorder (AUD) but the underlying brain mechanisms are still not well understood. Despite the initiation of several clinical trials for psychiatric disorders, unexpectedly little preclinical research has been conducted so far using psychedelics. Here, we used two relevant animal models of alcohol use disorders in rats to better understand their behavioral effects and their brain targets. We previously demonstrated that psilocybin reduced alcohol relapse after abstinence in the post-dependent state model of AUD possibly through rescuing mGluR2 expression in the nucleus accumbens (Meinhardt 2019). Now we are providing new unpublished results showing the effectiveness of psilocybin injected either i.p. or directly into brain structures to reduce alcohol self-administration and the blockade of its effect after the injection of a 5-HT_{2A}R antagonist directly into the brain. We also show that this effect may be mediated, at least in part, through increased expression of dopamine receptors. Finally, we also tested the effects of other psychedelics and psychedelic-like such as LSD and ketamine. To the best of our knowledge, we are the first to demonstrate the effectiveness of psychedelics directly administered into the brain and our results bring new important perspectives in terms of the mechanisms of action of psychedelics as AUD treatments. Several clinical trials on psychedelics in AUD will be launched soon in France.

S35.3

Perinatal stress and alcohol drinking on sleep cycle: role of metabotropic receptors

S Maccari[1,2*#], S Morley-Fletcher[1*#], H Bouwalerh[1*#], G Van Camp[1*#], F Nicoletti[3,4*], M Kabbaj[5#]

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The animal model of maternal stress (PRS) induces chronic stress and sleep abnormalities that are associated with an increased vulnerability to psychostimulants and natural rewards. We

have previously demonstrated that PRS increases the preference for ethanol in heavy-drinking females following severe stress. Conversely, in PRS males, activation of the stress axis is reduced in response to alcohol consumption. We investigated the link between early-life stress and alcohol consumption/sensitivity in both sexes, as well as the strategies implemented in the sleep-wake cycle by exposing PRS rats to chronic intermittent alcohol consumption (20%) in a two-bottle choice paradigm during either adolescence or adulthood. Our findings reveal the following: 1) Adolescent PRS rats consume more alcohol than non-stressed controls, with a more pronounced effect observed in PRS females. 2) Adult females exhibit higher alcohol consumption than males. 3) Analysis of sleep architecture reveals increased REM sleep and sleep fragmentation in both male and female PRS animals compared to controls. 4) After two months of intermittent alcohol intake, PRS rats consume less alcohol than control rats that have been drinking alcohol. 5) Additionally, PRS groups experience a reduction in REM sleep compared to controls. 6) In adult PRS rats that consume water, we observed an increase in glutamate mGlu 1 receptor expression in the striatum compared to controls. This increase is more pronounced in male PRS rats than in PRS females following

alcohol intake. In conclusion, our results support the evidence of an interplay between glutamate and early-life stress in alcohol dependence, which is sex-dependent.

S35.4

A reverse translational approach to evaluate individual variability in treatment response in alcoholism.

Sara De Carlo[1], Min Li[1], Hela Mizrak[1], Veronica Lunerti[1], Antonio Lacorte[1], Andrea Della Valle[1], Leah Solberg-Woods[2], Massimo Ubaldi[1], Laura Soverchia[1], Roberto Ciccocioppo[1], and Nazzareno Cannella[1]

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Due to the large heterogeneity of alcohol use disorders (AUD), treatments efficacy varies between patient subgroups and many promising targets failed clinical expectations. Using a reverse translational we verified that preclinical models of heterogeneous AUD-like behavior would predict the efficacy of approved an AUD medication (Naltrexone) and the lack of efficacy of a drug that failed clinical trials (Memantine). Innate exploratory activity, anxiety and pain sensitivity were initially screened in forty NIH heterogeneous-stock (HS) rats (sex balanced), then subjected to multiple alcohol seeking behavioral screening (motivation under progressive ratio contingency, quinine adulterated alcohol intake, and cued relapse) to allocate them into three clusters: AUD-cluster-2 scored the lowest in every behavior (AUD resilience-like); AUD-cluster-1 and 3 showed similar alcohol intake and cued relapse and were differentiated by higher motivation in AUD-cluster-1 and higher quinine resistance in AUD-cluster-3 representing two different AUD-like profiles. Both doses of Naltrexone (0, 0.3 and 1.0 mg/kg) reduced alcohol self-administration in AUD-Clusters-1 and 3, with the lowest dose being selective for alcohol as the highest also reduced saccharin self-administration. Conversely, the highest dose of memantine (0, 6, 12, 25 mg/kg) reduced both alcohol and saccharin self-administration in all AUD-clusters, showing lack of selectivity and confirming our hypothesis. Naltrexone effect size inversely correlated with anxiety, thus we applied k-mean to divide rats into naltrexone-responder and non-responder subjects and demonstrated that naltrexone-responder showed higher innate anxiety than non-responder. Our results demonstrated that models of individual variability can predict treatment efficacy and allow to spot and predict drug non-responder subjects.

S36

New insights in brain homeostasis

CHAIR: Thiriet Nathalie[1]

[1]*Experimental and Clinical Neurosciences Laboratory, University of Poitiers, Poitiers, France*

The symposium titled "New Insights in Brain Homeostasis" brought together five speakers to shed light on various aspects of brain homeostasis. The first presentation by Thiriet N. et al. explored how acute and chronic exposure to cocaine and nicotine can impact the expression of genes related to cholesterol homeostasis in the rat dorsal striatum. Their study revealed that while a single dose of cocaine increased the mRNA levels of certain genes, chronic exposure to cocaine did not lead to lasting modifications, whereas nicotine had distinct effects on gene expression in this brain region.

Moving on to the second presentation, Mélodie Devère et al. discussed the chemogenetic activation of a unique subpopulation of neurons expressing 26RFa and orexins in the lateral hypothalamic area (LHA) and its implications for glucose and energy homeostasis. Surprisingly, the stimulation of these neurons resulted in prohyperglycemic and anorexigenic effects, suggesting the involvement of another peptidergic system. The study also highlighted a complex interaction between the 26RFa and orexin systems.

The third presentation by Laila Berroug et al. delved into the sex-specific neurobehavioral and biochemical effects of developmental exposure to malathion in mice. Their research revealed that malathion exposure led to various deficits in both males and females, including changes in body weight, social behavior, and memory, along with alterations in oxidative stress markers and acetylcholinesterase activity. These findings underscored the importance of considering sex-specific effects when assessing neurotoxicants.

In the fourth presentation, Meriem Laaroussi et al. explored the impact of chronic exposure to inorganic mercury on neurobehavioral and oxidative stress in female mice. Their study showed that mercury exposure resulted in reduced body weight, increased anxiety-like behavior, impaired motor performance, and memory deficits. Additionally, alterations in antioxidant enzyme activity and increased oxidative stress markers were observed in various brain structures. This research highlighted the neurotoxic effects of mercury and emphasized the importance of monitoring and mitigating mercury exposure.

Overall, the symposium provided valuable insights into the intricate mechanisms governing brain homeostasis and the diverse ways in which external factors, such as drug exposure and environmental contaminants, can disrupt this delicate balance, with potential implications for understanding and addressing neurological disorders.

S36.1

Role of the brain cholesterol metabolism in relapse to drug addiction

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Cholesterol, the major sterol found in the central nervous system, plays an important role in different brain functions. Some studies show that drugs of abuse alter brain cholesterol metabolism, suggesting that cholesterol may participate in the mechanisms of addiction, a chronic relapsing brain disease. Since cholesterol has been shown to participate in both structural and functional neuroplasticity, it may participate in drug-induced mechanisms underlying the persistent risks of relapse. In order to test this hypothesis, we first investigated whether administrations of two different drugs of abuse (cocaine and nicotine) would alter the expression of genes involved in cholesterol homeostasis in brain areas playing role in addiction and relapse. We also tested whether modulating cholesterol metabolism by overexpressing the enzyme CYP46A1, which is responsible for the degradation of cholesterol, during abstinence could alter drug seeking in rat models of cocaine addiction. For this, rats underwent 10 sessions of cocaine self-administration; then at the beginning of abstinence period, using viral approaches we overexpressed CYP46A1 (the main enzyme responsible for cholesterol degradation) or GFP (for control animals) in the dorsal striatum (DSt) or the anterior cingulate cortex (ACC). Six weeks after the last self-administration session, drug seeking was measured in an extinction session. Using a similar protocol, we also investigated the effects of striatal CYP46A1 overexpression on sucrose seeking. Our results suggest that drugs dysregulate cholesterol metabolism. Therefore, cholesterol metabolism may represent a new therapeutic target for the treatment of this costly psychiatric disorder.

S36.2

The Chemogenetic Activation of a Novel Key Subpopulation of Neurons, Expressing 26rfa and Orexins, Elucidates Part of The Fine and Complex Hypothalamic Regulation of Glucose and Energy Homeostasis

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26RFa (QRFP) is a biologically active neuropeptide known to promote feeding behaviour and to exert a both a central and peripheral antihyperglycemic effect. Recently, we found that the 26RFa (QRFP)/GPR103 neuropeptidergic system in mice relays insulin signalling into the brain to regulate glucose homeostasis
To go further, we investigated, the effect of a chemogenetic activation of the 26RFa-expressing neurons in the Lateral Hypothalamic Area (LHA), in 26RFa deficient and 26RFa-expressing mice. Surprisingly, we found that stimulation of the 26RFa neurons induces prohyperglycemic and anorexigenic effects, opposite to those of a central administration of 26RFa. The same effects were found in 26RFa deficient mice, suggesting therefore the implication of another peptidergic system in these neurons that is responsible of these effects. Interestingly, double labelling RNAscope® experiment revealed that a subpopulation of the LHA 26RFa neurons also express the orexins, another orexigenic neuropeptides, and we found that a central injection of orexin induces an antihyperglycemic effect similar to that observed with 26RFa. Interestingly, the chemogenetic activation of 26RFa neurons also decreases the mRNA expression of both the 26RFa and orexin systems.
To conclude, we highlighted that the neuronal networks regulating glucose and energy homeostasis involve the 26RFa/orexin-expressing neurons of the LHA. Indeed, activation of the 26RFa/orexin neurons induces a down-regulation of the 26RFa and orexin systems, leading to the observed prohyperglycemic effect. Orexin neurons being glucose-inhibited neurons, a hyperglycemia could inhibit this subpopulation of neurons, leading to the activation of these neuropeptidergic systems, thus ensuring the maintenance of energy and glucose homeostasis.

Key words: glucose and energy homeostasis; 26RFa; orexins; hypothalamus

S36.3

Sex-specific neurobehavioral and biochemical effects of developmental exposure to Malathion in offspring

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Malathion is an organophosphate pesticide (OP) commonly used in agriculture, industry, and veterinary medicine. Sex is a crucial factor in responding to neurotoxicants, yet the sex-specific effects of OP exposure, particularly neurological impairments following chronic low-level exposure, remain limited. Our study aims to evaluate the neurobehavioral and biochemical effects of developmental exposure to Malathion across sexes. Pregnant mice

were exposed to a low oral dose of Malathion from gestation up to weaning of the pups, which were individually gavaged with a similar dose regimen until PND70. Our results show that Malathion decreased body weight and food intake, reduced locomotor activity and recognition memory. Motor coordination and special memory were only altered in females, whereas we found a male-specific effect of Malathion on social behavior and marble burying. These deficits were accompanied by an increase of malondialdehyde (MDA) as a biomarker for lipid peroxidation, as well as the alteration of the activity of superoxide dismutase, catalase, and glutathione peroxidase, indicating a disruption of brain redox homeostasis. Additionally, Malathion exposure decreased brain AChE activity at varying degrees between sexes in some brain structures. Our findings about the effects of Malathion exposure across sexes may, in part, contribute to understanding the dimorphic susceptibilities observed in neurological disorders.

S36.4

Chronic Exposure to Inorganic Mercury Affects Neurobehavioral and Oxidative Stress in Female Mice

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Mercury is known as one of the most neurotoxic elements. Contamination with mercury is a real health issue for Humans with physiological and neurobehavioral consequences. The present study aims to evaluate the neurotoxicological effect of chronic exposure to mercuric chloride (HgCl2) on mice. Both mating male and female mice were divided into two groups; the treated groups were exposed to a low level of metal in drinking water; treatment continued throughout gestation, lactation, and during the adult period when their behavior and antioxidant status were analyzed. Our Results indicated that HgCl2 decreased body weight and food intake, as well as increased anxiety-like behavior in treated animals compared to controls, and impaired motor performance. In addition, the treated group displayed reduced spatial working and recognition memory. The enzymatic activity of the antioxidant system was assessed in eight brain structures, including the cerebral cortex, olfactory bulb, hippocampus, hypothalamus, and cerebellum. The results show that chronic exposure to HgCl2 caused alternations in the activity of catalase, thioredoxin reductase, glutathione peroxidase, superoxide dismutase, and glutathione S-transferase, accompanied by peroxidation of membrane lipids, indicating a disturbance in intracellular redox homeostasis with subsequent increased intracellular oxidative stress.

S37

The “invisible” disability: neurological disorders including chronic pain, and epilepsy

CHAIR: Katarzyna Starowicz[1], Livio Luongo[2]

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Both chronic pain (e.g. neuropathic), fibromyalgia and epilepsy are common chronic disorders which result in significant morbidity to the sufferers, and have a major impact on health resources. While vastly different in their clinical manifestations, abnormal nerve excitability is implicated in the pathogenesis of both chronic pain and epilepsy. Therefore, we aim to study these conditions in tandem to evaluate the mechanism by which abnormal nerve excitability results in symptoms. In Europe, it is estimated that 0.6–0.7% of the general population suffers from epilepsy, and up to 20% will experience chronic pain at some point in their lives. Despite the impressive array of drugs available to treat these disorders, a significant proportion of patients remains resistant to traditional pharmacotherapy; 25% of epilepsies are refractory in nature, and as many as two-thirds of chronic pain sufferers are dissatisfied with treatment efficacy. Refractoriness is not the only concern. Many antiepileptic and analgesic drugs elicit a range of unpleasant side effects that place restrictive limits on dosing and opioid agents used to treat more severe forms of chronic pain are at high risk of abuse. Because surgical intervention is only possible in a small number of cases, there is a pressing need to develop therapeutic alternatives. Attention has therefore focused on advancing new pain therapies directed at the cannabinoid system because of its key role in pain modulation.

Speakers will cover different disciplines, including basic neurobiology, pharmacology, experimental pain research, psychology and neuroimaging. All 5 speakers have established track records in neurological disorders and the endocannabinoid system, as evidenced by their peer-reviewed publications and international conference presentations.

S37.1

Therapeutic potential of endocannabinoids for the treatment of chronic pain and associated cognitive impairment

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Almost half of the chronic pain patients have been reported to suffer from co-morbid depression. Recognition of the potential occurrence of pain-depression cycle is essential, only few studies have examined the pain-depression link in osteoarthritis (OA) - the most common form of arthritis. OA pain is a combination of inflammatory, nociceptive, and neuropathic pain, each requiring specific analgesics. The body's innate endocannabinoid system (ECS) has been shown to ameliorate all of these pain types, being one of the main biological systems linking pain transmission and affective processes.
The mutual involvement of brain structures (the frontal cortex, striatum and nucleus accumbens) in the affective processing of pain is poorly understood. Therefore, we evaluated the development of affective symptoms and the underlying neurotransmission. As depressive-like behavior and cognitive impairment co-occur with decreased survival of newly generated cells in the dentate gyrus of the hippocampus we also assessed the contribution of ECS on the alteration in LTP and monoamine levels in the lateral entorhinal cortex-dentate gyrus pathway. Network analysis revealed noradrenaline (NA) and serotonin (5-HT) neurotransmission in the nucleus accumbens as the key structures affected by chronic pain. We also demonstrated the role of ECS in restoring maladaptive neuroplasticity at the level of LEC-DG pathway and restoring physiological levels of DA and 5-HT in the CA3 hippocampus, respectively.

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S37.2

Potential role of the hydroxyl carboxylic acid receptor type 2 (HCAR2) in microglia pathophysiology and pain implications

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Following insults or injury, microglia cells are activated contributing to the cytotoxic response or by promoting an immune-mediated damage resolution. Besides its protective role, microglia activation can result in detrimental neurotoxic effects due to the excessive production of cytotoxic mediators and pro-inflammatory cytokines implicated in neuronal dysfunctions and brain damage. Microglia cells express HCA2R, a hydroxy carboxylic acid (HCA) receptor, which has been shown to mediate neuroprotective and anti-inflammatory effects. HCAR2 is responsible for mediating the pharmacologic actions of nicotinic acid. Endogenous ligands for HCA2 include the ketone body, β-OHB (β-hydroxybutyrate), nutrient sources for cells under various physiological conditions. Given the crucial role of microglia in the induction and maintaining of neuropathic pain states, was investigated in this study the effects of HCRA2 stimulation on primary microglia cell.

MK1903, a potent full agonist of HCAR2, was tested on LPS-primed microglia, by measuring cells viability, morphological activation. In addition, the functional activity of HCAR2 was evaluated through electrophysiological recordings in vivo.
The results showed that HCAR2 expression levels were increased in LPS-primed microglia cells. Moreover, was observed HCAR2 stimulation prevented cells viability, morphological activation and pro/anti-inflammatory mediator's production in LPS-treated cells. Finally, was found that spinal application of MK1903, before fractalkine, prevented the spinal fractalkine-induced hypersensitivity, indicating the HCAR2/CX3CR1 involvement in the cross-talk between neuron and glia.
This study paves the way for further investigations aimed at understanding the role HCAR2 as potential target in neuroinflammation-based CNS disorders.

S37.3
5-HT2C Receptors/Endocannabinoids Interaction in Absence Epilepsy

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Absence seizures (ASs), with their characteristic EEG spike and wave discharges (SWDs) and concomitant lack of consciousness, are the hallmark of childhood absence epilepsy, though they can present in many other epilepsies. Monotherapy with first-line anti-absence drugs only controls ASs in 25% of patients, and there is therefore a need for novel therapeutic targets. In this study, we investigated the role of 5-HT_{2C} receptors and their interaction with the endocannabinoid system (i.e., 2-AG) on ASs and the modulation of tonic and phasic $GABA_A$ currents in ventral basal (VB) thalamocortical (TC) neurons. In Wistar rats and GeneticAbsence Epilepsy Rats from Strasbourg (GAERS), the 5-HT_{2C}R agonist RO60-0175 decreases tonic $GABA_A$ current with a postsynaptic mechanism involving a G-protein and phospholipase-C pathway. Moreover, the agonist decreases phasic $GABA_A$ current with a mechanism involving an endocannabinoid retrograde signaling pathway. In GAERS, an animal model of ASs, RO60-0175 dose-dependently suppressed ASs and normalized their aberrant tonic current. In the present study, we also used immunohistochemical methods to evaluate the immunoreactivity of enzyme diacylglycerol lipase alpha (DAGLα) essential for 2-AG synthesis,cannabinoid type 1 receptor (CB_1R), and serotonin 2C receptor (5-HT_{2C}R) in the nucleus reticolaris thalami (NRT) and ventrobasal thalamus (VB) of genetic absence epilepsy rats fromStrasbourg (GAERS), non-epileptic control rats (NEC) and Wistar rats at postnatal day 15 (P15),25 (P25), and 90 (P90). Our study indicates that immunohistochemical abnormalities involving

the expression of endocannabinoid and 5-HT2CR may underline the origin of cortico-thalamic networks of an absence seizure model.
In summary, our research demonstrates that 5-HT_{2C} receptors play a regulatory role in tonic current in Wistar rats by acting postsynaptically. Additionally, they represent promising therapeutic targets for absence epilepsy, and their reduction of tonic current may occur through the release of 2-AG.

