EBPS2025 Biennial Meeting

17-20th September, 2025

Almería, Spain

Program and Abstracts

EUROPEAN BEHAVIOURAL PHARMACOLOGY SOCIETY

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Welcome to #EBPS2025 Almería!

Dear EBPS 2025 Attendees,

It is our great pleasure to welcome you to the 21st Biennial Meeting of the European Behavioural Pharmacology Society (EBPS), taking place from 17–20 September 2025 in the sunny coastal city of Almería, Spain.

We are excited to share a rich and diverse scientific program, including:

- 3 Plenary Lectures
- 2 Awardee Talks
- 2 Featured Symposia
- 24 Parallel Symposia
- 3 Nanosymposia
- 170 Poster Presentations

In addition, we invite you to attend a satellite event on 17 September titled *"From Bench to Bedside: How to Improve the Translational Aspect of Your Research".* This event is free for registered trainees and postdoctoral fellows.

Both EBPS and the Local Organizing Committee are deeply committed to the principles of **Inclusion, Diversity, Equity, and Accessibility (IDEA)** in science. These values are central to our mission and essential to the vitality of our field. We are proud of the diverse representation throughout this year's program—including participants at various career stages and from countries that have historically been underrepresented at EBPS meetings.

This year, we received over 100 applications for travel grants. Thanks to the generous support of EBPS, Aelis Farma, Med Associates, and *Psychopharmacology*, we are thrilled to support 24 awardees from around the globe. Our awardees represent Australia, Brazil, Cameroon, Canada, France, Germany, Iran, Ireland, Nigeria, Spain, the United Kingdom, and the United States.

Further support from Aelis Farma has enabled us to offer **on-site childcare at no cost** to attendees traveling with families. We hope this effort helps to reduce stigma and demonstrates that family care and a research career can be compatible.

Throughout the meeting, you will find several IDEA-focused activities addressing topics such as:

- Work–Life Balance
- Animal Research Ethics
- Language Barriers in Science
- Impostor Syndrome

We encourage your participation in these sessions so we can learn from one another and grow as a community.

Finally, we are pleased to continue our **Mentor–Mentee Program**, designed to help trainees expand their networks and access mentorship during the meeting and beyond.

We look forward to a stimulating and inclusive meeting, filled with scientific discovery, collaboration, and community.

We hope you enjoy #EBPS2025!

Shelly Flagel, President of EBPS
Margarita Moreno, Chair of the Local Organizing Committee

MEETING ORGANIZATION

Chairs of the Local Organizing Committee

Margarita Moreno Montoya (Chair)
María del Pilar Flores Cubos (Co-chair)
Ana Sanchez Kuhn (Co-chair)
Elena Martín González (Co-chair)

Local Organizing Committee Team

Abel Fabrega Leal
Álvaro López Villegas
Ángel García Pérez
Antonio José Rodríguez Sánchez
Cristian Antonio Pérez Fernández
Darío Puertas López
Diego Ruiz Sobremazas
Isabel Galiana Camacho
Manuela Olmedo Córdoba
Mara Morales González
María del Rocío Rodríguez Herrera
Mario Ruiz Coca
Miguel Morales Navas
Nerea Rios Nieto
Neus Ibáñez Sempere
Paula Bermúdez Martínez
Roberto Álvarez Gómez
Rocío Rodulfo Cárdenas

ACKNOWLEDGMENTS

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Aelis Farma
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Cajamar
Med Associates Inc
Metris
Psychopharmacology
OTRI, Universidad de Almería
Vicerrectorado de Igualdad, Inclusión y Compromiso Social, Universidad de Almería
Dept. Psicología, Universidad de Almería
Facultad de Psicología, Universidad de Almería
EIDUAL, Universidad de Almería
Escuela de Master, Universidad de Almería

GENERAL INFORMATION

Meeting venue

Location: Palacio de Exposiciones y Congresos Cabo de Gata – Ciudad de Almería.
Address: C. de los Juegos de Casablanca, 1, 04131 Almería, Spain
Email: ebps2025@ual.es
Link to location in Google Maps

Registration

Date and time: Wednesday, September 17 – from 12:00 to 15:00 PM at Main Hall of Palacio de Exposiciones y Congresos Cabo de Gata – Ciudad de Almería

Badges

Badges must be always worn during the meeting.
No one will be admitted to the Congress Palace without a badge, for security reasons.

Lectures and Symposia

Plenary Lectures and **Featured Symposia** will take place in **Sala 1 – Las Salinas**.
Symposia and **Nanosymposia** will be distributed across three parallel rooms:
Sala 1 Las Salinas
Sala 2 Nueva Almería
Sala 4 La Fabriquilla

The Chairs of the Symposia are responsible for upload all Speaker's presentations via a link to a specific folder corresponding to their session in a Google drive. Chairs and Speakers can ask the organizers or check on the laptop located next to the registration desk if all presentations have been uploaded. This needs to be done at least 60 min prior to the start of the session. The presentations need to be in PowerPoint or PDF format. Chairs and Speakers must also plan to be in their session room at least 20 minutes prior to start time to check their presentations.

Posters

The **poster area** is in **Sala 5 Las Almoladeras**. Posters should be in place before 11:00 AM on the day of presentation. Presentations will take place between 13:00 and 15:00. Presenters are expected to be available at their posters **during the first hour (for even numbers)** and the **second hour (for odd numbers)** for discussion and questions. Posters should be removed before 18:00 on the day of the presentation session.

Catering / Coffee Breaks

Coffee breaks will take place at the **Main Hall (Ground Floor)**.
Opening reception and **Lunch** service will take place at the **Plaza Interior (-1 Floor)**.
Food, refreshments, coffee and tea will be available for free for registered participants.
If you would like to include a Guest or have any food restrictions or allergies that you did not inform us of previously, please contact the Local Organizing Committee at ebps2025@ual.es

Internet

RED WIFI: EBPS2025 guest
PASSWORD: almeria2025

Mobile Phones

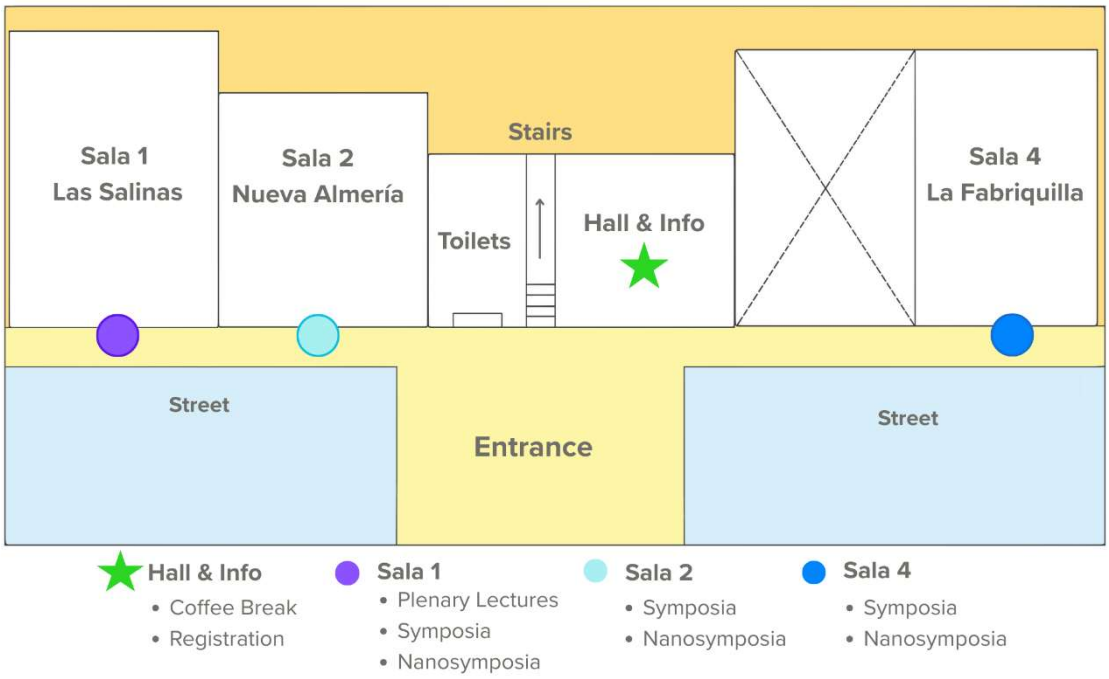
To avoid disruptions, please have your phone in silent mode throughout the meeting. Phone calls are not allowed inside session rooms.

Abstract Book & Attendance certificates

The book of abstracts is available online at the www.ebps2025.com website.
Attendance certificates will be sent by email to each attendee once the meeting has concluded. If an attendee needs a certificate of poster or talk presentation you can ask for them by email ebps2025@ual.es.

MAP OF THE VENUE

GROUNDFLOOR



FLOOR -1

Wednesday 17th Sept	Thursday 18th Sept	Friday 19th Sept	Saturday 20th Sept
	8:30-9:15 Plenary Lecture Angela Roberts	8:30-9:15 Plenary Lecture Marta Miquel	9:00-9:45 Plenary Lecture John Cryan
10:00-14:00 Pre-meeting Workshop	9:30-11:00 Featured Symposia 1	9:30-11:00 Featured Symposia 2	10:00-11:30 Parallel Symposia S19, S20 & S21
12:00-15:00 Registration Opens	11:00-11:30 Coffee Break	11:00-11:30 Coffee Break	11:30-12:00 Coffee Break
13:30-14:30 By invitation, EBPS Full Committee Meeting	11:30-13:00 Parallel Symposia S1, S2 &S3	11:30-13:00 Parallel Symposia S10, S11 & S12	12:00-13:30 Parallel Symposia S22, S23 & S24
15:00-15:10 Welcome EBPS 2025	13:00-15:00 Lunch & Posters 14:00-15:00 Roundtables	13:00-15:00 Lunch & Posters 14:00-15:00 Roundtables	13:30-13:45 Closing Remarks
15:10-16:10 Travel Award Data Blitz	15:00-16:30 Parallel Symposia S4, S5 & S6	15:00-16:30 Parallel Symposia S13, S14 & S15	14:00-14:30 EBPS Executive Committee Meeting
16:10-17:15 IDEA Panel Marianne Jöels	16:45-18:15 Parallel Symposia S7, S8 & S9	16:45-18:15 Parallel Symposia S16, S17 & S18	
17:00-17:30 Coffee Break Mentor-Mentee Meeting	18:30 - 19:30 Parallel Nanosymposia	18:30-19:15 EBPS General Assembly, All Members	
17:45-19:15 Awardee Ceremony Ida Fredriksson Thedora Duka		20:30 Gala Dinner	
19:15 - 19:30 Welcome Local Authorities 19:30 - 21:30 Opening Reception			

PROGRAM

Wednesday, 17th September 2025

10:00 - 14:00 Pre-meeting Workshop (Sala 6 San Telmo)
From Bench to Bedside: How to Improve the Translational Aspect of Your Research
Organized by Merce Correa and Lucía Hipólito *(Spain)*

Computational Techniques to Measure Behaviour
Santiago Mora and **Anna Stuckert** *(United Kingdom)*
** Includes a short coffee break*

Meet the Experts: Improve Your Skills in Translational Science
Trevor Robbins *(UK),* **John Salamone** *(USA)* and **Paula Banca** *(Portugal)*
Panel discussion + Q&A + brief interactive exercise

13:30 - 14:30 By invitation, EBPS Full Committee Meeting

12:00 - 15:00 Registration (Hall of Palacio de Congresos Cabo de Gata)

15:00 - 15:10 Welcome Remarks (Sala 1 Las Salinas)

Shelly Flagel, EBPS President *(USA)*
Margarita Moreno Montoya, EBPS2025 Chair *(Spain)*

15:10 - 16:10 Travel Awardee Data Blitz (Sala 1 Las Salinas)
Chair: Leah Mayo *(Canada)*

16:10 - 17:15 Elevating Global Perspectives in Neuroscience: Barriers, Opportunities, Action. Panel on Inclusion, Diversity, Equity and Accessibility ✪ IDEA activity **(Sala 1 Las Salinas)**
Chair: Marco Venniro (Italy)

Plenary Speaker: Marianne Jöels *(Netherlands)*
IDEA Panelists: Tania Romacho *(Spain),* **Stephanie Garnier** *(France)*, **Ana Deutsch** (Canada) **and Luis Contreras** *(Canada)*

17:15 - 17:45 Break and Mentor-Mentee meeting (Sala 1 Las Salinas)

17:45 – 19:15 Awardee Ceremony (Sala 1 Las Salinas)
Chairs: Shelly Flagel and Aldo Badiani (Italy)

Early Career Investigator Award lecture - Ida Fredriksson *(Sweden)*
The role of the ventral subiculum and claustrum in incubation of opioid craving

Distinguished Investigator Award lecture - Theodora Duka *(United Kingdom)*
A life on the borders of drug addiction

19:15 – 19:30 Welcome from the Local Authorities (Sala 1 Las Salinas)
Chair: Margarita Moreno (Spain)

Jose Antonio Sánchez Pérez, Vice-chancellor of Scientific Policy
Universidad de Almería *(Spain)*
Vanesa Lara de la Cruz, Deputy Councilor for Economy, Innovation and Procurement
Almeria City Council *(Spain)*

19:30 - 21:30 Opening Reception (Plaza Interior)

Thursday, 18th September 2025

8:30 - 9:15 Plenary Lecture (Sala 1 Las Salinas)

Prefrontal Regulation of Emotion: Insights into Anhedonia, Anxiety and Pharmacotherapy
Angela C Roberts *(UK)*
Chair: Amy Milton (UK)

9:30 - 11:00 Featured Symposia 1 (Sala 1 Las Salinas)
EBPS Chair: Shelly Flagel *(USA)*

Global Perspectives on Neuropsychiatric Research: Stress, Cognition, and Innovative Therapeutics
Session Chair: Princess Felix *(USA)*

Vidita Vaidya *(India)*
FS.1.1 - Neurocircuitry and molecular regulation of stress and emotion in mood disorders
Oritoke Okeowo *(Nigeria)*
FS.1.2 - Novel pharmacological approaches for stress related disorders
Inna Gaisler-Salomon *(Israel)*
FS.1.3 - Glutamate dysregulation, stress and cognitive dysfunction: novel therapeutic venues
Gwladys Ngoupaye *(Cameroon)*
FS.1.4 - Cameroonian medicinal plants: mechanistic insights on stress-induced cognitive deficits

11:00 - 11:30 Coffee Break (Hall)

11:30 - 13:00 Parallel Symposia

Symposium 1 • Endocannabinoids and Sex-dependent Behavior: Insights from Development to Adulthood (Sala 1 Las Salinas)
Chair: Carmen Sandi *(Switzerland)*

Miriam Melis *(Italy)*
S.1.1 - Sex-specific phenotypes induced by prenatal perturbation of endocannabinoid signaling
Olivier Manzoni *(France)*
S.1.2 - Lifelong sex-specific impacts of prenatal cannabis exposure
Arnau Busquets Garcia *(Spain)*
S.1.3 - Cannabinoid receptors and higher-order conditioning
Silvie Ruigrok *(Switzerland)*
S.1.4 - Estrous cycle modulation of anxiety and motivation - focus on the endocannabinoid system

Symposium 2 • Recent Advances in Addiction Vulnerability in Animal Models and Humans
(Sala 2 Nueva Almería)
Chair: Ginevra D'Ottavio *(USA)*

Nazzareno Cannella *(Italy)*
S.2.1 - Multisymptomatic screening reveals differences of addiction behavior and treatment outcome
Ginevra D'Ottavio *(USA)*
S.2.2 - Exploring addiction vulnerability in preclinical models using drug vs social choice tasks
Irene Perini *(Sweden)*
S.2.3 - Choice preference for alcohol over a natural reward in heavy versus light drinkers
Philip Jean-Richard Dit Bressel *(Australia)*
S.2.4 - A cognitive pathway to maladaptive choice.

Symposium 3 • A Translational Perspective on Safety Learning and Safety Behaviours
(Sala 4 La Fabriquilla)
Chair: Joanna Yau *(Australia)*

Heidi Meyer *(USA)*
S.3.1 - Experience with safety learning can scale later fear responding
Alba López Moraga *(Belgium)*
S.3.2 - Differential effects of chronic stress on active avoidance procedures
Emma Cahill *(United Kingdom)*
S.3.3 - Hypervigilant responses to ambiguous threat cues by rats
Sarah Tashjian *(Australia)*
S.3.4 - vmPFC integration of safety information in humans

13:00 - 15:00 Posters and Lunch
Sala 5 Las Amoladeras and Plaza Interior

14:00 - 15:00 Roundtables ✪ IDEA activity

Work-Life Balance for Women in Science (Sala 6 San Telmo)
Leah Mayo *(Canada)* & Leslie Ramsey *(USA)*

Language Barriers as an International Scientist (Sala 7 Las Conchas)
Marco Venniro *(USA)* & Paula Banca *(Portugal)*

15:00 - 16:30 Parallel Symposia

Symposium 4 • Innovations and Challenges of Psychedelics in Behavioral Health Disorders
(Sala 1 Las Salinas)
Chair: Harriet de Wit *(USA)*

Kathryn Cunningham *(USA)*
S.4.1 - Probing mechanisms and novel 5-HT2R modulators as psychedelic-inspired therapeutics for cocaine use disorder
Charles Nichols *(USA)*
S.4.2 - Novel 5-HT2A receptor agonists with treatment potential without acute behavioral effects
Friederike Holze *(Switzerland)*
S.4.3 - Clinical pharmacology of different psychedelic drugs in healthy human volunteers
Leah Mayo *(Canada)*
S.4.4 - Challenges and opportunities in psychedelic clinical trial design

Symposium 5 • Using Computational & Cognitive Methods to Study Substance Use Over the Addiction Course (Sala 2 Nueva Almería)
Chair: Justin Strickland *(USA)*

Justin Strickland *(USA)*
S.5.1 - Evaluating value-based decision-making mechanisms underlying opioid use disorder
Amber Copeland *(UK)*
S.5.2 - Modelling changes in value-based decision-making in response to contingency management
Samuel Acuff *(USA)*
S.5.3 - Exploring trajectories between behavioral economic reward and cannabis use
José C. Perales *(Spain)*
S.5.4 - The role of emotion regulation mechanisms in gambling and gaming craving

Symposium 6 • Motivational and Cognitive Effects of Manipulating the Dopamine Transporter: Potential Therapeutic Actions of Atypical DAT Inhibitors **(Sala 4 La Fabriquilla)**
Chair: Mercè Correa *(Spain)*

Mercè Correa *(Spain)*
S.6.1 - Vigor and work selection after bupropion administration in mice
John D. Salamone *(USA)*
S.6.2 - Effort-related motivational effects of novel atypical DAT inhibitors in rats of both sexes
Marta Pardo *(Spain)*
S.6.3 - DAT transgenic rats as a new model for vulnerability to stress

16:45 - 18:15 Parallel Symposia

Symposium 7 • From Synapse to Nucleus: An Integrated View of Neuronal Ensembles
(Sala 1 Las Salinas)
Chair: F. Javier Rubio *(USA)*

F. Javier Rubio *(USA)*
S.7.1 - Plasticity changes in synapses from neuronal ensembles: seeking the synaptic ensemble
Eisuke Koya *(UK)*
S.7.2 - Environmental enrichment suppresses food seeking and induces Prelimbic ensemble overdrive
Leslie Ramsey *(USA)*
S.7.3 - Searching for the engram in prefrontal cortical neuronal ensembles: mechanisms that mediate drug and social learning
Sophie Tronel *(France)*
S.7.4 - Looking for the engram of PTSD-like memory: focus on the role of NMDA receptors of the Anterior Cingulate cortex in traumatic memory maintenance

Symposium 8 • New Insights on Individual Differences in Pain and Interoception Using Dense Sampling Techniques in Humans **(Sala 2 Nueva Almería)**
Chair: Siri Leknes *(Norway)*

Siri Leknes *(Norway)*
S.8.1 - Understanding individual treatment effects through dense sampling N-of-1 single case experimental designs: a primer
Micah Allen *(Denmark)*
S.8.2 - Brain-gut functional interactions in response to semagludide treatment: a dense sampling N-of-1 fMRI study
Julie Klinke *(Sweden)*
S.8.3 - Neural learning mechanisms in the development of nociplastic pain: a dense sampling prospective longitudinal study of chronic non-specific pain
Marie Eikemo *(Norway)*
S.8.4 - Predicting opioid responses and opioid use in surgery patients in the U.S. and Norway

Symposium 9 • Behavioural and Neurobiological Mechanisms of Choice in Rodent Models of Addiction **(Sala 4 La Fabriquilla)**
Chair: Nathan Marchant (Netherlands)

Nathan Marchant *(Netherlands)*
S.9.1 - Role of anterior Insula cortex in choice between alcohol and social reward
Marco Venniro *(USA)*
S.9.2 - Neurobiological mechanisms mediating social and drug craving
Youna Vandaele *(France)*
S.9.3 - Investigation of the decision-making processes underlying choice between drug and nondrug rewards
Jamie Peters *(USA)*
S.9.4 - Mu opioid receptors and heroin vs. alcohol choice

18:30 - 19:30 Parallel Nanosymposia

Nanosymposium 1 • Amyotrophic Lateral Sclerosis: From the Bench to the Clinic (Sala 1 Las Salinas)
Chair: Santiago Mora *(UK)*

Xavier Navarro *(Spain)*
N.1.1 - Pharmacological targeting Kv7 and TSPO as a therapeutical strategy for ALS
Beatriz Vélez-Gómez *(Spain)*
N.1.2 - Comprehensive pharmacological approach in ALS: quality of life beyond motor symptoms
Ilary Allodi *(UK)*
N.1.3 - Gene therapy strategies for the treatment of Amyotrophic Lateral Sclerosis

Nanosymposium 2 • Cannabinoid Regulation of Behaviour: Addiction, Cell Specificity and Development (Sala 2 Nueva Almería)
Chair: Alejandro Higuera-Matas *(Spain)*

Luigi Bellocchio *(France)*
N.2.1 - Cellular and sub-cellular targets of cannabinoids: from signaling to behavior and beyond
Mireia Medrano *(Spain)*
N.2.2 - The role of PPAR-gamma as a modulator of cocaine-seeking behaviour in male and female mice
Alejandro Higuera-Matas *(Spain)*
N.2.3 - Exposure to cannabinoids during adolescence as a risk factor for psychopathology
Erika Zamberletti *(Italy)*
N.2.4 - Sex-dependent consequences of adolescent exposure to different THC and CBD combinations

Nanosymposium 3 • Beyond D1 and D2 Dopamine Receptor-Expressing Neurons: Modulating Circuits and Behavior (Sala 4 La Fabriquilla)
Chair: Michelle W. Antoine *(USA)*

Bernard Le Foll *(Canada)*
N.3.1 - Dopamine D3 receptors in nicotine addiction: from preclinical to clinical studies
Melissa Perreault *(Canada)*
N.3.2 - Exploring the functional role of Gq-Coupled dopamine receptors in the brain
Michelle W. Antoine *(USA)*
N.3.3 - Roles of striatal neurons co-expressing dopamine D1/D2 receptors in autism mouse models

Friday, 19th September 2025

8:30 - 9:15 Plenary Lecture (Sala 1 Las Salinas)

Cerebellar Modulation of Drug-Induced Reward: How Cinderella Came to the Ball
Marta Miquel *(Spain)*
Chair: Margarita Moreno *(Spain)*

9:30 - 11:00 Featured Symposia 2 (Sala 1 Las Salinas)
EBPS Chair: Shelly Flagel *(USA)*

Advanced Technologies and Big Data in Behavioral Pharmacology and Psychiatry
Session Chair: Brenda Curtis *(USA)*

Brenda Curtis *(USA)*
FS.2.1 - Digital surveillance for substance use trends: social media and behavioral data analysis
Peter R. Chai *(USA)*
FS.2.2 - Smartphone phenotypes of PrEP adherence in substance use
Ignacio Obeso *(Spain)*
FS.2.3 - Neurocognitive dynamics in pre-addiction states using big data and neurotechnology
Stephanie Carreiro *(USA)*
FS.2.4 - Craving-based digital phenotyping for MOUD pharmacovigilance

11:00 - 11:30 Coffee Break (Hall)

11:30 - 13:00 Parallel Symposia

Symposium 10 • Triggered Temptations: New Findings on How Environmental Cues Fuel Addiction and Gambling (Sala 1 Las Salinas)
Chair: Anne-Noel Samaha *(Canada)*

Anne-Noel Samaha *(Canada)*
S.10.1 - Modeling cue-triggered relapse to cocaine use in rats
Muhammad Parvaz *(USA)*
S.10.2 - Neurobiology of incubation of cue-reactivity in individuals with stimulants use disorders
Catharine Winstanley *(Canada)*
S.10.3 - Win-paired cues drive risky choice through divergent mechanisms in male and female rats
Rajita Sinha *(USA)*
S.10.4 - Drugs, stress cues or both? Prospective effects on craving and drug use in the real world

Symposium 11 • Neurohormonal Dysregulations Underlying Alcohol and Opioid Use Disorders
(Sala 2 Nueva Almería)
Chair: Brendan Tunstall *(USA)*

Brendan Tunstall *(USA)*
S.11.1 - Oxytocin against hyperalgesia and intensified alcohol drinking in alcohol dependence
Daniele Caprioli *(Italy)*
S.11.2 - Targeting gut microbiota to regulate heroin induced gut dysbiosis and addiction behaviors
Brandon Warren *(USA)*
S.11.3 - Novel MOR-partial agonist against opioid self-administration, withdrawal, and pain
Hayley Manke *(USA)*
S.11.4 - Role of PKCε in alcohol dependence

Symposium 12 • Pharmacology and Neural Mechanisms of Comorbid Pain and Drug Use
(Sala 4 La Fabriquilla)
Chair: Nicholas W. Gilpin *(USA)*

Lucía Hipólito-Cubedo *(Spain)*
S.12.1 - Modeling negative affective states comorbid with pain and drug intake: insights from rat models and translational perspectives
Jose Moron-Concepcion *(USA)*
S.12.2 - Sex-specific effects of inflammatory pain on fentanyl self-administration and modulation by ovarian hormones
Anushree Karkhanis *(USA)*
S.12.3 - Nucleus Accumbens at the Intersection of Adolescent Alcohol Use and Pain in Adulthood
Nicholas W. Gilpin *(USA)*
S.12.4 - Vaporized cannabinoid inhalation effects on chronic inflammatory pain outcomes

13:00 - 15:00 Posters and Lunch **(Sala 5 Las Amoladeras and Plaza Interior)**

14:00 - 15:00 Roundtables ⛤ IDEA activity

The Threat on Animal Use in Research **(Sala 6 San Telmo)**
Heidi Lesscher *(Netherlands),* Amy Milton *(United Kingdom)*, Lucía Hipólito *(Spain)* and Christelle Baunez *(France)*

Imposter Syndrome **(Sala 7 Las Conchas)**
Connor Haggarty *(USA)* & Marco Venniro *(USA)*

15:00 - 16:30 Parallel Symposia

Symposium 13 • The Stress of the Trip: Interactions between Psychedelics and the Stress Response
(Sala 1 Las Salinas)
Chair: Ana Deutsch *(Canada)*

Ana Deutsch *(Canada)*
S.13.1 - The impact of LSD and MDMA on stress-related biomarkers & the eCB system in healthy humans
Sarah Gibson Cook *(Canada)*
S.13.2 - Psilocybin induces sex- and context-specific recruitment of the stress axis
Helena Aicher (Switzerland)
S.13.3 - Impact of Ayahuasca-inspired DMT/Harmine formulation on stress reactivity & the ANS in healthy Humans

Symposium 14 • Beyond Reward Prediction Error: Translational Conceptualizations, Findings, and Applications that Shed a New Light on Dopamine's Function in Complex Behavior
(Sala 2 Nueva Almería)
Chair: Rita Z. Goldstein *(USA)*

Vijay Mohan K Namboodiri *(USA)*
S.14.1 - Extinction and retrospective learning
Geoffrey Schoenbaum *(USA)*
S.14.2 - Striatal dopamine signals errors in cue prediction during sensory preconditioning
Rita Goldstein *(USA)*
S.14.3 - Methylphenidate- and reconsolidation-enhanced drug memory forgetting in human addiction
Roshan Cools (Netherlands)
S.14.4 - Role of dopamine in controllability inference for human cognitive control

Symposium 15 • Addictive Substances and Their Impact on Brain and Molecular Pathways
(Sala 4 La Fabriquilla)
***Chair: Mohamed Kabbaj** (USA)*

Stefania Maccari *(France)*
S.15.1 - Prenatal stress effects on alcohol drinking: role of oxytocin and metabotropic receptors
Mary K Lobo *(USA)*
S.15.2 - Perinatal fentanyl exposure impacts behavioral and brain molecular mechanisms
Mohamed Kabbaj *(USA)*
S.15.3 - Role of medium spiny neurons in ketamine reinstatement
Marcelo Wood *(USA)*
S.15.4 - Investigating the opposing roles of the nuclear orphan receptor NR4A2 in drug-seeking and relapse of drug-seeking