S37.4
Old skulls tie new tricks: the therapeutic potential of the novel cannabimimetic substance Δ^9-Tetrahydrocannabiphorol in the Central Post-Stroke Pain

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Central post-stroke pain (CPSP) is a neuropathic pain syndrome whose pathogenetic mechanisms is poorly understood, remaining difficult to treat [1]. Increasing evidence suggests cannabinoids effectiveness in different types of drug-resistant chronic pain, with a multitarget mechanism but prominent role of CB1 receptor mediated signalling [2,3]. However, the cannabinoids-based therapy is not yet optimised as pain control is often accompanied by important side effects. Recently, a novel phytocannabinoid, the Δ9-Tetrahydrocannabiphorol (THCP), has been isolated from the Italian FM2 cannabis variety, showing a potency higher than Δ9-Tetrahydrocannabinol (THC), and suggesting potential low-doses analgesia [4].
The aim of the study was to pharmacologically characterize the THCP testing its effect on WT and different mutant lines for the CB1 receptor. At the same time, test the drug in a CPSP model, obtained injecting collagenase-IV in thalamic ventral posterolateral (VPL) nucleus.
The compound showed an antinociceptive effect higher than THC not accompanied by increased adverse effects, suggesting a peculiar pharmacodynamics and a differential action on plasmamembrane and subcellular CB1 location, recently correlated to main adverse effects like catalepsy and cognitive impairment [5,6]. Low doses (0.3-2.5 mg/kg) of THCP were tested in CPSP, obtaining a significant anti-allodynic effect, with minimal side effect.
This study proposes, in a translational point of view, the THCP as a new therapeutic strategy for CPSP. Moreover, our results suggest a pivotal role of CB1 receptor in post-stroke pain paving the way to better investigate its involvement in CPSP pathophysiology.

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S37.5
Neuro-glia-vascular interactions in health and disease: Time for translation

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The dynamic functional unit of the neurovascular unit (NVU) consisting of cerebral blood vessels, neurons, astrocytes, microglia and pericytes play a crucial role in the regulation of blood flow and proper function of neural circuits. This is permitted partly by the unique blood-brain barrier (BBB) that acts as an anatomical and functional interface. Clinical studies have confirmed that BBB dysfunction (BBBD) is a hallmark of most neurological disorders and can result in neural dysfunction and disease. Our research has demonstrated that BBBD leads to transforming growth factor beta (TGFβ)-mediated transformation of astrocytes andactivation of the innate neuroinflammatory system, changes in the extracellular matrix and pathological plasticity – which in-turn is associated with abnormal function of the cortical circuit and reduced seizure threshold. Blocking TGFβ signaling and associated pro- inflammatory pathway prevents the enitire cascade, reduce neuroinflammation, repairsBBBD and prevents post-injury epilepsy in pre-clinical studies. We therefore established andimplemented a novel imaging approach to quantitative assess BBBD as a diagnostic, predictive and pharmacodynamic biomarker. We confirmed that BBBD is common in brain injury, patients with drug-resistant epilepsy and severe bipolar disorder. In patients with systemic lupus erythematous BBBD was associated with cognitive deficits. We bring evidence that microvascular injury and BBBD are novel diagnostic and therapeutic targets in brain disorders.

S38

Maternal environment during perinatal life affects offspring brain development and life-long brain functions.

CHAIR: Marialetizia Rastelli[1], Sebastien bouret[1, *]

[1]*INSERM UMR-S1172, Lille Neuroscience & Cognition*
[*]*Co-chair*

The growing prevalence of obesity, metabolic and behavioral disorders is a major health concern.
It is now widely accepted that alterations in maternal environment during perinatal life (nutrition, stress, hormonal imbalances, dysbiosis) are associated with increased health risk in the offspring.
However, the mechanisms underlying the enduring impact of early life experience on neurodevelopmental disorders still remain largely unknown.

This symposium will present the state-of-the-art research related to the importance of maternal environment during critical period of perinatal life. It will also give an overview of our current knowledge on the role of neurodevelopmental, molecular and environmental clues mediating the effects of perinatal insults on neurobiological and behavioral outcomes, ringing from metabolic to behavioral disorders.

The proposed speakers are world experts in the fields of the developmental programming and will cover various aspects of maternal environment (nutrition, hormonal imbalance, stress, dysbiosis) as well as a variety of life-long disorders in the offspring (obesity, anxiety and social behavior). They will also shed lights on the potential mechanisms that have been recently pinpointed, as well as potential interventional approaches. These emerging concepts open new perspectives in the management of obesity, metabolic and behavioral disorders.

Due to the interdisciplinary nature of this symposium and the potential translational nature of the proposed topic, it should be of interest to a wide audience of neurobiologist.

S38.1
Early life programming of obesity via a hypothalamic miRNA involved in fatty acid sensing

Laura Dearden

University of Cambridge, UK

In utero exposure to maternal obesity programs an increased risk of an individual developing obesity themselves later in life. Animal models show that offspring obesity is often preceded by increased food intake, however, the mechanisms that mediate these changes are not understood. Using a mouse model of maternal diet-induced obesity we observed increased intake specifically of a high-fat pellet in adult offspring of obese mothers. Using small RNA

sequencing, we identified programmed overexpression of miR-505-5p in the hypothalamus

of offspring of obese mothers, that is established in the fetus and remains to adulthood, and showed *in vitro* that fatty acid exposure increases expression of miR-505-5p in hypothalamic neurons. Pulsed SILAC analysis demonstrated protein targets of miR-505-5p are enriched in pathways involved in fatty acid metabolism. These include key components of neuronal fatty acid sensing pathways that we find to be associated with BMI in human genetic studies. Over-expression of miR-505-5p decreased neuronal fatty acid uptake and metabolism in neurons *in vitro*. Importantly, intra-cerebroventricular injection of a miR-505-5p mimic in mice resulted in increased intake specifically of a high-fat pellet. Collectively these data suggest that maternal obesity induces over-expression of miR-505-5p in offspring hypothalamus, resulting in altered fatty acid sensing and increased intake of high-fat diet. This represents a novel mechanism by which exposure to obesity in pregnancy programs obesity in offspring.

S38.2

Prenatal restraint stress affects maternal behavior, early neurobehavioral response and oxidative stress in mice pups.

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Prenatal stress (PS), in both humans and animals, presents a potential risk threatening the mother and her fetus throughout gestation. PS is always associated with physiological changes that alter embryonic development and predispose the individual to lifelong health problems, including susceptibility to mental illness. The purpose of this study is to identify the deleterious effects of restraint stress (PRS) which is commonly employed to induce stress during gestation. This stress is applied to pregnant Swiss albino mice from E7.5 to parturition for three hours daily. This study is mostly interested in neurodevelopment, especially the neurodevelopmental reflexes using a battery of developmental tests such as Surface righting reflex, Cliff avoidance, Negative geotaxis, and finally Swimming development. Our results show that PS affected the weight gain of dams as well as some of their maternal behaviors including nesting. As far as offspring are concerned, this stress appears to play a major role in the impairment of different neurobehavioral responses such as the delay of some reflexes. These alterations were accompanied by an increase in the level of Malondialdehyde activity (MDA) at PND17 and 21, and a downregulation of AchE activity in the whole brain of pups in postnatal days 7,9, and 13. These findings demonstrated that PS causes deleterious neurodevelopmental impairments that can alter a wide range of behaviors later in life.

S38.3

Neuronal circuits underlying maternal dietary habits and the programming of offspring health

Roberta Haddad-Tóvolli

Neuronal Control of Metabolism (NeuCoMe) Laboratory Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS) Barcelona, Spain

Maternal physiological and behavioural adaptations during pregnancy and lactation are set to provide an adequate environment for the correct growth and nurture of the infant. Disturbances in this delicate balance during critical periods of embryonic and perinatal development may exert life-long influences on disease predisposition in early life and adulthood. In this talk, I will describe our latest findings on how maternal unbalanced dietary habits, including HFD exposure, food cravings and emulsifiers consumption directly influence the development of key neuronal centers that control feeding and metabolism, aswell as its impact in offspring´s neuropsychiatric health. I will conclude the talk with new data in which we show that iron deficiency during perinatal life directly influences POMC neuron maturation, highlighting a new fundamental role of iron in hypothalamic development.

S38.4

The intergenerational inheritance of early life stress is transmitted by maternal oxytocin

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Perinatal Stress (PRS) in rats induces long-term alterations, which can be predicted by reduced maternal behavior resulting from gestational stress. We examined the intergenerational effects of PRS by mating first-generation (F1) PRS female rats with naïve males and exploring the phenotypes of both F1 and F2 offspring. PRS was associated with reduced maternal behavior in both mothers (F1) and grandmothers (F0). In both F1 and F2 offspring, we observed consistent results in risk-taking behavior, which were associated with neurobiological alterations related to stress and anti-stress responses across the two generations. It is noteworthy that F2 offspring were not directly exposed to stress in utero. Given the well-established role of maternal care in inducing epigenetic transmissible effects to the second generation, we focused on epigenetic modifications influenced by maternal care and behavior. Through our analysis, we identified differential gene expression patterns transmitted across F1 and F2 generations, along with key canonical pathways implicated in glutamatergic synaptic transmission and the balance between stress and anti-stress systems via IPA analysis. Post-partum treatment with carbetocin, which enhances maternal care,

reversed the long-term effects induced by PRS in the offspring of both F1 and F2 generations. This reversal highlights the crucial epigenetic role played by maternal care in imprinting the HPA axis of the offspring and underscores the potential therapeutic role of the oxytocinergic system.

S39

Neural Cell Metabolism in Health and Disease

CHAIR: Natalie Rasgon[1]

[1]*Stanford University School of Medicine*

In this symposium cellular and molecular mechanisms underpinning metabolism and receptor actions of neurotransmitters and neuromodulators will be addressed. Specifically these mechanisms will be considered under disease conditions, including psychiatric, neurodevelopmental and neurodegenerative conditions. Dr Rasenik will describe their recent experiments unveiling the interactions between lipid metabolism and lipid structures have long been linked with both depression and the action of antidepressant drugs. Specifically, presentation will focus on direct and indirect interactions between antidepressant compounds and lipid structures. Dr. Vardjan will present her recent findings studying signalling and metabolism in aged drosophila. Dr. Zorec will discuss adrenergic astroglial mechanisms mediating neurodegeneration and ketamine induced inhibition of neuroinfection in astrocytes by viruses, including the SARS-Cov-2. Dr Rasgon will present evidence of in vivo biomarkers of central metabolic dysfunction in depressive disorders and specific correlations between peripheral and central biomarkers related to disease state and severity. The speakers come from a diverse basic and clinical backgrounds.

S39.1

AS15.1 biosignature for depression and antidepressant response: Roles of G proteins, lipid rafts and the cytoskeleton.

Jeffrey Schappi, Aksu Gunay, Olusola Ajilore and Mark.M.

Rasenick Depts of Physiology & Biophysics and Psychiatry, U. Illinois College of Medicine and Jesse Brown VAMC Chicago USA

Lipid rafts are specialized membrane structures, rich in cholesterol and (sometimes) caveolin, that have extensive interaction with cytoskeletal elements. Lipid rafts can be disrupted with caveolin or cholesterol depletion or disruption of the microtubule cytoskeleton. Lipid raft disruption frees the G protein, Gsα yielding a more facile interaction with adenylyl cyclase and an increase in cAMP signaling in neurons or glia. Both post-mortem and peripheral blood studies have demonstrated that the degree to which the G protein, Gsα, is associated with lipid rafts is a biomarker for depression. More recent studies reveal a strong negative correlation between Gsα-raft association (as determined by Gsα-activated adenylyl cyclase) and HAM-D scores. Preclinical studies with neural and glial cells reveal that decreased association between Gsα and lipid rafts results from sustained treatment with monoaminergic antidepressants and brief treatment with ketamine or the psychedelics LSD or psilocin. Antidepressant treatment resulted in dissociation of Gsα from tubulin in lipid rafts

and this mirrored the decrease in tubulin acetylation seen in lipid rafts from depressed

subjects. Antidepressant treatments also modify G protein lipidation. Antidepressant treatment has no apparent effect on raft composition or structure, or on any G protein other than Gsα, Disruption of rafts by cholesterol depletion or microtubule disruption elicits translocation of many raft proteins, which contrasts with the specific effects on Gsα elicited by antidepressant treatment. Treatment with antidepressants, but not mood stabilizers or antipsychotics, reveals a gradual coalescence of antidepressant in lipid raft fractions of cultured astrocytes. Together these observations suggest a confluence of lipid and cytoskeletal elements may be involved in both depression and its reversal.

S39.2
Lipids as triggers of astrocyte glucose metabolism and stress response

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In a pathological state of the brain, the content of lipid droplets (LDs), lipid storage organelles, is increased, especially in glial cells but rarely in neurons. The biology and mechanisms leading to the accumulation of LDs in astrocytes, glial cells with important homeostatic functions, are poorly understood. We examined fluorescently labelled LDs by microscopy in isolated and brain tissue rat astrocytes and in glia-like cells in the *Drosophila* brain under basal and stress conditions characteristic of brain pathologies. LDs in astrocytes showed limited mobility near mitochondria and endoplasmic reticulum, which was attenuated by metabolic stress and increased intracellular Ca^{2+}, likely enhancing the interaction between LDs and organelles as imaged by electron microscopy. When *de novo* biogenesis of LDs was blocked, astrocyte cell number decreased, suggesting that turnover of LD in astrocytes is important for cell survival and/or proliferation. Exposure to noradrenaline, a neuromodulator of the brain stress response system, as well as metabolic and hypoxic stress strongly promoted the accumulation of LD in astrocytes. Moreover, excess of extracellular free fatty acids (docosahexaenoic acid and oleic acid) induced intracellular Ca^{2+}- and cAMP-signalling that triggered aerobic glycolysis and LD accumulation. The observed lipid-related responses of stressed astrocytes may be considered to support energy provision but also to be neuroprotective against stress-induced lipotoxicity.

S39.3
Astroglial mechanisms of neurodegeneration and viral infection

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We study how subcellular vesicle traffic and membrane fusion contributes to various diseases.

Studying lysosomal fusion in electrofused dendritic and tumor hybridomas, led to the development of a cell-based immunotherapy for prostate cancer (1), a personalized treatment already approved. Here we focus into pathophysiology of astrocytes, neuroglial

cells sharing metabolic properties with cancer cells. Age-dependent demise of the main noradrenergic brain nucleus, *Locus coeruleus* (LC), represents a defining factor of neurodegeneration. LC axons release noradrenaline, which stimulates astrocytes, functionally heterogeneous neuroglial cells, providing homeostatic neuronal support. Astrocytes are enriched with adrenergic receptors and mediate increases in cytosolic Ca^{2+} and cAMP, regulating cell growth and morphology, inhibition of neuroinflammation and control of aerobic glycolysis (AE). AE was observed by Warburg in cancer cells, which exhibit a high rate of glycolysis even in the presence of oxygen (AE) (2). Deficits in the noradrenergic innervation promote pathologic processes leading to neurodegeneration, trauma and infection by neurotropic viruses, which preferentially proliferate in astrocytes which exhibit AE (3,4). We will discuss how the activation of adrenergic receptors modulate the morphology (cytotoxic edema), aerobic glycolysis and vesicle-based processes in normal and reactive astrocytes. In particular we will address how adrenergic stimuli and established drugs (i.e. ketamine) affect astrocyte function in health and disease.

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S39.4
Peripheral and Central Metabolic Dysfunction in CNS Diseases

Natalie Rasgon

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Insulin resistance (IR) is a known metabolic state underlying many diseases of brain and body. Multiple levels of evidence support pathophysiological role of IR in mood disorders, with peripheral biomarkers of IR serving as predictors of disease onset, clinical course and treatment response. We and others illustrated need for more precise mechanistic exploration of IR in CNS. This presentation will focus on biosignature of central IR in major depression and bipolar disorder. Specific focus will be on presentation of age, sex and type of illness phenotypes of mood disorders associated with central IR and its correlations with established peripheral IR biomarkers. Precision medicine approach in development of mechanistic treatments will be discussed as well.

S40
NEW INSIGHTS IN NEUROPROTECTION, LEARNING AND MEMORY MECHANISMS
CHAIR: Aldo Donizzetti (IT) & James Olopade (NG)

The symposium titled "New Insights in Neuroprotection, Learning, and Memory Mechanisms" explores various facets of neuroprotection, learning, and memory mechanisms, bringing together experts in the field to discuss groundbreaking research. The symposium's agenda encompasses a range of topics, each contributing valuable insights to the broader understanding of neurological processes.
First, the study by Anna Maria Carrese and her team delves into the molecular mechanisms

of synaptic plasticity and neuroprotection. They emphasize the critical role of synaptic activity in brain development, neuronal health, and cognitive functions such as learning and memory.

Their work introduces an in vitro model based on SH-SY5Y cells to investigate these processes, shedding light on the specific genes involved and their implications for neurological diseases. M working The second presentation by Mohamed Ksila and colleagues explores the neurotrophic potentials of Imine Analogs of Trans-Resveratrol, addressing the challenge of RSV's rapid metabolism and the need for effective analogs with similar properties. Their research highlights the potential anti-tumor activities of these analogs and underscores their distinctiveness from RSV, offering promising avenues for therapeutic development in age-related diseases.

The third abstract by Olopade, Ojurongbe, Happi, Oluwayelu, Happi, and Groschup focuses on the surveillance of neurotropic viruses in Nigeria and the urgent need for novel therapies. They present data from their ongoing surveillance efforts, emphasizing the vulnerability of developing countries' healthcare systems to endemic viruses. Their proposal to explore novel therapies from herbal plants against neurodegenerative diseases and neuroinfections represents a forward-looking approach to address this pressing issue.

In the fourth presentation, Georgios S. Kogias and Siqiong June Liu investigate the role of the transcription factor PPARα in memory reconsolidation. They uncover the impact of PPARα on the degradation of endocannabinoids and its modulation of fear memory. Their findings highlight the significance of PPARα activity in memory reconsolidation and provide insights into potential therapeutic interventions.

Collectively, these abstracts reflect the diverse and innovative research being conducted in the fields of neuroprotection, learning, and memory mechanisms. They underscore the importance of interdisciplinary collaboration and the pursuit of novel therapeutic approaches to address the complex challenges of neurological disorders and cognitive function.

S40.1

In vitro model of synaptic activity for the investigation of molecular mechanisms of synaptic plasticity and neuroprotection

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Neurons communicate by means of synaptic activity, a process that affects brain development, neuronal health, and the ability to strengthen the connections between neurons and thus to regulate high order functions including learning and memory.

Synaptic activity acts through the involvement of a fine regulated expression of several genes (activity-regulated genes) in different waves of induction: a rapid activation of immediate-early genes and then the expression of late effector genes.