16:45 - 18:15 Parallel Symposia

Symposium 16 • Oxytocin: A Promising Old Acquaintance (Sala 1 Las Salinas)
***Chair: Rossella Ventura** (Italy)*

Valery Grinevich *(Germany)*
S.16.1 - Oxytocin signaling in the prefrontal cortex
Inga D. Neumann *(Germany)*
S.16.2 - Prosocial, anxiolytic, and stress-protective effects of oxytocin in rodents
Bice Chini *(Italy)*
S.16.3 - Long-lasting effects of early life Oxytocin administration in mice models of neurodevelopmental disorders
Simona Cabib *(Italy)*
S.16.4 - Role of oxytocin in the development of the motivational salience neurocircuitry

Symposium 17 • New Insights into Neuromodulatory Underpinnings of Adaptive Behaviour
(Sala 2 Nueva Almería)
***Chair: Philip Jean-Richard-dit-Bressel** (Australia)*

Emmanuel Valjent *(France)*
S.17.1 - Deconstructing the role of dopamine D2 receptors in motivated behaviors
Philip Jean-Richard-dit-Bressel *(Australia)*
S.17.2 - Monoamine release during instrumental versus Pavlovian aversive learning
Laura Corbit *(Canada)*
S.17.3 - Locus coeruleus activity promotes learning updates following changes in reward
Jay Bertran-Gonzalez *(Australia)*
S.17.4 - At D2-neuron's discretion: revealing dominant D2-to D1-neuron modulation in learning

Symposium 18 • The Use of Non-Human Primates in Addiction-Related Research **(Sala 4 La Fabriquilla)**
Chair: Christelle Baunez *(France)*

Daniel Borgatti *(USA)*
S.18.1 - Role of sleep disruption in cognitive impairment associated with methamphetamine use in rhesus monkeys
Paul Czoty *(USA)*
S.18.2 - Nociceptin-orphanin FQ peptide (NOP) receptors as promising targets for substance use disorder medications: evidence from nonhuman primate models.
Christelle Baunez *(France)*
S.18.3 - Motivation for cocaine is reduced by subthalamic nucleus deep brain stimulation in macaques
Anders Fink-Jensen *(Denmark)*
S.18.4 - Effect of semaglutide and other glucagon-like peptide-1 (GLP-1) receptor agonists on alcohol consumption in alcohol-preferring vervet monkeys

18:30 - 19:15 EBPS General Assembly Meeting, All Members **(Sala 1 Las Salinas)**

20:30 Social Event at Hotel Barceló Cabo de Gata (Gala Dinner)

Saturday, 20th September 2025

9:00 - 9:45 Plenary Lecture (Sala 1 Las Salinas)

Bugs, Drugs & Behaviour: Microbiome as a Key Regulator of Brain Function Across the Lifespan
John Cryan *(Ireland)*
Chair: Gavan McNally *(Australia)*

10:00 - 11:30 Parallel Symposia

Symposium 19 • The Role of Prefrontal Cortical Networks in Flexible and Compulsive Reward-Related Behavior (Sala 1 Las Salinas)
Chair: Ingo Willuhn *(Netherlands)*

Catharine Winstanley *(Canada)*
S.19.1 - Frontal contributions to risky choice in rats
Ingo Willuhn (Netherlands)
S.19.2 - Cortico-striatal circuits mediate compulsive behavior in schedule-induced polydipsia
Frank Meye (Netherlands)
S.19.3 - A prefrontal cortex-lateral hypothalamus circuit controls stress-driven food intake
Stephanie Borgland *(Canada)*
S.19.4 - Effect of astrocyte dysfunction in the OFC on goal-directed behaviour

Symposium 20 • The Dual Impact of Cannabis: Chronic and Acute Effects of Cannabinoids on Human Behaviour (Sala 2 Nueva Almería)
Chair: Sara Kroll *(Switzerland)*

Lukas Eggenberger *(Switzerland)*
S.20.1 - Linking THC and CBD hair analytes to cognitive and mental health outcomes
Ziva Cooper *(USA)*
S.20.2 - Sex-dependent effects of cannabis: Does use frequency impact outcomes?
Amir Englund *(UK)*
S.20.3 - The interactive effects of THC and CBD in healthy volunteers and schizophrenia patients
Connor Haggarty *(USA)*
S.20.4 - Harnessing the cannabinoid system for the treatment of PTSD

Symposium 21 • Uncovering the Behavioral and Biological Factors Underlying Individual Differences in Risk for Alcohol Use Disorder (Sala 4 La Fabriquilla)
Chair: Andrew Holmes *(USA)*

Esi Domi *(Italy)*
S.21.1 - Individual differences and neural substrates in compulsive alcohol self- administration
Céline Nicolas *(France)*
S.21.2 - Contribution of the insular cortex to persistent alcohol drinking in mice
Andrew Holmes *(USA)*
S.21.3 - Artificial intelligence-based prediction of individual differences in mouse alcohol binge-drinking
Markus Heilig *(Sweden)*
S.21.4 - Massive single-nucleus transcriptional profiling reveals a novel molecular substrate of compulsive alcohol use

11:30 - 12:00 Coffee Break (Hall)

12:00 - 13:30 Parallel Symposia

Symposium 22 • New Therapies for Psychostimulant Addiction (Sala 1 Las Salinas)
Chair: Malgorzata Filip/Christian P. Müller *(Poland/Germany)*

Malgorzata Filip *(Poland)*
S.22.1 - Cocaine seeking during abstinence: effects of esketamine and Tat-NR2B9c peptide
Judith R. Homberg *(Netherlands)*
S.22.2 - Controlling cocaine reward and self-administration by targeting dopaminergic and serotonergic storage vesicles
Rainer Spanagel *(Germany)*
S.22.3 - Cell type-specific multi-omics analysis of cocaine use disorder in the addiction circuitry reveals new drug targets
Christian P. Müller *(Germany)*
S.22.4 - The pharmacotherapy of psychostimulant use disorders – past, present, and future ideas

Symposium 23 • Sex Differences in the Risk, Pathophysiology, and Treatment of Neuropsychiatric Disorders (Sala 2 Nueva Almería)
Chair: Christina Dalla *(Greece)*

Debra Bangasser *(USA)*
S.23.1 - Sex differences in the effects of early resource scarcity on motivated behavior
Christina Dalla *(Greece)*
S.23.2 - Sex differences in psycho-pharmacological effects of GPER1 estrogen membrane receptor
Patrizia Campolongo *(Italy)*
S.23.3 - Sex differences in fear expression and persistence in an animal model of PTSD
Ivan Nalvarte *(Sweden)*
S.23.4 - Sex hormones, gender, and the aging brain

Symposium 24 • Role of Microglia in Synaptic Plasticity Associated with Substance Use Disorders (Sala 4 La Fabriquilla)
Chair: Daniele Caprioli *(Italy)*

Ingrid Reverte *(Italy)*
S.24.1 - Microglia and AMPA receptor plasticity during cocaine withdrawal
Marie-Eve Tremblay *(Canada)*
S.24.2 - The outcomes of cannabinoids and psychedelics on microglia
Jacqueline Barker *(USA)*
S.24.3 - Neuroimmune mechanisms of dysregulated cocaine seeking in a mouse model of HIV infection
Anne Mathia Klawonn *(Denmark)*
S.24.4 - Microglia in affective and motivational regulation – Striatal circuits and beyond

13:30 - 13:45 Closing Remarks (Sala 1 Las Salinas)

14:00 - 14:30 EBPS Executive Committee Meeting (by invitation including new members)

LIST OF POSTERS

Poster Session 1
Thursday, 18 September • 13:00-15:00
Even numbers presented 13:00-14:00, odd numbers presented 14:00-15:00

P1.1 Ines Erkizia-Santamaria *(Spain)*
Endogenous serotonin modulates psychedelic-like effects of psilocybin in mice

P1.2 Margareth Nogueira *(USA)*
Therapeutic effects of the psychedelic 5-MeO-DMT in opioid use disorder

P1.3 Nathaniel Kregar *(USA)*
Psilocybin disrupts heroin cue reactivity in prefrontal cortex neuronal ensembles

P1.4 Jordi Jornet-Plaza *(Spain)*
Signs of antidepressant-like effects following adolescent ketamine in selectively bred low-responder rats

P1.5 Elena Hernández Hernández *(Spain)*
Characterization of the acute effects of psilocybin in male and female aging mice

P1.6 Adiia Stone *(Canada)*
Challenges with the use of sweet additives in an oral morphine self-administration task in male and female rats

P1.7 Irene Garcia Manzanares *(Spain)*
Novel behavioral approaches to evaluate psychotic-like states induced by Delta-9-Tetrahidrocannabinol in mice

P1.8 Valeria Serra *(Italy)*
Role of the lateral hypothalamus in the hyperdopaminergic phenotype induced by prenatal THC exposure

P1.9 Roberta Leone *(Italy)*
Dysregulation of tryptophan metabolism and the disinhibition of dopamine neurons induced by in utero cannabis exposure

P1.10 Laura Galvez Melero *(Spain)*
A preclinical study evaluating the impact of temozolomide on affective- and cognitive-like responses in adult rats of both sexes

P1.11 Ana Belén Sanz Martos *(Spain)*
Tributyrin reverses the deleterious effect of saturated fat on memory and plasticity in juvenile mice in a sex dependent manner

P1.12 Antonio Pérez-Colorado *(Spain)*
Chronic methylphenidate consumption during adolescence reduces parvalbumin neurons in prelimbic and disrupt long-term attentional maintenance

P1.13 Reyes Martinez Marin *(Spain)*
Behavioral effects of different methylphenidate doses on fear conditioning and locomotor activity in adolescent and adult Wistar rats: sex-specific differences

P1.14 Tylah Doolan *(Australia)*
Deciphering the involvement of the Paraventricular Nucleus in Oxytocin's regulation of methamphetamine addiction behaviours: A chemogenetic approach

P1.15 **Joel Raymond** *(USA)*
Stimulant solutions, sleepless nights: dexamphetamine and lisdexamfetamine suppress binge eating but disrupt sleep in female rats

P1.16 **Alice Minard** *(France)*
Role of the olfactory system in the vulnerability to flavored nicotine addiction in electronic cigarettes

P1.17 **Anita Sikic** *(Canada)*
Discriminative and proteomic effects of nicotine vs cigarette smoke extract in rats

P1.18 **Yaiza Jiménez Marín** *(Spain)*
Ascertaining the behavioral responses induced by different anesthetic drugs administered during adolescence in rats of both sexes

P1.19 **Spatika Jayaram** *(UK)*
Critical periods of development across prefrontal sub-regions: insights from magnetic resonance spectroscopy in marmosets

P1.20 **Sofia Vellere** *(Italy)*
Adolescent social exclusion and fear of missing out on the vulnerability to alcohol and stress-related disorders: a preclinical approach

P1.21 **Camilla Mancini** *(Italy)*
The role of oxytocin in mediating long-term consequences of early attachment disruption

P1.22 **Ann-Sofie Bjerre** *(Australia)*
Neural signatures of social reward: oxytocin and dopamine signalling in the Nucleus Accumbens

P1.23 **Neda Assareh** *(Australia)*
Whole brain activity mapping of the effects of a novel small molecule on chronic social isolation-induced aggression in mice

P1.24 **Marta Pardo** *(Spain)*
Transgenic DAT rat model reveals vulnerability to early life stress and protective effects of exercise on neurobehavioral outcomes

P1.25 **Oritoke Okeowo** *(Nigeria)*
Chronic unpredictable stress alters social behavior in adult male rats: association with serotonergic and dopaminergic changes

P1.26 **Alberto Fernández Teruel** *(Spain)*
Neonatal handling modulates behavioral and neurobiological processes in a genetic rat model of schizophrenia: Age- and strain-dependent effects on frontocortical neuroplasticity

P1.27 **Wei-li Chang** *(USA)*
Neural signatures of impaired behavioral discrimination in the ventral hippocampal CA1 after early life adversity in mice

P1.28 **Lucía Hipólito** *(Spain)*
Effect of peripheral inflammatory insults on anxiety-like behaviour and microglial responses within the mesocorticolimbic system

P1.29 **Amber Besseling** *(UK)*
Effects of sex and inhibitory neuron type on fear memory suppression by extinction

P1.30 Valeria Tarmati *(Italy)*
Genotype-dependent functional role of the anterior and posterior paraventricular Thalamus in the incubation of conditioned fear

P1.31 McKenna Williams *(Ireland)*
The gut microbiota shapes the endocannabinoid system throughout development

P1.32 Lucas Hassib Camina *(Brazil)*
Involvement of gut microbiota in the behavioral therapeutic effects of cannabidiol in an autism animal model

P1.33 Samin Davoody *(Iran)*
Gut-brain axis modulation by Limosilactobacillus reuteri in a maternal separation animal model of autism: exploring underlying mechanisms

P1.34 Carla Ramon Duaso *(Spain)*
Astrocyte dynamics in alzheimer's disease: unraveling sex-, genotype-, and cannabinoid-dependent mechanisms

P1.35 Lorena Roselló-Jiménez *(Spain)*
Noradrenaline and the astrocyte-neuron lactate shuttle: The critical role of β2-adrenergic receptors in glycogenolysis and object recognition memory in female mice

P1.36 Serafina Manila Guzzo *(Italy)*
Guanidinoacetate methyltransferase deficiency in mice: a window into behavioral dysfunction and RNA therapy potential

P1.37 Amelie Essmann *(USA)*
Deciphering the effects and neurochemical identity of projections into the nucleus accumbens

P1.38 Javier Cuitavi *(Ireland)*
Age-related changes in the metabolic and cognitive effects of systemic Tumour Necrosis Factor α

P1.39 Yury Lages *(France)*
miR-10a-5p modulates impulsive choice in rats: insights into the role of PI3K and the AKT/MTOR pathway

P1.40 Brianna Ramos *(USA)*
Identifying a neurochemical signature of the paraventricular nucleus of the thalamus that predicts individual variability in cue-reward learning

P1.41 Zuzana Pedan *(UK)*
Sex differences in the role of cue-reactive nucleus accumbens neuronal ensembles in spontaneous recovery of food seeking

P1.42 Princess Felix *(USA)*
Knockdown of the glucocorticoid receptor (GR) in a corticostriatal pathway increases the propensity to attribute incentive salience to a reward cue

P1.43 Małgorzata Filip *(Poland)*
Study of potential behavioral predictors of obesity phenotypes in male rats

P1.44 Merridee Lefner *(USA)*
Distinct roles for ventral tegmental area GABA and dopamine neurons underlying flexible updating of reward and punishment contingencies

P1.45 Christakis Kagios *(Sweden)*
Effects of cafeteria diet on pituitary hormones and behaviour in male Wistar rats

P1.46 Matthew Bailey *(UK)*
Inhibitory brain dynamics for adaptive behaviour: The role of GABAergic neurotransmission in temporal discrimination based visual perceptual learning

P1.47 Matthew Hilton *(UK)*
The effects of selective serotonin reuptake inhibitors and beta-blockers on learning in dynamically changing environments

P1.48 Rita El Azali *(Canada)*
Individual differences in sensitivity and resistance to punished self-administration of a sweetened oral morphine solution

P1.49 Stephanie Desrochers *(USA)*
Differential engagement of top-down and bottom-up pathways in the paraventricular thalamus in sign-trackers versus goal-trackers

P1.50 Alexandra Gregory *(Australia))*
Brain networks for punishment learning

P1.51 Kendra Loedige *(Canada)*
Parsing the role of Cell Adhesion Molecule 2 in externalizing traits using Pavlovian conditioning and RNA sequencing in transgenic mice

P1.52 Zengyou Ye *(USA)*
An open-source, budget-friendly tail suspension test platform with high temporal resolution for behavioral and neural correlation studies

P1.53 Davin Peart *(Canada)*
Neural substrates of potentiation of cocaine-primed reinstatement by 17β-estradiol in ovariectomized rats

P1.54 Iva Tic *(USA)*
TRPV1 antagonism modulates drug-seeking behavior in cocaine self-administration in male but not female mice

P1.55 Natalia Morales Pagán *(USA)*
The impact of a GLP-1 receptor agonist on cue- and drug-induced reinstatement of cocaine-seeking behavior

P1.56 Jeanne-Laure de Peretti *(France)*
Can correlated pathological oscillations in the cortex and the subthalamic nucleus predict compulsive-like cocaine seeking in rats?

P1.57 Veronika Llerena *(USA)*
PPAR-gamma agonism induces distinctive effects on cocaine-reinforced behaviour in male and female mice

P1.58 Cristian Bis-Humbert *(Spain)*
Increased vulnerability to cocaine addiction in male rats exhibiting maladaptive sucrose self-administration behavior

P1.59 Maria Carolina Machado da Silva *(Brazil)*
Disruption of immune homeostasis mediates neural and behavioral alterations induced by cocaine

P1.60 Maria Ros *(Spain)*
Effect of isolation and binge alcohol drinking in decision-making behaviour rats: study of the sex and age differences

P1.61 **Javier Orihuel Menéndez** *(Spain)*
A Senotherapeutic approach alleviate alcohol-induce cellular damage and reduce compulsive like alcohol consumption in mice

P1.62 **Leandro Ruiz Leyva** *(USA)*
Therapeutic potential of an Ibogaine analog for polydrug opioid and alcohol misuse

P1.63 **Sofie van Koppen** *(Netherlands)*
Effects of age of onset of voluntary alcohol consumption on reward sensitivity, impulsivity, and cognitive flexibility in rats

P1.64 **Jairo Steffan Acosta Vargas** *(Spain)*
Long-term effects of adolescent THC-CBD vapor exposure on alcohol-related behaviour: evidence from schedule-induced polydipsia and self-administration paradigms

P1.65 **Bart Cooley** *(Australia)*
Satiety-related treatments on alcohol motivation and choice

P1.66 **Lauri Elsilä** *(Finland)*
Voluntary ethanol consumption disrupts circadian rhythm in female mice: preliminary observations exploring the utility of automated home cage monitoring

P1.67 **Lauren Ursich** *(Australia)*
Assessing the utility of zuranolone to modify alcohol-related behaviours

P1.68 **Esther Visser** *(Sweden)*
PKC-δ neurons in the central amygdala promote compulsive alcohol use

P1.69 **Jonathan Aguirre** *(USA)*
Effect of ventral tegmental area dopamine neuron inhibition on stress-induced reinstatement

P1.70 **Andrea Coppola** *(Sweden)*
A role for social status and social status loss in alcohol-related behaviors in Wistar male and female rats

P1.71 **Keira Aubin** *(Canada)*
Exploring the relationship between early-life trauma, circulating endocannabinoids, and problematic cannabis use among young adults

P1.72 **Zachary Pierce-Messick** *(USA)*
Effect of nicotine dose and dose expectancy on puff- and bout-level analysis of smoking topography

P1.73 **Abigail Lunge** *(Canada)*
The impact of childhood maltreatment on the endocannabinoid system and the processing of socially relevant information in healthy humans

P1.74 **Marc D. Ferger** *(Canada)*
Longitudinal changes in endocannabinoids and clinical course in adolescents with non-suicidal self-injury

P1.75 **Berta Escudero** *(Spain)*
Longitudinal changes in apolipoproteins correlate with alterations in cognitive decline in alcohol use disorder: a prospective cohort study

P1.76 **Luis Contreras** *(Canada)*
Exploring access to psychedelics among canadian veterans: pathways, barriers, and experiences

P1.77 Rocío Rodríguez-Herrera *(Spain)*
Neurofunctional mechanisms of behavioural inhibition in ADHD and OCD: A comparative study using the stop-signal task and resting-state functional connectivity

P1.78 Thomas Zandonai *(Italy)*
Co-prescription of anticholinergics and benzodiazepines in chronic pain patients treated with opioids: a population-based case-control study

P1.79 Paula Banca *(Spain)*
Action-sequence learning, habits and automaticity in obsessive-compulsive disorder: implications for treatment

P1.80 Tania Romacho *(Spain)*
Repurposing antidepressants for diabetic neuropathic pain: in combination or alone?

P1.81 Páleníček Tomáš *(CZ)*
The effects of Ayahuasca on inter-brain synchrony during the ritual in the Amazon – a field study

P1.82 Tatum Sevenoaks *(UK)*
The effect of caffeine consumption and acute withdrawal on mood, cognition, and resting state brain activity

Poster Session 2
Friday, 19th September • 13:00-15:00
Even numbers presented 13:00-14:00, odd numbers presented 14:00-15:00

P2.1 Harry Robson *(UK)*
Investigating the role of the alpha-7 nicotinic acetylcholine receptor during a signal detection task: pharmacological modulation and molecular analysis

P2.2 Marion Annie Ponserre *(Germany)*
GlyT1 inhibitor, Bitopertin redistributes the excitatory and inhibitory network connectivity in mouse medial prefrontal cortex

P2.3 Maria Llach Folcrà *(USA)*
Behavioral and molecular effects of CBD in a peripartum depression mouse model

P2.4 Zheng-Xiong Xi *(USA)*
Brain CB2 receptor: A new target in medication development for treating opioid use disorder in rodents

P2.5 Luigi Bellocchio *(France)*
To flee or not to flee: the role of the endocannabinoid system

P2.6 Yolanda Mateo *(USA)*
Endocannabinoid modulation of cortical dopamine release

P2.7 Courtney S. Wilkinson1 *(USA)*
Is there a role for extended amygdala dynorphin/κ-opioid receptor in opioid addiction-like behaviors?

P2.8 Alexander Athanasopoulos *(Australia)*
Exploring behavioural interactions between methamphetamine and psilocybin in mouse models of methamphetamine sensitization and head twitch response

P2.9 **Álvaro López Villegas** *(Spain)*
Effects of the 5-HT2A agonist DOI on compulsivity and reversal learning in preclinical models

P2.10 **Itziar Beruete Fresnillo** *(Spain)*
Characterizing the antidepressant-like effects of psilocybin in adolescent rats of both sexes

P2.11 **María Teresa Colomina** *(Spain)*
Transcriptomic and metabolomic signatures of ibogaine treatment: preclinical and clinical investigation

P2.12 **Maria Asuncion Aguilar** *(Spain)*
Ketamine prevented the anxiety- and depression-like symptoms and the enhanced sensitivity to cocaine induced by social defeat in mice

P2.13 **Olivia Gilmore McKimm** *(Australia)*
Acute and enduring effects of psilocybin on EEG power spectra and sleep architecture in mice

P2.14 **Pedro Bergas-Cladera** *(Spain)*
Exploring the Prosocial Impact of Psilocybin in Male and Female Adult Mice

P2.15 **Annika Hästbacka Schäfer** *(Finland)*
BDNF/TrkB signalling in tolerance development to diazepam in mice

P2.16 **Gladys Pinto** *(Spain)*
Cognitive and emotional consequences of new psychoactive substances chronic use: investigation with Alkyl Nitrites (Poppers)

P2.17 **Nerea Ríos Nieto** *(Spain)*
Comparative Effects of Serotonergic and Glutamatergic Modulators to remediate behavioral alterations in anhedonia, anxiety and compulsivity in preclinical models

P2.18 **Satoshi Ikemoto** *(US)*
Reinforcing effects of nicotine in the hypothalamic supramammillary region involve activation of glutamatergic projections to the medial septum

P2.19 **Livia Wilod Versprille** *(UK)*
Amphetamine selectively reduces dopamine transients in the nucleus accumbens core during decision-making and distraction in a visual signal detection task

P2.20 **Roberto Alvarez** *(Spain)*
Psychedelics, stimulants, and habituation: behavioral effects of DOI and Amphetamine in the earthworm *Dendrobaena veneta*

P2.21 **Maria Zelai Garçon** *(USA)*
Inflammatory cytokine profile in plasma and brain during chronic pain progression

P2.22 **Natalia de las Heras Martínez** *(Spain)*
Maternal immune activation and vulnerability to develop adjunctive behaviours in adulthood: an exploratory study

P2.23 **Antonino Casile** *(Italy)*
Dysregulation of the oxytocin system and disruption of social reward processing in a rat model of gaming disorder

P2.24 **Gregorio Sonsini** *(Italy)*
An efficient raw pixel approach for machine learning-based annotation of novel object recognition videos

P2.25 **Fernando Sánchez-Santed** *(Spain)*
A systematic review focused on micro-/nano-plastic developmental neurotoxicity. in search for common biological target across different models

P2.26 **Michele Petrella** *(Sweden)*
Dissecting the role of lateral septum PKCδ neurons

P2.27 **Andrea Sepe** *(Italy)*
Genotype-dependent corticolimbic network differences in cue-induced fear responses: A data-driven c-Fos-based analysis

P2.28 **Antonio Cañete Ramírez** *(Spain)*
Cognitive Impairments in the RHA vs RLA rats: Insights into Schizophrenia-Related Deficits

P2.29 **Daniel Sampedro Viana** *(Spain)*
Neonatal handling enhances exploratory and social behaviour, and neuroplasticity in a genetic rat model of schizophrenia-relevant traits

P2.30 **Antonio José Rodríguez Sánchez** *(Spain)*
Anodal tDCS improves anxiety-like behavior in rats with ischemic stroke

P2.31 **Bianca Bobotis** *(Canada)*
Sex chromosomes and sex hormones differently shape microglial properties during normal physiological conditions in the adult mouse hippocampus

P2.32 **Bianca De Filippis** *(Italy)*
In search of molecular signatures preceding full symptoms appearance: towards early interventions for Rett syndrome

P2.33 **Diana Cardona** *(Spain)*
Influence of ingestion of live microalgae rich in omega-3 acids on biochemistry, behaviour and gut microbiota in mice

P2.34 **Ketki Mulay** *(Ireland)*
Sex-specific effects of gut microbial depletion on adult hippocampal neurogenesis and spatial and contextual memory

P2.35 **Elena Martín-González** *(Spain)*
Brain metabolomic alterations in compulsive rats selected by Schedule-Induced Polydipsia

P2.36 **Ewa Litwa** *(Poland)*
Effects of deep brain stimulation on BDNF-ERK-CREB signaling pathway in animal model of treatment-resistant depression

P2.37 **Ezgi Selcuk Filizoglu** *(Spain)*
The D3 receptor knock-out mutation in dopamine deficient aphakia mice reverses activational impairments: impact on the cerebral dopamine neurotrophic factor

P2.38 **Francesca Sansó-Elle** *(Spain)*
Validating a preclinical model of PMDD in female Sprague-Dawley rats

P2.39 **María Jose Simón** *(Spain)*
Conditioned place aversion induced by electrical stimulation of the Lateral Parabrachial area is blocked by selective mu-opioid antagonists

P2.40 **Margarita Moreno Montoya** *(Spain)*
Habits study network in experimental psychology

P2.41 **Pedro Vidal** *(Spain)*
Time-based diminishing returns task: effects of d-amphetamine on decision-making strategies under multiple schedules

P2.42 **Rocío Rodulfo** *(Spain)*
Enhancing impulsivity assessment in mice: validation of the variable delay-to-signal task

P2.43 **Blanca Cativiela Campos** *(Spain)*
Where you live matters: air pollution affects cognitive and emotional health along with changes in the inflammatory response during aging

P2.44 **Elena Tittarelli** *(Italy)*
MicroRNA-34a as a possible functional marker of the innate freezing defensive response

P2.45 **Heidi Lesscher** *(Netherlands)*
Sleep Deprivation and risky play during early life: Implications for cognitive control in rats

P2.46 **Isabel Galiana Camacho** *(Spain)*
Impact of combined prenatal exposure to Chlorpyrifos and particulate matter on early neurodevelopmental outcomes in Wistar rats

P2.47 **Mario Ruiz Coca** *(Spain)*
Long-Term effects of prenatal exposure to PM10 and Chlorpyrifos in aging: impact on memory and hippocampal gene expression in offspring

P2.48 **Paula Matas Navarro** *(Spain)*
Aphakia dopamine deficient mice show anergia but not anhedonia: the role of cerebral dopamine neurotrophic factor in dopaminergic terminal areas

P2.49 **Kelly Zhuang** *(Australia)*
A cognitive pathway to maladaptive choice

P2.50 **Amanda C. Lee** *(Canada)*
Outcomes of CADM2 recursive splice site variation on rodent neuroimaging and ADHD-related behaviours

P2.51 **Matthew C. Broomer** *(USA)*
Neural representation of altered reward-seeking behavior following punishment

P2.52 **Elisa Marín-Sampietro** *(Spain)*
Cerebellar modulation in cocaine self-administration and drug-seeking behavior

P2.53 **Claudia Fornari** *(France)*
Role of progesterone on cue-induced cocaine seeking in rats

P2.54 **Giulia De Maio** *(France)*
Knock-down of the histone methyltransferase Prdm2 in the dorsomedial prefrontal cortex: effect on cocaine-related behaviors in male rats

P2.55 **Hannah L. Robinson** *(USA)*
Effects of chemogenetic modulation of the mesocorticolimbic dopamine pathway on cocaine choice

P2.56 **M. Flavia Barbano** *(US)*
Role of Dorsal Raphe glutamatergic neurons in cocaine-seeking behavior