A growing amount of genome-wide expression data is showing that some of those genes are associated with neurological diseases and have specifically evolved in primates or humans. This feature constraints the right choice of the experimental model to be used not only for a

descriptive analysis but also for functional studies to uncover the specific role of that genes. In this regard, among in vitro human models, the SH-SY5Y is a popular cell line largely used in neurobiology and represents a cost-effective and user-friendly platform for several molecular investigation.
We developed a synaptic activity model on differentiated SH-SY5Y cells by using high potassium solution to induce depolarization. The differentiation protocol was based on combined used of retinoic acid and BDNF for 12 days. Depolarization process was monitored by fluorescent analysis of synaptic vesicles release and recycle, and induction of immediate-early genes. The effectiveness of the model was also confirmed analyzing the expression of several coding and non-coding genes after 8 hours of depolarization, including genes involved in neuroprotection.

S40.2

Characterization of neurotrophic potentials of Imine Analogs of Trans-Resveratrol

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Trans-resveratrol (RSV) is a non-flavonoid polyphenol (stilbene) with numerous biological activities, such as anti-tumor activities. However, RSV is rapidly metabolized, which limits its therapeutic use. The availability of RSV analogues with similar activities for use in vivo is therefore a major challenge. A better understanding of ageing and the prevention of age-related diseases is a public health challenge. Several types of compounds have been studied: (a) trans-resveratrol (RSV) derivatives produced in the laboratory, aza-stilbenes, for their cytotoxicity compared to RSV in anti-tumour perspectives, (b) C7 oxysterols (7-ketocholesterol (7KC), 7α-hydroxycholesterol (7α-OHC), 7β-hydroxycholesterol (7β-OHC)) involved in age-related diseases; c) pomegranate seed oil and α-tocopherol to evaluate their cytoprotective activities; d) Mediterranean essential oils (Thyme, Jasmine) to better understand their biological activity. In this perspective, in comparison with the RSV, our study first consisted in evaluating the cytotoxic and antioxidant properties of AZA-STs and their impact on mitochondrial status using murine N2a neuronal cells. The antioxidant activities of AZA-STs, assessed by different techniques (DPPH, FRAP, KRL, PAOT), are often more important than those of RSV. The cytotoxic effects of AZA-STs have shown a decrease in esterase activity associated with a decrease in cell adhesion, mitochondrial dysfunction, overproduction of reactive oxygen species and changes in cell cycle distribution. The synthesised AZA-STs are therefore distinct from RSV and, like RSV, have potential anti-tumour activities. Furthermore, as an increase in oxidised cholesterol derivatives, especially C7-oxysterols (7KC, 7α-OHC, 7β-OHC), is often observed in biological fluids and diseased organs of patients with age-related diseases, cell death induced by these oxysterols was

characterised in N2a cells at 72 h and the cytoprotective activities of pomegranate seed oil

and α-tocopherol were evaluated in this model. 7α-OHC is not toxic, while 7KC and 7β-OHC induce oxyapoptophagy (including OXYdant stress, APOPTOsis and autoPHAGY criteria) which is attenuated by pomegranate seed oil and α-tocopherol.

S40.3

Surveillance of neurotropic viruses in Nigeria: What are plans to develop novel therapies?

Olopade, J.O., Ojurongbe, O., Happi, C., Oluwayelu, D., Happi, A and Groschup, M

Alexander von Humboldt Center of Excellence for Arboviral Diseases, Faculty of Veterinary Medicine, University of Ibadan

The aftermath of the COVID-19 pandemic and the report of detection of the virus in animals has called for constant surveillance of the SARS-CoV2 and other endemic viruses in both the human and animal species. In the last one year, we have been conducting surveillance of animals as reservoir host for the SAR-CoV2 and some other neurotropic viruses in domestic animals and different wildlife species. There is the fear that disease burden of endemic viruses in developing countries will affect an already fragile medical system with minimal infrastructure; it is thus imperative that novel therapies that are home grown but based on good science is invested upon and developed. In this meeting, I shall be presenting data set from surveillance of COVID-19 and arboviral disease reservoirs, and on the proposal of the development of novel therapies from herbal plants against neurodegenerative diseases and neuroinfections

S40.4

The transcription factor peroxisome proliferator-activated receptor alpha PPARα promotes the eCB degradation and enhances memory reconsolidation

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Cerebellar activity is critical for memory reconsolidation as inhibition of protein synthesis in the cerebellar vermis during the reconsolidation period impairs memory recall. Since the transcription factor peroxisome proliferator-activated receptor alpha (PPARα) regulates the primary enzyme responsible for the degradation of 2-AG, monoacylglycerol lipase (MAGL), we determined the role of PPARα in the reconsolidation of fear memory. Here we show in vitro findings demonstrating that PPARα, modulates the activity of MAGL, and thereby reduced endocannabinoid signaling. We show that a PPARα agonist can increase the activity of MAGL and thereby reduces endocannabinoid signaling. At the behavioral level, administration of a PPARα antagonist disrupted both original and reconsolidated memories. We used a reconsolidation behavioral protocol that consists of three sessions: i) Acquisition

(CS+US; Day 1). ii) Reactivation (CS only; absence of CS; Day 11). iii) Retention (CS only; Day 14). Administration of a PPARα antagonist 1 hour before reactivation impaired memory retention (day 14) only when the memory was reactivated. In a different set of experiments, when we measured the activity of MAGL during the retention day (day 14), we noticed a marked increase in MAGL activity, in lobules V/VI, in mice receiving reactivation. Administration of a PPARα antagonist 1 hour before reactivation completely prevented the increase in MAGL activity compared to the saline control, whereas the PPARα antagonist did not alter MAGL activity when the memory was not re-activated. Thus, these results suggest that PPARα activity is required for both the increase in MAGL levels and memory re-consolidation.

S40.5

Cellular and molecular aspects of neurotoxicity induced in rats and rabbits by pesticides: Thiamethoxam and Voliam-Targo

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The use of pesticides, such as insecticides in the world is intensifying despite the warnings of specialists about their potentially harmful effects on human health. Compared to traditional insecticides, neonicotinoids were long considered to be of low toxicity to mammals. However, recent studies have shown that exposure to neonicotinoids poses a potential risk to humans. Among the most concerning effects of neonicotinoids are those that affect the nervous system.

Our objective aims both to know the real effects of Thiamethoxam, an insecticide from the neonicotinoid family, on brain development, but also on neuroinflammation, implicated in the pathogenesis of many neurodegenerative disorders in adult brain.We found that repeated oral exposure for 10 weeks to thiamethoxam (5.2 mg/kg) elicits stress apoptosis and an increase in markers of neuro-inflammation, such as microglial activation and increased expression of TNFα, IL6 and also iNOS in neurons of hypothamic nuclei of adult male rats. These changes were preceded by the induction of oxydatif stress markers increased.

At the same time, work on rats and rabbits has made it possible to assess the consequences of exposure to thiamethoxam, as well as to Voliamtargo®, another neurotoxic insecticide, on the peripheral organs and endocrine glands dependent on the hypothalamus, such as: the reproductive organs, the thyroid and the adrenal gland. We observed significant histological changesunder the light microscope and confirmed by morphometric analysis.

Together, these results demonstrate that exposure to thiamethoxamor Voliamtargo® leads to stress-mediated neuro-inflammation, which may subsequently contribute to neurodegeneration impairment and disorders of peripheral functions.

Key words: insecticide, neuro-inflammation, thiomethoxam, voliamtargo, rat

S41

Preclinical and clinical novel insights on the mechanisms underlying human obesity and eating disorders.

CHAIR: Mariangela Pucci[1], Paola Fadda[2]

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This symposium delves into the complex world of eating behaviors, neurobiology, and their implications in eating disorders and obesity. Four distinct presentations explore various aspects of this intricate relationship, from the role of the dopaminergic system in binge eating to the neurobiological mechanisms underlying anorexia nervosa. Additionally, the interplay between the gut microbiome, eating behaviors, and psychological stress is examined, shedding light on the potential influence of the gut on these conditions. Lastly, the symposium investigates the involvement of bitter taste receptors in the jejunum of morbidly obese patients undergoing bariatric surgery, uncovering intriguing connections between taste receptors and weight loss outcomes. Collectively, these presentations offer valuable insights into the underlying factors driving eating disorders and obesity, providing a deeper understanding of these challenging conditions.

S41.1

Preclinical and clinical evidence of dopaminergic system regulation in Binge Eating

Mariangela Pucci

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Changes in reward processing play a role in the onset and maintenance of binge eating (BE), a compulsive overeating behavior, often associated with stress, and characterizing for some eating disorders as well as obesity. The dopaminergic system has attracted growing attention due its ability to modify behavioral responses to various environmental stimuli associated with reward behaviors. We will here show our results on the role of dopaminergic system genes in regulating BE, using both preclinical models and clinical studies.
DNA promoter sequences of dopamine transporter (*DAT*) and dopamine D2 receptor (*DRD2*), analyzed from saliva samples of patients suffering from BE disorders, result hypomethylated on selective CpG site in both genes. Moreover, the same genes regulation was evaluated in different brain regions of an animal model showing recurrent episodes of BE. In addition, studying *C. elegans* feeding behaviors as a possible model resembling BE behavior, we observed changes in the pharyngeal pumping rate ("worm eating") in animals, wild-type and dat-1 and dop-2 mutants, orthologs of human *DAT* and *DRD2*, exposed to starvation and acute stress.
These findings highlight an important evolutionarily conserved role of dopaminergic system genes in BE behavior. Their epigenetic modulation is relevant to suggest possible biomarkers and new targets to treat BE behavior. Moreover, the BE model in *C. elegans* could improve

the understanding of the roles played by brain circuits and by environmental triggers in affecting food intake.

S41.2

Neurobiological and molecular mechanisms implicated in the development of anorexia nervosa: focus on the experimental model of Activity-Based-Anorexia (ABA)

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Anorexia nervosa (AN) is a severe eating disorder characterized by a reduction of food intake to achieve body weight loss. Furthermore, over-exercise is commonly reported. AN typically occurs in young women and tends towards a chronic course. Although it is widely acknowledged that biological factors contribute to the course and progression of AN, its pathogenesis has not yet been fully elucidated. The “activity-based anorexia” (ABA) paradigm represents the most well-known and validated animal model to better investigate the biological basis of AN. In this experimental paradigm, animals undergo restricted feeding schedule with free access to a running wheel. These two factors applied simultaneously cause a significant decline in body weight together with a progressive increase in running wheel activity. Moreover, other clinical manifestations described in patients, such as neuroendocrine disturbances and dysregulation of appetite regulating hormones, are also reproduced. Using the ABA model, we performed different studies to deeply investigate neurobiological and molecular mechanisms implicated in the development of AN. For example, we highlighted the potential of cannabinoid agonists in the treatment of AN in accordance with an altered endocannabinoid tone. Moreover, we supported the notion that AN could be related to a dysregulated inflammatory status. Finally, we provided further proof of the impairment of the dopaminergic and serotoninergic systems and supported the knowledge of the involvement of these two important neurotransmitter systems in the development and progression of AN.

S41.3

Feeding the gut, feeding the host: insights on the interplay between gut microbiome and eating behaviours in eating disorders and obesity

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The potential implication of the gut microbiome in several health conditions, including eating disorders and obesity, has recently captured the attention of the medical community. Gut microbiome may influence appetite control and brain functions through the gut-brain axis, potentially contributing to the development of eating disorders and obesity. As these conditions progress, altered eating behaviours and psychological stress can, in turn, affect the gut ecosystem, further perpetuating the disorders.

Although the gut microbiome may be crucial in understanding the complex pathophysiology of eating disorders, research in this area is still in its infancy, and more robust evidence is required before drawing definitive conclusions.
In this spotlight, the bi-directional association between gut microbiota and eating disorders, as well as the underlying etiopathogenic hypotheses, will be critically reviewed in light of actual knowledges.
Additionally, preliminary results on the association between salivary microbiota, eating behaviours and epigenetic regulation known to be involved in appetite regulation, food intake, metabolic processes, and inflammation will be discussed.

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S41.4

Profile of Bitter Taste Receptors in the Jejunum of Morbid Obese Patients that undergo Bariatric Surgery

Authors: Florijan Jalševac[1], Margalida Fontcuberta-Rigo[1], Teresa Auguet[1,2], Esther Rodríguez-Gallego[1,2], Raúl Beltrán-Debón[1,2], Ximena Terra[1,2], Maria Teresa Blay[1,2], Anna Ardévol[1,2], Montserrat Pinent[1,2]

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Pandemics of obesity, diabetes and metabolic syndrome are ever more. A novel way of combating these illnesses might be the use of bitter taste receptors (TAS2Rs), which are involved in the control of enterohormone secretion, and through their actions, control of metabolic processes.
We aimed to describe the profile of expression of TAS2Rs in the jejunum of obese patients and investigate their possible involvement on the success of bariatric surgery.
In this study, participants were obese women (BMI > 40 kg/m^2) with metabolic syndrome (n=21). During bariatric procedure, jejunal biopsies were obtained. Patients were divided into 2 groups; a group which lost less than 35 kg 12 months after the surgery; and a group which lost more than 35 kg. Expression of specific receptors was analysed with the use of qPCR.
From the expression profile, it was observed that TAS2R14 was the receptor expressed at the highest level. On the other side, receptors TAS2R5, TAS2R13, TAS2R20, TAS2R31 and TAS2R39 were the ones expressed at the lowest levels. Additionally, only the expression of TAS2R39 was different between the groups, being the group that lost more weight displaying higher levels.
Correlation analysis of the expression and global parameters showed that TAS2R13 negatively correlated with insulin levels and BMI 12 months after the procedure.

In conclusion, the results obtained suggest a possible involvement of TAS2R39 in the positive outcome of the weight loss after bariatric surgery. Additionally, it is interesting to see a possible connection between TAS2R13 and metabolic syndrome parameters.

S41.5

Endocannabinoid system regulations in the reward system in obesity and binge eating disorder.

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Binge eating disorder and obesity are multifactorial diseases both involving maladaptive feeding behaviors, that are mostly directed toward palatable foods. The mesocorticolimbic dopamine system, also called the "reward system", plays a major role in hedonic food intake and is altered in eating disorders and obesity. The endocannabinoid system (ECS) is expressed in the reward system and represents a potent regulator of feeding, but the impact of binge eating and obesity on its expression is not fully known. Recent research has strongly highlighted its predominant role in feeding behaviors, with specific modulation of addictive-like eating behaviors.

We investigated whether obesity or binge eating behavior could affect ECS gene expression in the reward system. Rats were exposed either to a 6-week continuous (obesity model) or intermittent (binge eating disorder model) diet with a free choice access to both fat and sucrose solution (fcHFHS). We assessed the consequences of diet exposure on ECS gene expression in cortical, striatal, and mesencephalic brain regions using qPCR.

Our results show differential regulation of ECS genes depending on the schedule of palatable food access, suggesting that binge eating behavior and obesity differentially affect ECS genes expression in the reward system. Interestingly, correlation analysis demonstrated that the macronutrient profile (sucrose, fat) of highly consumed food can specifically influence ECS gene expression.

Taken together, our results broaden the understanding of ECS molecular adaptation in obesity and binge-eating disorder models and could potentially help to identify new ECS targets for therapy.

S42

Sensory alterations in autism: From preclinical models to human studies

CHAIR: Ourania Semelidou[1]

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Altered sensory experience has been recently added as one of the core features of autism spectrum disorder (ASD), a neurodevelopmental disorder characterized by alterations in social communication and repetitive behaviors. These sensory alterations are observed across

modalities and affect the majority of autistic individuals, with approximately 90% of them

experiencing altered reactivity to sensory stimulation. Importantly, differences in sensory perception exert a strong negative influence on day-to-day life and contribute to the development of higher-order cognitive symptoms and repetitive behaviors. A strong link has also been found between the manifestation of sensory symptoms and neurodivergences or medical conditions that co-occur with autism (e.g. anxiety). Sensory alterations can be detected as early as in the sixth month of life in infants with ASD, thus preceding other core symptoms, and sensory sensitivity scores correlate with clinical diagnosis – a finding that accentuates their predictive power. In addition, alterations in the sensory domain have a strong neurophysiological basis, which shows great promise in our endeavor to identify the neurobiological mechanisms of autism.

The symposium 'Sensory alterations in autism: From preclinical models to human studies' aims to bring together researchers who study changes in sensory perception in autism using a variety of methods in humans and in animal models. The speakers of the symposium will address emerging topics such as the diverse sensory phenotypes in autism and how they correlate with neural network alterations and clinical profiles, the heterogeneity of hyper-/hypo-sensitivity, the alterations in perceptual decision-making in autistic individuals, and finally, sensory perception alterations in rodent models of autism and their neurobiological mechanisms. In a round table at the end of the session, our current approach to the study of sensory symptoms will be discussed. Up to date, the study of sensory alterations in autism has demonstrated the impact of these symptoms in the daily life of autistic individuals but has also led to contradictory findings, mainly due to the wide variety of methods used in different studies. This symposium will give the opportunity to discuss not only the importantfindings in the field but also the hindrances and misconceptions in human studies as well as caveats in the design and translatability of preclinical studies.

The symposium's objective is to bridge preclinical and clinical research; a crucial step to develop objective diagnostic biomarkers and preclinical models that can be used to test new mechanism-based treatments. To this end, researchers from both fields were invited to promote an open discussion on our progress and further contemplate on the ways we can ameliorate and combine our approaches to better understand sensory alterations in autism. In addition, the symposium aims to host a dynamic, inclusive conversation with the participation of speakers at different stages of their career (from postdoctoral researchers to team leaders with newly-established or well-established laboratories all over the globe). A collective effort is required to advance in the field, and this symposium aspires to provide a platform for communication, which is necessary to reach this goal.

S42.1

Sensory phenotypes in Autism: From neural networks to clinical profiles

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Autistic individuals report sensory differences in all modalities. While symptoms vary across individuals, we recently identified five distinct sensory phenotypes that differed in behavioral and clinical profiles. The neural mechanisms underlying sensory phenotypes in autism have not been investigated. We used resting-state functional connectivity to examine neural differences between sensory phenotypes in autism.

Data were extracted from the Province of Ontario Neurodevelopmental Disorders Network. 638 autistic participants' (M_{age}=9.8) parents completed the Short Sensory Profile (SSP). A k-means clustering analysis grouped participants on their pattern of scores on the SSP. Five phenotypes were identified, 1) sensory adaptive, 2) generalized sensory differences, 3) taste/smell sensitivity, 4) under-responsive/sensory seeking, and 5) movement difficulties with low energy.

We then analyzed resting-state fMRI data in a subgroup of participants (N=147, M_{age}=11.8). We parcellated the brain based on the Schaefer Atlas and calculated functional connectivity matrices for each participant. We calculated strength of connectivity across 7 functional networks from the Yeo parcellation. Pairwise comparisons for the strength of within- and between-network connectivity were conducted across each phenotype ($p<0.05$, FRD-corrected at $q=0.2$). Numerous differences in network connectivity were observed across phenotypes, including differences in limbic, default mode, visual, and sensorimotor networks, including selective hyper- and hypo-connectivity.

These results suggest that these distinct sensory phenotypes are associated with broad differences in the brain's functional architecture, not only in low-level sensory networks, but also networks associated with higher-level cognitive processes. This reflects findings over the past decade that have shown that sensory differences cascade to influence higher-level cognitive development.