P2.57 **Oscar Solis Castrejon** *(US)*
Synaptic zinc and dopamine dynamics in response to cocaine and locomotion

P2.58 **Abel Fabrega Leal** *(Spain)*
Role of cerebellum projecting neurons to the VTA in cocaine-induced conditioned memory

P2.59 **Palmira Acosta Mares** *(Italy)*
Impulsivity as a risk factor for alcohol use disorders: development and validation of a go-nogo model of impulsivity

P2.60 **Lucía Hipólito** *(Spain)*
Inflammatory pain impairs alcohol reward processing without affecting motivation for sucrose or alcohol in female rats

P2.61 **Tetiana Kardash** *(Sweden)*
The role of a positive allosteric modulator of the GABAB receptor (ADX71441) on ethanol vapor dependence-induced compulsive alcohol drinking

P2.62 **Eva Bonilla Gonzalez** *(Spain)*
Sexual dimorphism in the behavioural impact of binge drinking during adolescence

P2.63 **Francisca Carvajal** *(Spain)*
Modulation of binge-like consumption of ethanol and other salient reinforcers by acute DHA administration in C56BL/6J mice

P2.64 **Hannah Machet** *(Australia)*
Decision-making in electric barrier-induced voluntary abstinence

P2.65 **Jolanta Kotlinska** *(Poland)*
New preclinical research on pathogenesis of fetal alcohol spectrum disorders: The role of myelination and endocannabinoids

P2.66 **José Manuel Lerma-Cabrera** *(Spain)*
Neuroprotective effects of chronic DHA on ethanol intake in a mouse model of adolescent alcohol exposure

P2.67 **Laura Orío** *(Spain)*
Functional consequences of apolipoprotein AI potentiation in females exposed to intensive alcohol consumption

P2.68 **Manuela Olmedo Córdoba** *(Spain)*
Combined 5-HT2A receptor agonist and anodal tdcs for modulating compulsive alcohol drinking in a preclinical model

P2.69 **Mara Morales González** *(Spain)*
Compulsivity and alcohol abuse: sexual dimorphism and disruption of social interaction in a preclinical model

P2.70 **Mateo Leganes-Fonteneau** *(Belgium)*
Mapping acute alcohol effects on bodily sensations

P2.71 **Cecilia Bergeria** *(USA)*
Examining the relationship between drug demand, craving, and withdrawal during a buprenorphine taper among individuals with opioid use disorder

P2.72 **Darío Puertas-López** *(Spain)*
Learning contingencies and uncertainty: a modified probabilistic reversal learning task

P2.73 **Suky Martinez** *(USA)*
Emerging evidence of heterogeneity in the opioid withdrawal syndrome: spontaneous and precipitated withdrawal

P2.74 **Neus Ibáñez Sempere** *(Spain)*
Mechanisms of Risky Decision-Making in ADHD and OCD: A Transdiagnostic Approach

P2.75 **Diego Ruiz** *(Spain)*
Variability in cognitive reserve across the aging process: structural equation modeling evidence based on rural contexts and sociodemographic determinants

P2.76 **Isabell Meier** *(Norway)*
Endogenous opioid modulation of safety learning in humans

P2.77 **Jose Manuel Cimadevilla** *(Spain)*
Differential brain activity between young and older adults associated with performance on a spatial recognition task

P2.78 **Laura Brandt** *(USA)*
From clinical trials to real-world impact: introducing a computational framework to detect endpoint bias in opioid use disorder research

P2.79 **Lola Rueda** *(Spain)*
Effects of a multi-strain probiotic on mental and emotional health in older adults: a randomized crossover study

P2.80 **María Luisa Ruiz Franco** *(Spain)*
Treatment of apathy in stroke patients. A systematic review

P2.81 **Thomas Zandonai** *(Italy)*
The emergence of Ketamine use as an adjunct to physical exercise: a netnographic analysis

P2.82 **Ana Sánchez-Kuhn** *(Spain)*
Higher smartphone addiction is associated with more impulsive decision-making in young adults

ABSTRACTS

Panel discussion on Inclusion, Diversity, Equity and Accessibility

Marian Jöels *(Netherlands)*

Biography

We are excited to introduce our upcoming EBPS IDEA event featuring keynote speaker Dr. Marian Joëls. Her book FINISHED (open access) highlights a range of dilemmas in the academic world:

"The way we deal with frequently occurring situations in the academic world may not always be the only or even the best option. Too often, we—scientists—accept the situation as a given. "This is how the system works, and if you want to survive, you better adapt." But we are the system and if particular aspects are wrong, we better mend them!...
Let the story foster a discussion with the ultimate goal of making the great world of science an even more excellent and enjoyable place to live"

Dr. Joëls will provide an overview of global issues related to inclusion, diversity, equity, and accessibility, examining both historical contexts and future directions. Following the keynote, a panel discussion will bring together panelists from diverse countries and career stages, fostering an open and dynamic conversation. This event aims to engage all attendees in meaningful discussions and collectively contribute to improving these critical issues in our society and beyond.

See book at this link: Finished

Early career Investigator EBPS Award

Ida Fredriksson *(Sweden)*

Biography

Ida Fredriksson was recently appointed as an assistant professor in the Centre for Social and Affective Neuroscience at Linkoping University. Her lab's research focuses on the behavioral and neurobiological mechanisms of opioid relapse and craving.

Ida obtained her Ph.D. in Neuroscience from the Karolinska Institutet (Sweden) in 2017. Her Ph.D. work focused on testing potential new treatments in rodent models of alcohol addiction. In 2017, Ida joined the laboratory of Dr. Yavin Shaham at NIDA as a Postdoctoral Fellow.

As a Postdoctoral Fellow, she studied the neuronal circuitry and mechanisms that mediate incubation of oxycodone craving after abstinence due to negative consequences of drug seeking. Ida has been the recipient of a Fellows Award for Research Excellence from the NIH, NIDA Women in Science Excellence in Research Award and the Women Scientist Advisors Scholar Award of NIH. Ida has also received the Swedish Research Council International postdoctoral grant as well as two prestigious Starting Grants from the Swedish Research Council and the Swedish Society for Medical Research.

Award Lecture
The Role of the Ventral Subiculum and Claustrum in Incubation of Opioid Craving

The lecture describes studies using a human relevant animal model of incubation of craving combined with modern neuroscience techniques. Dr. Fredriksson will present new data showing an important role of a ventral subiculum-claustrum circuit on incubation of opioid seeking after voluntary abstinence. She will also show that longitudinal functional connectivity (fMRI) changes in ventral subiculum and claustrum-related circuits predict incubation.

Distinguished Investigator EBPS Award

Theodora Duka *(United Kingdom)*

Biography

Dora Duka is Professor of Experimental Psychology in the Behavioural and Clinical Neuroscience group of the School of Psychology at the University of Sussex.

Dora qualified in Medicine in Athens where she also completed her PhD in Pharmacology, followed by postdoctoral research in Neuropsychopharmacology with Albert Herz at the Max Planck Institute for Psychiatry in Munich, Germany. The development of a severe allergy to lab animals encouraged Dora to complete her training as an Anaesthetist in Germany and to move to human psychopharmacology research. Subsequently she worked in the pharmaceutical industry as head of Clinical Psychopharmacology Department, at Schering (now Bayer) in Berlin. She returned to Academia in 1995 as a Reader (Associate Professor) at Sussex University in the UK where she became established as an experimental psychologist. Her work translating ideas and methodologies from animals to humans has been pivotal for research in cognitive and emotional processes in addictive behaviours.

Dora's early-career investigations led to the first demonstration of a relationship between benzodiazepines and endogenous opiate systems and the first suggestion that benzodiazepine use may lead to dependence. Her more recent work has focused on brain mechanisms underlying the acute effects of alcohol on cognition and emotional sensitivity in social drinkers, and in particular the long term effects of alcohol in binge drinkers and alcoholics. She has used functional and structural imaging to reveal these mechanisms. Her work has been supported over the years at Sussex by the UK Medical Research Council and by the UK Biotechnology and Biological Sciences Research Council, the NIH and the European Commission.

Award lecture
A Life on the Borders of Drug Addiction

Humans have used plants and drugs since earliest time to feel animated, relaxed or creative. Among these psychoactive substances, opiates and alcohol are those that have dominated my scientific research path. My early work with opiates focused on the interaction of opiates with the benzodiazepines and the implications of this relationship for dependence. Although my talk will refer to my early career, I will concentrate on my work over the last 30 years, focusing especially on alcohol. This simple molecule has a multitude of effects ranging from reducing anxiety to inducing elation and pleasure. At the same time, it impairs memory and dampens our ability to control our behaviour. My research has shown that alcohol impairs the ability to plan, to make efficient decisions, and to inhibit inappropriate responses. All these effects contribute to alcohol's addictive nature. Most importantly, misuse of alcohol frequently leads to dependency - an inability to abstain from misuse. I will present alcohol-influences contributing to this inability to abstain, and the brain mechanisms underlying them. I will emphasise the importance of binge drinking and the behavioural and cognitive impairments associated with it. The talk will also refer to individual psychological aspects which may predispose to binge drinking. Finally brain mechanisms underlying changes in behavioural and cognitive function associated with binge drinking will be revealed and implications for the prevention of alcohol abuse will be discussed.

Plenary Lecture 1

Prefrontal Regulation of Emotion: Insights into Anhedonia, Anxiety and Pharmacotherapy

Angela C Roberts *(UK)*

Biography

Angela Roberts obtained a PhD in neuroendocrinology, University of Cambridge (1985) and then undertook postdoctoral studies into the neural and neurochemical basis of cognitive flexibility. She was appointed Lecturer in Department of Anatomy, Cambridge in 1996, becoming Professor of Behavioural Neuroscience in 2010.

Recent scientific contributions include establishing non-human primate models of positive and negative emotion regulation, identifying distinct prefrontal networks underlying the varied aetiology of affective disorders and elucidating the sensitivity of these networks to anxiolytics/antidepressants.

She is a Fellow of the Academy of Medical Sciences and a recipient of the Goldman-Rakic Prize for outstanding achievements in Cognitive Neuroscience.

Abstract

This lecture explores the multiple contributions of prefrontal and anterior cingulate cortices to the regulation of positive and negative emotion in a non-human primate. It reviews the effects of acute interventions in frontal pathways on cardiovascular and behavioural reactivity to reward and threat, on network dynamics derived from neuroimaging and on responsivity to anti-depressants/anxiolytics, in the marmoset. Results from these studies provide insights into the functional organisation of threat regulation across the frontal lobes, network interactions between subcallosal cingulate and dorsolateral prefrontal cortex in relation to both anxiety and anhedonia-like symptoms and differential responsiveness of these frontal networks to SSRI's and Ketamine.

Plenary Lecture 2

Cerebellar Modulation of Drug-Induced Reward: How Cinderella Came to the Ball

Marta Miquel *(Spain)*

Biography

Marta Miquel is a Professor of Psychobiology at Universitat Jaume I (UJI, Spain) and a visiting professor at the Dominick Purpura Department of Neuroscience. Albert Einstein College of Medicine (NY, USA).
She serves as the Director of the Addiction and Neuroplasticity research group. Dr. Miquel earned her PhD. from Valencia University and completed post-doctoral training at the Department of Pharmacology, University of Toronto (Canada), and at CIFA (Center for Research in Applied Pharmacobiology. University of Navarra (Spain).

Her research has pioneered the role of the cerebellum in the neurobiological mechanisms of addiction. She has drawn attention to the cerebellum involvement in higher brain functions when chronic drug abuse compromises the prefrontal function. One of the main findings in her lab indicates that the cerebellum-infralimbic cortex loop controls the formation of cocaine-induced memory in a compensatory manner. Additional interests include investigating the function of perineuronal nets (PNNs) in the cerebellum as a mechanism for synaptic stabilization and consolidation of drug-induced memory. Dr. Miquel is best recognized for her expertise in addiction and cerebellum.

Abstract

It is now increasingly clear that the cerebellum may modulate brain functions altered in drug addiction. The cerebellum appears to be closely connected to the functional loops that support addictive behavior, including the Ventral Tegmental Area. In this lecture, I will discuss evidence regarding how the cerebellum can regulate reward-related processes and, in particular, drug-induced reward. Our findings identified the posterior vermis as the locus of drug-related learning hallmarks. Neurotoxic lesions and chemogenetic studies suggest that reduction in the inhibitory modulation from the posterior vermis onto the cerebellar output neurons facilitates cocaine-induced reward learning. However, increasing the inhibitory control from the cerebellar cortex prevents it. We hypothesized that the cerebellum would acquire higher functional relevance when prefrontal function is compromised by other mental disorders or chronic drug use. Our findings indicate that the cerebellum-infralimbic cortex loop, but not the prelimbic loop, regulates cocaine-induced memory in a compensatory manner. Impairment of each region is sufficient to enhance neural activity and encourage mechanisms for synaptic stabilization in the other region, boosting cocaine-induced conditioning. Our results also showed a never-described- before descending pathway through which IL sends monosynaptic projections to the Interposed DCN and the Inferior Olive, possibly through collateral projections, and then the Interposed and Inferior Olive reach the posterior vermis. We have also been interested in the function of cerebellar PNNs in cocaine-related reward from the beginning. We showed that the increased PNN expression surrounding Golgi interneurons is a hallmark of cocaine-induced conditioned preference. Our results also argue in favor of the dynamic regulation of cerebellar PNNs during the incubation period. PNN expression in the posterior vermis increases throughout the first month of abstinence in animals with extended access to cocaine. According to the proposed role of PNNs in synaptic stabilization, degradation of cerebellar PNNs with the enzyme ChABC prevents cocaine-induced short-term memory and reduces the stability of the cocaine-seeking response. Therefore, evidence suggests that the posterior cerebellum is a general controller for reward-related processes and open a window for treatments involving the modulation of cerebellar activity.

Plenary Lecture 3

Bugs, Drugs & Behaviour: Microbiome as a Key Regulator of Brain Function Across the Lifespan

John Cryan *(Ireland)*

Biography

John F. Cryan is Professor & Chair, Dept. of Anatomy & Neuroscience, University College Cork and was appointed Vice President for Research & Innovation in 2021. He is also a Principal Investigator in the APC Microbiome Ireland Institute.

Prof. Cryan's current research is focused on understanding the interaction between brain, gut & microbiome and how it applies to stress, psychiatric and immune-related disorders at key time-windows across the lifespan. Prof. Cryan has published over 700 peer-reviewed articles and book chapters. He has co-edited four books and is co-author of the bestselling “The Psychobiotic Revolution: Mood, Food, and the New Science of the Gut-Brain Connection”.

He is a Senior Editor of Neuropharmacology and of Neurobiology of Stress and is on the editorial board of a further 10 journals. He has received numerous awards including UCC Researcher of the Year in 2012, the University of Utrecht Award for Excellence in Pharmaceutical Research in 2013, UCC Research Communicator of the Year 2017, and being named on the Thomson Reuters/Clarivate Highly Cited Researcher list in 2014 and each year from 2017 to the present. He was elected a Member of the Royal Irish Academy in 2017. He also received a Research Mentor Award from the American Gastroenterology Association and the Tom Connor Distinguished Scientist Award from Neuroscience Ireland in 2017 and was awarded an honorary degree from the University of Antwerp, Belgium in 2018. He was a TEDMED & TEDx speaker and is a Past-President of the European Behavioural Pharmacology Society.

Abstract

The microbiota-gut-brain axis is emerging as a research area of increasing interest for those investigating the biological and physiological basis of neurodevelopmental, age-related and neuropsychiatric disorders. The routes of communication between the gut and brain are being unravelled and include the vagus nerve, the immune system, tryptophan metabolism, via the enteric nervous system or via microbial metabolites such as short chain fatty acids. Studies in animal models have been key in delineating that neurodevelopment and the programming of an appropriate stress response is dependent on the microbiota. Developmentally, a variety of factors can impact the microbiota in early life including mode of birth delivery, antibiotic exposure, mode of nutritional provision, infection, stress as well as host genetics. Stress can significantly impact the microbiota-gut-brain axis at all stages across the lifespan. Moreover, animal models have been key in linking the regulation of fundamental brain processes ranging from adult hippocampal neurogenesis to myelination to microglia activation by the microbiome. Our lab is particularly interested in the role of the microbiome in reward processes. The interaction between xenobiotics including psychotropic medication, drugs of abuse, pesticides and environmental disrupters are gaining more attention with a growing attention to exposome-microbiome interactions. Finally, studies examining the translation of these effects from animals to humans are currently ongoing. Further studies will focus on understanding the mechanisms underlying such brain effects and developing nutritional and microbial-based psychobiotic intervention strategies and how these interact with various systems in the body across the lifespan.

Featured Symposia 1 - Global Perspectives on Neuropsychiatric Research: Stress, Cognition, and Innovative Therapeutics

Chair: Princess *Felix* *(USA)*

Advancing neuropsychiatric research requires a comprehensive understanding of the biological, environmental, and societal factors that shape mental health outcomes. However, in many regions of the world, scientific progress is hindered by economic constraints, cultural stigma, and limited access to research infrastructure. Despite these challenges, researchers in these areas are making significant contributions to understanding the neurobiology of stress, cognition, and psychiatric disorders. This symposium will highlight cutting-edge work from scientists in Africa, Asia, and the Middle East, offering novel perspectives on the mechanisms underlying stress-related psychiatric conditions and potential therapeutic approaches. This session will feature four distinguished speakers whose research spans molecular, pharmacological, and neurocircuitry-based approaches to better understand neuropsychiatric disorders. Dr. Vidita Vaidya will discuss the stress neurocircuitry and molecular regulation of emotion in animal models of relevance to psychiatric disorders, demonstrating how pharmacological and genetic approaches can uncover novel treatment strategies. Dr. Oritoke Modupe Okeowo will present her work on the molecular properties of methyl jasmonate, a bioactive compound with potential for modulating stress responses and psychiatric symptoms. Dr. Inna Gaisler-Salomon will present on epigenetic and glutamatergic mechanisms underlying stress-induced cognitive dysfunction, highlighting how stress before conception alters neurobiological outcomes in offspring. Finally, Dr. Gwladys Ngoupaye will discuss the pharmacological properties of traditional Cameroonian medicinal plants used for psychiatric disorders, shedding light on the untapped potential of indigenous compounds in treatment. Together, these presentations will provide a global perspective on neuropsychiatric research, emphasizing how social, cultural, economic, and environmental conditions shape both challenges and innovations in the field.

Vidita Vaidya *(India)*
FS.1.1 - Neurocircuitry and molecular regulation of stress and emotion in mood disorders
Oritoke Okeowo *(Nigeria)*
FS.1.2 - Novel pharmacological approaches for stress related disorders
Inna Gaisler-Salomon *(Israel)*
FS.1.3 - Glutamate dysregulation, stress and cognitive dysfunction: novel therapeutic venues
Gwladys Ngoupaye *(Cameroon)*
FS.1.4 - Cameroonian medicinal plants: mechanistic insights on stress-induced cognitive deficits

Featured Symposia 2 - Advanced Technologies and Big Data in Behavioral Pharmacology and Psychiatry

Chair: Brenda Curtis *(USA)*

The integration of advanced technologies and big data into biobehavioral pharmacology and psychiatry is revolutionizing personalized approaches to mental health and behavioral addictions. This symposium will explore cutting-edge innovations, including biometric monitoring, body sensor networks, digital phenotyping, and neurotechnology, to uncover novel insights into psychiatric conditions and addictions. Given the increasing prevalence of mental health challenges, this timely topic highlights the transformative potential of emerging tools for personalized care and enhanced interventions. The symposium will showcase interdisciplinary approaches such as wearable devices, ingestible sensors, and digital phenotyping through big data and social media analytics. These methods address critical challenges in the field, including improving diagnosis accuracy, enhancing medication adherence, predicting behaviors, and tracking pre-addiction states. Featuring international experts, the session will demonstrate the synergy between advanced technology and behavioral pharmacology, fostering discussion on practical applications in research and clinical practice.

Brenda Curtis *(USA)*
FS.2.1 - Digital surveillance for substance use trends: social media and behavioral data analysis
Peter R. Chai *(USA)*
FS.2.2 - Smartphone phenotypes of PrEP adherence in substance use
Ignacio Obeso *(Spain)*
FS.2.3 - Neurocognitive dynamics in pre-addiction states using big data and neurotechnology
Stephanie Carreiro *(USA)*
FS.2.4 - Craving-based digital phenotyping for MOUD pharmacovigilance

Symposium 1 · Endocannabinoids and Sex-Dependent Behavior: Insights from Development to Adulthood

Chair: Carmen Sandi *(Switzerland)*

The endocannabinoid system plays a pivotal role in regulating brain function and behavior, with growing evidence pointing to sex-specific effects across development and adulthood. We will explore how endocannabinoid signaling shapes behavioral outcomes, highlighting the critical interplay between sex, stress, and neurodevelopmental processes. Miriam Mellis (Professor of Pharmacology, University of Cagliari, Italy) will present findings on how prenatal perturbations of endocannabinoid signaling predispose rats to stress-related, dopamine-dependent psychopathological phenotypes in a sex-specific manner. This work emphasizes the importance of understanding early-life disruptions in endocannabinoid pathways for long-term mental health. Olivier Manzoni (Directeur de Recherche, INSERM, INMED, Marseille, France) will discuss longitudinal studies examining the lifelong consequences of prenatal cannabis exposure, revealing sex-specific impacts on neurodevelopment, synaptic plasticity, and behavior. His findings emphasize the need for a deeper understanding of cannabis exposure during pregnancy, given its prevalence. Silvie Ruigrok (Postdoc, Brain Mind Institute, EPFL, Switzerland) will explore how the estrous cycle influences anxiety, motivation, and related changes in the nucleus accumbens' endocannabinoid system. Her data highlights the need to address the knowledge gap in female mental health and its neurobiological underpinnings. Arnau Busquets-Garcia (Assistant Professor, Hospital del Mar Research Institute, Spain) will discuss the role of cannabinoid receptors in higher-order cognitive processes, such as incidental learning and psychotic-like states. His work highlights how these receptors modulate complex behaviors and their implications for pathological conditions. The symposium, co-chaired by Carmen Sandi (Switzerland) and Miriam Mellis, will advance our understanding of sex-dependent endocannabinoid mechanisms, providing a basis for targeted interventions in mental health.

Miriam Melis *(Italy)*
S.1.1 - Sex-specific phenotypes induced by prenatal perturbation of endocannabinoid signaling
Olivier Manzoni *(France)*
S.1.2 - Lifelong sex-specific impacts of prenatal cannabis exposure
Arnau Busquets Garcia *(Spain)*
S.1.3 - Cannabinoid receptors and higher-order conditioning
Silvie Ruigrok *(Switzerland)*
S.1.4 - Estrous cycle modulation of anxiety and motivation - focus on the endocannabinoid system

Symposium 2 • Recent Advances in Addiction Vulnerability in Animal Models and Humans

Chair: Ginevra D'Ottavio *(USA)*

Drug use is a necessary but not sufficient for development of drug addiction; only a small proportion of individuals exposed to drugs develop addiction. Addiction vulnerability is shaped by an interplay of complex genetic, environmental, and behavioral factors. Individuals with addiction often exhibit extreme drug use, high craving, and high drive to seek and consume drugs. Notably, this drive for drugs is often accompanied by a reduced interest in natural rewards, with substances outweighing healthier options. Our panel will present new research on factors that influence vulnerability and resilience to drug addiction. We will explore recent advances in animal models, human research and computational models examining genetic variations, behavioral traits, as well as the neurobiological mechanisms of addiction vulnerability. Cannella will present data on individual differences in heroin self-administration, relapse, brain response to heroin cues, and responses to approved and novel medications for opioid addiction, using a multi-symptomatic addiction vulnerability model in genetically diverse rats. D'Ottavio will present data from recent studies on a social-vs-heroin choice task to identify individual differences in vulnerability to heroin self-administration and relapse in a rat model. Perini will present findings from a personalized concurrent choice procedure, examining preference for alcohol versus non-drug rewards in light and heavy drinkers and their neurobiological correlates. Gu will present a novel computational framework that examines how drug craving and reinforcement learning mutually influence each other during decision-making, offering insights into the mutually escalating effect of these processes on each other and how they might predict addiction vulnerability.

Nazzareno Cannella *(Italy)*
S.2.1 - Multisymptomatic screening reveals differences of addiction behavior and treatment outcome
Ginevra D'Ottavio *(USA)*
S.2.2 - Exploring addiction vulnerability in preclinical models using drug vs social choice tasks
Irene Perini *(Sweden)*
S.2.3 - Choice preference for alcohol over a natural reward in heavy versus light drinkers
Philip Jean-Richard Dit Bressel *(Australia)*
S.2.4 - A cognitive pathway to maladaptive choice

Symposium 3 · A Translational Perspective on Safety Learning and Safety Behaviours

Chair: Joanna Yau *(Australia)*

Safety learning is the learning about the absence of danger. For example, we may learn that a loud noise signals danger in one environment (e.g., combat), but not another (e.g., home). The safety cue (e.g. home) predicts the absence of danger and prevents fear from switching on. However, sufferers of anxiety and stress-related disorders (e.g., post-traumatic stress disorder [PTSD]) disorders show impairments in safety and they overgeneralise fear to safe places and people. This symposium reconciles rodent and human research to bring a new translational perspective on safety as a unique and powerful form of fear inhibition. To begin, Dr. Heidi Meyer will be discussing how safety is studied in rodents and her work showing safety signals can inhibit fear. Dr. Alba Lopez Moraga will be talking about how stress influences safety behaviours such as avoidance. Lastly, Dr. Sarah Tashjian will conclude the symposium by discussing how the ventromedial prefrontal cortex integrate safety information in humans. These collection of talks will highlight the mechanisms of safety and their relevance to anxiety and trauma-related disorders, and potential translational implications for exposure-based therapies. By integrating animal and human research, this symposium will highlight converging evidence on the neural and cognitive mechanisms of safety learning. The talks will address how insights from rodent models can inform therapeutic approaches in humans, fostering cross-disciplinary dialogue to advance translational neuroscience in fear inhibition.

Heidi Meyer *(USA)*
S.3.1 - Experience with safety learning can scale later fear responding
Alba López Moraga *(Belgium)*
S.3.2 - Differential effects of chronic stress on active avoidance procedures
Emma Cahill *(United Kingdom)*
S.3.3 - Hypervigilant responses to ambiguous threat cues by rats
Sarah Tashjian *(Australia)*
S.3.4 - vmPFC integration of safety information in humans

Symposium 4 • Innovations and Challenges of Psychedelics in Behavioral Health Disorders

Chair: Harriet de Wit *(USA)*

Mental health and drug abuse crises affect ~300 million people globally with considerable personal and economic impacts. The need to innovate toward therapeutics to support affected individuals, families and communities has never been greater. Psychedelics, mainly serotonin 5-HT2A receptor (5-HT2AR) agonists, show promise as psychopharmacological medicines, but are challenged mainly related to their profound hallucinogenic effects. Chemical biology efforts are developing novel modulators that lack acute psychedelic effects, and clinical researchers are adapting psychotherapeutic treatment to powerful subjective experiences. Kathryn A. Cunningham will present recent preclinical advances in probing behavioral psychedelic mechanisms, developing novel 5-HT2R modulators, and addressing knowledge gaps to guide integration of psychedelic-inspired therapeutics into cocaine use disorder treatment. Dr. Charles Nichols will discuss the rational design of novel 5-HT2AR agonists that do not elicit behavioral effects and have therapeutic potential to treat psychiatric, and inflammatory disorders. Dr. Friederike Holze will present recent findings on the clinical pharmacology of different psychedelic drugs in healthy human volunteers including physiological and psychological risks, interactions, and dose-optimization. Dr. Leah Mayo will draw on her experience with clinical trials of psilocybin for a range of indications, including alcohol use disorder, concussion, and intimate partner violence to describe challenges in design, setup and recruitment specific to psychedelic clinical trials. Speakers will discuss challenges in harmonizing preclinical and clinical data to optimize therapeutically useful medications. This is a timely, relevant topic in the behavioral pharmacology, psychology and neuroscience of psychotherapeutics as well as pharmacology and circuit mechanisms of behavior in both animal models and human subjects.

Kathryn Cunningham *(USA)*
S.4.1 - Probing mechanisms and novel 5-HT2R modulators as psychedelic-inspired therapeutics for cocaine use disorder
Charles Nichols *(USA)*
S.4.2 - The rational design of novel 5-HT2A receptor agonists that do not elicit behavioral effects and have therapeutic potential to treat psychiatric and inflammatory disorders
Friederike Holze *(Switzerland)*
S.4.3 - Clinical pharmacology of different psychedelic drugs in healthy human volunteers
Leah Mayo *(Canada)*
S.4.4 - Challenges and opportunities in psychedelic clinical trial design

Symposium 5 • Using Computational & Cognitive Methods to Study Substance Use Over the Addiction Course

***Chair: Justin Strickland** (USA)*

This symposium will explore how computational models can reveal mechanistic and targetable determinants of substance use and substance-free choice. Diverse perspectives will be discussed including multiple drug classes and behavioral addictions, and how these mechanisms apply across distinct stages of the addiction process from addiction etiology to recovery. First, Dr. Strickland will introduce value-based decision-making (VBDM) and discuss whether computational parameters of choice for opioid and drug-free rewards distinguish people with opioid use disorder and those in recovery, while considering how environmental factors, such as cue presentation, influence decision-making. Then, Dr. Copeland will extend these findings to an interventional setting by describing a randomized controlled trial of contingency management for alcohol use disorder, exploring whether computational parameters of VBDM for alcohol and alcohol-free choice change over the course of treatment and predict treatment response. Dr. Acuff will investigate mechanisms underlying varying latent trajectories of “aging out” of harmful cannabis consumption across three years in a combined sample of emerging adults from the United States and Canada and how changes in computational indices of reward and cannabis consumption impact each other in bidirectional pathways. Dr. Perales will extend the discussion to behavioral addictions and will provide a summary of recent findings on the computational underpinnings of how emotion regulation mechanisms influence sensitivity to cravings for gambling and video games. This discussion will illuminate similarities and differences across substance and behavioral domains, offering insights into the extent to which gambling and gaming may (or may not) be conceptualized as addictive behaviors.

Justin Strickland *(USA)*
S.5.1 - Evaluating value-based decision-making mechanisms underlying opioid use disorder
Amber Copeland *(UK)*
S.5.2 - Modelling changes in value-based decision-making in response to contingency management
Samuel Acuff *(USA)*
S.5.3 - Exploring trajectories between behavioral economic reward and cannabis use
José C. Perales *(Spain)*
S.5.4 - The role of emotion regulation mechanisms in gambling and gaming craving

Symposium 6 • Motivational and Cognitive Effects of Manipulating the Dopamine Transporter: Potential Therapeutic Actions of Atypical DAT Inhibitors

Chair: Mercè Correa *(Spain)*

Although most research on the functions of the dopamine (DA) transporter (DAT) have focused on studies related to substance use and abuse, there is enormous potential for using DAT inhibitors as treatments in psychopathology. While classical DAT inhibitors such as cocaine are well known for their abuse liability, there is considerable variability in how different DAT ligands interact with the DAT protein, and not all DAT ligands are major psychomotor stimulants. Drugs such as vanoxerine, modafinil, and bupropion bind to the DAT in ways that differ from cocaine. The proposed symposium will focus on the neurochemical, physiological, cognitive, stress response and effort-related motivational effects of interference with DAT function. Four speakers will approach this subject from different perspectives. Pardo will provide background on DAT transgenic rats as a new model for vulnerability to stress. Salamone will focus on the effort-related motivational effects of novel atypical DAT inhibitors in rats, as well as antidepressant drugs that act on various monoamine transporters, including DAT. Characterization of sex differences will be a theme running through these presentations. Taken together, this symposium will provide a broad but integrated perspective on current research in this important area.

Mercè Correa *(Spain)*
S.6.1 - Vigor and work selection after bupropion administration in mice
John D. Salamone *(USA)*
S.6.2 - Effort-related motivational effects of novel atypical DAT inhibitors in rats of both sexes
Marta Pardo *(Spain)*
S.6.3 - DAT transgenic rats as a new model for vulnerability to stress

Symposium 7 • From Synapse to Nucleus: An Integrated View of Neuronal Ensembles

Chair: F. Javier Rubio *(USA)*

In the past 25 years, the study of neuronal activity markers like Fos and Arc has advanced our understanding of Donald Hebb's neuronal ensemble hypothesis, demonstrating that these ensembles play a causal role in learned behavior. Within individual ensemble neurons, the nucleus initiates expression of immediate early genes such as Fos and Arc, as well as other gene expression programs critical for plasticity and protein synthesis. However, synapses are the site of communication between neurons, receiving specific input from other brain regions through synaptic transmission. Thus, the signaling and integration of activated synapses to the nucleus works cooperatively to encode associative memories. Synapses that are activated by specific inputs are referred to as synaptic ensembles, which are postulated to be involved in learning and memory. The recent development of novel, high resolution, selective tools have enabled researchers to examine neuronal ensembles at the nuclear level as well as the synaptic level. This symposium will highlight different approaches used to identify and analyze neuronal ensembles from the synapse to the nucleus, focusing on technologies used to understand unique molecular alterations, structural alterations within dendritic spines, and electrophysiological alterations at the synapse in response to reward-based associative learning and memory formation.

F. Javier Rubio *(USA)*
S.7.1 - Plasticity changes in synapses from neuronal ensembles: seeking the synaptic ensemble
Eisuke Koya *(UK)*
S.7.2 - Environmental enrichment suppresses food seeking and induces Prelimbic ensemble overdrive
Leslie Ramsey *(USA)*
S.7.3 - Searching for the engram in prefrontal cortical neuronal ensembles: mechanisms that mediate drug and social learning
Sophie Tronel *(France)*
S.7.4 - Looking for the engram of PTSD-like memory: focus on the role of NMDA receptors of the Anterior Cingulate cortex in traumatic memory maintenance

Symposium 8 • New Insights on Individual Differences in Pain and Interoception Using Dense Sampling Techniques in Humans

Chair: Siri Leknes *(Norway)*

Over the last decades, preclinical research has identified several promising targets for psychiatric and/or pain treatment that have failed in human trials. All psychoactive medications and analgesics are known to show substantial variability in humans. The desired effects are typically only evident in subgroups. Dense sampling and single case experimental designs are now emerging as important techniques to understand the mechanisms of individual differences in treatment responses. Here, we will discuss new insights into sources of variability of human experience and drug responses, focusing on drug effects, autonomic and neurohormonal responses related to pain and interoception.
First, Micah Allen will describe his groundbreaking, still ongoing N-of-1 dense sampling study of semaglutide (Ozempic) treatment. The longitudinal study involves resting state stomach brain connectivity measures using an electrogastrogram and fMRI, along with movie watching during appetitive vs control clips, collected during baseline and every two weeks synched to the timing up monthly treatment.
Karin Jensen will report on new results from dense sampling using behavioural and repeated fMRI measures of pain and cognitive functioning to determine cognitive signatures of chronic pain and predictors of pain exacerbation.
Complementing these approaches, Marie Eikemo's talk will describe predictors of perioperative opioid responses and postoperative opioid use in large samples of Norwegian and U.S. surgical patients, with a focus on how repeated opioid use changes brain and subjective responses to subsequent opioids.
The series of talks will have a strong translational focus and pave the way for a better integrated behavioural neuroscience within psychiatry, pain, addiction and obesity research.

Siri Leknes *(Norway)*
S.8.1 - Understanding individual treatment effects through dense sampling N-of-1 single case experimental designs: a primer
Micah Allen *(Denmark)*
S.8.2 - Brain-gut functional interactions in response to semagludide treatment: a dense sampling N-of-1 fMRI study
Julie Klinke *(Sweden)*
S.8.3 - Neural learning mechanisms in the development of nociplastic pain: a dense sampling prospective longitudinal study of chronic non-specific pain
Marie Eikemo *(Norway)*
S.8.4 - Predicting opioid responses and opioid use in surgery patients in the U.S. and Norway

Symposium 9 • Behavioural and Neurobiological Mechanisms of Choice in Rodent Models of Addiction

Chair: Nathan Marchant *(Netherlands)*

A core feature of drug addiction is the allocation of behaviour towards drug use, at the expense of healthier non-drug alternatives. This maladaptive behaviour is modelled in rodents using choice models, where rats are typically given the choice between a drug and a non-drug alternative. In this session the speakers will present data describing the behavioural and neurobiological mechanisms that are involved in the choice of drug in addiction. Dr Nathan Marchant (Amsterdam UMC) will describe the behavioural factors which contribute to choice preferences for alcohol over social reward. He will also present experiments describing how activity in anterior insula cortex is related to choice-preference for alcohol over social reward. Dr Marco Venniro (U Maryland) will present data on the neural mechanisms mediating craving for drug or social rewards. The presentation will highlight the protective effects of social reward and its sensory components on drug craving, as well as data on the neural circuits underlying craving for social interaction. Dr. Youna Vandaele (INSERM) will describe decision-making processes governing choice between drug and non-drug rewards. Her findings suggest that, depending on individual preferences, choice can become habitual. The implications of these findings to behavioural control in addiction will be discussed. Finally, Dr. Jamie Peters (U Alabama Birmingham) will describe a polydrug model of alcohol and heroin co-use, and the role of mu opioid receptors in choice. Break points for alcohol and heroin on a progressive ratio schedule indicate heroin is significantly more reinforcing than alcohol in rats with a polydrug history. Nonetheless, the data suggest the two substances are at least partial substitutes.

Nathan Marchant *(Netherlands)*
S.9.1 - Role of anterior insula cortex in choice between alcohol and social reward
Marco Venniro *(USA)*
S.9.2 - Neurobiological mechanisms mediating social and drug craving
Youna Vandaele *(France)*
S.9.3 - Investigation of the decision-making processes underlying choice between drug and nondrug rewards
Jamie Peters *(USA)*
S.9.4 - Mu opioid receptors and heroin vs. alcohol choice

Symposium 10 • Triggered Temptations: New Findings on How Environmental Cues Fuel Addiction and Gambling

Chair: Anne-Noel Samaha *(Canada)*

Drug users experience cravings triggered by drug-associated cues, leading to relapse. While animal models of relapse focus on cues presented after drug-seeking responses (conditioned stimuli), humans also encounter passive cues that signal drug availability (discriminative stimuli), which are critical to craving before, during, and after drug-seeking actions. Dr. Samaha (Université de Montréal) will show how conditioned and discriminative stimuli affect relapse behaviour in rats post-cocaine abstinence, highlighting the role of corticostriatal pathways. In rats, cue-induced craving intensifies over time, but similar evidence in humans is limited. Dr. Parvaz (Icahn School of Medicine) will present data from individuals with cocaine use disorders (iCUD), showing an increase in cue-reactivity during abstinence, along with greater activation in frontoparietal and sensorimotor regions. This provides evidence for the incubation of craving and its neural substrates in iCUD. Reward-associated cues also play a key role in gambling, particularly in electronic machines that use lights and sounds to trigger risky decisions. Dr. Winstanley (University of British Columbia) will show that both males and females are equally susceptible to these cues, but their underlying computational processes differ. Understanding how win-associated cues influence risky behavior may reveal why gambling disorder manifests differently across the sexes. Dr. Sinha (Yale University) will show data from daily ecological momentary assessment of drug and stress cues and their effects on drug use decisions in the real world. She will also show that distinct cortico-striatal-limbic circuits may underlie alcohol use outcomes in women and men, further underscoring the importance of sex-specific therapeutics.

Anne-Noel Samaha *(Canada)*
S.10.1 - Modeling cue-triggered relapse to cocaine use in rats
Muhammad Parvaz *(USA)*
S.10.2 - Neurobiology of incubation of cue-reactivity in individuals with stimulants use disorders
Catharine Winstanley *(Canada)*
S.10.3 - Win-paired cues drive risky choice through divergent mechanisms in male and female rats
Rajita Sinha *(USA)*
S.10.4 - Drugs, stress cues or both? prospective effects on craving and drug use in the real world

Symposium 11 • Neurohormonal Dysregulations Underlying Alcohol and Opioid Use Disorders

Chair: Brendan Tunstall *(USA)*

This collection of preclinical and behavioral-pharmacology-heavy presentations provides a look at new directions and developments from four independent investigators at various career stages who are studying the neurobiological underpinnings of alcohol and opioid addiction using rat and mouse models. All speakers are interested in neurohormonal systems which are dysregulated by use (in particular, heavy use) of alcohol and opioids, and which may present opportunities for intervention in the addiction process (i.e., via treatments designed to replace or rectify dysregulated signaling). The series of talks will be thematically linked by the conceptual approach taken to identify target mechanisms in alcohol and opioid use disorder (i.e., considering their findings relating to the addiction process as smaller pieces of a larger, overarching deviation from homeostasis that is induced by alcohol and opioid consumption). Each speaker plans to present a combination of recently published and new, unpublished data on these independent lines of work, ensuring that this symposium will be interesting and timely for the EBPS. In brief, Dr. Brendan Tunstall (Chair and Organizer) will present new data on the role of oxytocin in alcohol drinking and hyperalgesia in alcohol dependence. Dr. Kristen Pleil will present new data on the role of estrogen signaling in binge alcohol drinking. Dr. Leandro Vendruscolo will present novel data on the role of glucocorticoids and mineralocorticoids in opioid use disorder. Dr. Brandon Warren will present novel data on the mu-opioid receptor and ability of new partial-MOR agonist compounds to restore homeostasis in opioid use and pain.

Dr. Brendan Tunstall *(USA)*
S.11.1 - Oxytocin against hyperalgesia and intensified alcohol drinking in alcohol dependence
Dr. Kristen Pleil *(USA)*
S.11.2 - Estrogen enhancement of risky alcohol drinking behavior
Dr. Brandon Warren *(USA)*
S.11.3 - Novel MOR-partial agonist against opioid self-administration, withdrawal, and pain
Dr. Hayley Manke *(USA)*
S.11.4 - Role of PKCε in alcohol dependence

Symposium 12 • Pharmacology and Neural Mechanisms of Comorbid Pain and Drug Use

Chair: Nicholas W. Gilpin *(USA)*

Pain and drug use are highly comorbid in humans. Pain increases the use of specific drugs, and excessive drug use can lead to higher pain sensitivity and worsening of pre-existing pain conditions. Animal models and human imaging are being used to uncover the pharmacological and neural mechanisms underlying these comorbidities. Dr. Lucia Hipolito will present clinical and pre-clinical data on negative affective states that are comorbid with pain and high intake of opioids and alcohol. Her data will show a role for dynorphin signaling and kappa-opioid receptors in regulating these behaviors, and she will emphasize sex differences in these outcome measures. Dr. Jose Moron-Concepcion will discuss how sex differences in fentanyl self-administration, motivation, and reinstatement emerge under conditions of persistent inflammatory pain. He will highlight mechanisms related to dopamine signaling and ovarian hormones that promote and protect against pain-facilitated fentanyl use in males, respectively. The findings highlight sex- and age-related differences, revealing that older females are particularly vulnerable to chronic pain and a potentially heightened risk of opioid addiction. Finally, Dr. Nicholas Gilpin will discuss the effects of chronic inhalation of vaporized cannabinoids (delta-9-THC, cannabichromene (CBC), cannabigerol (CBG)) on nociceptive, affective and physiological aspects of chronic inflammatory pain in male and female rats over time.

Lucía Hipólito-Cubedo *(Spain)*
S.12.1 - Modeling negative affective states comorbid with pain and drug intake: insights from rat models and translational perspectives
Jose Moron-Concepcion *(USA)*
S.12.2 - Sex-specific effects of inflammatory pain on fentanyl self-administration and modulation by ovarian hormones
Anushree Karkhanis *(USA)*
S.12.3 - Nucleus Accumbens at the Intersection of Adolescent Alcohol Use and Pain in Adulthood
Nicholas W. Gilpin *(USA)*
S.12.4 - Vaporized cannabinoid inhalation effects on chronic inflammatory pain outcomes

Symposium 13 • The Stress of the Trip: Interactions between Psychedelics and the Stress Response

Chair: Ana Deutsch *(Canada)*

There has been a resurgence in the study of psychedelic drugs, both as novel therapeutics in the treatment of various stress-related disorders and as compounds that can improve well-being and life satisfaction in healthy populations. Work across species is exploring how just 1-2 doses of these compounds can produce long-lasting effects, though attempts to study the psychedelic subjective effects in animal models are fraught with interpretive issues. Here, we instead look to other translationally relevant ways to explore which mechanisms may be critical to understanding the short- and long-term impacts of psychedelics, with a specific focus on the stress response.
The first speaker will describe how acute administration of LSD and MDMA impact cortisol, BDNF, and endocannabinoids in relation to subjective effects in healthy humans.
The next speaker will use fiber photometry to demonstrate acute effects of psilocybin on stress-driving CRH neurons in the paraventricular nucleus of the hypothalamus – highlighting important context-dependent and sex-divergent effects in mice.
The third speaker will demonstrate how acute administration of a DMT formulation influences stress-related outcomes following an acute laboratory stress challenge in healthy humans.
The final speaker will explore how a single dose of 5-MeO-DMT impacts immediate early gene expression in anxiety-related brain regions and promotes long-lasting anxiolytic effects in stressed mice.
Together, this panel will highlight the stress response as a novel mechanism that may be critical to the psychedelic experience and related prolonged effects, providing foundation for understanding how psychedelics may improve outcomes for those with stress-related psychiatric disorders.

Ana Deutsch *(Canada)*
S.13.1 - The impact of LSD and MDMA on stress-related biomarkers & the eCB system in healthy humans
Sarah Gibson Cook *(Canada)*
S.13.2 - Psilocybin induces sex- and context-specific recruitment of the stress axis
Helena Aicher (Switzerland)
S.13.3 - Impact of Ayahuasca-Inspired DMT/Harmine formulation on stress reactivity & the ANS in healthy humans

Symposium 14 • Beyond Reward Prediction Error: Translational Conceptualizations, Findings, and Applications that Shed a New Light on Dopamine's Function in Complex Behavior

Chair: Rita Z. Goldstein *(USA)*

Dopamine has been implicated in signaling RPEs plus a myriad added functions from value processing, to movement and action discovery, to salience and learning rate control. In this symposium we will emphasize novel concepts, and supporting computational modeling, preclinical experimental findings, and human research, which shed new light on dopamine's role in complex behavior. Vijay Namboodiri (UCSF) will discuss extinction and forgetting to highlight learning of retrospective associations between cues and rewards. He will use behavioral, dopaminergic and orbitofrontal cortical data collected using photometry and two-photon calcium imaging in mouse models to test predictions of an algorithmic framework of learning. Geoffrey Schoenbaum (NIDA) will show prediction-error like correlates in dopamine release in striatum during latent stimulus-stimulus learning in a sensory preconditioning task, in which dopamine transients were previously shown to play a causal role. Rita Goldstein (Mount Sinai) will present results in people with cocaine addiction suggesting that methylphenidate (a dopamine agonist) normalizes ventromedial prefrontal cortical signaling (and its connectivity with the amygdala) during standard extinction (of drug associated conditioning), an effect that was strongest when combined with post-retrieval extinction (during memory reconsolidation). Roshan Cools (Donders) will explore dopamine's role in meta-decisions about control and in tracking the controllability of the environment. Together, these talks will broaden views of dopamine's role in RPE encoding to accommodate alternative accounts, from abstract theoretical accounts to basic preclinical research in rodents to human higher order executive function in both health and disease.

Vijay Mohan K Namboodiri *(USA)*
S.14.1 - Extinction and retrospective learning
Geoffrey Schoenbaum *(USA)*
S.14.2 - Striatal dopamine signals errors in cue prediction during sensory preconditioning
Rita Goldstein *(USA)*
S.14.3 - Methylphenidate- and reconsolidation-enhanced drug memory forgetting in human addiction
Roshan Cools (Netherlands)
S.14.4 - Role of dopamine in controllability inference for human cognitive control

Symposium 15 • Addictive Substances and Their Impact on Brain and Molecular Pathways

Chair: Mohamed Kabbaj *(USA)*

Despite the widespread abuse of drugs, effective treatments remain elusive, largely due to a limited understanding of the molecular mechanisms and brain circuits underlying their long-term effects. This symposium, utilizing animal models, will explore key molecular pathways and specific brain circuits involved in addiction while highlighting potential targeted therapies for substance use disorders.
Dr. Maccari will open the session by discussing how perinatal stress influences alcohol consumption and sleep patterns in male and female rats, emphasizing the role of the glutamate receptors mGlu1 in mediating the interplay between stress and alcohol. Dr. Lobo will present findings on how perinatal fentanyl exposure induces molecular adaptations in the brain throughout development, leading to enduring behavioral consequences. Next, Dr. Kabbaj will follow with insights into the mechanisms behind ketamine's abuse potential, focusing on the involvement of medium spiny neurons (MSNs) in the nucleus accumbens. Finally, Dr. Wood will share recent research on the role of cholinergic neurons in the medial habenula in driving drug-seeking behavior, highlighting the necessity of the nuclear orphan receptor and transcription factor NR4A2 in regulating cocaine reinstatement.
Together, the presenters will provide an in-depth look at the mechanisms and brain circuits underlying some of the effects of alcohol, ketamine, opioids, and cocaine, offering insights into potential avenues for treatment.

Stefania Maccari *(France)*
S.15.1 - Prenatal stress effects on alcohol drinking: role of oxytocin and metabotropic receptors
Mary K Lobo *(USA)*
S.15.2 - Perinatal fentanyl exposure impacts behavioral and brain molecular mechanisms
Mohamed Kabbaj *(USA)*
S.15.3 - Role of medium spiny neurons in ketamine reinstatement
Marcelo Wood *(USA)*
S.15.4 - Investigating the opposing roles of the nuclear orphan receptor NR4A2 in drug-seeking and relapse of drug-seeking

Symposium 16 • Oxytocin: A Promising Old Acquaintance

Chair: Rossella Ventura *(Italy)*

The pharmacological story of the peptide oxytocin (OT) starts in the early 50s, with OT being used in gynecology for its action on the smooth muscle of the uterus. It proceeds through the 70s and 80s with the treatment of social difficulties in schizophrenia based on the discovery of OT acting as a peptide neurotransmitter and the compelling evidence of its role in affiliative processes. This ancient story is far from complete. Indeed, in the beginning of the second millennium evidence of OT transmission in brain circuits not specifically involved in social behaviour opened new areas of intervention.
The proposed symposium brings together researchers working on OT in this new context with different perspectives. Prof. Valery Grinevich (Heidelberg University, Germany) will provide a mechanistic view of OT's role in social behavior through specific corticolimbic pathways. Prof. Inga D. Neumann (University of Regensburg, Germany) will present the complex brain network engaged by OT to modulate social salience and buffering social stress. Dr. Bice Chini will present data collected in mice models of atypical neurodevelopment supporting the conclusion that OT, by integrating sensory inputs in newborns, promotes the development of the sensory-motor system (CNR, Italy). Finally, Prof. Simona Cabib (Sapienza University of Rome, Italy) will discuss the involvement of brain OT in the development of the corticolimbic circuitry involved in the attribution of motivational salience.

Valery Grinevich *(Germany)*
S.16.1 - Oxytocin signaling in the prefrontal cortex
Inga D. Neumann *(Germany)*
S.16.2 - Prosocial, anxiolytic, and Stress-protective effects of oxytocin in rodents
Bice Chini *(Italy)*
S.16.3 - Long-lasting effects of early life oxytocin administration in mice models of neurodevelopmental disorders
Simona Cabib *(Italy)*
S.16.4 - Role of oxytocin in the development of the motivational salience neurocircuitry

Symposium 17 • New Insights into Neuromodulatory Underpinnings of Adaptive Behaviour

Chair: Philip Jean-Richard-dit-Bressel *(Australia)*

Neuromodulators—like dopamine, serotonin, and norepinephrine—are known to mediate adaptive learning and behaviour. Correspondingly, perturbations in these systems are critically implicated in a variety of psychiatric conditions, and remain key targets for pharmacotherapies. However, the precise ways in which neuromodulators contribute to learning and decision-making remain unclear. This symposium brings together eminent researchers from across the world to showcase new findings on how neuromodulators act within different circuits to support different forms of adaptive behaviour, something that can open new avenues for the treatment of neuropsychiatric disease. Dr. Philip Jean-Richard-dit-Bressel (UNSW Sydney, Australia) will present unpublished data revealing dynamic and dissociated patterns of serotonin, noradrenaline, and dopamine release within the basolateral amygdala as animals learn to resolve different forms of motivational conflict. Dr. Emmanuel Valjent (INSERM, France) will present recent work showing how coordinated presynaptic and postsynaptic activation of dopamine D2 receptors (D2r) within the central extended amygdala jointly yet differentially regulate defensive behaviours. Dr. Laura Corbit (University of Toronto, Canada) will describe recent work from her lab showing how the locus coeruleus and forebrain noradrenaline signal deviations from expected reward across various tasks to support beneficial behaviour change. Finally, Dr. Jay Bertran-Gonzalez (UNSW Sydney, Australia) will present new findings showing how horizontal cell-to-cell neuromodulation involving two major cell types in the striatum dominate the plasticity landscape supporting adaptive goal-directed action. This symposium synthesises research using different behavioural and neuroscientific approaches to offer new insight into the neuromodulatory mechanisms of adaptive behaviour.

Emmanuel Valjent *(France)*
S.17.1 - Deconstructing the role of dopamine D2 receptors in motivated behaviors
Philip Jean-Richard-dit-Bressel *(Australia)*
S.17.2 - Monoamine release during instrumental versus Pavlovian aversive learning
Laura Corbit *(Canada)*
S.17.3 - Locus coeruleus activity promotes learning updates following changes in reward
Jay Bertran-Gonzalez *(Australia)*
S.17.4 - At D2-neuron’s discretion: revealing dominant D2-to D1-neuron modulation in learning

Symposium 18 • The Use of Non-Human Primates in Addiction-Related Research

Chair: Christelle Baunez *(France)*

The question of translatability of findings obtained in animals to humans is a recurrent issue, especially for psychiatric disorders. It is however important to maintain research using non-human primates in the field of psychopharmacology and this is why this symposium is important at EBPS meeting. The need for treatments for addiction remains and the search for pharmacological or surgical treatment requires the use of non-human primate models before validating results from rodents to a use in humans. In this session, we will review a few studies using drugs of abuse intake/self-administration in vervets or macaques and how these are used for the search of treatments. Sally Huskinson (University of Mississippi Medical Center, Jackson, USA) will present how male and female macaques self-administer food, cocaine, fentanyl, in various schedules of reinforcement. Then Paul Czoty (Univ. Wake Forest, North Carolina, USA) will present how cocaine use can affect ethanol drinking in macaques. The second part of the symposium will focus on therapies. The first one will focus on Glucagon-like peptide 1 on alcohol consumption in vervet monkeys, presented by Anders Fink-Jensen (University of Copenhagen, Denmark), while the second, presented by Christelle Baunez (CNRS & Aix-Marseille University, France) will show effects of Deep Brain Stimulation (DBS) applied in the subthalamic nucleus of macaques on their motivation for either apple sauce or cocaine. This symposium has 2 US speakers and 2 Europeans (Denmark and France). It is gender balanced with 2 female speakers (Huskinson and Baunez) and 2 male speakers (Czoty and Fink-Jensen).

Daniel Borgatti *(USA)*
S.18.1 - Role of sleep disruption in cognitive impairment associated with methamphetamine use in rhesus monkeys
Paul Czoty *(USA)*
S.18.2 - Nociceptin-orphanin FQ peptide (NOP) receptors as promising targets for substance use disorder medications: evidence from nonhuman primate models.
Christelle Baunez *(France)*
S.18.3 - Motivation for cocaine is reduced by subthalamic nucleus deep brain stimulation in macaques
Anders Fink-Jensen *(Denmark)*
S.18.4 - Effect of semaglutide and other glucagon-like peptide-1 (GLP-1) receptor agonists on alcohol consumption in alcohol-preferring vervet monkeys

Symposium 19 • The Role of Prefrontal Cortical Networks in Flexible and Compulsive Reward-Related Behavior

Chair: Ingo Willuhn *(Netherlands)*

The prefrontal cortex (PFC) is crucially involved in the regulation and control of motivated behavior and is thought to serve as the executive center for decision making, impulse control, and goal-directed actions. Its functional architecture encompasses several subregions, including the orbitofrontal cortex (OFC) and the ventral and dorsal aspects of the medial prefrontal cortex (vmPFC / dmPFC), each of which have been associated with critical but overlapping roles ranging from learning and adaptively responding to reward, signaling value, and supporting economic decisions, to name a few. Consistently, dysfunction or damage to the PFC is associated with a range of neuropsychiatric conditions, including ones that are characterized by impulsive and compulsive behavior. The first two panel speakers, Catherine Winstanley and Ingo Willuhn, will present studies that probed regional differences in the behavioral function of vmPFC, dmPFC, and OFC in rats preforming in custom-designed behavioral paradigms using lesions, in-vivo tetrode electrophysiology and calcium imaging with miniaturized fluorescence microscopes. Then, Frank Meye will demonstrate how stress can drive excessive intake of high-caloric food in mice via specific mPFC output pathways using optogenetics, in-vivo and ex vivo electrophysiology and ensemble tagging. Finally, Stephanie Borgland will show that obesity alters OFC function to impair goal-directed behavior via hypertrophic astrocytes in the OFC which lead to a dysregulation of neuronal signaling. The panel will discuss clinical and translational relevance of their findings, including the significance of the PFC in impulsive and compulsive behavior, as well as implications for our understanding of PFC contributions across species.