S42.2

Tackling hypo and hyper sensory processing heterogeneity in Autism: from clinical stratification to genetic pathways

Aline Lefebvre[1,2], Julian Tillmann[3], Freddy Cliquet[2], Frederique Amsellem[1,2], Anna Maruani[1,2], Claire Leblond[2], Anita Beggiato[1,2], David Germanaud[4], Anouck Amestoy[5,7], Myriam Ly-Le Moal[6], Daniel Umbricht[3], Christopher Chatham[3], Lorraine Murtagh[3], Manuel Bouvard[5,7], Marion Leboyer[7,8,9], Tony Charman[10], Thomas Bourgeron[2,7], Richard Delorme[1,2, #,7] & Guillaume Dumas[2, 11, #]; and the EU-AIMS LEAP group.

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As an integral part of autism spectrum symptoms, sensory processing issues including both hypo and hyper sensory sensitivities. These sensory specificities may result from an excitation/inhibition imbalance with a poorly understood of their level of convergence with genetic alterations in GABA-ergic and glutamatergic pathways. In our study, we aimed to characterize the hypo/hyper-sensory profile among autistic individuals. We then explored its link with the burden of deleterious mutations in a subset of individuals with available whole-genome sequencing data. To characterize the hypo/hyper-sensory profile, the differential Short Sensory Profile (dSSP) was defined as a normalized and centralized hypo/hypersensitivity ratio from the Short Sensory Profile (SSP). Including 1136 participants (533 autistic individuals, 210 first-degree relatives, and 267 controls) from two independent study samples (PARIS and LEAP), we observed a statistically significant dSSP mean difference between autistic individuals and controls, driven mostly by a high dSSP variability, with an intermediated profile represented by relatives. Our genetic analysis tended to associate the dSSP and the hyposensitivity with mutations of the GABAergic pathway. The major limitation was the dSSP difficulty to discriminate subjects with a similar quantum of hypo- and hyper-sensory symptoms to those with no such symptoms, resulting both in a similar ratio score of 0. However, the dSSP could be a relevant clinical score, and combined with additional sensory descriptions, genetics and endophenotypic substrates, will improve the exploration of the underlying neurobiological mechanisms of sensory processing differences in autismspectrum.

S42.3

Auditory perceptual and circuit alterations in a rat model of fragile X syndrome

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Atypical sensory processing is a hallmark of autism spectrum disorders (ASD) and related neurodevelopmental disorders like Fragile X syndrome (FXS), most notably manifesting as extreme sensitivity to sound (i.e. hyperacusis). Auditory hypersensitivity is not only a pressing clinical problem in FXS and ASD, but it also likely reflects fundamental circuit defects that

extend to more complex but less accessible features of the disorders, such as impaired communication and language development. Using a combination of novel operant and innate perceptual-decision making paradigms, we found that a recently developed *Fmr1* KO rat model of FXS exhibits behavioral evidence for sound hypersensitivity in the form of abnormally fast auditory reaction times, increased sound avoidance behavior, and altered perceptual integration of sound duration and bandwidth. High density *in vivo* electrophysiological recordings from multiple points along the auditory pathway demonstrated that these perceptual changes were associated with sound-evoked hyperactivity and hypersynchrony in the central auditory system. These results suggest that increased auditory sensitivity in FXS is due to central auditory hyperexcitability and disrupted temporal and spatial integration of sound input. This novel symptoms-to-circuit approach has the potential to uncover fundamental deficits at the core of FXS and ASD pathophysiology while also having direct clinical implications for one of the most disruptive features of these disorders.

S42.4

Altered detection of tactile stimuli in a mouse model of autism during a translational task

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Altered sensory experience is one of the core features of autism spectrum disorder (ASD), a neurodevelopmental disorder characterized by alterations in social interaction and repetitive behaviours. Sensory alterations affect the majority of autistic individuals, exert a strong negative influence on day-to-day life, and contribute to the development of other core symptoms and medical conditions that co-occur with autism. Importantly, alterations in the sensory domain have a strong neurophysiological basis, which can be exploited in our endeavor to identify the neurobiological mechanisms of autism.

In this study we aim to characterize sensory alterations in $Fmr1^{-/y}$ mice, a genetic mouse model of autism. We developed a novel perceptual decision-making task that can be combined with measurements of neuronal activity and can be translated in human studies, to assess changes in tactile sensitivity. We observed slower acquisition of the task for $Fmr1^{-/y}$ mice and higher detection thresholds, demonstrating hyposensitivity during tactile perception. Notably, a high variance in the detection thresholds was observed in $Fmr1^{-/y}$ mice, with increased inter-individual variability, as was previously reported in autistic individuals. Parallel *in vivo* calcium imaging recordings of neuronal activity in the somatosensory cortex during the behavioural task revealed altered patterns of activity in the $Fmr1^{-/y}$ mice, with less stimulus-specific responses both in excitatory and in inhibitory neurons. Finally, using a complementary approach we observed that tactile hyposensitivity is accompanied by decreased tactile reactivity. These results expand our knowledge of tactile alterations in autism at the behavioural and neuronal level and contribute to the establishment of objective

biomarkers.

S43

Understanding the role of neuronal integrative processing through oligomeric receptor complexes in health and brain disorders.

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The concept of allosteric receptor–receptor interactions in membrane homo and heteroreceptor complexes of the CNS provides a new dimension to brain integration and neuropsychopharmacology. Allosteric receptor–receptor interactions, made possible through receptor oligomerization, lead to novel receptor dynamics where the receptor protomers change their recognition, pharmacology, signaling and trafficking. Membrane heteroreceptor complexes represent novel targets for drug development in molecular medicine in general and not only for the treatment of CNS disease like schizophrenia, depression, Parkinson's disease, and addiction. Prof. Fang Liu has previously identified a protein complex composed of the α7 nicotinic acetylcholine receptor (nAChR) and NMDA glutamate receptors (NMDARs), through which α7nAChR upregulates NMDAR function. Disruption of the α7nAChR-NMDAR complex with an interfering peptide blocked α7nAChR-mediated upregulation of NMDAR function and cue-induced reinstatement of nicotine seeking in rat models of relapse. Her team has recently shown that disrupting the α7nAChR-NMDAR complex also has antidepressant-like effects in the forced swim test. The interfering peptide significantly increases extracellular signal-regulated kinase (ERK) activity in the animals subjected to the FST. Overall, these exciting results provide a novel potential therapeutic target for the development of new antidepressant medications. Dr. Fores-Pons will provide evidence that adenosine A_{2A} receptor ($A_{2A}R$), dopamine D_2 receptor (D_2R) and metabotropic glutamate receptor type 5 ($mGluR_5$) form $A_{2A}R$-D_2R-$mGluR_5$ heteroreceptor complexes in living cells and in rat striatal neurons. Also, will present experimental data supporting the view that the $A_{2A}R$protomer plays a major role in the inhibitory modulation of the density and the allosteric receptor-receptor interaction within the D_2R-$mGluR_5$ heteromeric component of the $A_{2A}R$- D_2R-$mGluR_5$ complex in vitro and in vivo. These results represent a relevant example of integrative activity within higher order heteroreceptor complexes. Finally, Dr. Borroto- Escuela will present data describing the role of several vulnerable serotonin heteroreceptor complexes in major depressive disorder (MDD), and how antidepressant drugs such as fast- acting antidepressant drugs can directly bind to several serotonin heteroreceptor complexes.Thus, it provides a novel mechanism for their rapid antidepressant actions.

S43.1

Dual effects of α7nAChR-NR2A receptor complex on nicotine addiction and major depression

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The α7 nicotinic acetylcholine receptor (nAchR) and NMDA glutamate receptor (NMDAR) are both ligand-gated ion channels permeable to Ca2+ and Na+. Previous studies have demonstrated functional modulation of NMDARs by nAchRs, although the molecular mechanism remains largely unknown. We have previously reported that α7nAchR forms a protein complex with the NMDAR through a protein-protein interaction. We also developed an interfering peptide that is able to disrupt the α7nAchR-NMDAR complex and blocks cue-induced reinstatement of nicotine-seeking in rat models of relapse. Furthermore, we found that the α7nAchR-NMDAR interaction is responsible for the functional modulation of NMDAR by α7nAchR using both electrophysiological and behavioral tests. Thus, activation of α7nAchR upregulates NMDAR-mediated whole cell currents and LTP of mEPSC in cultured hippocampal neurons, which can be abolished by the interfering peptide that disrupts the α7nAchR-NMDAR interaction. Moreover, administration of the interfering peptide in mice impairs novel object recognition but not Morris water maze performance, suggesting that α7nAchR/NMDAR coupling may selectively affect some aspects of learning and memory. Recently, we reported that disrupting the α7nAChR-NMDAR complex with the interfering peptide also has antidepressant-like effects in the forced swim test (FST), a common rat behaviour screening test for antidepressant effects. Furthermore, the interfering peptide significantly increases extracellular signal-regulated kinase (ERK) activity in the animals subjected to the FST. Our results provide a potential therapeutic target for the development of novel therapeutics for nicotine addiction as well as major depression.

S43.2

The $mGlu_5$ receptor protomer-mediated dopamine D_2 receptor trans-inhibition is dependent on the adenosine A_{2A} receptor protomer: implications for Parkinson's disease.

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The adenosine A_{2A} receptor ($A_{2A}R$), dopamine D_2 receptor (D_2R), and metabotropic glutamate receptor type 5 ($mGluR_5$) form $A_{2A}R$-D_2R-$mGluR_5$ heteroreceptor complexes in living cells and in rat striatal neurons[1,2]. In the current study, we present experimental data supporting the view that the $A_{2A}R$ protomer plays a major role in the inhibitory modulation of the density and the allosteric receptor-receptor interaction within the D_2R-$mGluR_5$ heteromeric component of the $A_{2A}R$-D_2R-$mGluR_5$ complex *in vitro* and *in vivo*. The $A_{2A}R$ and $mGluR_5$ protomers interact and modulate D_2R protomer recognition and signaling upon forming a trimeric complex from these receptors. Expression of $A_{2A}R$ in HEK293T cells co-expressing D_2R and $mGluR_5$ resulted in a significant and marked increase in the formation of the D_2R-$mGluR_5$ heteromeric

component in both bioluminescence resonance energy transfer and proximity ligation assays. A highly significant increase of the the high affinity component of D_2R ($D2R_{Ki\ High}$) values was found upon cotreatment with the $mGluR_5$ and $A_{2A}R$ agonists in the cells expressing $A_{2A}R$, D_2R, and $mGluR_5$ with a significant effect observed also with the $mGluR_5$ agonist alone compared to cells expressing only D_2R and $mGluR_5$. In cells co-expressing $A_{2A}R$, D_2R, and $mGluR_5$, stimulation of the cells with an $mGluR_5$ agonist like or D_2R antagonist fully counteracted the D_2R agonist induced inhibition of the cAMP levels which was not true in cells only expressing $mGluR_5$ and D_2R. In agreement, the $mGluR_5$ negative allosteric modulator raseglurant significantly reduced the haloperidol induced catalepsy in mice and in $A_{2A}R$ knockout mice the haloperidol action had almost disappeared, supporting a functional role for $mGluR_5$ and $A_{2A}R$ in enhancing D_2R blockade resulting in catalepsy. The results represent a relevant example of integrative activity within higher order heteroreceptor complexes[3].

1 *Pintsuk, J. et al. Cocaine self-administration differentially affects allosteric A2A-D2 receptor-receptor interactions in the striatum. Relevance for cocaine use disorder. Pharmacol Biochem Behav **144**, 85-91, doi:10.1016/j.pbb.2016.03.004 (2016).*

2 *Feltmann, K. et al. Effects of Long-Term Alcohol Drinking on the Dopamine D2 Receptor: Gene Expression and Heteroreceptor Complexes in the Striatum in Rats. Alcohol Clin Exp Res **42**, 338-351, doi:10.1111/acer.13568 (2018).*

3 *Romero-Fernandez, W. et al. The mGlu5 Receptor Protomer-Mediated Dopamine D2 Receptor Trans-Inhibition Is Dependent on the Adenosine A2A Receptor Protomer: Implications for Parkinson's Disease. Mol Neurobiol **59**, 5955-5969, doi:10.1007/s12035-022-02946-9 (2022).*

S43.3
Dysfunctional serotonin heteroreceptor complexes as novel targets for the treatment of Major Depressive Disorders

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Among mental diseases, major depressive disorder (MD) deserves a special place due to their high prevalence and their negative impact. Consequently, the development of novel strategies designed to treat them quickly and efficiently is considered a highly important goal. Growing evidence indicates that serotonin (5-HT) homo, hetero and iso-receptor complexes in the brain give new targets for drug development in MD[1]. One emerging concept is that direct physical receptor-receptor interactions in serotonin heteroreceptor complexes and/or altered balance with their homo-receptor complexes can contribute to mental disorders and become novel

targets for treatment. For instance, a disruption and/ or dysfunction in the 5-HT1A-FGFR1 heteroreceptor complexes in the raphe-hippocampal serotonin neuron systems can contribute to the development of MD[2]. It leads inter alia to reduced neuroplasticity and potential atrophy in the raphe-cortical and raphe-striatal 5-HT pathways and in all its forebrain networks. Reduced 5-HT1A auto-receptor function, increased plasticity and trophic activity in the midbrain raphe 5-HT neurons can develop via agonist activation of allosteric receptor-receptor interactions in the 5-HT1A-FGFR1 heterocomplex. Also, the inhibitory allosteric receptor-receptor interactions in the 5-HT1AR-5-HT2AR iso-receptor complex therefore likely have a significant role in modulating mood[3], involving a reduction of postjunctional 5-HT1AR protomer signaling in the forebrain upon activation of the 5-HT2AR protomer. In addition, OXTRs play a significant and impressive role in modulating social and cognitive related behaviors like bonding and attachment, reward and motivation. Pathological blunting of the OXTR protomers in 5-HT2AR and especially in 5-HT2CR[4] heteroreceptor complexes can contribute to development of depression and other types of psychiatric diseases involving disturbances in social behaviors.

1 *Perez de la Mora, M. et al. Dysfunctional Heteroreceptor Complexes as Novel Targets for the Treatment of Major Depressive and Anxiety Disorders. Cells **11**, doi:10.3390/cells11111826 (2022).*

2 *Borroto-Escuela, D. O., Tarakanov, A. O. & Fuxe, K. FGFR1-5-HT1A Heteroreceptor Complexes: Implications for Understanding and Treating Major Depression. Trends Neurosci **39**, 5-15, doi:10.1016/j.tins.2015.11.003 (2016).*

3 *Borroto-Escuela, D. O. et al. Existence of Brain 5-HT1A-5-HT2A Isoreceptor Complexes with Antagonistic Allosteric Receptor-Receptor Interactions Regulating 5-HT1A Receptor Recognition. ACS omega **2**, 4779-4789, doi:10.1021/acsomega.7b00629 (2017).*

4 *Borroto-Escuela, D. O. et al. The oxytocin receptor represents a key hub in the GPCR heteroreceptor network: potential relevance for brain and behavior. Frontiers in molecular neuroscience **15**, 1055344, doi:10.3389/fnmol.2022.1055344 (2022).*

Poster presentations

P1 Psychiatric disorders and Comorbidities caused by pollution in the Mediterranean area

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**Project Coordinator*

Over the past 20 years, there has been an increase in mental illnesses and neurological conditions in the countries bordering the Mediterranean Sea, one of the seas most affected by marine pollutants of anthropogenic origin in the world. According to the Horizon2020 Mediterranean Report, many human activities are degrading the Mediterranean Sea, contributing to the accumulation and diffusion of anthropogenic pollutants in the entire region, as recently described for microplastic hotspots. Exposure to pollutants, in turn, threatens the health and well-being of people living along the coast, among which the incidence of psychiatric illnesses is recently increased. Numerous studies indicate adverse associations between pollution and mental illnesses; yet the biological mechanistic pathways responsible remain elusive. However, pollutants are persistent sources of neuroinflammation and reactive oxygen species production, two processes that are strongly related to the pathogenesis of brain diseases. We hypothesize that pollutants present in the Mediterranean Sea expose nearby populations to an increased risk of psychiatric disease and comorbid conditions. To date, no therapeutic treatment is designed to target pollution-based psychiatric diseases and associated neurological conditions. The major objective of the PsyCoMed project is to form an international and inter-sectoral consortium (i) to characterize the effect of pollutants on symptoms reflective of psychiatric disorders and comorbidity in validated animal models, in light of the clinical incidence of these pathologies in the Mediterranean area, (ii) to determine the role of the neuroinflammatory response in the development of these pathologies in the two sexes, and (iii) to propose innovative anti-inflammatory therapeutic treatments based on natural products.

P2 Role of Cannabinoids in Neuropsychiatric Comorbidities in Absence Seizures

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Childhood Absence Epilepsy (CAE) is a form of pediatric epilepsy that inflicts substantial suffering upon both male and female patients. It is characterized by the presence of absence seizures, which manifest as episodes of vacant staring coupled with a loss of consciousness and are identifiable through spike-wave discharges (SWDs) on electroencephalogram (EEG). However, it is crucial to acknowledge that absence seizures represent only a partial contributor to the diminished quality of life experienced by individuals with CAE. Extensive research has demonstrated that approximately 60% of CAE patients report the coexistence of neuropsychiatric comorbidities, with particular emphasis on attention deficit disorders, anxiety, and depression. While previous research has indicated a pivotal role of the endocannabinoid system (ECS) and its interaction with monoamine systems in the development of CAE, their involvement in psychiatric comorbidities remains unexplored.

The present study focuses on examining anxiety-related behavioral alterations in genetic absence epilepsy rats from Strasburg (GAERS), an animal model of CAE, following the administration of the potent non-selective cannabinoid 1 and 2 receptor (CB1/2R) agonist, WIN55,212-2, and its vehicle. A separate group of non-epileptic control rats (NEC) was also subjected to the same drug regimen, and anxiety-related and motor behavioral changes were assessed through two commonly employed behavioral tests for anxiety, namely the hole board (HB) and elevated plus maze (EPM) tests. Furthermore, we explored the monoamine systems in absence epilepsy and their interaction with the ECS by quantifying the levels of serotonin, noradrenaline, and dopamine in the brain.

Our findings reveal that NEC rats exhibit a higher level of anxiety when compared to GAERS rats with CAE treated with the vehicle of WIN55,212-2. Additionally, the administration of WIN55,212-2 results in strain-dependent alterations in the behavior of the animals, inducing an anxiolytic effect in NEC rats and a sedative effect in GAERS rats. These behavioral changes are paralleled by neurochemical modifications in specific brain regions; for instance, reduced serotonin levels were observed in the cortex, dorsal hippocampus, and substantia nigra of GAERS rats compared to NEC rats.

While numerous questions remain unanswered, our collective findings contribute to the body of evidence supporting pathological changes in the endocannabinoid system in individuals with absence epilepsy. Further mechanistic investigations are warranted to elucidate the current evidence, which may ultimately enhance the treatment prospects for patients.