Catharine Winstanley *(Canada)*
S.19.1 - Frontal contributions to risky choice in rats
Ingo Willuhn (Netherlands)
S.19.2 - Cortico-striatal circuits mediate compulsive behavior in schedule-induced polydipsia
Frank Meye (Netherlands)
S.19.3 - A prefrontal cortex-lateral hypothalamus circuit controls stress-driven food intake
Stephanie Borgland *(Canada)*
S.19.4 - Effect of astrocyte dysfunction in the OFC on goal-directed behaviour

Symposium 20 • The Dual Impact of Cannabis: Chronic and Acute Effects of Cannabinoids on Human Behaviour

Chair: Sara Kroll *(Switzerland)*

In recent years, there have been increasing efforts to legalize (non-)medical use of cannabis worldwide. Despite the putative therapeutic potential of phytocannabinoids such as ∆9-tetrahydrocannabinol (THC) and cannabidiol (CBD), frequent cannabis use has also been associated with adverse cognitive functioning, psychotic symptoms, and psychopathologies such as schizophrenia and cannabis use disorder. Therefore, a comprehensive understanding of cannabis effects in healthy individuals as well as in psychopathologies is needed. This symposium will showcase recent and novel pharmacological findings of chronic and acute phytocannabinoid effects on human behaviour and in the development as well as treatment of psychopathologies. Lukas Eggenberger will present unpublished data from an ongoing Zurich cohort study of young adults showing increased cannabis use over a 4-year period based on THC and CBD hair concentration, and how this might modulate cognitive performance and internalizing/externalizing problems. Ziva Cooper will present findings on the impact of cannabis use frequency on the pharmacokinetic and pharmacodynamic effects of acute phytocannabinoid administration with a specific focus on analgesia and abuse liability as well as sex-differences. Amir Englund will follow up on acute pharmacological effects of THC and CBD, presenting recently published findings on cognition at 4 different ratios of CBD:THC in healthy volunteers, as well as novel data on potential protective effects of CBD on acute THC effects in individuals with schizophrenia. Connor Haggarty will close the symposium by presenting unpublished data from their current clinical trial exploring the role of THC and prolonged exposure therapy, as a potential treatment for post-traumatic stress disorder.

S.20.1 - Linking THC and CBD hair analytes to cognitive and mental health outcomes
Lukas Eggenberger *(Switzerland)*
S.20.2 - Sex-dependent effects of cannabis: Does use frequency impact outcomes?
Ziva Cooper *(USA)*
S.20.3 - The interactive effects of THC and CBD in healthy volunteers and schizophrenia patients
Amir Englund *(UK)*
S.20.4 - Harnessing the cannabinoid system for the treatment of PTSD
Connor Haggarty *(USA)*

Symposium 21 • Uncovering the Behavioral and Biological Factors Underlying Individual Differences in Risk for Alcohol Use Disorder

Chair: Andrew Holmes *(USA)*

Alcohol use disorder (AUD) has an enormous global health and economic burden, but the behavioral and biological factors that underlie individual differences in risk for AUD remain incompletely understood. This symposium will provide new insights into this critical question by showcasing largely unpublished preclinical (rodent) studies using state-of-the-art neuroscience techniques, coupled with sophisticated measures of alcohol-related behaviors. Because the speakers are at different career stages and backgrounds, the symposium aims to bring a range of perspectives to the central theme. Esi Domi (University of Camerino) will first present data showing a subset of female rats maintain alcohol-administration despite footshock and will relate this compulsive-like phenotype to an amygdala microcircuit. Next, Andrew Holmes (National Institute of Alcohol Abuse and Alcoholism) will discuss how emerging technologies exploiting computer vison and artificial intelligence can be effectively used to identify home-cage behavioral signatures that are predictive of later alcohol bring-drinking in mice. Céline Nicolas (INSERM) will then outline a comprehensive series of studies that employ neuronal recordings and causal manipulations to define a key role for the insular cortex in persistent mouse alcohol drinking. Finally, new work presented by Markus Heilig (Linkoping University) will show how transcriptional profiling of central amygdala neurons is being employed to identify novel molecular signaling pathways underlying individual variation in rat compulsive-like alcohol-seeking. Together, these presentations will provide the audience with a new perspective on preclinical efforts to understand the biological and behavioral basis of excessive alcohol drinking, with potential implications for the treatment of AUD.

Esi Domi *(Italy)*
S.21.1 - Individual differences and neural substrates in compulsive alcohol self- administration
Céline Nicolas *(France)*
S.21.2 - Contribution of the insular cortex to persistent alcohol drinking in mice
Andrew Holmes *(USA)*
S.21.3 - Artificial intelligence-based prediction of individual differences in mouse alcohol binge-drinking
Markus Heilig *(Sweden)*
S.21.4 - Massive single-nucleus transcriptional profiling reveals a novel molecular substrate of compulsive alcohol use

Symposium 22 • New Therapies for Psychostimulant Addiction

Chair: Malgorzata Filip and Christian P. Müller *(Poland/Germany)*

Psychostimulants are one the most frequently consumed drugs in the world addiction. Their consumption is linked with a loss of control over drug intake and is associated with structural, functional, and molecular alterations in the human or animal brain. Currently available clinical treatments on psychostimulant addiction exhibit limited or no efficacy, and new druggable targets are required. Investigating the pathophysiology of psychostimulant addiction enables the characterization of the underlying disease processes and provides a basis for the development of novel therapeutic approaches. This proposal aimes brand-new therapies for the psychostimulant addiction based on drug instrumentization theory for addiction, recent novel omics data, and novel pharmacoterapeutic agents.

Malgorzata Filip *(Poland)*
S.22.1 - Cocaine seeking during abstinence: effects of esketamine and Tat-NR2B9c peptide
Judith R. Homberg *(Netherlands)*
S.22.2 - Controlling cocaine reward and self-administration by targeting dopaminergic and serotonergic storage vesicles
Rainer Spanagel *(Germany)*
S.22.3 - Cell type-specific multi-omics analysis of cocaine use disorder in the addiction circuitry reveals new drug targets addiction circuitry reveals new drug targets
Christian P. Müller *(Germany)*
S.22.4 - The pharmacotherapy of psychostimulant use disorders – past, present, and future ideas

Symposium 23 • Sex Differences in the Risk, Pathophysiology, and Treatment of Neuropsychiatric Disorders

Chair: Christina Dalla *(Greece)*

Psychiatric and neurological disorders are often characterized by sex differences in prevalence, symptomatology, and treatment response. Major depression, as well as anxiety disorders, such as specific phobias, social anxiety, and generalized anxiety disorder, as well as post-traumatic stress disorder (PTSD) and Alzheimer's disease (AD), are more common in women than in men. This symposium will use both animal models and human studies to describe how sex-related variables interact with other environmental factors to alter psychiatric and neurodegenerative disorders and their treatment. Bangasser (GSU) will discuss the lasting effect of early-life resource scarcity on adult rat motivated behaviors. She will describe how alterations in glial function can mediate these effects. Dalla (NKUA) will present behavior, neurochemical, and neuroplasticity data on sex differences in the estrogen membrane GPER1 receptor in the rat brain, which could serve as a potential target for rapid-acting drugs. Campolongo (Sapienza) will present experimental evidence showing how adverse life experiences can lay the groundwork to psychopathologies development and discuss potential sex-specific therapeutics to treat pathologies such as PTSD. Nalvarte (Karolinska) will present novel data, derived from human cohorts and AD mouse models, on sex hormone treatments in relation to AD risk in postmenopausal women and in gender-affirming hormone therapy. Overall, these studies highlight the importance of studying sex differences and aim to improve sex-and gender-oriented neuropsychopharmacological treatments. The topics covered include a range of species and approaches and are relevant to many brain diseases. The panel speakers represent a diverse range of nationalities, countries, genders, and career stages.

Debra Bangasser *(USA)*
S.23.1 - Sex differences in the effects of early resource scarcity on motivated behavior
Christina Dalla *(Greece)*
S.23.2 - Sex differences in psycho-pharmacological effects of GPER1 estrogen membrane receptor
Patrizia Campolongo *(Italy)*
S.23.3 - Sex differences in fear expression and persistence in an animal model of PTSD
Ivan Nalvarte *(Sweden)*
S.23.4 - Sex hormones, gender, and the aging brain

Symposium 24 • Role of Microglia in Synaptic Plasticity Associated with Substance Use Disorders

Chair: Daniele Caprioli *(Italy)*

Drugs of abuse significantly impact neuroimmune functioning, with microglia playing a central role in these effects. Microglia are the brain's resident immune cells, responsible for maintaining homeostasis, responding to injury, and facilitating repair. However, prolonged drug abuse can dysregulate their activity, leading to chronic neuroinflammation and neuronal damage. In turn a compromised neuroimmune system by chronic stress or infections might exacerbate microglial reactivity, amplifying neuroinflammation and increasing susceptibility to addiction-related behaviors. To date, preclinical studies of addiction have mostly focused on neuronal mechanisms. However, a body of work increasingly recognizes the contribution of glia to the development and maintenance of addiction. Drugs of abuse induce microglia reactivity, causing an inflammatory cascade that disrupts neural signaling and plasticity. These alterations might reinforce drug use and craving, thus perpetuating the cycle of drug addiction. We believe that a symposium on microglia and addiction is timely and relevant due to emerging evidence of microglia's role in synaptic plasticity and circuit regulation, all critical to addiction. This topic aligns with the need for innovative strategies to address addiction and its connection to stress and mental health, making it highly relevant to behavioral pharmacology. The proposed talks delve into the mechanisms by which microglia influence neuronal function in brain regions crucial to drug use and relapse, particularly in response to psychostimulants, cannabis, and psychedelics. Furthermore, they examine microglia as central mediators of peripheral inflammation and stress that shape vulnerability to drug abuse. By bridging these perspectives, the talks highlight microglia's role in addiction-related behaviors.

Ingrid Reverte *(Italy)*
S.24.1 - Microglia and AMPA receptor plasticity during cocaine withdrawal
Marie-Eve Tremblay *(Canada)*
S.24.2 - The outcomes of cannabinoids and psychedelics on microglia
Jacqueline Barker *(USA)*
S.24.3 - Neuroimmune mechanisms of dysregulated cocaine seeking in a mouse model of HIV infection
Anne Mathia Klawonn *(Denmark)*
S.24.4 - Microglia in affective and motivational regulation – Striatal circuits and beyond

Nanosymposium 1 • Amyotrophic Lateral Sclerosis: From the Bench to the Clinic

Chair: Santiago Mora *(UK)*

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by death of corticospinal and somatic motor neurons, that leads to motor behavior impairments due to muscle paralysis and wasting and premature death. It has been known for a long time and intensively studied, however the reason is still unknown: although motor neuron degeneration is well-established and the main pathophysiological feature, recent evidence has pointed towards other mechanisms such as connectivity and metabolic alterations. Moreover, current Medicine does not have tools for early detection or proper treatments against the degeneration. Aside from the dramatic consequences to the patient, this debilitating condition carries a devastating load for the family, the community, and the health system in general, since every effort in providing good quality of life and larger life expectancy results in monumental health-related expenses. However, very little is known about the pathophysiology and putative treatments. The present symposium will shed light on the most recent findings regarding this condition from different research fields trying to extensively cover the evidence from an interdisciplinary approach. Thus, the speakers will cover the deficits observed in transgenic and mutant animal models, how cutting-edge therapy is aiming to tackle the disease, and the ultimate impact on life quality of patients.

Xavier Navarro *(Spain)*
N.1.1 - Pharmacological targeting Kv7 and TSPO as a therapeutical strategy for ALS
Beatriz Vélez-Gómez *(Spain)*
N.1.2 - Comprehensive pharmacological approach in ALS: quality of life beyond motor symptoms
Ilary Allodi *(UK)*
N.1.3 - Gene therapy strategies for the treatment of Amyotrophic Lateral Sclerosis

Nanosymposium 2 • Cannabinoid Regulation of Behaviour: Addiction, Cell Specificity and Development

Chair: Alejandro Higuera-Matas *(Spain)*

The endocannabinoid system plays a central role in regulating a wide range of behavioural and physiological processes and is essential for the proper development of the nervous system. In this symposium, we will examine how the endocannabinoid system functions as a key regulator of these processes and how its regulation can be influenced by exogenous cannabinoids. The first talk will focus on the heterogeneity of CB1 receptor actions, highlighting how signalling varies across brain regions, cell populations, and subcellular compartments, selectively modulating behaviours such as feeding, motor activity, cognition, and pain perception. The second talk will expand on this theme by exploring the "extended endocannabinoid system," with an emphasis on the PPAR-gamma receptor and its role in modulating cocaine-seeking behaviour in male and female mice. The role of cannabinoids in reward will be then discussed in more detail in the third talk, which will address the impact of adolescent exposure to natural cannabinoids (THC and CBD) and synthetic cannabinoids (e.g., those found in Spice). This presentation will provide data on how such exposure affects brain structure and function (as assessed by neuroimaging), gene expression, and behaviours related to cocaine or alcohol self-administration and self-medication. The crucial role of sex differences will be emphasised. Finally, the fourth talk will examine the specific contributions of THC and CBD to behavioural alterations, with a particular focus on differences observed in female subjects.

Luigi Bellocchio *(France)*
N.2.1 - Cellular and Sub-cellular targets of cannabinoids: from signaling to behavior and beyond
Mireia Medrano *(Spain)*
N.2.2 - The role of PPAR-gamma as a modulator of cocaine-seeking behaviour in male and female mice
Alejandro Higuera-Matas *(Spain)*
N.2.3 - Exposure to cannabinoids during adolescence as a risk factor for psychopathology
Erika Zamberletti *(Italy)*
N.2.4 - Sex-dependent consequences of adolescent exposure to different THC and CBD combinations

Nanosymposium 3 • Beyond D1 and D2 Dopamine Receptor-Expressing Neurons: Modulating Circuits and Behavior

Chair: Michelle W. Antoine *(USA)*

Dopamine plays a crucial role in movement and cognition by binding to five G protein-coupled receptor subtypes: D1-like (D1, D5) and D2-like (D2, D3, D4). While D1 and D2 receptors have been extensively studied due to their prominence in the basal ganglia, the roles of D3, D4, and D5 remain less understood despite growing evidence of their involvement in addiction and cognitive processes. This symposium will explore how D1 and D2 neuron innervation of globus pallidus interneurons influences motor control and rewarded actions. Moreover, it will largely examine the pharmacology and functions of lesser-studied dopamine receptors, as well as striatal cells co-expressing D1 and D2 receptors and the debated existence of D1-D2 heteromers in rodent and non-human primate brains. These topics challenge traditional dopamine receptor models by highlighting underexplored receptor subtypes and their roles in brain function and disease. Focusing on D3 and D4 receptors in addiction-related behaviors and D5 receptor function in memory, this symposium will provide insights to inform therapeutic strategies for substance use disorders and cognitive dysfunction. Additionally, investigating D1-D2 heteromers and co-expressing striatal cells in typical and neurodevelopmentally altered brains, such as in autism, may uncover novel dopamine signaling mechanisms underlying behavioral impairments. Ultimately, this symposium aims to challenge existing paradigms and open new avenues for targeted therapeutic interventions.

Bernard Le Foll *(Canada)*
N.3.1 - Dopamine D3 receptors in nicotine addiction: from preclinical to clinical studies
Melissa Perreault *(Canada)*
N.3.2 - Exploring the functional role of Gq-coupled dopamine receptors in the brain
Michelle W. Antoine *(USA)*
N.3.3 - Roles of striatal neurons co-expressing dopamine D1/D2 receptors in autism mouse models

POSTERS SESSION 1

P.1.1 - Endogenous serotonin modulates psychedelic-like effects of psilocybin in mice

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The psychedelic serotonin 2A receptor (5HT2AR) agonist psilocybin has been posited as efficacious for the treatment of depression. However, the potential link between the intensity of acute psychedelic effects and long-term therapeutic outcomes remains undiscovered. Moreover, the impact of classical antidepressant drugs that modulate serotonergic activity on psilocybin's effects is a clinically relevant concern. We aimed to assess serotonergic mechanisms implicated in the regulation of the intensity of psilocybin-induced acute effects. In the present work, we performed the head-twitch response (HTR), deemed as the most translational behavioural assay to characterize psychedelic-like effect in rodents. Furthermore, in vivo brain microdialysis technique was employed to study the role of endogenous brain cortex synaptic serotonin (5-HT) on psilocybin-induced HTR.Synaptic increase of 5-HT by citalopram dose-dependently attenuated HTR induced by maximally effective psilocybin dose (1 mg/kg, i.p.), after both acute and chronic dosing regimens. Conversely, cortical depletion of 5-HT by tryptophan hydroxylase inhibitor p-chlorophenylalanine (PCPA) potentiated psilocybin-evoked HTR. Moreover, a significant inverse correlation was found between cortical 5-HT and HTR. Serotonin 1A receptor (5HT1AR) agonist 8-OH-DPAT dose-dependently decreased psilocybin-induced HTR, demonstrating functional interaction between 5HT2AR and 5HT1AR for psychedelic effects.In conclusion, cortical 5-HT and acute psychedelic-like effects of psilocybin are inversely correlated. Therefore, the enhancement of serotonergic activity induced by prior antidepressant treatment may underlie interindividual variability in the acute response to psychedelics. Further research on these mechanisms in the context of sustained therapeutic outcomes of psilocybin could contribute to optimizing the efficacy of psychedelic-based therapies.

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Keywords. Psychedelics, psilocybin, head-twitch response, serotonin, antidepressant

P.1.2 - Therapeutic effects of the psychedelic 5-MeO-DMT in opioid use disorder

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Opioid use disorder (OUD) is a severe problem worldwide, and opioid overdose related deaths continue to soar. Serotonergic psychedelics and psychedelics-inspired non-hallucinogenic compounds have recently re-emerged as promising treatments for psychiatric disorders. Importantly, their plasticity-promoting properties may produce long-lasting therapeutic changes in the functioning of neural circuits. This is particularly important given the known disruptions in cognition and the functioning of the reward system after extended periods of drug use. 5-methoxy-dimethyltryptamine (5-MeO-DMT), a classic serotonergic psychedelic, acts mainly through serotonin 1A and 2A (5-HT1A/2A) receptors, which are widely expressed in the medial prefrontal cortex (mPFC) - a key brain region involved in cognition, motivation and impulse control that shows reduced activity in substance use disorders. Here we show that 5-MeO-DMT decreases drug-seeking behavior in a mouse model of heroin self-administration under a progressive ratio of reinforcement. We also investigated whether chemogenetic activation of 5-HT2A expressing neurons could mimic the therapeutic effects of psychedelics. To this end we utilized a Htr2a-IRES-Cre transgenic mouse line for chemogenetic manipulations of 5-HT2A expressing neurons in the mPFC. Chemogenetic stimulation of 5-HT2A expressing neurons significantly reduced opioid-seeking behavior during cue-induced reinstatement. Ongoing studies are examining the effects of chemogenetic inhibition of these neurons, and mechanistic insights into the role of the 5-HT2A receptor in the mPFC in the therapeutic effects of psychedelics. In sum, our findings indicate that targeting 5-HT2A expressing neurons may offer a novel approach for reducing opioid relapse, and support the use of psychedelic and psychedelic-like interventions for the treatment of OUD.

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Keywords. Opioid use disorder, heroin, 5-MeO-DMT, chemogenetics, 5-HT2A receptors

P.1.3 - Psilocybin disrupts heroin cue reactivity in prefrontal cortex neuronal ensembles

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Current pharmacological treatments for opioid use disorder (OUD) often fail to provide long-term protection against relapse and present risk of misuse and abuse. In recent years, psychedelics, a group of drugs that promote structural and functional neuroplasticity, have gained traction as powerful therapeutic tools for a variety of neuropsychiatric disorders, including OUD. The ability of psychedelics to mitigate relapse triggered by heroin cues suggests that one possible mechanism of action may involve regulation of opioid cue reactivity at the level of cue-encoding neuronal ensembles. Previous work in our lab has identified distinct ensembles in the infralimbic prefrontal cortex (IL-PFC) that exhibit heroin cue reactivity measured as increased calcium transients with in vivo fiber photometry. Furthermore, separate cue-reactive ensembles projecting to the lateral hypothalamus (LH) or the nucleus accumbens shell (NAsh) drive or limit heroin seeking, respectively. In this study, we used fiber photometry to investigate how psilocybin changes activity in these IL-PFC heroin-cue reactive ensembles that regulate heroin seeking. Administration of psilocybin (3.0 mg/kg) 24 hours prior to a test of cued heroin relapse reduced heroin-cue reactivity in both IL-PFC ensembles, an effect that lasted at least 72 hours. These findings suggest psilocybin modulates activity in heroin-cue reactive neuronal ensembles that regulate heroin seeking during relapse. This highlights the therapeutic potential of psilocybin and other psychedelic compounds for the treatment of OUD.

Funding. R01DA056660 and R01DA061766

Keywords. Psilocybin, psychedelic, heroin, fiber photometry, addiction

P.1.4 - Signs of antidepressant-like effects following adolescent ketamine in selectively bred low-responder rats

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Previous studies from our group proved sex- and dose-dependent antidepressant-like effects of subanesthetic doses of ketamine in rats of both sexes. This follow-up and collaborative study aimed at validating the effects of ketamine in an animal model of innate internalizing behavior (bred low-responder, bLR, rats). To do so, bLR rats of both sexes (male, n=33; female, n=39) were selected after breeding at the University of Michigan facilities based on their locomotor response in a novel environment which was tested after weaning. Then, during mid-adolescence rats were treated i.p. with ketamine (5 or 10 mg/kg) or vehicle (saline) for 7 days. Antidepressant-like responses were assessed under the stress of the forced-swim test (FST) 30 min after a single dose (acute effects), and 24 h after the 7-day treatment (repeated effects). Statistical evaluations were done through two-way ANOVAs (independent variables: Sex and Treatment) followed by post-hocanalysis when appropriate. The main results proved that the highest dose tested of ketamine (10 mg/kg) induced acute and repeated antidepressant-like responses by improving swimming behavior in the FST, although exclusively in male bLR rats (acute: vehicle=7±1 s; ketamine=15±2 s; p=0.023; repeated: vehicle=5±1s; ketamine=10±2 s; p=0.027). Ongoing experiments are processing biological samples from another group of allocated bLR rats (male, n=18; female, n=18) that were treated with ketamine (or vehicle) and sacrificed after 30 min, in order to evaluate potential molecular correlates underlying the sex-specific effects of ketamine in particular brain regions. In conclusion, and in line with our prior studies, the present results validated the antidepressant-like potential of ketamine in a sex-specific manner, as now observed in an inborn model of internalizing behavior. Future studies should better understand the mechanisms behind the observed sex differences.

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Keywords. Depression, Adolescence, Ketamine

P.1.5 - Characterization of the acute effects of psilocybin in male and female aging mice

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Anatomical and physiological changes during aging predispose to the development of late-life depression and reduce the efficacy of classical antidepressants. The psychedelic serotonin 2A receptor (5HT2AR) agonist psilocybin has been proposed as a novel, fast-acting antidepressant. However, the impact of age-associated changes in the serotonergic system on the effects of psilocybin remains unknown. Here, we used the head-twitch response (HTR) paradigm to evaluate possible age- and/or sex-related differences on the acute psychedelic-like response to psilocybin in mice. Male and female adult (3 months, n=16) and aged (16-22 months, n=18) C57BL/6J mice were treated with two doses of psilocybin (1 mg/kg, i.p.; n=4-5/group) or saline (n=4-5/group) on days 1 and 7. Mice were immediately placed in an open field arena and 25 min of free behavior were recorded. HTRs were counted (5-25 minutes) by a blinded experimenter, and locomotor activity was assessed using ANY-maze software. Data were analyzed by three-way ANOVA to address the interactions between age, sex and psilocybin treatment. Regarding HTR, significant effects of treatment ($F(1,21)=79.38$; $p<0.0001$), sex ($F(1,21)=10.28$; $p<0.01$), and sex xtreatment ($F(1,21)=9.42$; $p<0.01$) were observed, with no effects attributable to age alone or in combination with sex and/or treatment. For locomotor activity, only a sex xage effect ($F(1,21)=0.5.79$; $p<0.05$) on the travelled distance was observed. In conclusion, psilocybin-induced acute effects were not affected by aging. The present findings prompts further investigation into the potential antidepressant effects of psilocybin in late-life depression. Furthermore, these results highlight the need to explore potential sex differences in the effects of psilocybin in both preclinical and clinical research.

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Keywords. psilocybin, antidepressant, aging, head-twitch response, sex-differences, psychedelic

P.1.6 - Challenges with the use of sweet additives in an oral morphine self-administration task in male and female rats.

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Introduction:To improve translatability of morphine self-administration (SA), we developed a two-lever oral morphine SA task with a reinforcer solution containing grapefruit juice (GFJ), thought to enhance morphine's bioavailability, and a sucrose (SUC) fading procedure. Despite our original hypotheses, following stable self-administration, pre-session injections of methamphetamine, fentanyl, morphine, and naloxone evoked minimal effects on SA. Questioning of morphine's role in lever reinforcement then arose due to the sweet additives and limited knowledge of GFJ's pharmacokinetic impact on morphine's metabolism in rats. Methods: Exp 1: Male and female rats were trained to lever press using a SUC fading procedure: half with GFJ, half without. Seven 10-session phases followed, each modifying a component of the solution to assess additive-dependent differences in responding. Exp 2: In a separate set of rats, to discern morphine's pharmacological role, a two-day test cycle followed acquisition under the same training conditions. Day 1, rats were pretreated with saline, Day 2 with 1mg/kg naloxone. Results:Exp 1: Training history altered behavior across phases. Removal of SUC extinguished lever pressing for SUC-trained rats, but not GFJ-trained rats. Presenting GFJ alone increased lever pressing for both training histories. Exp 2: Sex and additive dependent differences were present throughout acquisition. Naloxone pretreatment decreased lever pressing in both sexes; however, the magnitude of difference was significantly greater in males. Conclusions: These findings suggest a large role for sweet additives in the reinforcer solution, primarily GFJ, on operandum responding over the pharmacological effects of morphine. Thus, utilizing GFJ in oral morphine SA ambiguates characterization of drug-specific seeking.

Keywords. Morphine, Oral self-administration, Poly-substance

P.1.7 - Novel behavioral approaches to evaluate psychotic-like states induced by Delta-9-Tetrahidrocannabinol in mice

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Cannabis is the most widely consumed illicit drug, and its use is associated with an increased risk of developing psychotic symptoms, including positive psychotic-like states and impairments in social and emotional skills. However, the neurobiology of these psychotic-like states remains poorly understood, partly due to the limitations of existing animal behavioral paradigms. Recent studies suggest that complex cognitive processes, such as higher-order conditioning, may help to model and study the drug-induced psychotic-like states. In rodents, higher-order conditioning is explored through sensory preconditioning, where two low-salience stimuli are paired in the preconditioning phase and later, one stimulus is conditioned with a reinforcer. This leads to conditioned responses not only to the directly conditioned stimulus, but also to the non-conditioned stimulus through mediated learning (ML). As the preconditioning phase increases, ML transitions into "reality testing" (RT), which enhances stimuli discrimination. RT impairment is considered a hallmark of psychotic-like states. In this study, we established a light-tone sensory preconditioning task in male and female mice and developed a RT protocol by enhancing light-tone associations during preconditioning. We found that an acute injection of Delta-9-tetrahydrocannabinol (THC,1mg/kg) impaired RT in male mice, suggesting disruption in mental sensory processing. Additionally, we used advanced behavioral tracking tools to assess THC's impact on social and emotional recognition. Future research will investigate the molecular mechanisms of THC-induced psychotic-like effects, focusing on mitochondrial cannabinoid receptor-1 dependent processes, with the goal of identifying new therapeutic targets for psychiatric disorders.

Funding. Caixa Health Research

Keywords. THC, psychotic-like states, sensory preconditioning

P.1.8 - Role of the lateral hypothalamus in the hyperdopaminergic phenotype induced by prenatal THC exposure

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Cannabis is the most commonly used illicit drug in Europe. Latest reports show an increased cannabis use among the female population, especially among pregnant and breastfeeding women. This concern is amplified by the availability of cannabis preparations containing increasingly higher concentrations of delta-9-tetrahydrocannabinol (THC), the main psychoactive component of cannabis, thus increasing the risk of adverse effects in the progeny. THC crosses the placenta and the fetal blood-brain barrier, thus affecting neurodevelopment. Clinical evidence demonstrates that fetal exposure to cannabis increases the risk to manifest psychopathologies throughout the lifespan. In an animal model of prenatal cannabis exposure (PCE), we have previously shown a sex-dependent aberrant sensorimotor gating function in response to an acute exposure to THC or stress, and deficits in social behavior at preadolescence. In PCE males, these behavioral alterations are associated with a hyperdopaminergic tone arising from the ventral tegmental area (VTA) and a reduced inhibitory transmission on dopaminergic neurons. Females do not show any of these alterations. The lateral hypothalamus (LH) provides one of the most robust inhibitory inputs to the VTA and plays a critical role in social interaction. Here, by combining optogenetic manipulation with ex vivorecordings and behavioral assessment, we interrogate LH GABAergic input to VTA dopamine neurons to disclose its role in the PCE-induced sex-specific hyperdopaminergia and social deficits. These findings may help to elucidate the underpinnings of the increased susceptibility to the manifestation of psychopathologies in the progeny exposed in utero to THC.

Funding. The present study is funded by the Horizon Europe 2022 Excellent Science - European Research Council (101088207 to M.M.)

Keywords. Cannabis, dopamine, lateral hypothalamus, neurodevelopment, optogenetic, vulnerability

P.1.9 - Dysregulation of tryptophan metabolism and the disinhibition of dopamine neurons induced by in utero cannabis exposure

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Cannabis use among pregnant women for both medical and recreational purposes has followed an increasing trend over the last decades. Clinical evidence is accumulating on the effects of prenatal cannabis exposure (PCE) leading to deviations of neurodevelopmental trajectories with behavioral manifestation including impulsivity, hyperactivity, emotional dysregulation and increased risk for ASD, ADHD and psychotic-like experiences. Similarly to other psychiatric conditions, PCE causes a dysregulation of tryptophan metabolism, particularly through the kynurenine pathway, thereby leading to the accumulation of brain kynurenic acid (KYNA), as observed in the medial prefrontal cortex of PCE male progeny. KYNA accumulation in post-mortem brain is also a typical sign of schizophrenia.We previously demonstrated that PCE in rats leads to a male-specific hyperdopaminergic state tied to a stress-induced sensorimotor gating disruption (a measure of psychotic-like experiences), thus recapitulating the effects observed in PCE children. An imbalance between excitation and inhibition in dopamine neurons is a key determinant of this hyperdopaminergia. By combining pharmacological, electrophysiological and optogenetic approaches, we dissected the molecular and circuit mechanisms implicated in PCE-induced disinhibition of dopamine neurons driving stress-induced sensorimotor gating disruption. By counteracting the effect of KYNA, we rescue mesolimbic dopamine pathway function. Collectively, our findings are paving the way for early therapeutic intervention to confer resilience towards mental conditions falling under psychotic spectrum.

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Keywords. cannabinoid, dopamine, kynurenic acid, neurodevelopmental disorders, psychotic spectrum

P.1.10 - A preclinical study evaluating the impact of temozolomide on affective- and cognitive-like responses in adult rats of both sexes

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In the context of cancer-depression comorbidity, the main chemotherapeutic drug used for the treatment of glioblastoma, temozolomide, is known to affect healthy brain cells by inhibiting adult hippocampal neurogenesis. Given that a decrease in this process is associated with depressive-like symptomatology, and since depression is often comorbid in many patients with brain cancer, this preclinical study aimed at evaluating how temozolomide might impact affective- and cognitive-like responses in rodents while including sex as a biological variable. To do so, adult Sprague-Dawley rats (n=39 females, n=40 males) were treated with temozolomide (2 cycles: 25 mg/kg, i.p., 5 days/cycle, 1 dose/day, 10 days total with 2 resting days in between cycles, n=9-11) or vehicle (DMSO, 1ml/kg, n=9-11). Groups of allocated rats were scored through specific behavioral tests that capture different manifestations of affective-like responses (i.e., forced-swim, novelty-suppressed feeding, sucrose preference and/or open field). Moreover, the long-term effects of temozolomide on cognition were evaluated with the Barnes maze (short- and long-term memory). Data were analyzed through two-way ANOVAs (independent variables: Sex and Treatment) and showed that temozolomide did not induce any significant changes in the behavioral tests evaluated. In conclusion, even though temozolomide decreases hippocampal neurogenesis, it did not seem to have a negative impact on affective-like behavior and/or long-term cognition in adult rats of both sexes. Yet, future studies should evaluate the pharmacological interactions of this chemotherapeutic drug with potential antidepressants in order to select appropriate treatments in the context of cancer-associated depression.

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Keywords. temozolomide, neurogenesis, depression

P.1.11 - Tributyrin reverses the deleterious effect of saturated fat on memory and plasticity in juvenile mice in a sex dependent manner

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Short-chain fatty acids derived from the intestinal fermentation of dietary fiber, have been proposed as a treatment for certain pathologies of the central nervous system. Our research group has shown that tributyrin (TB), a butyric acid prodrug, reverses deficits in spatial memory and modulates hippocampal synaptic plasticity. Diets enriched in saturated (SOLF; Saturated OiL-enriched Food) or unsaturated (UOLF; Unsaturated OiL-enriched Food) fats were administered to young male and female mice for either 2 hours or 8 weeks, and the effect of a TB-enriched diet administration was studied on spatial learning and memory (SLM) using both the Y-maze and the eight-arm radial maze. Additionally, hippocampal expression of genes involved in glutamatergic transmission and synaptic plasticity, as long-term potentiation (LTP) were also analyzed. Our results demonstrate that a TB-treatment reversed the impairment of working memory and synaptic plasticity induced by enriched-fat diets and these effects are dependent on the diet, treatment duration, and sex. Specifically, 2 hours-SOLF intake impaired LTP and spatial memory only in male mice. In contrast, 8-week treatment with SOLF/UOLF deteriorated SLM measured in the RAM in both sexes. Moreover, TB reversed the detrimental effects of SOLF in males and UOLF in females in SLM and synaptic plasticity, suggesting a potential beneficial influence of this molecule in learning and memory processes. These effects appear to be associated to the LTP-facilitation induced by TB through PPARγ and AMPK molecular pathways. Our study suggests that TB may offer therapeutic benefits for memory impairment by improving hippocampal synaptic plasticity and spatial memory.

Funding. Ministerio de Ciencia e Innovación (PID2020-117422RB-C22)

Keywords. tributyrin, hippocampus, synaptic plasticity, high-fat diets

P.1.12 - Chronic methylphenidate consumption during adolescence reduces parvalbumin neurons in prelimbic and disrupt long-term attentional maintenance

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Adolescence is marked by a profound reorganization of the medial prefrontal cortex (mPFC), particularly within the GABAergic inhibitory network mediated by parvalbumin (PV+) interneurons. Methylphenidate (MPH) is the primary drug prescribed to treat patients with attention-deficit/hyperactivity disorder (ADHD). Most patients are diagnosed at an early age and consequently consume MPH over extended periods. However, ADHD's complex diagnosis, coupled with a false perception of safety, have led to its global misuse by healthy individuals seeking to enhance memory and attention. This study examined whether chronic MPH exposure during adolescence could influence PV+ neurons acquisition and, as a result, whether fluctuations in GABAergic neuronal activity persist into adulthood, impairing mPFC-dependent functions like sustained attention. Male and female Wistar rats received ad libitum 5mg/kg MPH – equivalent to human therapeutic dose– dissolved in their water bottle for 20 days from different onsets: early (PD35-55), middle (PD42-62) and late adolescence (PD49-69). From PD100 onwards, they underwent attentional behavioral testing, where pressing a lever in presence ('hit') or absence ('correct rejection') of a visual light stimulus was required. After reaching>75% correct hits and CR criteria, exposure time was shortened to 500ms, 100ms and 25ms. Our findings revealed a selective impairment of PV+ neurons acquisition in prelimbic, but not infralimbic, only in animals exposed to MPH during PD49-69. This alteration disrupted attentional maintenance and visual discrimination abilities, with effects persisting into adulthood. These results underscore the crucial relationship between PV+ and attentional processes, identifying specific windows of vulnerability in the functional maturation of mPFC during adolescence.

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Keywords. Parvalbumin, adolescence, methylphenidate, attention, prelimbic

P.1.13 - Behavioral effects of different methylphenidate doses on fear conditioning and locomotor activity in adolescent and adult Wistar rats: sex-specific differences

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Methylphenidate (MPH) is commonly used as a psychostimulant to treat Attention Deficit Hyperactivity Disorder (ADHD). Recent studies suggest that the maturation of the prefrontal cortex during adolescence plays a crucial role in the development of cognitive abilities and emotional regulation. As a result, the use of psychoactive substances during this developmental stage may disrupt the typical progression of the prefrontal cortex. This research analyses the effects of both chronic and acute MPH consumption during adolescence and adulthood in male and female Wistar rats. With this aim, we used tasks such as extinction fear conditioning and locomotor activity.In fear conditioning procedure, we used adult Wistar rats (40 weeks old) divided into four groups based on: drug (MPH vs. saline) and period of development for drug application (adolescence vs. adulthood). Thus, the four groups were SAL-SAL (no drug), MPH-SAL (drug during adolescence), SAL-MPH (drug during adulthood), and MPH-MPH (drug during both periods). For the conditioning phase, animals were exposed to five trials with a tone (85 dB, 1500 Hz, 10 s) paired with a footshock (0.8 mA, 0.5 s). The day before we started an extinction phase with four sessions (one per day), where the conditioned stimulus was presented without the electric shock for 10 trials. We also used a drug-free test.For locomotor activity, we conducted four days of testing in 40 weeks old rats. Similar to the former experiment, three groups receiving either saline or MPH during adolescence and tested during adulthood. On the third day of testing, all of them received acute MPH 30 minutes before the behavioral test. All animals were re-tested on the fifth day after withdrawal.Results showed significant effects based on age, sex, and dosage of MPH. This study underscores the importance of considering individual differences in the effects of pharmacological treatments, especially during adolescence, and emphasizes the need for further research in this area.

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Keywords. Methylphenidate, Wistar Rats, Extinction Fear, Locomotor Activity

P.1.14 - Deciphering the involvement of the Paraventricular Nucleus in oxytocin's regulation of methamphetamine addiction behaviours: a chemogenetic approach

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No approved pharmacotherapies exist for methamphetamine (METH) addiction, highlighting an urgent need for therapies addressing neurobiological changes driving the disorder's onset and maintenance. Oxytocin (OXT) has emerged as a promising candidate due to its interaction with addiction-relevant brain regions and encouraging preclinical results following exogenous OXT administration. While these effects are known to result from binding to brain reward circuit receptors, it remains unclear whether this is direct binding of exogenous OXT, or if exogenous OXT binds peripheral receptors and stimulates central release via a feed-forward mechanism in the paraventricular nucleus (PVN) of the hypothalamus. We utilised chemogenetics to activate or inhibit PVN OXT neurons in a METH self-administration model. Rats receive bilateral PVN intracranial injections of Otp-Gq-mCherry or Otp-Gi-mCherry and jugular vein catheters for METH delivery. After METH acquisition, deschloroclozapine will be administered to modulate PVN OXT neuron activity. Subjects undergo testing at multiple fixed-ratios to assess contribution of PVN OXT signalling at various efforts. While ongoing, we hypothesise activation of PVN OXT neurons will reduce METH self-administration, and inhibition of PVN OXT neurons alone will not impact METH self-administration, however, may block low i.p. OXT doses, and dampen the effects of high i.p. doses. Understanding PVN's role in exogenous OXT signalling is crucial for developing effective OXT-based therapies. Given OXTs low blood-brain barrier penetration and poor drug-like properties, the molecule itself has little therapeutic utility. However, if peripheral OXT receptor binding and subsequent PVN-mediated central release is sufficient to reduce drug-seeking, this insight could significantly advance OXT-targeted pharmacotherapies.

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Keywords. Oxytocin Methamphetamine Addiction Chemogenetics

P.1.15 - Stimulant solutions, sleepless nights: dexamphetamine and lisdexamfetamine suppress binge eating but disrupt sleep in female rats

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Introduction: Individuals with binge eating disorder (BED), which is characterised by recurrent episodes of excessive, fast-paced food intake over a short period, often report comorbid sleep disturbances such as insomnia. The only FDA-approved medication for BED, lisdexamfetamine, which is endogenously metabolised to dexamphetamine, can suppress appetite and reduce binge episode frequency. However, lisdexamfetamine treatment has also been reported to cause iatrogenic sleep disturbances, especially when administered in the evening when most binge episodes occur. At present, no quantitative studies (clinical or preclinical) have assessed lisdexamfetamine- and dexamphetamine-induced sleep disturbances at doses that suppress binge eating. Methods: Adult female Long Evans rats were surgically implanted with radiotelemetry probes to record electroencephalographic and electromyographic data. Polysomnographic (PSG) recordings were scored for wake, NREM, and REM sleep to assess sleep outcomes. Binge-like eating was measured using an intermittent access model, where rats with ad libitumchow received a sweetened fat mixture (8.6 kcal/g) for 30 min twice weekly on nonconsecutive days. Dexamphetamine hemisulfate (0.1875, 0.375, 0.75, 1.5 mg/kg) and lisdexamfetamine mesylate (0.463, 0.927, 1.854, 3.371 mg/kg) were administered via the intraperitoneal route. For sleep assessment, 19-h PSG recordings (ZT23-ZT18) were conducted with drug administration at ZT23. For assessment of binge-like eating, drugs were administered 30 min before testing (ZT20-22). Results: Dexamphetamine and equivalent doses of lisdexamfetamine dose-dependently suppressed binge-like eating and disrupted sleep. At the lowest effective doses that attenuated binge-like eating, both drugs markedly delayed sleep and REMS onset, increased wake time, and reduced both NREM and REM sleep during the first 3 hours of the light phase, with little to no rebound sleep recovery observed at later timepoints. Conclusion: We confirm qualitative clinical reports of significant iatrogenic sleep disturbances induced by lisdexamfetamine and its active metabolite used as a treatment to suppress binge eating. As poor sleep can itself enhance appetite and shift preferences to calorie-dense palatable foods (i.e., those typically consumed during binge episodes), novel treatments that suppress binge eating without causing iatrogenic sleep problems are warranted.

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Keywords. sleep, dexamphetamine, lisdexamfetamine, binge eating, rat

P.1.16 - Role of the olfactory system in the vulnerability to flavored nicotine addiction in electronic cigarettes

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The use of electronic cigarettes (e-cigs) has surged in the past 20 years. These devices heat e-liquid containing nicotine and flavor additives into an aerosol form. While studies suggest flavors increase e-cigs use, neurobiological mechanism behind this remain understudied. Therefore, this study aims to understand the neurobiological substrate involved in the rewarding properties of inhaled flavored nicotine using complementary approaches combining an innovative behavioral paradigm of vaping exposure and neurobiological investigation. We first developed a nicotine-vaping induced conditioned place preference (CPP) protocol to test the rewarding effect of nicotine and flavors in a mouse model. In males, flavored nicotine dose-dependently increases CPP and decreases conditioned response variability. In females, increasing nicotine doses induce significant conditioned place aversion, which is prevented with the addition of flavors. Sex differences in behavioral response were supported by differences in nicotine metabolism. A large-scale c-fos analysis targeting key brain regions was then performed. Following exposure to flavored nicotine, increased c-fos expression was observed in the olfactory tubercle (OT) a key structure receiving direct projections from both the ventral tegmental area (VTA) and the olfactory bulb (OB), supporting its role in both olfactory and reward processes. Using fiber photometry coupled with fluorescent calcium marker, we recorded OT neurons dynamic changes in vivo upon passive exposure to vaping and observed a modification in the activity pattern specifically with flavored nicotine vape inhalation. Altogether, these findings provide insight into the role of the OT in processing the sensorial aspect of e-cig reward, which is essential to further understand increased approach and attractiveness induced by flavors in e-cigs.

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Keywords. E-cigarette, flavored nicotine, addiction vulnerability, olfactory reward, olfactory tubercle

P.1.17 - Discriminative and proteomic effects of nicotine vs cigarette smoke extract in rats

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Introduction:Although nicotine (NIC) is generally the primary alkaloid investigated for tobacco use disorder, the other ~8000 constituents in cigarette smoke are thought to interact with NIC to affect its etiology. The behavioural study used a Pavlovian drug discrimination task; we hypothesized that rats could discriminate between NIC and cigarette smoke extract (CSE) of the same NIC concentration based on the presence of constituent chemicals. We have also begun investigation of brain proteomic changes resulting from long-term exposure to CSE, NIC, or vehicle (VEH). Methods: Behaviour is assessed using three types of occasion setting training: NIC discriminating from VEH, CSE discriminating from VEH, and CSE discriminating from NIC. Separate rats were injected daily for 28d with CSE, NIC, or VEH, and brains were excised for proteomic processing. Results:Subjects discriminate between NIC and VEH and between CSE and VEH; they are unable to discriminate between CSE and NIC after 72 sessions. However, preliminary results suggest differential proteomic changes evoked by CSE vs NIC. Conclusions: Our results confirm that CSE is a successful occasion setter and adds to prior NIC literature. Interestingly, we demonstrate that CSE and NIC do not create distinct interoceptive environments under these training conditions and differences may be occurring at the cellular level instead. This has implications for ongoing discussions regarding nicotine as a proxy for tobacco in animal models.

Keywords. Nicotine, Cigarette Smoke Extract, Proteomics, Occasion Setting, Rats

P.1.18 - Ascertaining the behavioral responses induced by different anesthetic drugs administered during adolescence in rats of both sexes

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The induction of electroconvulsive seizures (ECS) is a safe option for adolescent treatment-resistant depression, although more studies are needed to improve its used in humans, which is applied under anesthesia. In fact, the choice of anesthetic is important for ECS' effectiveness, as some modern hypnotics offer better seizure quality and fewer side effects, making them more suitable for adolescents. In this context, we ascertained the behavioral responses induced by different anesthetics drugs during adolescence in rats of both sexes, as a preliminary study to later determine its interaction with ECS. To achieve this, male and female adolescent rats were treated with ketamine (20, 50, 75 mg/kg), propofol (50, 75 mg/kg) or vehicle (saline, 1 ml/kg) for 5 days (1 dose/day, i.p.). The onset of loss of righting reflex (LORR) and the duration of LORR was monitored daily after treatment. The behavioral responses scored potential antidepressant-like responses in adolescence (forced-swim and novelty-suppressed-feeding tests), as well as long-term cognitive changes in adulthood (Barnes maze: short- and long-term memory). The results proved clear sex differences in the onset and duration of LORR by both anesthetic drugs evaluated, with females showing faster onsets and longer durations of LORR. The effects of anesthetics were dose-dependent and showed signs of pharmacological tolerance across days for both sexes. The behavioral data was analyzed for each sex separately through one-way ANOVAs and found no changes on affective-like responses during adolescence or in long-term cognitive performance in adulthood for ketamine or propofol, as evaluated with the doses and tests described. These findings proved that these drugs would be a good choice to combine with ECS, since no individual effects on behavior were observed following their exposure in adolescence.

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Keywords. ECS, anesthetics, ketamine, propofol, affective behavior, long-term safety profile

P.1.19 - Critical periods of development across prefrontal sub-regions: insights from magnetic resonance spectroscopy in marmosets

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Mood disorders are commonly diagnosed in adolescence, a period of significant prefrontal cortical development. Two regions implicated in depression are the subgenual anterior cingulate cortex (sgACC-25) and the dorsolateral prefrontal cortex (dlPFC-46). Both are targets for treatment, with success related to the extent of their anti-correlated activity. Earlier studies in marmoset monkeys outlined distinct trajectories of morphological development for these subregions. In this study, we examined the potential metabolic mechanisms underlying these differences by analysing magnetic resonance spectroscopy data from 68 monkeys, imaged 1-5 times from infancy to adulthood (3-30 months, 180 scans). Inositol, creatine, n-Acetylaspartate (NAA) and choline showed significant differences between both regions. Inositol and creatine (involved in membrane turnover and energy metabolism) were significantly higher in sgACC-25 and increased across development, reflective of an actively developing region. Development in dlPFC-46 was marked by a decrease in choline, likely reflective of earlier myelination here since decreasing choline levels are linked to its incorporation into the myelin sheath. As myelination is one of the last developmental processes, this highlights the earlier metabolic maturation of area 46. Comparison of metabolic and structural milestones suggested that the onset of metabolic changes in dlPFC-46 overlapped considerably with the onset of structural changes, while those of sgACC-25 appeared displaced later in development, as compared to its structural profile. We hypothesise that the prolonged and elevated metabolic demands in sgACC-25 may be driven by its extended structural development, potentially increasing its susceptibility to dysregulation across adolescence and into adulthood. This may, in turn, disrupt circuit development, including its interaction with dlPFC-46, contributing to heightened vulnerability to mood disorders.

Keywords. prefrontal, MRS, depression

P.1.20 - Adolescent social exclusion and fear of missing out on the vulnerability to alcohol and stress-related disorders: a preclinical approach

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Shifts in adolescent lifestyles and social dynamics have contributed to a rise in psychiatric disorders, with social exclusion emerging as a significant risk factor. Unlike traditional preclinical models that focus on early-life maternal separation or social isolation, human adolescents are more commonly exposed to bullying and exclusion, experiences that can often elicit Fear of Missing Out (FoMO).We developed a novel preclinical model of FoMO to investigate the long-term impact of adolescent social exclusion on alcohol- and stress-related disorders. Male and female Wistar rats were subjected to social exclusion from postnatal day 21 (PND21) to PND60, a period paralleling early-to-late adolescence in humans. In this paradigm, the excluded rat observed two conspecifics engaging in rewarding social interaction on the opposite, inaccessible side of the arena. To quantify FoMO-related behaviors, we implemented a deep learning-based classifier capable of quantitively assessing social performance. This approach enables detection and analysis of: attempts to engage socially, peer interactions, and background behaviors like locomotion.Results in adulthood showed that socially excluded (SE) females exhibited increased alcohol self-administration, while SE males showed reduced stress-induced relapse following foot-shock. These behavioral outcomes were accompanied by sex-specific alterations in fear responses and corticosterone levels: SE males showed enhanced fear expression, SE females showed elevated fear conditioning, and corticosterone levels were reduced in SE females compared to socially interacting controls.Altogether, these findings suggest that social exclusion in adolescence leads to long-lasting effects in adulthood. Further investigating the underlying neurobiological mechanisms of FoMO will be crucial for developing both sex-specific preventive and treatment strategies in psychiatric disorders.

Keywords. Social exclusion, adolescence, alcohol use disorder, stress

P.1.21 - The role of oxytocin in mediating long-term consequences of early attachment disruption

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Early-life experiences affecting attachment bond increase vulnerability to psychopthology, such as depression, in adulthood. However, the presence of a significant alternative caregiver (SAC) promoting earned-secure attachment (ESA) can counteract these negatve effects. While clinically relevant, the mechanism underlying attachment and ESA remain largely not understood. We have previously reported that Repeated Cross-Fostering (RCF) manipulation, that alters attachment bond, led to increased depressive-like behaviour and altered intrinsic neuronal properties of Dopamine (DA) neurons into the Ventral Tegmental Area (VTA), a key region of the mesocorticolimbic circuitry, of DBA/2J female mice. Moreover, we established an RCF+SAC model of ESA, which successfully reversed these alterations. Here, we hypothesize that these effects are mediated by the neuropeptide oxytocin (OXT) whitin the mesocorticolimbic system. To test this hypothesis, DBA/2J mice exposed to RCF, Cont or RCF+SAC conditions were used for biochemical and behavioural analysis. OXT levels and OXT receptor (OXTr) were investigated through rt-qPCR, RNA scope, ELISA and Western Blot. Forced Swimming Test (FST) and Tail Suspension Test (TST) were used to assess depressive-like behaviour. We found a strong alteration of OXT and OXTr in VTA and Nucleus Accumbens (NAc) of RCF mice, that show increased passive coping strategies. Interestingly, SAC exposure was able to prevent these alterations. This study points to the oxytocin system as a critical mediator of the long-term consequences of early attachment disruption and shed light on the neurobiological mechanism underlying the ESA effects. Understanding these mechanims may provide valuable insights into novel therapeutic strategies for attachment-related disorders.

Keywords. oxytocin, attachment, earned-attachment, depression, mice model, mesocorticolimbic system

P.1.22 - Neural signatures of social reward: dopamine signalling in the Nucleus Accumbens

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Social dysfunction is a core feature of many psychiatric conditions, including depression, schizophrenia, autism spectrum disorder, and dementia. A key contributor to this dysfunction stems from disrupted social reward processing. Neuromodulators such as dopamine and oxytocin play vital roles in reward processing, including motivation and reward prediction. However, while non-social reward circuitry is well characterised, the mechanisms underpinning social reward remain poorly understood. This is partly due to limitations in monitoring endogenous neuromodulator dynamics and behavioural paradigms lacking volitional engagement, a key component of social motivation. To address this, we used fibre photometry to record real-time dopamine signalling in the nucleus accumbens (NAc) of rats performing a volitional social operant task. This task was designed to separate anticipatory and consummatory phases of social reward, allowing us to examine when and in response to what dopamine is engaged by aligning neuromodulator activity to discrete behavioural events. Preliminary findings suggest that the NAc selectively encodes social-predictive cues and the consumption phase of social reward, but not anticipatory signals or the goal-directed actions required to obtain it. However, dopamine responses are markedly stronger when social rewards are contingent on an action, suggesting that social motivation amplifies dopaminergic signalling. Together, these results reveal a functional dissociation within the social reward circuitry and highlight a motivational gating of dopamine signals within the NAc. Experiments are still underway but will fully characterise the temporal dynamics of dopamine and oxytocin signalling in the NAc across phases of volitional social behaviour. These insights will advance our understanding of the neurobiology of social deficits and support the development of pro-social therapeutics.*Funding*. NHMRC, Kinoxis Therapeutics Pty Ltd

Keywords. Oxytocin, Dopamine, Social reward, Nucleus accumbens, fibre photometry

P.1.23 - Whole brain activity mapping of the effects of a novel small molecule on chronic social isolation-induced aggression in mice

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Background: Chronic social isolation in mice is a well-established model for studying aggression and its underlying neurobiological mechanisms. Aim: This study explores the effects of a novel small molecule, KNX100, on isolation-induced aggression (AGG) and whole-brain activity, utilising c-Fos, a neuronal activity marker. Method: Male Swiss mice were either socially isolated for 10 weeks to induce aggression or grouped- housed as controls. Post-isolation, mice were treated with KNX100, risperidone, or vehicle. Aggression was measured using semi-automated behavioural classification in a neutral open field. Whole-brain activity was examined using iDISCO clearing, c-Fos immunolabeling, light-sheet imaging, and computational analysis. Results: Isolated mice exhibited significantly more aggression than socially housed mice, with increased fights, longer fight durations, and shorter latencies to the first fight. Both KNX100 and risperidone significantly inhibited aggressive behavior in isolated mice compared to vehicle, reducing the number of fights, time spent fighting, and fight latency. C-Fos mapping revealed distinct activity patterns for KNX100 and risperidone. KNX100-associated pathways include regions involved in threat detection, emotional regulation, aggression, and sensory-emotional integration. Risperidone-associated pathways include regions involved in motor control, attentional filtering, and sensory processing. Notably, KNX100 reduces aggression without affecting locomotor activity, unlike risperidone, which works at sedative doses. Conclusion: The KNX100 shows great promise in reducing aggression in mice, likewise risperidone. The study highlighting this effect is linked to specific neuronal activation in brain regions tied to aggression and social behavior. These encouraging preclinical findings are in line with ongoing clinical trials, suggesting KNX100 could be a new therapeutic option for aggression-related disorders.

Keywords. aggression, KNX100 , c-Fos

P.1.24 - Transgenic DAT rat model reveals vulnerability to early life stress and protective effects of exercise on neurobehavioral outcomes

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Chronic stress-related psychiatric conditions are an enormous public health concern. Early trauma and stress (ELS) can contribute to several psychiatric disorders that develop in late adolescence as well as adulthood. Not everyone with high levels of stress exposure will develop psychiatric disorders. ELS events can be associated with mesolimbic dopamine (DA) release, which in turn affects the neurobiology of the stress response. Dopamine Transporter (DAT) disruptions have captured some attention in this field. Exercise training may play a protective role in stress system dysregulation and comorbidities. Regular engagement in physical activity is associated with substantial physical and mental health benefits, including reductions in stress response and anxiety. Using Maternal Separation (MS) as a model of ELS, we investigated whether ELS affects later adolescence, based on genetic vulnerability (transgenic DAT rat model (DAT+/+ (WT) versus DAT+/- (HET)). Our data supports that: a) HET DAT rats are more vulnerable to MS in measures of anxiety, depression and memory, b) voluntary running wheel exercise during adolescence has protective effects against MS-induced changes in the brain and behavior. Additional dysregulation on underlying mechanisms (steroid hormones, glutamate) are being confirmed.

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Keywords. DAT, stress, vulnerability, exercise

P.1.25 - Chronic unpredictable stress alters social behavior in adult male rats: association with serotonergic and dopaminergic changes

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Exposure to chronic unpredictable stress has profound effects on mental and physical health. Previous research demonstrated that a Chronic Unpredictable Movement Restraint (CUMR) paradigm increases immobility in the forced swim test and hippocampal pro-inflammatory cytokines. In this study, we investigated the impact of CUMR on social behavior and its underlying neurobiological mechanisms. Adult male rats were assigned to either a control or CUMR group and subjected to 2, 4, or 6 hours of restraint daily for three weeks. Following exposure, social behaviors, including social investigation and interaction, were assessed alongside synaptophysin, serotonin, and dopamine levels in key brain regions. The CUMR-exposed rats exhibited reduced body weight gain, decreased social investigation, and increased dominant behavior. Neurochemically, CUMR resulted in reduced serotonin levels in the hippocampus, increased dopamine levels in the amygdala and hypothalamus, and elevated serotonin turnover in the amygdala compared to controls. Notably, hippocampal serotonin levels were positively correlated with social interaction, whereas amygdala serotonin levels were negatively correlated. Additionally, dominant behavior was positively correlated with hypothalamic dopamine levels. These findings suggest that chronic unpredictable restraint stress disrupts social behaviors, potentially through region-specific alterations in serotonergic and dopaminergic signaling. This study provides further insight into the neurobiological basis of stress-induced social deficits.