P3 Study of the protective effect of PACAP on brain development and oxidative stress in mice exposed in utero to glyphosate

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Glyphosate-based herbicides (GBH) are the most used herbicides in the world, responsible for potentially harmful effects on the environment and toxic effects on different species due to their massive and inappropriate use. Pituitary adenylate cyclase-activating polypeptide (PACAP) is a well-known neurotrophic and neuroprotective neuropeptide. PACAP promotes cell survival in numerous cells and tissues exposed to various stimuli. The present study focused on the ability of PACAP to protect the brain of 35-day-old mice (PND35) from prenatal glyphosate exposure induced oxidative damage and neurotoxicity. Pregnant mice were divided randomly into 4 groups, i.e. control group, glyphosate group (250 mg/kg oral gavage daily injection), PACAP group (1µg/µl intranasal daily injection) and a glyphosate plus PACAP group. Behavioural tests revealed that PND-35-aged mice exposed to glyphosate during the prenatal period exhibited reduced exploratory interest, increased anxiety and altered spatial and recognition memory, as determined by the open field test, the object location test and the object recognition test. However, PACAP treatment attenuated these behavioural impairments. Moreover, production of ROS was sharply enhanced in the cerebral cortex and in the cerebellum of prenatally glyphosate-exposed animals, associated with an elevation in the activity of the antioxidant enzymes, and an increase of oxidative damage as shown by the accumulation of the lipid peroxidation marker malondialdehyde. Furthermore, in-utero glyphosate exposure downregulated Mtor gene expression. Intranasal administration of PACAP during the gestation period restored the endogenous antioxidant system, prevented ROS overproduction and blocked oxidative damage of cellular constituents by modulating the expression of Mtor and Nos1 genes in animals prenatally exposed to glyphosate. This study indicates that PACAP and/or PACAP analogues might be useful tools for the treatment of glyphosate intoxication during pregnancy.

P4 Neuroprotective effects of neuropeptides PACAP and ODN against prenatal glyphosate exposure induced oxidative damage and neurotoxicity

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Pre- and post-natal exposure to environmental pollutants have been associated with neurodegenerative diseases. Glyphosate, the most used herbicide worldwide that can persist in the environment for days or months and its intensive use can be a major environmental and health problem. Exposure to glyphosate induces several neurotoxic effects leading It has been suggested to induce neurotoxicity and behavioral and motor disorders. Pituitary adenylate cyclase activating polypeptide (PACAP) is a neuropeptide with several neuromodulatory functions and an important neurotrophic and neuroprotective factor. In addition, PACAP can act indirectly by stimulating glial cells to generate various neurotrophic factors such as the OctaDecaNeuropeptide or ODN, a family of biologically active peptides that have been implicated in neuronal cell protection. The present study focused on the ability of PACAP to protect from prenatal glyphosate exposure induced oxidative damage and neurotoxicity. In particular, we analyzed the ability of ODN treatment to reduce oxidative stress and to promote cell survival in case of new brain aggression, in astrocytes of neonatal mice. Prenatal exposure to glyphosate induced morphological changes represented by a shrinkage in both cell body and cellular extension and a decrease in the number of cell clusters in comparison with the control and PACAP groups. When combined with glyphosate. PACAP was able to partially reverse the induced morphological alterations. Incubation of astrocytes isolated from animals exposed during the prenatal period to glyphosate with H2O2 induced a significant decrease of the proportion of surviving cells compared to cells isolated from control animals and PACAP-treated animals. H2O2-treated astroglial cells derived from glyphosate exposure showed more ROS and NO generation than H2O2-treated astroglial cells from control-and PACAP animals. Addition of ODN at sub nanomolar doses abrogated totally the effect of H202 on cell viability and oxidative damages. In conclusion, this study indicates that the present study demonstrates that glyphosate exposure in utero triggers oxidative damage and neuronal cell death which can be counteracted by prenatal PACAP treatments. In addition, astroglial cells derived from newborn rats exposed in utero to glyphosate are more vulnerable to oxidative assault than cultured astrocytes obtained from control and PACAP animals and treatment with ODN causes a very strong long-lasting neuroprotective action against progressive oxidative damage and inhibit cell death in offspring exposed prenatally to glyphosate.

P5 Biological Activities of Cumin and Nutmeg Essential Oils on N2A cells: Focus on Cytotoxic Effects

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Essential oils derived from various plant sources have gained significant attention in recent years, due to their remarkable and diverse range of biological activities, making them attractive candidates for potential therapeutic applications. We aimed to determine the chemical composition of essential oils and investigate their biological properties on neuroblastoma cell line (neuro-2a), with a specific focus on the cytotoxic effects exhibited by cumin (Cuminum cyminum) and nutmeg (Myristica fragrans) essential oils. The chemical composition of cumin essential oil was characterized using gas chromatography-mass spectrometry (GC/MS). Cell viability and cytotoxicity were assessed using FDA and LDH assays, while the formation of reactive oxygen and nitrogen species was measured using 2,7-dichlorofluorescein diacetate (DCF-DA) and DAF-FM diacetate assays. Malondialdehyde, superoxide dismutase (SOD), and catalase levels were determined using chemical assays. GC/MS analysis revealed that cumin essential oil was particularly rich in cuminaldehyde (42.01%), γ-terpinene (18.19%), β-pinene (13.48%), and p-cymene (12.14%). On the other hand, nutmeg essential oil exhibited a predominance of hydrocarbon monoterpenes (90.51%), with sabinene, α-pinene, and β-pinene being the most abundant components, accounting for 29.083%, 23.701%, and 17.597%, respectively. Cumin and nutmeg essential oils demonstrated cytotoxic properties, inhibiting the growth and proliferation of N2A cells. These oils induced oxidative stress, leading to an imbalance between the production of reactive oxygen species (ROS) and the antioxidant defense system within the cells. The increased ROS levels resulted in cellular damage and triggered apoptotic pathways in neuro-2a cells. In conclusion, cumin and nutmeg essential oils possess cytotoxic effects against neuroblastoma cells by inducing oxidative stress. Further research is needed to elucidate the mechanisms underlying their therapeutic potential.

P6 Sorbitol accumulation in ZDF rat's brain as new link between diabetes and Alzheimer's disease?

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Alzheimer's disease (AD) and type 2 diabetes (T2DM) are aged-related diseases characterized by impaired glucose metabolism, inadequate insulin response, inflammation, and oxidative stress. The most important energy source for the brain is glucose. Under hyperglycemic conditions cells metabolize glucose by polyol pathway. Glucose is reduced to sorbitol by an enzyme aldose reductase, which uses NADPH as a cofactor. NADPH is necessary for the reduction of glutathione dimer, whose monomer works as an endogenous antioxidant. Accumulation of sorbitol causes osmotic stress and cell destruction. Therefore, the aim of the study is to analyze the development of hyperglycemia and its effect on the accumulation of sorbitol in parts of the brain in animal model of T2DM. ZDF rats (n = 57), both lean (fa/+) and obese (fa/fa) phenotypes in aged gradient were used. In all categories of the diabetic groups increased level of sorbitol was detected in the brain tissue. The most affected parts of the brain from the obtained results were cerebellum, hippocampus, and spinal cord. The highest values of sorbitol were in the hippocampus of 7-month-old diabetic ZDF rats ($^{***}P \leq 0.001$) and a significant increase in the cerebellum between 9 and 12 months of age ($^{**}P \leq 0.01$) was observed. In the control group, the most significant increase was in the right posterior cortex ($^{***}P \leq 0.001$) and in the hippocampus ($^{**}P \leq 0.01$) between 7 and 9 months of age. This study demonstrates the increased sorbitol accumulation in brain tissues of diabetic rats. These findings may thus contribute to better understanding of the common mechanism of T2DM and AD formation.

P7 In silico, *in vitro* and *in vivo* pharmacological characterization of emerging novel synthetic opioids: focus on sex differences

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Novel Synthetic Opioids, in particulars fentanyl derivatives (FENS), have been implicated in many cases of intoxication and death with overdose worldwide. The aim of this study is to investigate the pharmaco-dynamic profiles of two fentanyl (FENT) analogues: Butyrylfentanyl (BUF) and 4-Fluoro-Butyrylfentanyl (4-FBUF). *In vitro*, we measured FENS opioid receptor efficacy, potency, and selectivity and their capability to promote the interaction of the mu receptor with G protein and β-arrestin 2. *In silico*, we evaluated the ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) profiles of BUF and 4-FBUF. *In vivo*, we evaluated the cardio-respiratory changes using the Electrocardiography (ECG) and plethysmography in female and male mice injected with BUF or 4F-BUF (0.1-6 mg.kg i.p.). Opioid receptor specificity was investigated using naloxone (NLX; 6 mg/kg i.p.) pre-treatment. Moreover, we investigated the possible role of stress in increasing cardiotoxicity in mice using the CRF-1 antagonist Antalarmin (10 mg/kg). In vitro, FENT, BUF and 4F-BUF mimicked the maximal effects of dermorphin displaying the following rank of potency: FENT= 4-FBUF> BUF. 4-FBUF displayed lower maximal effects behaving as a partial agonist. FENT and BUF behaved as partial agonists for the β-arrestin 2 pathway, whereas 4-FBUF did not promote β-arrestin 2 recruitment. *In silico* ADMET prediction revealed higher toxicity risk of 4F-BUF respect to BUF. *In vivo*, our results revealed sex difference in the cardio-respiratory impairments induced by BUF and 4-FBUF. The pre-treatment with NLX partially reduced the cardio-respiratory impairments while the pre-treatment with NLX in combination with Antalarmin totally prevented the impairments induced by BUF and 4-FBUF. These findings reveal the risks associated with the use of FENS and the importance of studying the pharmaco-dynamic properties of these drugs considering sex differences. Moreover, our study shed light on the role of stress in potentiating the toxic effects of opioids.

P8 Sex-specific effects of GPER1 modulation on behavioral and neurochemical profiles: Investigating GPER1 as a therapeutic target for mood and anxiety

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Affective and anxiety disorders impose a significant burden, with higher prevalence in adult women. Recent studies suggest the role for G protein-coupled estrogen receptor 1 (GPER1) in depression and anxiety, particularly via rapid neuroestrogen signaling. The rapid antidepressant effect of ketamine shares similarities with the GPER1 signaling pathway. This study aimed to understand GPER1's mechanism of action and therapeutic potential for mood disorders. Adult male and female rats received acute doses of vehicle, fluoxetine, ketamine, G1 (a GPER1 agonist), G15 (a GPER1 antagonist), or combinations. Behavioral tests were conducted, and brain tissue from the Prefrontal cortex and Hippocampus was analyzed using HPLC-ED for monoamines and metabolites. Results showed that G15 inhibited ketamine's effects on center entries in male rats during the Open field test (OF). Co-administration of ketamine and G15 reduced the delay to consume food in male rats during the Novelty suppressed feeding test (NSFT), indicating an anxiolytic effect. The combination of G1 and ketamine had an anxiolytic synergistic effect, reducing the latency to consume food in male rats. In female rats, G1 and ketamine reduced activity levels compared to G1 alone. Ketamine tended to reduce overall activity in female rats but not in males. These findings suggest sex-specific effects of GPER1 manipulation on ketamine-induced behaviors in rats. HPLC analysis provided insights into GPER1's mechanism of action by detecting and quantifying monoamine levels in brain tissues. These results contribute to identifying GPER1 as a potential target for novel mood disorder treatments.

P9 Neurochemical analysis of the brain monoamine status of CD mice, a genetic mouse model of Williams-Beuren syndrome

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Williams-Beuren syndrome (WBS) is a rare neurodevelopmental disorder caused by a genetic alteration identifed as a microdeletion on chromosome 7 (7q11.23). Behavioural disorders, including hypersociability, impaired visio-spatial memory, and anxiety have been observed in WBS patients. A mouse line reproducing the total gene deletion observed in humans has been generated (CD mice). The behaviour of these mice resumes some of the expected alterations seen in humans, raising the issue of understanding the neurobiological bases of these

alterations. Beyond their implications in modulating behaviour, monoamines are involved in shaping the interaction between neurobiological networks during development and in adulthood. We hypothesised the existence of regionally specific alterations of the noradrenaline, dopamine or serotonin tissue contents and/or changes in connectivity of monoamines in the brains of CD mice. In female mice, samples were obtained from 10 brain regions and their monoamine content was analysed using high-performance liquid chromatography coupled with electrochemical detection. We found that there was a decrease in dopamine in the nucleus accumbens, a decrease in serotonin and its metabolite in the hypothalamus, and no changes for noradrenaline. Nevertheless, the pattern of correlations for a monoamine across brain regions differed between genotypes while the correlations for the index of serotonin metabolism (5-HIAA/5-HT) were suppressed in CD mice. These results indicate specific alterations of dopamine and serotonin in the brains of CD mice, with a reorganisation of the monoaminergic systems, particularly the serotonergic system, in this mouse model of Williams-Beuren disease.

P10 Emerging value of olfactory neuronal Prokineticin-2 as novel target in Parkinson's disease

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Prokineticin 2 (PK2) is an inducible chemokine that has shown remarkable neuroprotective effects in animal models of Parkinson's disease (PD). Specifically, PK2 increases in dopaminergic nigral cells in early stages of neurodegeneration, triggering positive bioenergetic and anti-inflammatory cascades[1]. Although a preliminary study measured higher PK2 levels in the blood and substantia nigra of PD patients[1,2], its actual contribution to PD in

humans remains to be elucidated. Because PK2 signaling is also critical for the proper development and survival of the olfactory system[3], which is affected early and has the specific neuropathological features of PD, we examined the expression of PK2 and its receptors (PKRs) in the olfactory neurons (ONs) of PD patients at different stages of disease and healthy controls (CTRLs). PK2 protein expression was also correlated with the expression of different α-synuclein species and with patients' clinical parameters. We found that PK2 expression was significantly increased in the ONs of PD patients compared with CTRLs. PK2 was higher in early disease stages, proportional to motor severity, and associated with accumulation of pathological α-synuclein forms. Conversely, PKR1 and PKR2 levels remained unchanged, suggesting that PK2 increase serves as a mediator and does not compensate for loss of receptors. In later stages of disease, in patients receiving dopaminergic therapy, PK2 expression instead decreased and did not correlate with key clinical features. These data, consistent with preclinical findings, support PK2 as a potential target in the PD early stages and confirm the reliability of olfactory neurons in reflecting PD pathological changes[4].

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P11 Chronic stress on neuronal cells converges on TDP43 endogenous cleavage and aggregation

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Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disease affecting the upper and lower motor neurons. The hallmark of ALS is the presence of inclusions made of TDP-43 formed through prion-like misfolding, a common process in neurodegenerative diseases. TDP-43 is a nuclear protein that localizes in the cytosol upon acute stress insults. However, little is known about TDP-43 biology upon milder and prolonged insults, a condition closer to pathology compared to acute stress. Here, we aim to set chronic stress paradigms on neuronal cell lines that would better mirror the long-lasting events leading to TDP-43 proteinopathy. We applied different chronic stress protocols and described TDP43 aggregation in a human neuroblastoma cell line by combining solubility assays, thioflavin-based microscopy and flow cytometry. This approach allowed us to detect, for the first time to our knowledge *in vitro*, the formation of 25 kDa C-terminal fragment of TDP43, a pathogenic hallmark of ALS. Our results indicate that chronic stress, compared to the more common acute stress paradigm, better recapitulates the cell biology of TDP43 proteinopathies. Moreover, we optimized a protocol for the flow cytofluorimetric detection of *bona fide* prions in living cells, suggesting that TDP43 may form amyloids as a stress response.

P12 Marine-derived extracts: effects of Polycarpa aurata and Sidnyum elegans in an *in vitro* model of cisplatin-induced neurotoxicity

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Cisplatin-induced peripheral neuropathy (CIPN) is a common adverse effect of chemotherapy[1]. Prevention and treatment strategies are unsatisfactory. The marine environment represents countless resources for pharmacologically-active products[2].

In this study, we evaluated the neuroprotective activity of twenty-nine fractions obtained by medium-pressure liquid chromatography of *Polycarpa aurata* (PAB) and *Sidnyum elegans* (SEB and SEA) extracts. A preliminary analysis by NMR and HR-MS means allowed the identification of the mainly featured chemical classes of more active fractions which range from sterols, alkyl sulfates, unsaturated fatty acids to 4-methoxybenzoyl derivatives. All fractions were tested in a CIPN *in vitro* model obtained treating RSC96, immortalized rat Schwann cells, with cisplatin. To select the non-cytotoxic concentrations, the fractions were tested at different concentrations (1-50 µg/ml) and MTT viability tests were performed. Informed by these results, we evaluated the neuroprotective activity of the fractions by testing them on cisplatin-treated RSC96 cells (30 µM). This first analysis allowed us to select PAB-4, PAB-5, SEA-1, SEA-2, SEA-3 (50 µg/ml), SEA-6, SEA-7 (5 µg/ml), SEA-8, SEA-9, and SEB-4 (1 µg/ml) as able to significantly preserve cells from cisplatin-induced mortality. Their effect was then evaluated on the oxidative imbalance evoked by cisplatin (10 µM). The selected fractions prevented the catalase activity enhancement and led to a further increase in superoxide dismutase activity. Furthermore, we demonstrated by flow cytometric analysis pro-proliferative and apoptotic effects of the active fractions tested on cisplatin-treated RSC96 cells (3-30 µM). The next steps will be aimed at investigating the mechanisms underlying the neuroprotective role of these fractions.

1. Chemotherapy-induced peripheral neuropathy-part 2: focus on the prevention of oxaliplatin-induced neurotoxicity - Kinga Salat. Pharmacol Rep ***2020*** *Jun - doi: 10.1007/s43440-020-00106-1.*
2. Exploring the ocean for new drug developments: Marine pharmacology – Harshd Malve. J Pharm Bioallied Sci ***2016*** *Apr-Jun - DOI: 10.4103/0975-7406.171700.*

P13 Characterization of neurotrophic potentials of Imine Analogs of Trans-Resveratrol

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Trans-resveratrol (RSV) is a non-flavonoid polyphenol (stilbene) with numerous biological activities, such as anti-tumor activities. However, RSV is rapidly metabolized, which limits its therapeutic use. The availability of RSV analogues with similar activities for use in vivo is therefore a major challenge. A better understanding of ageing and the prevention of age-related diseases is a public health challenge. Several types of compounds have been studied:

(a) trans-resveratrol (RSV) derivatives produced in the laboratory, aza-stilbenes, for their cytotoxicity compared to RSV in anti-tumour perspectives, (b) C7 oxysterols (7-ketocholesterol (7KC), 7α-hydroxycholesterol (7α-OHC), 7β-hydroxycholesterol (7β-OHC)) involved in age-related diseases; c) pomegranate seed oil and α-tocopherol to evaluate their cytoprotective activities; d) Mediterranean essential oils (Thyme, Jasmine) to better understand their biological activity. In this perspective, in comparison with the RSV, our study first consisted in evaluating the cytotoxic and antioxidant properties of AZA-STs and their impact on mitochondrial status using murine N2a neuronal cells. The antioxidant activities of AZA-STs, assessed by different techniques (DPPH, FRAP, KRL, PAOT), are often more important than those of RSV. The cytotoxic effects of AZA-STs have shown a decrease in esterase activity associated with a decrease in cell adhesion, mitochondrial dysfunction, overproduction of reactive oxygen species and changes in cell cycle distribution. The synthesised AZA-STs are therefore distinct from RSV and, like RSV, have potential anti-tumour activities. Furthermore, as an increase in oxidised cholesterol derivatives, especially C7-oxysterols (7KC, 7α-OHC, 7β-OHC), is often observed in biological fluids and diseased organs of patients with age-related diseases, cell death induced by these oxysterols was characterised in N2a cells at 72 h and the cytoprotective activities of pomegranate seed oil and α-tocopherol were evaluated in this model. 7α-OHC is not toxic, while 7KC and 7β-OHC induce oxyapoptophagy (including OXYdant stress, APOPTOsis and autoPHAGY criteria) which is attenuated by pomegranate seed oil and α-tocopherol.

P14 Distribution of tissue monoamines across the brain of young and old 3xTg-AD mice, a mouse model of Alzheimer's disease

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The function and status of monoaminergic systems encompassing serotonin (5-hydroxytryptamine, 5-HT), dopamine (DA), and noradrenaline (NA) are altered in Alzheimer's disease (AD). It has been suggested that the adjustment of monoamines may be involved in early signs of the disease. The aim of the present work was to explore the potential role of monoamines and related metabolites as biomarkers of AD. For this, we compared the tissue content of monoamines in 28 brain regions in the triple-transgenic mouse model 3xTgAD (expressing APPSwe, PS1M146V, and tauP301L, three genes associated with familial AD) and

their wild-type (WT) littermates. We included mice from two different age cohorts: 1 month (1-m, asymptomatic) and 4 months old (4-m). The quantification of monoamines and some metabolites (DOPAC, HVA, and 5-HIAA) was performed using HPLC coupled to electrochemical detection. Our results show that levels of monoamines are different between the age cohorts and between genotypes. 3xTgAD and WT showed different evolution of monoamines content between 1-m and 4-m. The regions exhibiting the highest changes were ventrolateral and ventromedial striatum, nucleus accumbens core (5-HT and DA), ventral and dorsal hippocampus (5-HT and NA), substantia nigra (DA), lateral orbitofrontal (HVA) and infralimbic cortex (5-HT, NA) and ventrolateral thalamus (HVA, DOPAC). In some of these regions, the content of monoamines was already altered at 1-m in 3xTg mice compared with WT. These data show that monoamines in AD are altered before the symptomatic stages in a subset of brain regions involved in different forms of memories (procedural and episodic).

P15 The mGlu5 receptor protomer-mediated dopamine D2 receptor trans-inhibition is dependent on the adenosine A2A receptor protomer: implications for Parkinson's disease

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The adenosine A_{2A} receptor ($A_{2A}R$), dopamine D_2 receptor (D_2R), and metabotropic glutamate receptor type 5 ($mGluR_5$) form $A_{2A}R$-D_2R-$mGluR_5$ heteroreceptor complexes in living cells and in rat striatal neurons[1,2]. In the current study, we present experimental data supporting the view that the $A_{2A}R$ protomer plays a major role in the inhibitory modulation of the density and the allosteric receptor-receptor interaction within the D_2R-$mGluR_5$ heteromeric component of the $A_{2A}R$-D_2R-$mGluR_5$ complex *in vitro* and *in vivo*. The $A_{2A}R$ and $mGluR_5$ protomers interact and modulate D_2R protomer recognition and signaling upon forming a trimeric complex from these receptors. Expression of $A_{2A}R$ in HEK293T cells co-expressing $D_2R$and $mGluR_5$ resulted in a significant and marked increase in the formation of the D_2R-$mGluR_5$ heteromeric component in both bioluminescence resonance energy transfer and proximity ligation assays. A highly significant increase of the the high affinity component of D_2R ($D2R_{Ki\ High}$) values was found upon cotreatment with the $mGluR_5$ and $A_{2A}R$ agonists in the cells expressing $A_{2A}R$, D_2R, and $mGluR_5$ with a significant effect observed also with the $mGluR_5$

agonist alone compared to cells expressing only D_2R and $mGluR_5$. In cells co-expressing $A_{2A}R$, D_2R, and $mGluR_5$, stimulation of the cells with an $mGluR_5$ agonist like or D_2R antagonist fully counteracted the D_2R agonist induced inhibition of the cAMP levels which was not true in cells only expressing $mGluR_5$ and D_2R. In agreement, the $mGluR_5$ negative allosteric modulator raseglurant significantly reduced the haloperidol induced catalepsy in mice and in $A_{2A}R$ knockout mice the haloperidol action had almost disappeared, supporting a functional role for $mGluR_5$ and $A_{2A}R$ in enhancing D_2R blockade resulting in catalepsy. The results represent a relevant example of integrative activity within higher order heteroreceptor complexes[3].

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P16 Maternal deprivation effects on recognition memory and depressive-like behavior in adolescent NMRI male mice

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Early-life stress (ELS) has been associated with an increased risk for cognitive disturbances and affective disorders. The adolescent, a critical developmental period, has been demonstrated extremely susceptible to stressful events. Maternal separation (MS) is a widely used model to study stress-related changes in brain and behavior in rodents. In this study, we examinedthe effect of MS (postnatal day 4–11, 3 h/day) on recognition memory and depression-like behaviour in adolescent male NMRI mice. We characterized for the first time the ontogeny of object and spatial memory performances, using object recognition memory task, in control mice at different ages across early development (P17, P26, P35) with short inter-trialinterval (5 min). Then, (ii) we investigate the effect of MS on both versants of recognition memory from P35 to P42. (iii) The anxiety-like behavior was evaluated using sucrose preference test. We found that control P26 and P35 mice, but not control P17 mice, recognizethe identity and the object location of objects. In addition, MD induced a deficit in object andspatial memory performances at adolescence whereas depressive-like behavior was spared. Taken together, these results indicate that, with short inter-trial interval, the age of memory onset in both types of recognition memory seems occurred in the same temporal windows. Moreover, MD impacts the development of object and spatial memory in

adolescent mice without development of an anhedonic phenotype. Further investigation is needed to determine the profile of cognitive performances and anhedonia at adulthood.

P17 Comparison between muscular biopsy and fibroblast as cell model to investigate mitochondrial activities in the neurometabolic disease "Melas Syndrome"

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Mitochondrial, Encephalomyopathy, Lactic Acidosis and Stroke-like episodes (MELAS) syndrome is a maternal inherited rare disease, which is clinically characterized by lactic acidosis, episodic vomiting, seizures, headaches, short stature, and stroke-like episodes causing hemiparesis, hemianopia and/or cortical blindness (3). The MELAS syndrome causal mutation affect the mitochondrial DNA and the respiratory complex activities such as complex I and/or complex IV. To diagnosis this disease, muscle biopsy is commonly used but the difficulties to obtain it are quiet multiple (consent, invasive chirurgical act, etc). Many alternatives have been proposed, in particular the culture of dermal fibroblasts from skin biopsy (obtained usually without chirurgical act). The present work propose a comparative study between two different samples obtained from same patient having MELAS Syndrome and diagnosis as porter of MT-TL1 mitochondrial mutation. Studies of respiratory complex activities revealed that the deficiency in complex I is more detectable in specific tissue (muscle) than fibroblasts. In fact, decrease of 14% in activity of Complex I has been observed in pathological Fibroblasts however deep deficit at about 90% have been found when studying the muscle biopsy (compared to control). Regarding complex IV (COX), we have found that any deficit has been recorded in muscle biopsy, however an important increase at about 6 fold has been observed in the COX activity setting in fibroblasts. These results confirmed the idea that the studies in specific tissue (muscle) is more efficient to detect respiratory chain deficiencies that in cellular model (fibroblasts).

P18 Increased MOP expression in the Ventral Tegmental Area mediates higher heroin self-administration and motivation expressed by marchigian sardinian alcohol preferring rats compared to non-preferring Wistars

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Marchigian Sardinian alcohol-preferring (msP) rat is an animal model genetically selected for high alcohol preference from outbred Wistars. MsPs show an innate dysregulation of Mu opioid receptors (MOP) in the amygdala and the nucleus accumbens. This prompted us to hypothesize that, similar to alcohol, msP rats may show a higher preference also for heroin compared to their non-preferring Wistar controls. We set out by comparing the dose/response of heroin (1, 7, 20, 60 µg/infusion) self-administration between msP and Wistar rats under fixed ratio 1 (FR1) contingency. Independently from sex, msPs self-administered higher number of heroin infusions than Wistars at the two intermediate doses. Next, we evaluated the motivation for the four doses of heroin measuring the break point reached under progressive ratio contingency. Male msP rats reached higher break-point than Wistars at the two intermediate heroin doses, whereas female msP rats showed higher break-point than Wistars at all heroin doses except the lowest. These data demonstrated that msP showed an increased preference for the primary reinforcing effect of heroin. Thus, we compared MOP expression in the ventral tegmental area (VTA) between heroin naïve msPs and Wistars finding that msPs show increased MOP expression in this area. Therefore, we next toned down the expression of MOP in the VTA of msPs by local viral transfection of a MOP short hairpin RNA (MOPshRNA) plasmid. Heroin (7 and 20 µg/infusion) self-administration and motivation of MOPshRNA rats were compared to that of scrambled virus infected rats. As expected, the MOPshRNA group showed lower heroin self-administration and motivation regardless of the heroin dose. Altogether, these findings demonstrate that msP rats have a higher preference for heroin compared to Wistar controls, which is mediated by a higher expression of MOP in the VTA.

P19 Investigation on the interplay between salivary microbiota and exosomal microrna in binge eating disorder

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Binge eating disorder (BED) is a serious eating disorder characterized by recurrent episodes of eating large quantities of food while feeling out of control. BED is associated with several psychiatric and somatic comorbidities, significantly affecting quality of life (McElroy, et al., 2018). Mechanisms underlying BED are not completely understood. Recently the potential role of the interplay between gut-microbiota and microRNAs (miRNAs) in vulnerability to eating disorders has been proposed (García-Blanco et al., 2022). Exosomes are small membrane-bound vesicles that are secreted by a variety of cells, including those in the gastrointestinal tract. They contain a variety of biomolecules, including miRNA, which can be absorbed by neighbouring or distant cells influencing their function. Recent research suggests that the gut microbiota may play a role in regulating host miRNA expression via exosomal communication (Belcheva, 2017). In the context of eating disorders, changes in the microbiota composition and function may alter exosomal miRNA expression, influencing the development and progression of these pathologic conditions. Our preliminary data show a dysbiosis in the salivary microbiota composition in individuals suffering from BED compared with healthy controls. Moreover, we also report significant alterations in the expression levels of exosomal miRNAs known to be involved in appetite regulation, food intake, metabolic processes, inflammation, and mood regulation. The emerging role of microbiota-exosomal miRNA interaction could aid in better understanding the complex pathophysiology underlying eating disorders and in developing new therapeutics targeting both the microbiota and exosomal miRNA.

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P20 Using fNIRS for studying self-motion perception induced by galvanic vestibular stimulation according to gravity

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The perception of self-movement is based on a central multisensory integration of somesthetic, visual and vestibular afferents. Galvanic stimulation (GVS), recently integrated into neuroimaging studies, allows to artificially stimulate the vestibular system. Thus, our team was able to demonstrate the activation of distinct cortical networks according to different configurations of GVS: anteroposterior or lateral (Aedo-Jury et al., 2020). Nevertheless, the conscious percept induced by GVS has been little described, as well as its sensitivity to head position as a function of gravity. Indeed, the otolithic apparatus of the vestibular system is affected by the suppression of gravity effects. This questions the relevance of using fMRI to study the sensitivity of head orientation to gravity in the brain construction of self-motion perception. Thus, the present study proposes to investigate anteroposterior and lateral GVS-induced perception in the sitting and lying-down positions, and its neural correlates, using functional near infrared spectroscopy (fNIRS). We used a similar GVS protocol as our previous study to 1/validate fNIRS as a tool for studying GVS-activated cortical networks and 2/assess the effect of gravity-dependent head position on induced percept and cortical activations. The studies are performed on 25 healthy young subjects, without vestibular pathology. We hypothesized that a decrease in the perception of illusory movements and an increase of latency in the perception of forward self-movement could be observed in the lying-down subjects. Thus, the present work will establish the effect of gravity on self-motion perception, which could have a valuable impact on future vestibular neuroimaging studies.

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P21 High-fat diet negatively affects the mucosal barrier function in the duodenum and trigger crucial changes along the gut-brain axis glial cells involved in anxiogenic and depressive-like behaviours

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Metabolic and behavioral disorders can be related to each other as they may share common etio-pathological processes. Autonomic neurons establish communication between the brain and the gastrointestinal tract and are involved in peripheral metabolic pathways affecting behavior change. The activity of neurons along this pathway is regulated by glia cells, which change their phenotype based on their environment. It is not clear how high-fat diet-induced changes in glia phenotype may contribute to affecting behavior. This study tested the hypothesis that high-fat diet leads to anxiogenic and depressive-like behaviors due to the compromised barrier of the duodenum and the subsequent phenotypic changes in glia and neurons along the gut-brain axis. The findings show that a high-fat diet caused duodenal mucosa damage and changes in glial cells along gut-brain axis, which resulted in anxiety and depression-like behavior in mice. Glial cells exhibited increased expression of GFAP and TLR4, with decreased BDNF and DCX expression, fewer neuronal dendritic spines, and anxiogenic/depressive symptoms in high-fat diet-treated mice. The use of fluorocitrate as a glial metabolic inhibitor prevented these effects in both the enteric and central nervous systems and stopped the behavioral alterations at week 20. These results indicate that a high-fat diet can impair duodenal barrier function, leading to glial-dependent behavioral changes, and suggests the potential role of glia in the alteration of gut-brain signaling that occurs during metabolic and psychiatric disorders.

P22 Neuroprotective activity of MT-POM in the LRRK2 genetic model of PD in drosophila melanogaster

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Parkinson's disease (PD) is a neurodegenerative disorder characterized by the selective loss of dopaminergic neurons and motor impairment. The pathogenesis of PD may involve both genetic susceptibility and environmental factors. Mutations in Leucine-rich repeat kinase 2 (LRRK2) locus contributes to genetic forms of PD[1]. The common fruit fly Drosophila melanogaster (Dm) carrying the mutation LRRK2 loss-of-function in the WD40 domain (LRRK2-Dm), is an *in vivo* model of PD that develops motor impairment, dopaminergic neuronal loss and damaged mitochondria[2]. Therefore, this model can be considered a valid tool to first test novel therapeutic approaches to the disease. Recent studies have identified several immunomodulatory agents with a neuroprotective effect in neurodegenerative disorders[2-3]. Here, in the LRRK2-Dm, we tested the novel pomalidomide derivative 3-monothiopomalidomide (MT-POM) that displayed increased potency in lowering TNF-alpha levels in *in vitro* tests. Changes in motor performance, number of brain dopaminergic neurons and mitochondria integrity were analyzed. Moreover, we studied the survival rate of LRRK2-Dm and wild type flies under life-long drug treatment. Mutant and wild type flies received 3 increasing MT-POM doses via diet from day 1 post eclosion, and efficacy was evaluated after 21 days. MT-POM significantly and dose-dependently improved climbing behavior respect to controls, prevented the loss of dopaminergic neurons and fully rescued damaged mitochondria with dilated cristae observed in non-treated LRRK2-Dm. Moreover, MT-POM significantly extended the survival of LRRK2-Dm. Our data indicate a neuroprotective effect of MT-POM in the LRRK2-Dm PD model, prompting further investigation of this drug in mammalian models of PD.

P23 QN6: A new 8-Hydroxyquinolylnitrone for the therapy of diseases of aging and stroke

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We have recently identified (*Z*)-*N*-benzyl-1-(8-hydroxyquinolin-2-yl)methanimine oxide (**QN6**), as a potent hBuChE (IC_{50} = 1.06 ± 0.31 nM) and hMAO-B (IC_{50} = 4.46 ± 0.18 µM) inhibitor, showing antioxidant and biometal chelator properties, able to cross the blood–brain barrier, no cytotoxic, acting as a neuroprotector agent in a 6-hydroxydopamine cell model of Parkinson's disease (PD),[1] as an anti-amnesic ligand in the scopolamine-induced mouse model of Alzheimer's disease (AD). Moreover, chronic treatment of double transgenic APPswe-

PS1δE9 mice with **QN6** reduced amyloid plaque load in the hippocampus and cortex of female mice[1]. Here we report the neuroprotective properties and the antioxidant power of **QN6** for their potential application in stroke. *In vitro* neuroprotection studies of **QN6** in an oxygen-glucose-deprivation model of cerebral ischemia, in human neuroblastoma cell cultures, indicate that **QN6** is a potent neuroprotective agent that prevents the decrease in neuronal metabolic activity (EC_{50} = 3.97 ± 0.78 µM) as well as necrotic (EC_{50} = 3.79 ± 0.83 µM) and apoptotic cell death (EC_{50} = 3.99 ± 0.21 µM),[2] showing high capacity to decrease superoxide production (EC_{50} = 3.94 ± 0.76 µM). Furthermore, in an experimental permanent focal ischemia model, **QN6** treated animals exhibited a very significant reduction (75.21 ± 5.31%) of the brain lesion volume size. Overall, previous[1] and present[2] results reported here confirm quinolylnitrone **QN6** as a unique, single and multivalent agent for the combined therapy of Neurodegenerative and Neurovascular Diseases.

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P24 Prenatal and postnatal exposure to inorganic mercury affects neurodevelopmental behavioral parameters in mice offspring

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Mercury is a heavy metal widely used in the world and is well recognized as causing human health problems. Contamination with mercury is not only a health issue for adults but has also been shown to have deleterious effects on the health of the fetus, newborn, child and adolescent, where brain maturation is still occurring and by consequent are sensitive to any toxic effects. In this study, we evaluated the effect of mercury on treated females during gestation and after parturition by maternal behaviour and retrieval test and in offspring during 21 days postnatal development using physical parameters. Furthermore, we assessed neurodevelopmental in offspring by using appropriate tests. For this, we have exposed pregnant mice during the entire gestational period and during the postnatal period after delivery to an inorganic form of mercury: $HgCl_2$. Our results indicate that newborn micefrom the intoxicated group show a decrease in their body weight, the size of the tail and a general delay in physical development (appearance of hair, incisor eruption and sex appearance). Concerning neurodevelopment; it is noteworthy that some parameters have

been affected negatively such as motor orientation and coordination as for negative geotaxis, cliff avoidance, swimming test and surface righting reflex.

P25 Inflammatory response in the retina in a mouse model of Alzheimer's disease is restrained by targeting the miRNA-155/TNFSF10 network

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Alzheimer's disease (AD) is the most common form of age-related dementia, characterized by an insidious onset of progressive cerebral atrophy and cognitive decline. According several studies, AD shares some features with retinal degenerative diseases such as glaucoma and age-related macular degeneration (AMD). In particular, retinal deposition of Aβ aggregates in AMD patients has suggested a potential link between AMD and AD. Here we analyzed, in the retina of a triple transgenic mouse model of AD (3xTg-AD), the expression pattern of a focused set of miRNAs, previously found to be involved in both AD and AMD. Results showed that several miRNAs were differentially expressed in the retina of 3xTg-AD mice, compared to the retina of age-matched wild-type (WT) mice. Bioinformatic analysis revealed that miR-155 played a central role in miRNA-gene network stability, regulating several pathways, including apoptotic and inflammatory signaling pathways modulated by TNF-related apoptosis-inducing ligand (TNFSF10). Chronic treatment of 3xTgAD mice with an anti-TNFSF10 monoclonal antibody was able to inhibit the retinal expression of miR-155, which inversely correlated with the expression of its molecular target SOCS-1. Moreover, TNFSF10 immunoneutralization was tightly linked to modulation of TNFSF10 itself and its death receptor TNFRSF10B, along with cytokine production by microglia, reactive gliosis, and specific AD-related neuropathological hallmarks (i.e., Aβ deposition and Tau phosphorylation) in the retina of 3xTgAD mice. In conclusion, the TNFSF10-neutralizing antibody treatment in 3xTg-AD mice significantly preserved the retinal tissue, suggesting novel therapeutic application in retinal degenerative disorders.