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Keywords. chronic stress, movement restraint, social behavior, hippocampus, amygdala, monoamine

P.1.26 - Neonatal handling modulates behavioral and neurobiological processes in a genetic rat model of schizophrenia: Age- and strain-dependent effects on frontocortical neuroplasticity

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Schizophrenia is a neurodevelopmental disorder influenced by gene-environment interactions, involving alterations of synaptic function and neuroplasticity. This study explores the impact of a “positive” infantile environmental intervention, namely neonatal handling (NH), on behavioral and neurobiological markers in a genetically-based rat model of schizophrenia-relevant features: Roman high-avoidance (RHA) and Roman low-avoidance (RLA) rat strains. Male RHA and RLA rats received NH (postnatal days 1–21) or left untreated (controls). Behavioral assessments were conducted during adolescence and adulthood, followed by frontal cortex (FC) gene expression analysis.Results revealed significant strain-dependent behavioral and attentional differences emerging in adolescence. NH increased novelty exploration and activity, and reduced anxiety-related self-grooming in RLAs, whereas it improved prepulse inhibition (PPI) in RHAs. In adult rats, NH increased novelty-induced activity in both strains, reduced self-grooming in RLA rats, and enhanced social interaction and PPI in RHAs.Gene expression analysis demonstrated that NH consistently increased the expression of pre- and post-synaptic and neuroplasticity (Cables1, Cdk5, Grin2b, Drd1, Homer1, Nrg1, Bdnf) markers in adolescent RHA rats, except for Snap25, which constitutively higher expression in RHAs was significantly reduced by NH in both adolescent and adult animals of this strain. NH also increased Nrg1and Bdnfexpression in adult RLA rats. These findings suggest for the first time that NH induces long-term neurodevelopmental changes, particularly in synaptic/neuroplasticity function, which are paralleled by behavioural and PPI improvements, with strain- and age-dependent effects.

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Keywords. Schizophrenia, Neonatal Handling, Synaptic Plasticity, Prefrontal Cortex, Roman Rat Model, Prepulse Inhibition, Social Interaction

P.1.27 - Neural signatures of impaired behavioral discrimination in the ventral hippocampal CA1 after early life adversity in mice

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Background:Early life adversity (ELA) increases vulnerability to psychiatric illnesses throughout the lifespan, and mouse models for ELA also exhibit changes in emotion-related behaviors. In the present study, we investigate the underlying circuit of these behavioral changes, focusing on the CA1 region of the ventral hippocampus and comparing behavioral discrimination for positive and negative stimuli.Methods:ELA is induced in c57BL6 pups using the limited bedding and nesting paradigm (p4-11). In adulthood, male and female mice express AAV-encoded GCaMP6f in excitatory cells, and a gradient-index (GRIN) lens is chronically implanted in the ventral CA1 (vCA1). vCA1 calcium activity is recorded during both a sucrose gustometer task and a fear context discrimination task.Results:In the gustometer task, post-consummatory licking increases with increasing concentrations of sucrose. This effect is significantly blunted in male but not female ELA mice (n=9-13/sex/group). In the fear conditioning task, female > male ELA mice show impaired contextual fear learning, and both sexes showed impaired fear context discrimination. ELA mice show significantly higher vCA1 calcium activity during the gustometer task, an effect more pronounced in males (n=~75 cells/mouse). ELA mice also exhibit alterations in vCA1 activity during various phases of the fear discrimination task. $p<0.05$ for significance in all analyses.Conclusion:Our findings demonstrate that ELA alters processing of both positive and negative valence stimuli in the vCA1, with some sex-specific effects. Given the vCA1 connections to both fear and reward circuits, these changes likely affect the broader network of emotion-related processing, contributing to vulnerabilities seen after ELA.

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Keywords. early life adversity, hippocampus, reward processing, fear conditioning, pattern separation, calcium imaging

P.1.28 - Effect of peripheral inflammatory insults on anxiety-like behaviour and microglial responses within the mesocorticolimbic system

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Pain-associated inflammatory insults impact the mesocorticolimbic system (MCLS), correlating with negative affective states such as anxiety, anhedonia, and depression. Although the molecular mechanisms behind these changes remain unclear, previous work from our group has linked pro-inflammatory microglial responses and Mu-Opioid Receptor (MOR) upregulation in the MCLS to Complete Freund Adjuvant (CFA)-induced inflammatory pain. This study further explores microglial activation by examining changes in the NLRP3 inflammasome pathway following CFA treatment or lung tumour-induced inflammation. Twenty-four male mice were divided into three groups (n=8): CFA-treated, tumour-bearing (novel CMT167 xenograft model, subcutaneously implanted), and controls. Anxiety-like behaviour was assessed using the light-dark box test seven days post-induction of the insult. On the same day, brain samples from the prefrontal cortex and nucleus accumbens were analysed via western blot for markers including MOR, ΔFOS-B, IBA1, CASP1, NLRP3, GSDMD, cGSDMD, IL-18, and IL-1β. Interestingly, only tumour-bearing mice exhibited increased anxiety-like behaviour. The CFA group showed a tendency for upregulation of NLRP3 inflammasome pathways proteins, particularly in the nucleus accumbens. Additionally, increased ΔFOS-B expression correlated with MOR upregulation in this group . These results shed light into the relationship between peripheral inflammatory changes and anxiety-related modifications in the brain, while highlighting the role of mesocorticolimbical microglia as the possible link. Nevertheless, further experiments must be carried out, including female mice as well, to be able to draw reliable conclusions.

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Keywords. Negative affective states, inflammatory pain, microglia, neuroinflammation, Mu Opioid Receptor

P.1.29 - Effects of sex and inhibitory neuron type on fear memory suppression by extinction

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Fear memory extinction is the process whereby a conditioned fear memory is suppressed after repeated presentation of the fear cues in absence of negative consequences. This memory process inhibits the expression of the original fear memory by the formation of a new inhibitory memory. However, fear returns over time or by specific environmental manipulations, implying a complex balance between the original fear memory and the so-called 'extinction neuronal ensemble'. It is therefore important to understand how fear memories are suppressed by extinction and to shed light into the transitory nature of the effect. The involvement of interneurons in fear memory formation has been studied, but the role of these neurons in the extinction memory is unknown. We used extinction of cued fear conditioning in male and female rats to study the recruitment of different inhibitory neuronal subtypes using immunohistochemistry. Eight different brain regions were included: infralimbic and prelimbic regions of the medial prefrontal cortex (mPFC), anterior to posterior basolateral amygdala (BLA), nucleus accumbens shell and core, and the dorsal dentate gyrus. We used Fos as a marker of neuronal activation and parvalbumin (PV) and somatostatin (SST) as markers of inhibitory neurons. Data was analysed using permutations and planned contrasts, with Bonferroni corrections. At the behavioural level, we observed successful fear memory suppression both in female and male rats. At the neuronal level, Fos activity was increased in the female extinction group (vs. controls) in the infralimbic cortex. There was a trend for significance between the same groups in the mPFC prelimbic region. Fos activity was not differentially increased in PV+ or SST+ neurons across all brain regions. All in all, despite finding robust fear suppression across sexes, the neuronal activity analysis contradicts earlier studies showing increased Fos levels in neurons in various brain regions. Our data indicates extinction may rely on recruitment of alternative molecular mechanisms to suppress fear.

Keywords. Fear memory extinction, Fos, inhibitory neurons, immunohistochemistry

P.1.30 - Genotype-dependent functional role of the anterior and posterior Paraventricular Thalamus in the incubation of conditioned fear

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Understanding the neural circuits underlying individual differences in psychiatric disorders is essential for advancing personalized treatment strategies. Using two inbred strains—C57BL/6J (C57) and DBA/2J (DBA)—it has been observed similar appetitive and aversive conditioned behaviors, but with distinct recruitment of cortico-limbic circuits. The paraventricular nucleus of the thalamus (PVT) plays a central role in these circuits, and recent findings have demonstrated that the anterior (aPVT) and posterior (pPVT) subregions function in opposing ways in C57 and DBA mice when exposed to appetitive conditioning. The present study aims to investigate the role of the aPVT and pPVT in both the acquisition and expression of aversive conditioned behaviors, modeled by the fear incubation paradigm, in C57 and DBA mice. To this aim, mice from both strains received selective lesions (NMDA) in the aPVT or pPVT prior to the fear incubation paradigm (acquisition, Exp. 1), or selective inactivation (by DREADDs technique) of these subregions before re-exposure to the cue 14 days after fear incubation training (expression, Exp. 2). The results confirmed an opposing role for these PVT subregions in C57 and DBA mice, both during acquisition and expression of conditioned fear incubation. This study identifies the PVT as a key source of heterogeneity in brain networks underlying psychopathological vulnerability and provides new insights into how genetic factors shape neural processes, in line with the precision psychiatry approach.

Keywords. Post-Traumatic Stress Disorder (PTSD), Conditioned Fear Incubation, Individual Differences, Inbred mouse strains, Paraventricular Nucleus of the Thalamus (PVT)

P.1.31 - The gut microbiota shapes the endocannabinoid system throughout development

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The endocannabinoid system (ECS) plays a pivotal role in the development and maintenance of neuronal function in the brain. It has been shown to modulate cell proliferation, migration, synaptogenesis and glial function during early-life, and neuro-plasticity and transmission in adulthood. Furthermore, the levels of endocannabinoids fluctuate across development. Whilst much is known of the role of the ECS in the brain, it also plays a key role in the gastrointestinal tract regulating motility, sensation and inflammation. Moreover, the gut microbiome has been shown to play a dynamic role in shaping neuronal functions across the lifespan. Although an interaction between the microbiome and the ECS has been suggested, this study aimed to directly query this, specifically, whether perturbations in the gut microbiota during early development affects the ECS. Germ-free male and female C57BL/6 mice were used, with conventionally-reared animals as controls. Prefrontal cortex and hippocampal tissue were collected at developmental ages: postnatal day (PND) 2, PND8, PND14, PND21 and adulthood, followed by RNA sequencing.In the prefrontal cortex, we observed a significant sex-dependent effect in the developmental trajectory of cannabinoid 1 receptor. Furthermore, an effect of the microbiome on the expression of FAAH and MAGL, genes responsible for key endocannabinoid degrading enzymes, was also observed. This study provides the first evidence of sex-dependent alterations in ECS due to microbiota perturbation. Ongoing research is focusing on the hippocampal ECS to elucidate the interplay between the ECS and the microbiome which may provide novel insights into the pathophysiology of neurodevelopmental disorders.

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Keywords. Endocannabionid System, Microbiota-Gut-Brain-Axis, Neurodevelopment

P.1.32 - Involvement of gut microbiota in the behavioral therapeutic effects of cannabidiol in an autism animal model

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This study explores how cannabidiol (CBD) influences gut microbiota composition and improves social behavior in models of neuropsychiatric disorders such as autism spectrum disorder (ASD). Experiments conducted with ten-week-old male C57BL/6 mice involved administering CBD orally (30 mg/kg/day) for 21 days. Fecal microbiome 16S rRNA sequencing revealed that CBD-treated mice exhibited an increase in probiotic bacteria like Akkermansia, Bifidobacterium, and Ruminococcuscompared to control groups. To assess behavioral relevance, ASD-like offspring were generated through prenatal Valproic Acid (VPA) administration. The pups were assigned to treatment groups during lactation, receiving CBD, vehicle, or microbiota from CBD-treated, vehicle-treated, or untreated (sham) animals. At ten weeks, sociability was assessed using the three-chamber test. VPA-exposed mice (VPA-vehicle: 4.64 ± 28.86, VPA-mSHAM: 17.90 ± 37.54, VPA-mVehicle: 9.94 ± 31.84) showed significant social deficits compared to control groups (63.21 ± 14.09, 73.05 ± 15.82, 59.67 ± 18.31, $p < 0.001$). These deficits were absent in groups treated with CBD (60.06 ± 20.53) and microbiota from CBD-treated mice (65.16 ± 16.21). Ongoing analyses include 16S rRNA sequencing and histological assessments to further characterize microbiota composition and microglial activation in the brain. This study suggests that CBD-mediated gut microbiota modulation may mitigate ASD-related social deficits, offering novel therapeutic perspectives.

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Keywords. Cannabidiol, Gut microbiota, Autism spectrum disorder, Microbiota-gut-brain axis, Social behavior

P.1.33 - Gut-brain axis modulation by Limosilactobacillus reuteri in a maternal separation animal model of autism: exploring underlying mechanisms

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Objective:Emerging evidence emphasizes the role of the gut-brain axis in neurodevelopment and the potential of probiotic therapy. Limosilactobacillus reuteri (LR), a probiotic strain, seems to modulate various brain and gut-related pathways in the context of autism spectrum disorder (ASD). This study examines the therapeutic potential of LR in ameliorating ASD-related abnormalities in a maternal separation rat model of autism. Methods:Male Wistar rats were divided into: 1) a maternal-separated LR-treated group (MS+LR), 2) a maternal-separated placebo-treated group (MS), and 3) a non-separated control group. A two-week period of MS followed by three weeks of probiotic administration was performed. Following the treatment, behavioral assessments were conducted, including three-chamber, marble-burying, and open-field tests. Oxytocin levels in the hypothalamus were evaluated by immunohistochemistry, and medial prefrontal cortex (mPFC) neuroplastic changes were explored using stereological analyses. Microscopy and behavioral data were analyzed using Cellpose and Deeplabcut, novel deep-learning-based tools. Absolute Quantification of Fecal LR was conducted by Quantitative Real-Time PCR. Results:Behavioral assessments indicated that LR treatment enhanced social and stereotyped behaviour. Immunohistochemical analysis revealed restored oxytocin expression after probiotic therapy, suggesting a neurobiological mechanism underlying the effects. The volume and number of neurons in infra-limbic area and anterior cingulate cortex were significantly altered in the MS group compared to other groups. The MS+LR group showed significantly higher LR colonization than other groups. Conclusion:This study demonstrated that L. reuterican have therapeutic effects on ASD-like symptoms induced by maternal separation by modulating neuroplasticity changes through oxytocin-dependent pathways.

Keywords. autism, gut-brain axis, neuropharmacology, animal model, oxytocin, probiotic therapy

P.1.34 - Astrocyte dynamics in Alzheimer's disease: Unraveling sex-, genotype-, and cannabinoid-dependent mechanisms

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Astrocytes are key players in Alzheimer's disease (AD), actively contributing to cognitive dysfunction. Gaining deeper insight into the mechanisms underlying their involvement in distinct AD phenotypes could pave the way for targeted therapeutic strategies. Using the APP/PS1 mouse model, we explored the interplay of sex, genotype, and cannabinoid treatment across multiple behavioral paradigms. A longitudinal assessment of behavior was performed using EzTrack® (background subtraction) and DeepLabCut™ (pose estimation) combined with custom Python scripts to precisely quantify more behavioral responses. Our analysis uncovered significant sex-, genotype-, and cannabinoid-related differences across cognitive domains. To investigate the molecular underpinnings of these differences, we conducted single-cell RNA sequencing on hippocampal tissue from male and female mice at six months of age, following cannabinoid or vehicle treatment during the presymptomatic phase (three months of age). This revealed distinct astrocytic gene expression patterns associated with astrocyte functions, the endocannabinoid system, and mitochondrial processes, among others. To further explore astrocytes' role in AD-related memory impairments, we employed in vivo fiber photometry to monitor astrocytic calcium dynamics. At five months of age, mice received hippocampal infusions of the viral vector pZac2.1gfaABC1D-cyto-GCaMP6f. After four weeks, they underwent the novel object recognition and light-tone sensory preconditioning tasks in a within-subject design. Preliminary results demonstrated sex-, genotype-, and cannabinoid-dependent alterations in astrocyte calcium signaling, reinforcing astroglial involvement in AD-related cognitive deficits. These findings offer new insights into astrocyte contributions to AD pathophysiology, underscoring their potential as therapeutic targets.

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Keywords. Alzheimer's Disease, Astrocytes, Cannabinoids

P.1.35 - Noradrenaline and the astrocyte-neuron lactate shuttle: The critical role of β2-adrenergic receptors in glycogenolysis and object recognition memory in female mice

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The noradrenergic (NA) system plays a crucial role in memory, particularly through β2-adrenergic receptors (AR), which are expressed in both neurons and astrocytes. NA binding to β2-AR in astrocytes stimulates lactate production via glycogenolysis, and lactate is subsequently transferred to neurons, where it supports synaptic plasticity. The Novel Object Recognition (NOR) task is commonly used to assess declarative memory in rodents by measuring their ability to distinguish between a familiar and a novel object. While it is known that NA influences NOR performance, the underlying mechanisms remain unclear. We hypothesize that NA's effects on memory are mediated by astrocyte-derived lactate. To test this hypothesis, we conducted both in vitro and in vivo studies. In Experiment 1, astrocyte cultures were treated with vehicle, NA, or NA + Butaxamine (a β2-AR antagonist). In behavioral experiments, female Swiss mice underwent a three-phase NOR protocol: habituation, training, and testing. In Experiment 2, different groups of mice were treated with vehicle, Atomoxetine (a NA reuptake inhibitor), or Atomoxetine + 4-CIN (which blocks lactate transport from astrocytes to neurons). In Experiment 3, animals received either vehicle, ICI-118,551 (a β2-AR antagonist), or ICI-118,551 + lactate. Our results showed that NA stimulates lactate production in astrocytes via β2-AR. Additionally, Atomoxetine enhanced memory, whereas 4-CIN completely abolished this effect. Blocking β2-AR disrupted object recognition memory, but this impairment was rescued by lactate administration. These findings highlight the critical role of β2-AR-mediated glycogenolysis and lactate signaling in astrocytes in the formation of object recognition memory.

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Keywords. β2-adrenergic receptors, Lactate, Noradrenaline, Astrocytes, Object recognition memory

P.1.36 - Guanidinoacetate methyltransferase deficiency in mice: a window into behavioral dysfunction and RNA therapy potential

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Guanidinoacetate methyltransferase deficiency (GAMT-D) is a rare metabolic disorder that leads to cerebral creatine depletion and is associated with intellectual disability, epilepsy, and autistic-like traits. While the GAMT knockout (KO) mouse model replicates key biochemical alterations observed in patients, its behavioral phenotype has remained largely unexplored.In this study, we present the most comprehensive behavioral characterization of GAMT-deficient mice to date, assessing both early developmental milestones and adult behavioral traits. We evaluated neonatal reflexes, ultrasonic vocalizations, and homing behavior during development, while in adulthood, we analyzed cognitive and social functions using the spatial novelty task and the social interaction test, incorporating social novelty exploration.This work represents the first in-depth investigation of the developmental and behavioral consequences of GAMT deficiency in a genetic mouse model. Our findings provide novel insights into the impact of creatine depletion on neurodevelopment and behavior, offering a valuable framework for future research into the pathophysiological mechanisms of GAMT-D and potential therapeutic approaches.Moreover, we test an innovative RNA-based therapy using red blood cell-derived extracellular vesicles (RBCEVs) loaded with modified GAMT mRNA in the validated GAMT-deficient mouse model. This approach aims to restore creatine biosynthesis and ameliorate the associated biochemical and behavioral phenotypes.

Keywords. Gamt-defict, Metabolic disorder, Behavioral Phenotype, Animal Models, mRNA treatment

P.1.37 - Deciphering the effects and neurochemical identity of projections into the Nucleus Accumbens

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The Nucleus accumbens (NAc) is a major network hub involved in behavioral and motivational regulation and mostly modulated by the mesolimbic dopaminergic pathway. It further has been shown to play a role in depression as well as other psychiatric conditions. While many inputs into the NAc have been identified, including the PVT, medial habenula (mHB), and mPFC, it is yet to be known whether these, mostly glutamatergic, inputs lead to aversive or rewarding experiences. Here we combine optogenetic tools with real time place preference (RT-CPP) tests to unravel the effects of these projections into the NAc. Additionally, we use fiber photometry to identify the neurochemical nature of these projections. Mice were injected with a retrograde ChR2 virus in the NAc and an optic fiber in the brain area of interest. After allowing enough time for virus expression, mice were placed in the CPP arena consisting of two compartments. Presence in one compartment turned on the 470 nm LED source (20 Hz) and therefore stimulating ChR2 in the desired brain area while presence in the other compartment turned the stimulation off. Preference of compartments indicates whether activation of the brain area is aversive or rewarding to the mice. Furthermore, viruses expressing dopamine and glutamate sensors were injected into the mice to detect changes in their activity when activating the pathways of interest. Results show both aversive and rewarding effects elicited from glutamatergic projections into the NAc, which could be related to changes in dopamine release. These observations are valuable for developing treatments for psychiatric disorders.

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Keywords. brain connectivity, optogenetics, behavior, fiber photometry

P.1.38 - Age-related changes in the metabolic and cognitive effects of systemic Tumour Necrosis Factor α

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Inflammation is essential for defence against infection or injury, but systemic inflammation can negatively impact the brain, particularly with ageing. Tumour Necrosis Factor α (TNFα) plays a central role in inflammatory responses during infection, sepsis, trauma, and chronic diseases. However, its effects on aged individuals remain poorly understood. This study investigated the acute impact of systemic TNFα on metabolism and cognition in young (7 ± 1 months) and aged (23 ± 2 months) male and female mice. Mice received 250 µg/kg TNFα intraperitoneally. Activity was assessed 2.5 hours later using the open field test, and tissues were collected 5 hours post-injection. TNFα increased inflammatory markers in all animals but elicited a significantly greater immune response in aged mice, with elevated blood TNFα and CCL2 levels and higher pro-inflammatory gene expression in several tissues. Blood glucose and motor activity dropped in all TNFα-treated mice, but only aged animals showed increased blood insulin and free fatty acids, suggesting a metabolic compensation attempt. However, ketogenic enzyme transcripts were downregulated in aged livers, with no rise in ketone bodies, indicating impaired lipid utilisation. Additionally, TNFα induced hypothermia exclusively in aged mice, alongside reduced CPT1A gene expression, which might indicate that free fatty acids are not entering the mitochondria, and unchanged protein UCP1 levels in white adipose tissue, preventing browning and, thus thermogenesis in that tissue. Microglial gene expression was higher in the aged hippocampus, suggesting increased vulnerability to neuroinflammation. Behaviourally, TNFα impaired cognitive flexibility in aged mice, as shown in the shallow water Y-maze. These findings highlight age-related susceptibility to systemic inflammation and potential metabolic targets to mitigate TNFα-driven cognitive decline.

Funding. Irish Research Council

Keywords. TNFα, systemic inflammation, metabolism, cognition deficit

P.1.39 - miR-10a-5p modulates impulsive choice in rats: insights into the role of PI3K and the AKT/MTOR pathway

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Impulsivity is a core symptom of various neuropsychiatric disorders, including Attention-Deficit Hyperactivity Disorder (ADHD) and impulse control disorders (ICDs), also called behavioral addictions. ICDs are exacerbated by dopamine replacement therapies in disorders such as Parkinson's disease or hyperprolactinemia, and are associated with a high impulsive choice—characterized by a preference for smaller, immediate rewards over larger, delayed ones. In this study, we applied the Delay Discounting Task (DDTs), a well-established method for measuring impulsive choice in humans and rodents, to investigate the role of miR-10a-5p in the development of cognitive impulsive behaviors. MicroRNAs (miRNAs) are small, non-coding RNA molecules that regulate gene expression primarily through post-transcriptional mechanisms, influencing the stability and translation of target messenger RNAs (mRNAs). Results obtained from NGS sequencing of miRNA-enriched fractions show that under sub chronic administration of pramipexole, a drug used for the treatment of human PD, the expression of miR-10a-5p is increased in the dorsal medial striatum and the nucleus accumbens (NAc) of highly impulsive rats in DDT. To investigate whether miR-10a-5p overexpression would increase impulsivity, we induced its overexpression in the NAc of low- and moderate-impulsive rats using viral infection. Our results show that increased miR-10a-5p expression, as measured by RT-qPCR, led to a heightened preference for larger rewards, particularly in the moderate-impulsive group, indicating increased impulsive behavior. Additionally, we have analyzed whether the expression of one of the miR-10a-5p's predicted target, PI3K, was altered as well as the expression of mRNAs for proteins of the AKT/MTOR pathway, in which PI3K is a key component. The results revealed reduced PI3K mRNA expression in the NAc, but no changes in the expression of AKT1, MTOR, or PTEN mRNAs. In summary, our findings suggest that miR-10a-5p directly promotes impulsive behaviors, potentially through its interaction with PI3K. Future studies will investigate protein expression and activation of the AKT/MTOR pathway, as well as the role of miR-10a-5p in compulsive behaviors.

Funding. ANR

Keywords. Impulsivity, microRNA, Delay Discounting Task (DDT), PI3K/AKT/MTOR Pathway

P.1.40 - Identifying a neurochemical signature of the paraventricular nucleus of the thalamus that predicts individual variability in cue-reward learning

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To examine the neurochemical correlates that may render one more susceptible to mental illness, we use an animal model that allows us to capture a “neurobehavioral endophenotype” of relevance to multiple psychiatric disorders. When exposed to a Pavlovian conditioned approach (PavCA) paradigm consisting of lever-cue presentation followed by reward delivery, rats learn the cue-reward relationship and attribute predictive value to the lever-cue, but a subset of rats, sign-trackers (STs), also attribute incentive value to the lever-cue. Relative to goal-trackers (GTs), who primarily attribute predictive value to the lever-cue, STs are more impulsive, have attentional deficits, and show greater reinstatement of drug-seeking behavior. The paraventricular nucleus of the thalamus (PVT) has emerged as a key neural node that may differentially integrate subcortical and cortical input in STs and GTs and, in turn, guide behavior. Utilizing microdialysis with liquid chromatography-tandem mass spectrometry (LC-MS/MS) we characterized multiple neurotransmitters, metabolites, and energy molecules in the PVT. Trends of increased dopamine and respective metabolites have been identified in STs relative to GTs. A significant correlation was found between glucose concentration and the PavCA index used to categorize behavioral phenotypes, with greater levels of glucose in STs. Mixed linear regression models revealed clusters of neurochemicals in the PVT under baseline conditions that could predict the PavCA index. This research identifies neurochemicals that may predispose an animal to a form of associative learning that promotes maladaptive behavior and may therefore be aid in the development of novel therapeutic targets for the treatment of psychiatric disorders.

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Keywords. behavior, psychiatric disorders, neurochemicals, neurotransmitters

P.1.41 - Sex differences in the role of cue-reactive Nucleus Accumbens neuronal ensembles in spontaneous recovery of food seeking

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Food-associated cues, such as fast-food advertisements can trigger food cravings and unhealthy overeating. Cue-evoked cravings can be attenuated using cue exposure therapy, which involves repeated food cue presentations in the absence of food, thereby utilising extinction learning to form inhibitory memories. However, extinction memories are often weak, leading to the spontaneous return of cravings, a phenomenon known as 'spontaneous recovery.' Promisingly in rodents, retrieval cues linked to extinction (extinction cues) reduce the spontaneous recovery of food seeking.We previously found that the expression of cue-evoked food seeking recruited nucleus accumbens (NAc) neuronal ensembles, while its extinction suppressed this recruitment. However, their role in spontaneous recovery of food seeking remains unestablished. Additionally, although previous studies have demonstrated sex differences in food motivation and regional brain activity, sex differences in neuronal ensemble function have not yet been clarified.Here, we investigated in mice the effect of extinction cues on the emergence of spontaneous recovery of cue-evoked sucrose seeking and whether sex differences existed in the role of NAc ensembles in mediating spontaneous recovery. Extinction retrieval cues suppressed the spontaneous recovery of cue-evoked sucrose seeking in male and female mice. Interestingly, the chemogenetic silencing of NAc ensembles inhibited and enhanced the spontaneous recovery of sucrose seeking in female and male mice, respectively.Our data provide new mechanistic insights into sex differences of NAc ensemble function. Ongoing studies aim to uncover sex-specific differences in in vivoneuronal activity patterns of cue-reactive NAc ensembles during the emergence and suppression of spontaneous recovery.