P26 Acute and chronic cocaine and nicotine change the expression of genes involved in cholesterol homeostasis in the rat dorsal striatum

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Cholesterol, the major sterol found in the central nervous system, has been shown to participate in both structural and functional neuroplasticity and may participate in drug-induced mechanisms underlying addiction. In this study, we investigated whether administrations of cocaine or nicotine would alter the expression of genes involved in cholesterol homeostasis in the dorsal striatum (DS), a brain area playing role in addiction and relapse. We investigated the rapid (1h after injection) effects of a single dose of cocaine (15mg/kg IP) or nicotine (0.7mg/kg SC) and the persistent effects (3 weeks after the last injection) of 10 injections of cocaine or nicotine. We used RT-PCR to evaluate the expression of genes involved in the synthesis of cholesterol (3-hydroxyl-3-methylglutaryl-coenzyme A (HMGCoA) reductase) or its regulation (sterol regulatory element-binding factor-2 SREBF2 ; Liver X Receptor type beta LXR B), in the cholesterol transport (ATP-binding cassette subfamily A member 1 ABCA1 ; Apolipoprotein E ApoE ; Low Density Lipoprotein receptor LDLr) and its degradation (CYP46A1). We found that a single cocaine injection increases the mRNA levels of HMGCoA reductase, SREBF2, LXRb, ApoE and CYP46A1, whereas a single injection of nicotine had no effect. On the other hand, we found that chronic exposure to cocaine does not durably modify the expression of these genes in this brain area, whereas chronic nicotine affects SREBF2, ABCA1, ApoE and LDLr mRNA levels. Altogether, these results indicate that drugs induce dysregulations in the cholesterol metabolism in DS and that these changes might participate in addiction.

P27 Impaired fronto-striatal excitation/inhibition balance underlies the repeated ketamine-induced schizophrenia-like bio-phenotype: The modulatory role of cannabidiol.

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The neurobiological underpinnings of repeated ketamine (KET) model of schizophrenia remain poorly understood. Cannabidiol (CBD), a non-addictive phytocannabinoid has been reported to present antipsychotic potential, but the mechanisms involved remain elusive. This study aims to investigate the KET-induced bio-phenotype, and the potential therapeutic effect of CBD by emphasizing on the glutamatergic system, and network function. After a repeated subanesthetic KET exposure, rats received a 5-day long treatment with CBD. Subsequently, they underwent behavioral analyses exploring positive, negative, and cognitive symptomatology. HPLC-ED provided estimates of GABA and glutamatergic activity, NMDA and AMPA receptors have been quantified using western blot, and specific interneuron densities have been calculated using immunohistochemistry. LFPs have been recorded from sevoflurane-anesthetized rats' mPFC (medial prefrontal cortex), simultaneously with dorsomedial striatum (DMS), and ventral hippocampus (VH). KET-treated rats displayed a schizophrenia-related behavioral bio-phenotype, with a parallel impairment in glutamatergic neurotransmission and excitation/inhibition balance in the PFC and DMS. CBD was able to ameliorate positive, negative, and cognitive symptomatology, while also positively modulated the excitation/inhibition imbalance with the concomitant reduced interneuron densities in the PFC. Current findings characterize further the schizophrenia-like bio-phenotype induced by repeated KET and enrich our understanding of the antipsychotic potential of CBD.

P28 Evidence suggesting that PLPPR3 tunes neuronal responses to Lysophosphatidic Acid.

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Phospholipid-phosphatase-related proteins (PLPPRs) are a five-member family of neuron-enriched, developmentally regulated membrane proteins that control glutamatergic synapses, filopodia and branch formation, as well as growth cone navigation. Although they display homology and similar topology to Lipid Phosphate Phosphatases, they lack Lysophosphatidic Acid (LPA) phosphatase activity. Previous studies have suggested the involvement of PLPPR4 in neuronal LPA signaling via an LPA transporter or scavenger function, but the role of other PLPPRs, including PLPPR3, a close PLPPR4 relative, in LPA signaling, remains elusive. The aim of present work is to study the molecular interactions of PLPPR3 and LPA and how this interaction could affect LPA-induced morphological effects in neurons. For this purpose, we investigated the physical interactions of 18:1 LPA and PLPPR3 via Microscale

Thermophoresis, and we assessed the extent of LPA uptake in different cell lines overexpressing PLPPRs using Flow Cytometry. Finally, we evaluated the effect of LPA treatment on neuronal morphology and axonal growth in primary hippocampal WT and PLPPR3 KO neurons at different developmental stages. Our results indicate that 18:1 LPA and PLPPR3 C-terminal domain physically interact with an apparent Kd in the micromolar range. Moreover, while PLPPR4 increases LPA uptake of cells, PLPPR3 exhibits biphasic effects on LPA uptake in a dose- time- and cell type- dependent manner. Importantly, PLPPR3 KO neurons resist to morphological changes caused by LPA in WT neurons, including axonal branch density alterations. Collectively, our results suggest that PLPPR3 functions by enabling or tuning LPA-responses in neurons which may involve direct interactions with LPA.

P29 Chronic intranasal administration of URB597 reverts short-term memory deficits in a rat model of metabolic syndrome

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The metabolic syndrome (MS) is a disorder characterized by metabolic disfunctions, but also memory impairment[1,2]. However, the neurobiological mechanisms underlying MS-related cognitive deficits are not clear. Scientific evidence has demonstrated an involvement of N-acylethanolamides (NAEs)[3,4], molecules structurally related to endocannabinoids, with which they share the inactivation by the fatty acid amide hydrolase enzyme (FAAH). The present study aims at investigating the therapeutic potential of the FAAH inhibitor URB597, which increases endogenous NAEs levels, on MS-related cognitive disorders. Sprague-Dawley rats were fed *ad libitum* with standard diet (CTRL) or high fat (60% Kcal from fat) and high carbohydrate (sucrose solution 20% w/v) diet (HF/HC), from post natal day 28 until the end of the experiment. Animals were treated chronically with URB597 (0.1 mg/Kg)[5,6], by daily intranasal administration. Our results demonstrated that HF/HC diet induced an increase of weight, body mass index and triglycerides. Furthermore, the HF/HC group showed spatial memory impairment in the Morris water maze task and short-term recognition memory deficits in the object recognition task. URB597 administration was able to counteract the recognition deficit effects but not the spatial ones. These findings introduce a potential therapeutic treatment to attenuate MS-related cognitive deficits.

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P30 Cyclodextrins decrease TRP ion channel activation via lipid raft disruption

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Transient Receptor Potential Ankyrin 1 (TRPA1) and Vanilloid 1 (TRPV1) are nociceptive ion channels involving in pain and inflammation and are located in the lipid rafts, the cholesterol-rich membrane domains of the plasma membrane of primary sensory neurons. Cyclodextrins (CDs) deplete cholesterol from lipid rafts, Methyl-β-cyclodextrin (MCD) inhibited TRP ion channel function and has analgesic effect in animal models. We tested five different CD derivatives (Randomly methylated β-cyclodextrin: RAMEB, (2-Hydroxypropyl)-γ-cyclodextrin: HPGCD, (2-Hydroxyproyil)-β-cyclodextrin: HPBCD, Sulfobutylated β-cyclodextrin sodium salt: SBECD and (2-Hydroxy-3-N,N,N-trimethylamino) propyl-β cyclodextrin: QABCD) in respect of their cytotoxicity (1, 3, 10, 50, 100 mM; 24 h) on CHO cells with CellTiter-Glo® Luminescent Cell Viability Assay. MitoTracker™ Red CMXRos fluorescent dye was used to reveal the effect of CD treatment on mitochondrial functioning. We performed radioactive $^{45}Ca^{2+}$-uptake measurements on TRPA1- and TRPV1-expressing CHO cells to detect alterations in receptor activation after CD treatment. In cell viability assay the methylated derivative RAMEB showed significant cytotoxic effect, but none of the non-methylated derivatives decreased cell viability. HPBCD and QABCD treatment resulted in significantly increased fluorescence intensities of CHO cells' mitochondria labeled with MitoTracker™ Red CMXRos. All of the investigated CDs were able to inhibit the $^{45}Ca^{2+}$-uptake in receptor-expressing CHO cells concentration dependently. In conclusion, non-methylated derivatives have much lower

cytotoxicity compared to RAMEB. HPBCD and QABCD affected significantly the mitochondrial function and all CD derivatives inhibited TRPA1 and TRPV1 channel activation, presumably via the disruption of lipid rafts. Targeting hydrophobic interactions of the protein-lipid interface might be promising as a novel mechanism of action in analgesia.

P31 Genetically modified Lactobacillus paracasei subsp paracasei F19 producing oleoylethanolamide (OEA) relieves peripheral and central symptoms associated with metabolic diseases

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The high-fat diet (HFD) causes intestinal dysbiosis and low-grade inflammation in the small intestine that leads to an alteration of the epithelial barrier. Prolonged intake of HFD leads to disruption of the neuroepithelial circuits that control energetic homeostasis through the gut-brain axis with the development of neuropsychological and behavioral complications [1]. Several probiotic species and gut-brain hormones secreted in the intestine after meals, such as N-oleoylethanolamide (OEA), shape the intestinal microbiota profile towards a “lean-like phenotype” and ameliorate pathological profiles of metabolic diseases. Exogenous OEA also displays beneficial effects in several cognitive paradigms and preserves the epithelial barrier integrity, acting as an intestinal “gate-keeper” [2, 3]. We integrated these OEA functions and developed a probiotic-based delivery system by engineering the *Lactobacillus paracasei F19* (LP) to express the human N-acylphosphatidylethanolamine- preferring phospholipase D (NAPE-PLD) gene and produce OEA in response to dietary ultra-low oleate supply. We treated 12-week HFD mice with oleate-probiotic formulations and assessed the impact on metabolic and behavioral dysfunctions, and intestinal microbiota composition after 8 weeks of the treatment. OEA issued by NAPE-LP-expressing LP (pNAPE-LP) led to significant weight loss and metabolic dysfunction betterment in HFD-treated mice. Further, a parallel improvement of depressive- and anxiety-like phenotypes was associated with duodenal barrier function retrieval, a restoration of the *Firmicutes/Bacteroidetes* ratio, and an increase in *Lactobacillus* and *Prevotella* species abundance. This oleate-regulated delivery system is a new probiotic-based strategy for the intestinal release of OEA in the treatment of metabolic syndrome and related behavioral disorders.

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P32 Role of cholesterol homeostasis in the dorsomedial striatum on the balance between habitual and goal-directed control

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The balance between habitual and goal-directed control is essential for appropriate decision-making and can be altered in several psychopathologies, including addiction. The dorsal striatum represents a central hub for action control and synaptic plasticity processes in this region are likely engaged in the balance between goal-directed and habitual control. Cholesterol, the major sterol compound of the brain, is thought to be involved in synaptic plasticity, notably by controlling glutamate receptor trafficking at the synapse. We hypothesized that manipulations of cholesterol metabolism in the dorsal striatum can affect the balance between habitual and goal-directed behavior. In this experiment, we used a viral strategy to overexpress the enzyme responsible for cholesterol degradation (CYP46A1) in the dorsomedial striatum and investigate the effects on habitual behavior. Preliminary results show that when rats are trained in a task promoting habit, overexpression of CYP46A1 promotes a reengagement of goal-directed control in a subset of animals. These results suggest that dorsomediostriatal cholesterol could be involved in the balance between habitual and goal-directed control.

P33 Investigation of the role and diagnostic, prognostic value of PACAP-38 in multiple myeloma

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Pituitary adenylate cyclase-activating polypeptide (PACAP) is a multifunctional neuropeptide with well known antiapoptotic, anti-inflammatory and antioxidant effects. The antitumor effect of PACAP in multiple myeloma (MM) has been demonstrated in numerous studies. PACAP inhibits the growth of myeloma cells, regulates osteolytic bone destruction, and protects proximal tubule cells in various models of MM. The peptide also has an immunomodulatory effect and may influence the complex cytokine network of the bone

marrow microenvironment. The aim of our study was to investigate the plasma PACAP-38 levels of patients with MM using ELISA method (n=66; control: n=10). We correlated the changes of PACAP levels with various clinical and laboratory parameters. Lower PACAP levels were measured in treated MM patients compared with the healthy control group, but this difference disappeared if the patient achieved better response than partial response after therapy. Significantly higher PACAP-38 levels were seen in younger individuals with lower stage, lower plasma cell fraction in bone marrow, lower tumor markers and in patients after lenalidomide therapy. Higher PACAP-38 levels in newly diagnosed MM patients predicted longer survival and higher probability of response to treatment. Based on our findings, we suggest that this peptide may play an important role in the pathophysiology of MM and PACAP could be used as a valuable noninvasive alternative biomarker. However, further studies are needed to describe the exact pathomechanism of the protective effect in this disease.

P34 Engaging Kenyan Communities in Dementia Research

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In the next decades, low- and middle-income countries (LMICs) will account for 85% of the population growth of people aged 65. However, The World Health Organization has warned that most countries are lagging in responding to dementia, particularly in Sub-Saharan Africa. Therefore, the Brain and Mind Institute (BMI) has established the *Center for Healthy Brain Aging*, serving East Africa and South/Central Asia, whose primary mission is to address dementia research gaps, and to improve treatment and care for people living with dementias in LMICs. To effectively address dementia globally, a proper understanding of the cultural context and individual/societal perceptions of dementia is necessary, but severely lacking in Sub-Saharan Africa. Therefore, the BMI *Center for Healthy Brain Aging* has developed a plan to engage urban and rural Kenyan communities in dementia research, using ethnographic design that entails both in-depth exploration interviews, observations and community participatory living lab approaches, including: (1) **consulting** with communities on dementia, (2) **informing** them about dementia diagnosis, research, and research methodologies, (3) **involving** them and **collaborating** with them in research conceptualization and implementation, and (4) **empowering** the communities in *co-creating* interventions and programs aimed to address drivers of dementia in their contexts. We are confident that our living lab and co-creation approaches to developing partnerships with communities will significantly contribute not only to a more effective treatment and care for people living with dementia in Africa but will also ensure a lasting and sustainable societal impact.

P35 The impact of Thiamethoxam on oxidative stress level in hypothalamic pituitary axis in Wistar rat.

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Neonicotinoid pesticides are a class of chemicals that are intentionally released into the environment, which is why their potential toxicity has been extensively studied. Pesticide-induced oxidative stress has also been the focus of toxicology research as a possible mechanism of toxicity over the past decade. Oxidative stress can be most simply defined as the excess production of reactive oxygen species (ROS) compared to antioxidant defenses. In this context, the present work consists in studying the effect of exposure of Wistar rats to increasing doses of Thiamethoxam on markers of oxidative stress, for this, 24 adult male rats of the *Wistar* strain were divided into four groups: group 1- controls (1 ml/day of water) and three other groups treated by gavage daily for 10 weeks with TMX at different doses: group 2-ADI (Acceptable Daily Intake): 0.026 mg/kg, group 3-NOAEL (No Observable Adverse Effect Level): 2.6 mg/kg and group 4-NOAELx2: 5.2 mg/kg. Food consumption, water, and body weight were measured weekly. In addition, at the end of the treatment period, the levels of pro-oxidative factors such as nitric oxide (NO) and Malondialdehyde (MDA) and the anti-oxidative factor Gluthathion reductase (GSH) were measured on total extracts of hpothalamic and pituitary gland. The results revealed a significant increase ($P < 0.001$) in body weight in NOAEL and NOAELx2 animals. Additionally, a significant increase in the rate of food consumption and water ingestion in ADI, NOAEL and NOAELx2 groups compared to the control group. Moreover, an alteration of the antioxidant defense system characterized by a decrease in GSH at the pituitary-hypothalamic axis, and by a significant increase in markers of oxidative stress, MDA and NO only on the hypothalamic region. These observations are in favor of a disruption of the function of the hypothalamic-pituitary axis via subtle changes of the different signaling pathways subsequently on the neuronal function in a direct or indirect way, by several phenomena such as inflammation, angiogenesis and cell death.

P36 Impact of type 2 diabetes on the organization and plasticity of the supraoptic and paraventricular hypothalamic nuclei in wistar rats subjected to high-calorie diet

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The prevalence of metabolic diseases such as type 2 diabetes (dt2) is steadily increasing in industrialized countries due to « fast-food » high calorie eating and sedentary lifestyles. The influence of nutritional stress on the hypothalamic nuclei results in an imbalance in energy homeostasis. The objective of this study is to better understand the impact of the "cafeteria" diet on the development of diabetes and its evolution into t2d and to determine the effects of the latter on the brain and mainly on the supraoptic nuclei (NSO) and paraventricular nuclei (NPV) hypothalamic in rats. We used an experimental model of nutritional diabetes. The Wistar rat (Rattus norvegicus) is fed a «cafeteria» diet for 6 months with free access to water. Our results showed interesting physiological changes in diabetic rats. At the plasma level, we notice an increase in the blood glucose level, hypernatremia and hyperosmolarity. At the central level, significant morphological changes represented by hypertrophy of the cell bodies of the magnocellular neurons concentrated at the level of NSO and NPV and a retraction of the glial cover which would allow neuronal apposition, hence an increase of the inter-neuronal communication. We also observe an organization of the magnocellular neurons adjacent to the vascular endothelium as well as neovascularization. It appears that hyperosmolarity, associated with diabetes mellitus, may trigger an increase in magnocellular neuronal activity, which is thought to be manifested by the production of the main antidiuretic hormone produced by this system, Arginine-Vasopressin.

P37 Dystrophins distribution in the median eminence of adult mice: effects of osmotic stimulation and reversibly normal hydration.

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Our team reported in several works that Dystrophins (Dps) seem to be implicated in the regulation of hydromineral homeostasis since they are expressed in hypothalamo-neurohypophyseal system (HNHS). Our aim is to determine Dps distribution in the median eminence (ME) one of the circumventricular organs and a part of the HNHS, which requires free access to blood circulation. For this study, mice were submitted to salt loading with 2% NaCl for 14 days, and for its reversibly, animals have access to the normal water drink for 30 days after 14 days dehydration. Our findings show distinct morphological changes in the ME during osmotic stimulation, we observed a structural reorganization of the cells bodies of tanycytes in the ependymal layer, and dilatation of the capillaries at the external zone. The constituents of the ME express GFAP and Dps in the ependymal layer and internal zone respectively. After 14 days of salt loading, Dps intensity signal increases in the fibre layer with an increase of tanycyte's cells expansion towards the internal zone. Normal hydration show a partial return to the control labelling intensity. Salt loading leads to an increase of liquid and food intake. Otherwise, 30 days of normal hydration show a return to control levels of liquid

intake but not food intake. Our finding suggest that tanycytes activity during osmotic stimulation may be modulated by dytrophins in the ependymal and fibre layer and this may have a potential implication in the regulation of the hydromineral homeostasis and neurosecretory process in the ME.

P38 Implication of Dp and α1-syntrophin in cellular plasticity and reversibility during water stress in wistar rats

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The supraoptic nuclei (SON) are hypothalamic structures where somas of magnocellular neurons (MCNs) are gathered. Axons of these neurons run through the median eminence toward neural lobe of hypophysis (NL/HP), where arginin-vasopressin (AVP) and oxytocin (OT) are secreted into the blood circulation. These two neurohormones are involved mainly in the regulation of hydroosmotic homeostasis. The SON has the particularity of undergoing a profound neuro-glial anatomical reorganization in response to intense stimuli such as dehydration. These modifications are reversible and strictly related to the structural and functional organization of the cytoskeleton. Among the proteins of the subcortical cytoskeleton are the dystrophins (Dp). Dp, the largest the Duchenne muscular dystrophy (DMD) gene product, firstly identified as a 427-kDa protein (Dp427) in muscle where it provides the stability and the integrity of the sarcolemma of muscle fibers in the contraction-relaxation cycles. In the brain, Dp427 and small products derived from different promoters of the DMD gene have been characterized, including with regard to their molecular weights: Dp260, Dp140, Dp116 and Dp71. In the brain, dystrophins are involved in metabolism, cortical excitability and in synaptic plasticity. In the hypothalamo-neurohypophyseal system, dystrophins have been demonstrated, for the first time by our team, with high proportion of Dp71 in mice. The involvement of these proteins is suggested in different processes, in neuroscretory granules storage, signal transduction and cellular plasticity. The aim of this study was to determine the importance of dystrophins and α1-syntrophin, one of the Dystrophin-Associated Protein Complex expressed in several tissues also in SON, in the response to dehydration of 14 days by soalt loading and in its reversibly after 30 days of normal hydration. All the results obtained during this work allowed the presence of Dp and α-1 Syn in the NSO. Dp was localized in magnocellular neurons (MCNs) and astrocytes, when α1Syn was observed essentially in astrocytes end feet. By an immunohistochemical technic, we showed a change in the distribution and expression of these proteins under the effect to dehydration of 14 days by soalt loading solution. This structural changs are reversible after 30

days of normal hydration. Dp71 is the most abundant form of dystrophin revealed by western bloting in the SON of control rat. After 14 days of salt-loading, Dp71 and α1Syn signals decreased, after 30 days of normal hydration, the intensity of the signal for the Dp71 and α1Syn, increased and approached that of control.

P39 The impact of intense endurance exercise on SOD1G93A ALS mouse model

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Amyotrophic lateral sclerosis (ALS) is a human neurodegenerative disease characterized by the loss of cortical, spinal motor neurons and muscle wasting. Although it is considered the prototype of motor neuron diseases, the compromission of metabolic homeostasis with high energy expenditure and defective energy production have been widely described in ALS patients and animal models of the disease (Ferri & Coccurello 2015). Since weight loss, energy stores depletion, hypermetabolism and alterations in glucose handling are common features of ALS, physical activity (PA) could be relevant in the pathology. In fact, PA could act as a risk factor exacerbating the existing energy imbalance and worsening the oxidative status of skeletal muscle (Scaricamazza et al. 2021), or, as widely recognized for PA, it could exert a protective effect improving the locomotor performances. This study aimed to evaluate the impact of PA in a mouse model of ALS, focusing the attention on locomotor alterations and neuromuscular dysfunctions, through the pre-onset administration of a specific endurance/oxidative training protocol. ALS mice, ($SOD1^{G93A}$) were trained on treadmill starting at P30 (early presymptomatic) until P90 (early symptomatic) for 5 days/week. Animals were monitored throughout the training protocol by assaying metabolic/molecular alterations and locomotor performance. We demonstrate that intense endurance training speeds up the progression of the disease, worsening the oxidative status of skeletal muscle and anticipating muscle denervation and motor neuron loss of $SOD1^{G93A}$.

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P40 The metabolic modulator Trimetazidine ameliorates mitochondrial dysfunction in Amyotrophic Lateral Sclerosis SOD1G93A cell models via autophagy activation

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Amyotrophic Lateral Sclerosis (ALS) is considered the prototype of motor neuron disease and is characterized by motor neuron loss and muscle waste. Mitochondrial failure, accompanied by bioenergetic deficits, is a well-established pathogenic hallmark extensively described in both patients and animal models. So far, pharmacological treatments of the disease failed and emerging evidence point to mitochondria as a potential "druggable" target in ALS(Candelise et al. 2022). Trimetazidine (TMZ) is a metabolic drug whose protective effect on SOD1^{G93A} mice has been previously reported (Scaricamazza et al. 2022). The drug is described as a metabolic modulator acting on different cellular pathways although its molecular target remains elusive. In SOD1^{G93A} mice TMZ plays a pivotal role in improving glucose handling and mitochondrial functionality. In the present study, on murine SOD1^{G93A} primary cultures of cortical and spinal enriched motor neurons, we elucidate the molecular pathways underlying the mechanism of action of TMZ. We first characterized the cell cultures bioenergetic profile pointing out a significant mitochondrial impairment that is improved by acute TMZ treatments. Electron microscopic analysis on the same primary cultures showed significant number of altered mitochondria, characterized by deranged cristae, whose ultrastructure was normalized by acute TMZ treatment. In this context, we highlighted the effect of TMZ in promoting autophagic/mitophagic processes, allowing to restore mitochondrial morphofunctional features, by the improved mitochondrial quality control.

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*-Scaricamazza S, et al. Repurposing of Trimetazidine for amyotrophic lateral sclerosis: A study in SOD1G93A mice. **Br J Pharmacol**. 2022 Apr;179(8):1732-1752. doi: 10.1111/bph.15738.*

P41 Behavioral correlates of fear memory in an animal model of Post-Traumatic Stress Disorder: Ultrasonic vocalizations and sex differences

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Post-Traumatic Stress Disorder (PTSD) is a chronic psychiatric disease characterized by over-consolidation, generalization and impaired extinction[1]. The return of fear following the acquisition of fear extinction learning is common[2] and often responsible for the PTSD-treatment unfailure[3,4]. While only few trauma-exposed individuals develop PTSD, women have a twofold greater risk, prevalence and duration of PTSD than men[5]. We have demonstrated that there is a link between fear extinction and 22-kHz USV emission in a fear conditioning paradigm, associated to profound sex differences[6]. Thus, in the present study we tested if 22-kHz USVs could mirror freezing behavior in an animal model of PTSD[7], and we examined potential sex differences in fear acquisition and extinction. Our results indicate that, although during trauma exposure males show higher freezing levels while females exhibit a greater reactivity to trauma, they both emit a similar number of alarm USVs. Moreover, along the extinction sessions, the number of USV emission gradually decreases in both sexes, mirroring the freezing response, although females show a higher extinction rate compared to males, in terms of both freezing and USV. Considering freezing, a single mild FS exposure induces a conditioned fear response in males only and reinstatement in both sexes. However, reinstatement of USV emission has been observed only in males. Taken together, the present findings reveal sex differences in trauma response and extinction process in our model of PTSD and underline the importance of 22-kHz USV analysis, in parallel with freezing,to provide a complete index of fear memory.

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P42 Neurobiological vs judiciary truth

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During a trial, judicial practice mobilises elements of a very diverse nature. These aim to establish the judicial truth, which makes it possible to define the responsibilities of the protagonists and the sentence to be applied. While the process thus tends towards objectivity and exhaustiveness, it comes up against the limits of the elements usually taken into account, notably the fallibility of human memory and intentional concealment. However, neurobiological evidence tends to upset this balance. Before it, DNA had been considered the "queen of evidence", leading some to say that solving crimes would now be easy. More generally, the history of modern judicial practice is marked by a permanent quest for tools that make it possible to overcome the intrinsic limits of the search for judicial truth. Yet the neurobiological element may seem to escape these ambivalences. Not only would it become possible to know a truth that escapes even the accused or that they want to hide, but the delicate question of criminal responsibility in the face of mental disorders would also be resolved thanks to these technologies. In this sense, the presentation will attempt to demonstrate the interests and limitations of neurobiology in relation to the main principles of forensic evidence and judicial truth. In particular, based on certain case studies, it will show the classic risks of the unconditional use of such tools but also, more fundamentally, to outline the more substantial changes that recourse to neurobiology would produce in the very conception of the judicial trial.

P43 Examination of pituitary adenylate cyclase-activating polypeptide in Parkinson's disease focusing on correlations with motor symptoms

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The neuroprotective effects of pituitary adenylate cyclase-activating polypeptide(PACAP) have been shown in numerous in vitro and in vivo models of Parkinson's disease(PD) supporting the theory that PACAP could have an important role in the pathomechanism of the disorder affecting mostly older patients. Earlier studies found changes in PACAP levels in neurological disorders, therefore, the aim of our study was to examine PACAP in plasma samples of PD patients. Peptide levels were measured with ELISA and correlated with clinical parameters e.g. age, stage of the disorder based on the Hoehn and Yahr (HY) scale, subtype of the disease, treatment and specific scores measuring motor and non-motor symptoms, such as Movement Disorder Society-Unified Parkinson's Disease Rating Scale(MDS-UPDRS), Epworth sleepiness scale(ESS), Parkinson's disease sleep scale(PDSS-2) and Beck-Depression Inventory(BDI). Our results showed significantly decreased PACAP levels in PD patients without deep brain stimulation (DBS) therapy and in akinetic-rigid subtype, additionally we also described further decrease in the HY stage 3 and 4. Elevated PACAP levels were found in patients with DBS. There were no significant correlations in PACAP level with MDS-UPDRS, type of pharmacological treatment, PDSS-2 sleepiness and depression (BDI) scales, but we found increased PACAP level in patients with more severe sleepiness problems based on the ESS scale. Based on these results we suggest that following the alterations of PACAP with other frequently used clinical biomarkers in PD patients might improve strategic planning of further therapeutic interventions and help to provide a clearer prognosis regarding the future perspective of the disease.

P44 A new potential therapeutic target in inflammatory retinopathy

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Retinal inflammation may lead to visual impairment, even blindness in most severe cases. Pituitary adenylate cyclase activating polypeptide (PACAP) is a neuropeptide, which has strong neuroprotective and general cytoprotective effects. It can also be found in the eye and it is involved in several ocular processes. Three receptors can be distinguished, however the specific PAC1 receptor plays the key role in its protective mechanisms. Our aim is to investigate the effectiveness of a specific, exogenous PAC1 receptor agonist agent, maxadilan, in inflammatory retinopathy. Inflammation was induced by bacterial lipopolysaccharide in mice. Maxadilan was administered by intravitreal injection. Optical coherence tomography was used to follow the changes in thickness of all retinal layers. Change of ganglion cell

number was evaluated after toluidine blue staining. Electroretinography provided functional information. Expression level of forty different types of cytokines was also analyzed. Our data show that maxadilan is able to prevent the decrease of the outer nuclear layer, outer plexiform layer, inner nuclear layer, inner plexiform layer and the photoreceptor layer. In addition, it improves the functional outcome. Significant ganglion cell degeneration was observed in inflamed group. However, ganglion cell number remained similar to control group after maxadilan treatment. Based on our results, PAC1 receptor-mediated signaling pathways significantly influence the level of several cytokines and chemokines. The specific, exogenous PAC1 receptor agonist maxadilan prevents the morphological and functional damage in inflammatory retinopathy. Based on our results PAC1 receptor is a new possible therapeutic target in this disease.

P45 Octadecaneuropeptide promotes the migration of astrocyte via ODN metabotropic receptor and calcium signaling pathway

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Background: Astrocytes specifically synthesize and release endozepines, a family of regulatory peptides, including the octadecaneuropeptide (ODN). ODN promotes proliferation and prevents oxidative damage induced cell death apoptosis on both neurons and astrocytes. However, little is known regarding the effects of ODN on neuronal cell migration. Migration is an essential characteristic of cells that occurs during many physiological and pathological processes. The purpose of the present study was to investigate the potential effect of ODN in induction of astrocytes migration, which is critical for formation of neurons during development and maintaining brain homeostasis
Materials/Methods To investigate the effect of ODN on cell migration, we used the wound healing technique. Then the wound edges were remicrographed 48 after treatment. Images of migratory cells from the scratched boundary were observed at 48h with different concentrations of ODN and using an inverted microscope. We measured astrocyte cells viability following injury with the fluorescein diacetate (FDA) and the thiazolyl blue tetrazolium blue (MTT) Assay with different concentrations of ODN. We therefore investigated the effect of ODN on intracellular Ca2+ levels. Finally, we tried to provide a new insight into the effect of ODN on mTOR gene expression for cell migration through RT-qPCR (luna universal One –step RT-qPCR kit) and data were corrected using the reference gene GAPDH.
Results: In the wound healing assay, the representative photomicrograph images of cultured astrocytes showed that administration of graded concentrations of ODN (10^{-16} to 10^{-8} M)

increased cell migration in a dose-dependent manner and adhesion. The effect of ODN in migration was maximal after 48 h of treatment and at very low concentrations. We have also observed that effect of ODN that was abrogated by the metabotropic ODN receptor antagonist cyclo1–8[DLeu5]OP, but not by the CBR antagonist flumazenil. We have also found that the metabotropic ODN receptor, which is positively coupled to adenylyl cyclase in astrocytes, activates calcium-signaling pathways. Downstream of calcium signaling pathways, ODN induced ERK phosphorylation, which in turn activated the expression of the anti-apoptotic TOR gene. **Conclusion**: These findings indicate that ODN potent action of ODN on astrocyte migration involves the metabotropic ODN receptor coupled to the Calcium/PKA/ERK-kinase pathway to inhibit TOR gene expression. Our results suggest that ODN may participate in the brain remodling during injuries such as brain wound healing.

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P46 Effects of binge alcohol exposure on the hippocampus in adolescent and adult mice

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Binge drinking refers to the consumption of alcohol, where a large amount is consumed within a period, with the intention of getting intoxicated quickly. This behavior is often associated with consuming drinks in than two hours. The goal of this study was to compare the effects of binge alcohol exposure on the hippocampus in adolescent and adult mice focusing on oxidative stress, neuroinflammation and cognitive abilities. To create a mouse model that mimics binge drinking ethanol was injected into mice three times through their peritoneum to maintain levels of alcohol for at least six hours. We selected 31 genes related to stress and neuroinflammatory mechanisms in order to examine their regulation in the brains of adolescent (P30) and adult (P95) mice four hours after treatment. Spectrophotometry was used to determine the activity of antioxidant systems and measure damage. Microfluorimetry allowed us to assess cell viability and accumulation of oxygen species (ROS). Anxiety levels, as memory and learning abilities were evaluated using the Barnes maze, T maze and elevated plus maze tests. Excessive drinking, in mice has been found to cause serious issues related to inflammation, oxidative stress and cognitive function. These complications include memory and cognition disruption in brain development heightened susceptibility to disorders and changes, in synaptic plasticity. Moreover alcohol can interfere with the brains ability to adapt and change. Elucidation of the cellular mechanisms of alcohol neurotoxicity will allow to understand the risks related to consumption according to age in order to propose a prevention message.

P47 Neuroinflammatory Mechanisms of Pain Hypersensitization in a Mouse Model of Attention-Deficit/Hyperactivity Disorder (ADHD)

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Attention-deficit/hyperactivity disorder (ADHD) is a complex neurodevelopmental disorder characterized by symptoms of inattention, hyperactivity, and impulsivity. It is one of the most common childhood disorders, with 8,4% of children diagnosed worldwide (APA, 2021). Clinical evidence suggests that pain hypersensitivity develops in subjects with ADHD. However, the mechanisms and neural circuits involved in these interactions remain unknown. We previously validated a mouse model of ADHD obtained by neonatal 6-hydroxydopamine (6-OHDA) intracerebroventricular injection. Here, we show that 6-OHDA mice exhibited a marked sensitization to thermal and mechanical stimuli, suggesting that ADHD conditions increase nociception. In addition, sensitization to pathological inflammatory pain is amplified in 6-OHDA mice as compared to shams. Moreover, by combining in vivo electrophysiology, optogenetics, and behavioral analyses, we demonstrated that the anterior cingulate cortex (ACC) hyperactivity alters the 'ACC – posterior insula' circuit, and triggers changes in spinal networks that underlie pain sensitization. We make the hypothesis that neuroinflammation is a major factor triggering ACC hyperactivity and the comorbidity between ADHD and pain. By using multiple techniques such as immunofluorescence staining and RT-qPCR, we demonstrated microglial and astrocytic activation and identified markers of inflammation and oxidative stress in different brain regions. Through high-throughput and unbiased phosphoproteomic assays, we also demonstrated changes in kinase activity under ADHD conditions. The identification of shared mechanisms, engaging overlapping neuronal circuits and inflammation, and underlying both disorders, is key to better treatments.

P48 Prenatal restraint stress affects maternal behavior, early neurobehavioral response and oxidative stress in mice pups

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Prenatal stress (PS), in both humans and animals, presents a potential risk threatening the mother and her fetus throughout gestation. PS is always associated with physiological changes that alter embryonic development and predispose the individual to lifelong health problems, including susceptibility to mental illness. The purpose of this study is to identify the deleterious effects of restraint stress (PRS) which is commonly employed to induce stress during gestation. This stress is applied to pregnant Swiss albino mice from E7.5 to parturition for three hours

daily. This study is mostly interested in neurodevelopment, especially the neurodevelopmental reflexes using a battery of developmental tests such as Surface righting reflex, Cliff avoidance, Negative geotaxis, and finally Swimming development. Our results show that PS affected the weight gain of dams as well as some of their maternal behaviors including nesting. As far as offspring are concerned, this stress appears to play a major role in the impairment of different neurobehavioral responses such as the delay of some reflexes. These alterations were accompanied by an increase in the level of Malondialdehyde activity (MDA) at PND17 and 21, and a downregulation of AchE activity in the whole brain of pups in postnatal days 7,9, and 13. These findings demonstrated that PS causes deleterious neurodevelopmental impairments that can alter a wide range of behaviors later in life.

P49 Chronic Exposure to Inorganic Mercury Affects Neurobehavioral and Oxidative Stress in Female Mice

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Mercury is known as one of the most neurotoxic elements. Contamination with mercury is a real health issue for Humans with physiological and neurobehavioral consequences. The present study aims to evaluate the neurotoxicological effect of chronic exposure to mercuric chloride (HgCl2) on mice. Both mating male and female mice were divided into two groups; the treated groups were exposed to a low level of metal in drinking water; treatment continued throughout gestation, lactation, and during the adult period when their behavior and antioxidant status were analyzed. Our Results indicated that HgCl2 decreased body weight and food intake, as well as increased anxiety-like behavior in treated animals compared to controls, and impaired motor performance. In addition, the treated group displayed reduced spatial working and recognition memory. The enzymatic activity of the antioxidant system was assessed in eight brain structures, including the cerebral cortex, olfactory bulb, hippocampus, hypothalamus, and cerebellum. The results show that chronic exposure to HgCl2 caused alternations in the activity of catalase, thioredoxin reductase, glutathione peroxidase, superoxide dismutase, and glutathione S-transferase, accompanied by peroxidation of membrane lipids, indicating a disturbance in intracellular redox homeostasis with subsequent increased intracellular oxidative stress.

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