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Keywords. extinction learning, spontaneous recovery, retrieval cues, nucleus accumbens, neuronal ensembles

P.1.42 - Knockdown of the glucocorticoid receptor (GR) in a corticostriatal pathway increases the propensity to attribute incentive salience to a reward cue

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Glucocorticoid receptors (GRs) are critical modulators of the stress response, yet their role in behavioral regulation outside of this remains unclear. Given that stress-related psychopathologies, such as substance use disorder (SUD) and impulse control disorders, are characterized by deficits in inhibitory control, we investigated the role of GR within a top-down cortico-striatal pathway in governing incentive motivation. Specifically, we used transgenic Sprague-Dawley rats with conditional GR knockdown to selectively reduce GR expression in glutamatergic projections from the prelimbic cortex (PrL) to the nucleus accumbens core (NAcC)—a pathway implicated in reward-seeking behavior and the regulation of dopamine signaling. To assess the effects of GR knockdown on incentive salience attribution, rats underwent a Pavlovian conditioned approach (PavCA) paradigm, in which a neutral cue was repeatedly paired with a food reward. Our results indicate that rats with GR knockdown in the PrL-NAcC pathway were significantly more likely to sign-track, or attribute heightened motivational value to the reward cue, compared to wildtype controls. Additionally, the degree of GR knockdown positively correlated with the magnitude of this behavior, further implicating GR in the regulation of incentive motivation. These effects were observed irrespective of sex. Since sign-tracking behavior is associated with increased impulsivity, attentional deficits, and susceptibility to cue-induced reinstatement of drug-seeking behavior, our findings suggest that GR signaling within the PrL-NAcC pathway plays an important role in inhibitory control and maladaptive behaviors. These results provide insight into the neuromolecular mechanisms underlying stress-induced vulnerabilities to impulsive reward-seeking and may have implications for stress-related psychiatric disorders.

Keywords. Reward learning; corticosterone; motivated behavior; prefrontal cortex; nucleus accumbens; Pavlovian conditioning

P.1.43 - Study of potential behavioral predictors of obesity phenotypes in male rats

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IntroductionObesity is a global issue, affecting more than 2.5 billion people worldwide. Although excessive consumption of high-energy foods contributes to the development of obesity, some individuals are resistant to this process. The experiment was aimed at searching for behavioral predictors of obesity phenotypes by measuring: locomotor activity, pro-depressive and pro-anxiety behaviors, and short-term memory, in juvenile rats fed with standard diet.Materials and MethodsWistar rats at 28 days postnatally were tested in behavioral tests: locomotor activity (LA), novel object recognition (NOR), forced swimming test (FST), and elevated zero maze (EZM). Then, after 12 weeks of feeding with an OID (obesity inducing diet) or standard diet (SD), animals fed with OID were divided into equal groups according to body weight change: rats with the lowest body weight gain were classified as obesity resistant (OR) and those with the highest body weight gain were classified as obesity prone (OP).ResultsYoung animals, classified later as OP and OR, did not differ (1) in entries to open space and time spent in open space in the EZM test, (2) and in immobility, swimming and climbing in the FST compared to themselves as well as to the SD group. Furthermore, no changes were observed for short-time memory after 1 hour and 24 hours in the NOR test and no changes in animal mobility were observed after 5 min and 1 hour of observation.ConclusionsIn male rats the exposure to OID leads to the development of obesity phenotypes: OP and OR. The tests did not show any behavioral predictors of the development of obesity phenotypes in animals.

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Keywords. obesity prone, obesity resistant, elevated zero maze, forced swimming test, novel object recognition, locomotor activity

P.1.44 - Distinct roles for ventral tegmental area GABA and dopamine neurons underlying flexible updating of reward and punishment contingencies

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In dynamic environments where stimuli predicting reward or punishment unexpectedly change, it is critical to flexibly update behavior while preserving recollection of previous associations. Dopamine and GABA neurons in the ventral tegmental area (VTA) are implicated in reward and punishment learning, yet little is known about how each population adapts when the predicted outcome valence changes. To address this, VTA GABA and dopamine population calcium activity fluctuations were measured with fiber photometry while male and female rats learned to associate three discrete auditory cues to three distinct outcomes: reward, punishment, or no outcome within the same session. After learning, the reward and punishment cue-outcome contingencies were reversed, and subsequently re-reversed. The dopamine population displayed the expected adaption to learning and contingency reversals by increasing the response to appetitive stimuli and decreasing the response to aversive stimuli. In contrast, the GABA population increased activity to all sensory events regardless of valence. Reversing learned contingencies selectively influenced GABA responses to the reward-predictive cue, prolonging increased activity both within and across sessions. Trial-by-trial analysis further confirmed that sustained GABA activity tracks contingency reversal. The valence-specific dissociations in the directionality and temporal progression of VTA GABA and dopamine neuronal activity indicates that these populations are independently recruited and serve distinct roles during reward or punishment associative learning and reversal. These findings also describe a novel role for VTA GABA in behavioral flexibility.

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Keywords. ventral tegmental area; dopamine; GABA; behavioral flexibility; fiber photometry; learning

P.1.45 - Effects of cafeteria diet on pituitary hormones and behaviour in male Wistar rats

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Background and aim: Obesity has become a global health crisis, posing a challenge to improve treatment strategies to provide long-term efficacy and safety. The impact obesity has on neuroendocrine markers and how those affect behaviours of animals is not fully explored. The aim of this study was to evaluate the impact of a cafeteria diet on pituitary hormonal and behavioural profiles of male Wistar rats.Materials and methodsTen-week-old male Wistar rats (RccHan:WI) were fed either an ad libitum standard rat chow diet (control group; n=12), or an ad libitum cafeteria diet (cheese doodles, chocolate balls and salted peanuts) in addition to standard chow (diet-induced obesity (DIO) group; n=12) for 12 weeks. DIO rats weighed more in comparison to controls (mean, 576 g, 493 g, respectively). At week 11 the animals were behaviourally profiled using the multivariate concentric square field™ (MCSF) test, which revealed no group differences in general activity, exploration, risk assessment, risk taking or shelter seeking. After 12 weeks of diet the animals were euthanized, blood collected, pituitary weight was assessed and plasma levels of pituitary hormones were measured.ResultsThe pituitary gland weight was significantly lower in the DIO group (mean 17.7 mg; $p<0.01$) compared to controls (mean 22.6 mg). ACTH, corticosterone, follicle-stimulating hormone (FSH), growth hormone, thyroid-stimulating hormone and triionthyronine (T3) did not differ between groups and neither did prolactin levels. In contrast, luteinizing hormone (LH) levels were significantly lower in the DIO group (mean 0.75 ng/ml; $p<0.05$) compared to controls (mean 1.21 ng/ml). With both animal groups combined, prolactin was inversely correlated with exploratory activity and the risk-taking behaviour but not with body weight.ConclusionBesides LH, the cafeteria diet did not seem to have any impact on circulating pituitary hormone levels or the behaviour of the animals. However, reduced growth of the pituitary gland could be observed. Furthermore, the inverse correlations of prolactin with exploratory activity and risk-taking behaviours, suggest a connection between prolactin and behavioural traits possibly orchestrated by central dopamine levels, but this is independent of the obesity status. Further research is needed to better understand this complex cross talk.

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Keywords. Diet-induced obesity, pituitary hormones, MCSF

P.1.46 - Inhibitory brain dynamics for adaptive behaviour: The role of GABAergic neurotransmission in temporal discrimination based visual perceptual learning

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Gamma-aminobutyric acid (GABA) plays a key role in learning and brain plasticity by regulating functional connectivity and oscillatory activity in local circuits and global brain networks. Altered cortical inhibition is associated with perceptual impairments in psychiatric disorders like Schizophrenia. Despite the importance of GABAergic inhibition for brain function, we lack a mechanistic understanding of the inhibitory network dynamics supporting adaptive behaviour from training.To unravel these mechanisms, we adapted our progressive 3-stimuli touchscreen orientation discrimination operant paradigm into a temporal discrimination paradigm, performing systemic GABAergic pharmacology to ascertain if spatial and temporal perceptual decisions are governed by analogous inhibitory microcircuitry. Here, 18 male Lister-hooded rats learned to distinguish between an 8Hz flashing LED target stimuli and a pair of distractors: 1 solid and a second flashing at block-wise frequencies in 150 trials (1Hz, 3Hz, 6Hz).Baseline validation showed effective perceptual challenge, with significant and orthogonal accuracy and distractor error rates between distractor frequency blocks. Full-task systemic GABAergic pharmacology revealed a negative impact of high-dose GABA-A α5 positive allosteric modulator on accuracy, whilst GABA metabolic potentiation, GABA-B receptor agonism and GABA-A α5 negative allosteric modulation did not alter accuracy. When target and flashing distractor were separated, high-dose α5-PAM reduced accuracy, whilst the α5-NAM exhibited a dose-distractor frequency interaction. These effects were not seen in other GABAergic compounds, or when target and flashing distractor were adjacent.Together this suggests that GABA-A α5 subunit containing receptors play a role in rodent temporal discrimination that appears to depend on attentional load and distractor interference.Project funded by Wellcome Trust (223131/Z/21/Z) and Boehringer Ingelheim Pharma

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Keywords. Visual-Perceptual-Learning, Inhibition, Pharmacology, Behaviour, GABA

P.1.47 - The effects of selective serotonin reuptake inhibitors and beta-blockers on learning in dynamically changing environments

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Depressive and anxiety-related disorders have been associated with altered processing of uncertainty within dynamically changing environments. In addition, it has been suggested that the targets of common pharmacological treatments for these disorders, such as selective serotonin reuptake inhibitors (SSRIs) and beta-blockers, may be involved in processing and representing uncertainty. However, it is unclear how SSRIs and beta-blockers may affect representations of uncertainty in dynamically changing environments. We tested male and female rats on a novel adaptation of the probabilistic reversal learning task (PRL). Our task systematically alters both volatility and noise, and is inspired by a task used with humans that has found changes in behaviour when moving from stable to noisy environments. Propranolol, a beta-blocker, and citalopram, an SSRI, was administered to each subject in a dose-dependent manner (1 mg/kg, 3 mg/kg and 10 mg/kg) and compared against a vehicle injection. We found that subjects performed significantly worse when moving from stable to uncertain environments. However, contrary to expectations, we found that subjects did not update their win-stay or lose-shift behaviour when moving from stable to noisy environments. Similarly, neither propranolol or citalopram affected overall performance or win-stay/lose-shift behaviour. Our results indicate that rats do not modulate their behaviour in uncertain environments in the same way that humans do. Furthermore, our results suggest that SSRIs and beta-blockers do not affect rodents' processing of uncertainty. These results have implications for the use of animal models to understand the cognitive processing underlying depressive and anxiety-related disorders.

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Keywords. uncertainty, learning, serotonin, noradrenaline

P.1.48 - Individual differences in sensitivity and resistance to punished self-administration of a sweetened oral morphine solution

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Purpose:Opioid and other substance use disorders are defined by persistent drug use despite adverse consequences. Stress further complicates opioid self-administration by either exacerbating or suppressing drug-seeking behavior, highlighting the need to understand its mechanisms for effective prevention and intervention strategies. Additionally, while most preclinical studies rely on intravenous self-administration, many opioids are initially prescribed and consumed orally in humans, underscoring the importance of models that better reflect real-world opioid exposure. The present study investigates the individual differences that emerge as a result of contingent and non-contingent punishment on oral morphine (OM) intake in a solution sweetened with grapefruit juice. Methods:Male and female rats were randomly assigned to: Morphine Control (MC); Punishment (P); Yoked (Y); Shock Control (SC); and Chamber Control (CC). Following OM acquisition, groups transitioned to the punishment phase. MC rats continued self-administration (SA) with no foot shocks (FS). P rats received FS at a 15% probability, contingent on active lever pressing for OM. Y rats were matched with P to receive time-matched non-contingent FS during SA sessions. SC rats received matched FS but never had access to OM; CC rats never experienced FS or had access to OM. Results: Male and female MCs are consuming similar amounts of drug in mg/kg, and this stabilizes over time. Contingent foot shock reduces drug intake in high and low consumers, but there are strong individual differences between animals more resistant versus more sensitive to foot shock when it is linked with morphine seeking. High or low levels of non-contingent foot shock does not decrease consumption in either high or low OM consumers. Notably, females show lower sensitivity to pain in the tail-flick test and both sexes show lower sensitivity at the end compared to baseline. Significance:These results have an impact on theoretical notions of the role of compulsivity in substance use disorders as well as provide insight into individual differences between those sensitive and resistant to punished seeking behaviour of a sweet morphine solution.

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Keywords. Opioid use disorder, Stress, Rats, Behavioural Neuroscience, Self-administration

P.1.49 - Differential engagement of top-down and bottom-up pathways in the paraventricular thalamus in sign-trackers versus goal-trackers

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Many of our everyday actions are guided by cues in our environment. For some individuals, cues can gain inordinate control over behavior. For example, in individuals with substance use disorder, the sight of drug paraphernalia may trigger cue-induced relapse. Such cues become powerful motivators when they are attributed with incentive value. We study individual differences in the propensity to attribute incentive value to cues using the sign-tracker/goal-tracker model. In this model, rats are exposed to a Pavlovian lever-cue which predicts delivery of food-reward. 'Sign-trackers' attribute incentive value to the lever-cue and preferentially interact with it upon presentation. In contrast, 'Goal-trackers' primarily attribute predictive value to the cue, instead interacting with the reward location. Previous research suggests that, in response to the lever-cue, sign-trackers more strongly engage bottom-up subcortical systems, while goal-trackers engage top-down cortical systems. These systems integrate in the paraventricular thalamus (PVT), which then sends projections to regions like the nucleus accumbens shell (NAcSh). However, we do not yet understand whether these two systems interact anatomically within the PVT to modulate sign- and goal-tracking behavior. In the present study, we use an anterograde transsynaptic tracing technique to examine how sign- and goal-trackers differentially engage the bottom-up lateral hypothalamus (LH) to PVT to NAcSh pathway compared to the top-down prelimbic cortex (PrL) to PVT to NAcSh pathway in response to the reward-predictive lever-cue. Preliminary data suggests that there is only a small amount of overlap in these pathways, and that different subregions within the PVT are differentially activated between phenotypes.

Funding. NIDA R01-DA054094 to SBF

Keywords. paraventricular thalamus, Pavlovian conditioning, incentive salience, sign-tracking

P.1.50 - Brain networks for punishment learning

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We constantly navigate choices, weigh risks, and learn from outcomes. When a choice leads to reward, we are more likely to repeat it; when it leads to punishment, we are not. This ability to learn from our mistakes, essential to survival, is called punishment learning. Impairments in punishment learning whereby individuals struggle to learn from their mistakes, have been implicated in several disorders such as depression, anxiety, substance use disorders, and behavioural addictions. Despite this, our knowledge of the brain mechanisms of punishment learning, and how these can go awry, is impoverished, especially compared with other forms of learning such as fear and reward. Here we studied the brain mechanisms of punishment learning. First, we used whole brain, single cell c-Fos imaging to identify the brain-wide networks for punishment learning. Graph theory and network analyses identified three brain regions – basolateral amygdala, zona incerta, and rostral linear nucleus- as key nodes in this punishment learning network. Next, we used multiplexed chemogenetic manipulation to assess the causal role of these key nodes in punishment learning. We expressed the inhibitory hM4Di DREADD in these three brain regions and showed that concurrent chemogenetic inhibition of basolateral amygdala, zona incerta, and rostral linear nucleus profoundly impaired punishment learning as shown by a lack of selective suppression of the punished action during chemogenetic inhibition and the following day when tested without chemogenetic inhibition. These results provide the first map of whole brain networks for punishment learning and demonstrate a causal role for this network in punishment learning. Ongoing work maps the specific cell-types within these brain networks that contribute to punishment learning.

Funding. ARC Discovery Projects DP220100040 and DP250100345 to Gavan P. McNally

Keywords. Punishment, Rostral Linear Nucleus, Basolateral Amygdala, Zona Incerta

P.1.51 - Parsing the role of cell adhesion molecule 2 in externalizing traits using Pavlovian conditioning and RNA sequencing in transgenic mice

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Substance use disorders (SUDs) frequently co-occur with psychiatric disorders, both sharing genetic and phenotypic underpinnings linked to behavioural disinhibition–collectively referred to as externalizing. These traits, which include risk tolerance, ADHD, problematic alcohol use, smoking initiation and cannabis use, are highly heritable (80%). Multivariate genome-wide association studies (GWAS) have identified over 500 loci associated with externalizing as a latent factor, with Cell Adhesion Molecule 2 (CADM2)emerging as a prominent locus. Cadm2 is highly expressed in regions involved in reward processing and plays a key role in synapse formation. While externalizing cannot be explicitly modeled in rodents, Pavlovian conditioned approach (autoshaping) paradigms have demonstrated that cue-directed approach (sign-tracking) correlates with externalizing traits and SUDs in humans.This study investigates the role of Cadm2in modulating externalizing-related phenotypes using a touchscreen-based autoshaping task in Cadm2knockout (KO), heterozygous (HT), and wildtype (WT) mice (n = 12/sex/genotype). During acquisition, KO and HT mice exhibited increased sign-tracking relative to WT controls. Following reversal of cue-reward contingencies, KO mice showed reduced sign-tracking and increased time at the reward tray, indicating a shift toward a more intermediate response strategy. Conversely, HT and WT mice increased sign-tracking after reversal. Whole-brain RNA sequencing (n = 3/sex/genotype) suggests that Cadm2may influence externalizing liability through disruptions in dopaminergic signaling and differential expression of genes involved in nicotine and cannabis metabolism. Ongoing studies using fiber photometry to monitor dopamine release in the nucleus accumbens during autoshaping aim to uncover the circuit-level mechanisms by which Cadm2contributes to externalizing phenotypes.

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Keywords. Externalizing, Autoshaping, RNA Sequencing, CADM2, GWAS

P.1.52 - An open-source, budget-friendly tail suspension test platform with high temporal resolution for behavioral and neural correlation studies

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The tail suspension test (TST) is a widely used assay for assessing stress-coping behaviors in rodents by subjecting mice to an acute, inescapable stressor. During the test, animals exhibit alternating active (struggling) and passive (immobile) behaviors, which serve as reliable proxies for screening antidepressant compounds. Here, we present an open-source, low-cost, and scalable platform for automated quantification of active and passive coping behaviors during the TST. The apparatus features four independent compartments, allowing simultaneous testing of up to four mice. A central stage facilitates secure tail attachment and accommodates head-mounted equipment, such as fiber photometry or optogenetic cables, ensuring compatibility with neural recording and manipulation techniques. Each suspension bar is equipped with a load cell sensor, interfaced with an Arduino Uno and controlled via a Bonsai-Rx software suite. The system records behavioral signals at 80 Hz, providing high temporal resolution for alignment with neural data. A custom Python-based algorithm processes the load cell outputs to extract periods of movement and immobility. To validate the system, we performed a double-blind comparison between sensor-derived measurements and manual video-based scoring. The load cell signals showed a strong correlation with human annotations ($r2=0.9978$, $p<0.0001$). As a proof of concept, we tested the effects of the antidepressant imipramine (15 mg/kg, i.p.), which significantly reduced immobility compared to saline controls ($p<0.0001$, $n=8$ for each group).

In summary, our automated TST platform enables efficient, high-throughput behavioral assessment with minimal experimenter bias. All hardware schematics, firmware, and analysis code will be freely available to the neuroscience community.

Funding. The present work was supported by the Intramural Research Program of NIDA, NIH.

Keywords. tail suspension test, open-source platform, automated scoring, imipramine

P.1.53 - Neural substrates of potentiation of cocaine-primed reinstatement by 17β-estradiol in ovariectomized rats

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Relapse-like behaviour is greater in cocaine-experienced female rats than males and this difference is driven by activational effects of the steroid hormone 17β-estradiol (E2) in females. The involvement of the striatum in this effect of E2 has been characterized well, but the sensitivity of other substrates of cocaine seeking to E2 has not been studied as thoroughly. To address this problem, cocaine-primed reinstatement was performed on ovariectomized rats receiving replacement of E2 or vehicle in conjunction with brainwide immunohistochemical quantification of the immediate-early gene c-Fos as a measure of neuronal activation. Reinstatement was induced by cocaine administration in both vehicle- and E2-treated rats and this effect was larger in E2-treated rats. Principal component regression indicated that there were distinct substrates of reinstatement in E2- and vehicle-treated rats. Fisher transformation of the Pearson's correlation matrices corresponding to each treatment group indicated that E2 increased the correlation between reinstatement and c-Fos+ cell counts in the ventral pallidum. Furthermore, E2 enhanced functional connectivity between the ventral pallidum and periventricular hypothalamus. There was an effect of E2 on functional connectivity between the periventricular hypothalamus and several regions, including the nucleus accumbens shell and the central amygdala. These findings suggest that E2 may enhance relapse-like behaviour by recruitment of the ventral pallidum via limbic and hypothalamic regions. Finally, it is notable and consistent with previous literature that there was a trend toward enhancement of functional connectivity between the ventral tegmental area and nucleus accumbens core by E2. The sensitivity of these substrates of cocaine seeking to E2 should be considered in the development of pharmacotherapies for cocaine use disorder.

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Keywords. Cocaine, Reinstatement, Estrogen, c-Fos

P.1.54 - TRPV1 antagonism modulates drug-seeking behavior in cocaine self-administration in male but not female mice

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Cocaine use disorder (CUD) is a chronic condition characterized by compulsive drug-seeking behavior and high relapse rates mostly triggered by stress. Experimental findings showed that the endocannabinoid system (ECS) plays a pivotal role in modulating reward pathways involved in addictive processes of CUD. In particular, transient receptor potential vanilloid 1 (TRPV1), well known as molecular integrator of painful stimuli, can get activated by endogenous ligands while its inhibition exerts anxiolytic-like effects in rodents. We hypothesize that TRPV1 plays an essential role in the reinstatement of cocaine-seeking behavior in mice. Therefore, this study aims to elucidate the effects of the selective TRPV1 antagonist SB366791 in short withdrawal (WD) period of cocaine self-administration (SA) in male and female mice. Indeed, dose of 0.6 mg/kg SB366791 significantly reduced number of active nose pokes in cue-induced seeking test on WD1 in males but the effect was lost on WD6. Notably, on WD5 treated mice showed anxiolytic-like behavior in elevated plus maze which was contrary to effects previously observed in handled mice. No significant effects were seen in females. To elucidate the molecular mechanisms underlying behavioral outcomes we assessed gene expression in areas of the mesocorticolimbic system. Results showed that SB366791 treated mice had significantly lower expression of Trpv1mRNA in VTA compared to controls, while in other areas it shows bimodal pattern of amplification. Our findings suggest that anxiolytic-like effects of SB366791 contribute to reduced drug-seeking behavior in SA while bimodal expression can potentially uncover a TRPV1 as a marker of vulnerability toward CUD.

Funding. FPI grant

Keywords. cocaine addiction, anxiolytic-like effect, TRPV1 antagonism

P.1.55 - The impact of a GLP-1 receptor agonist on cue- and drug-induced reinstatement of cocaine-seeking behavior

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Semaglutide, a glucagon-like-peptide-1 (GLP-1) receptor agonist, is the active ingredient in popular weight loss drugs like Ozempic®. Although primarily used for weight loss, patients have anecdotally reported reductions in addiction-related behaviors. Pre-clinical studies in rodents have shown that GLP-1 agonists decrease drug-taking and -seeking behaviors related to cocaine, opioids, and alcohol. However, most of these studies assessed the effects of acute semaglutide (SEMA) administration, and here we were interested in assessing the effects of "chronic" semaglutide administration, akin to the treatment regimen used by humans. Male and female rats underwent 14 days of cocaine (0.2-0.5 mg/kg/infusion) self-administration using an escalating infusion criteria paradigm such that rats had to reach 5, 10, 15, and 45 infusions. Following the final day of self-administration, rats underwent approximately 28 days of forced abstinence. During this period, and continuing for the duration of the experiment, rats received daily subcutaneous (s.c.) injections of VEH or SEMA, starting at a dose of 7 µg/kg and escalating by 7 µg/kg daily over the course of 10 days, reaching a final maintenance dose of 70 µg/kg. This treatment regimen significantly attenuated weight gain in male rats, with pronounced weight loss in females. This weight loss was, in part, due to decreased homecage chow consumption in rats treated with SEMA relative to VEH controls. We will next evaluate cue- and drug-induced reinstatement of cocaine-seeking behavior. We expect SEMA to attenuate drug-seeking behavior, which would suggest that chronic treatment with a GLP-1 receptor agonist during abstinence decreases the propensity to relapse.

Keywords. GLP-1 receptor agonist, drug self-administration, cocaine, addiction

P.1.56 - Can correlated pathological oscillations in the cortex and the subthalamic nucleus predict compulsive-like cocaine seeking in rats?

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Not everyone is equally vulnerable to addiction. In fact, only a small proportion of cocaine users (15–20%) lose controlover their intake and develop compulsive drug-seeking behavior. A key goal in addiction research is to identify these vulnerable individuals before they transition to pathological drug use. In rats, we identified low-frequency oscillations in the subthalamic nucleus(STN) that predict compulsive-like cocaine seeking. However, because of the deep location of the STN, recording these signals requires electrode implantation, limiting the translational potential of this biomarker. To explore whether a similar signal could be detected at a more superficial level, we performed simultaneous recordings of STNlocal field potentials (LFPs) and electrocorticographic (EcoG) activity in the prefrontal cortex, motor cortex, and cerebellum. These recordings were conducted during an escalation protocol, allowing rats to progressively lose control over their cocaine intake. Compulsive-like behavior was then assessed using a resistance-to-punishment test, in which cocaine seeking was randomly punished with a mild electrical shock to the paws, enabling us to identify compulsive-like individuals. Our data suggest that future addict rats exhibit a pathological increase in oscillations not only in the STN but also in the cortex. In contrast, this increase was absent in rats that did not develop compulsive cocaine seeking. These findings highlight the involvement of STN and cortical oscillations in the emergence of compulsive-like drug seekingin rats. More importantly, the presence of predictive oscillations at a superficial level raises the possibility of detecting this biomarker in humans using non-invasive recordings. This could facilitate early identification of at-risk individuals, paving the way for preventive strategies against addiction.

Keywords. Cocaine addiction, Subthalamic nucleus, Cortex, Oscillations

P.1.57 - PPAR-gamma agonism induces distinctive effects on cocaine-reinforced behaviour in male and female mice

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Cocaine use-disorder (CUD) is characterised by compulsive drug-seeking despite detrimental consequences and there are no effective pharmacological treatments for it. Sex differences are also reported in its development, negative effects, and impulsivity. Cocaine increases dopaminergic transmission in the mesocorticolimbic pathway, but endocannabinoids also modulate this circuitry by its interactions with CB1R, CB2R and other mediators including TRPVs and PPARs. PPARs are a family of nuclear receptors involved in metabolic activities and inflammatory responses. Specifically, PPAR-gamma isoform is expressed in areas from the mesocorticolimbic pathway like hippocampus or ventral tegmental area. Here, the aim is to evaluate the role of PPAR-gamma in different phases of cocaine addiction in both male and female mice using the paradigm of intravenous cocaine self-administration (SA). First, male and female mice were treated with 10 mg/kg of the PPAR-gamma agonist pioglitazone (PIO) during acquisition of cocaine SA. No significant differences were found in the acquisition of cocaine-reinforced behaviour in males, but females treated with PIO performed significantly less infusions and active nosepokes during this phase. Additional experiments were conducted in which mice from both sexes that acquired SA were treated with PIO during withdrawal. PIO significantly reduced cue-induced reinstatement of cocaine-seeking in males but not in females. OpenArray was performed to evaluate gene expression of main components involved in cocaine-seeking. Results suggest differential gene expression in males and females of genes like PPARGor DR2D. Our results show that PPAR-gamma agonism exerts differential effects on males and females depending on the phase of cocaine-reinforced behaviour explored.

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Keywords. cocaine, PPAR-gamma, operant behaviour, sex effects

P.1.58 - Increased vulnerability to cocaine addiction in male rats exhibiting maladaptive sucrose self-administration behavior

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Cocaine use is increasing in Europe, with approximately 20% of users developing cocaine use disorder. Previous research from our group identified early maladaptive cocaine seeking as a predictor of addiction-like behavior in 15-20% of male rats. This study aimed to investigate whether a pre-existing trait related to reward processing could influence vulnerability to cocaine addictive-like behavior. To do so, we clustered rats based on their oral sucrose self-administration (SA) behavior and then assessed their cocaine SA. Rats were trained for oral sucrose SA, alternating between periods of access and inaccessibility to sucrose, with distinct discriminative stimuli signaling each period. Motivation for sucrose was assessed using a Progressive Ratio (PR) schedule. Clustering analysis based on SA seeking (nose-pokes), consuming (licks) behaviors during sucrose unavailability periods and PR revealed two distinct groups. Cluster 2 exhibited significantly higher licking behavior when sucrose was unavailable and greater sucrose seeking in the PR. Notably, as the workload increased in the PR, the lick/nose-poke ratio decreased in Cluster 1 but increased in Cluster 2. The two clusters were further tested in a sucrose-induced reinstatement procedure. Non-contingent sucrose induced similar nose-poking behavior but higher licking behavior in Cluster 2, confirming their maladaptive avidity for sucrose. Following the ad hocsurgery, rats underwent cocaine SA testing. All rats exhibiting vulnerability markers for cocaine addiction were from Cluster 2. In conclusion, rats exhibiting maladaptive sucrose-seeking behavior may be at a higher risk of developing cocaine addiction-like behavior. Conversely, those with adaptive sucrose-seeking behavior would be at a lower risk.

Keywords. Cocaine, maladaptive, seeking, licking and vulnerability

P.1.59 - Disruption of immune homeostasis mediates neural and behavioral alterations induced by cocaine

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INTRODUCTION:Different data suggest that cocaine binds in the complex MD-2/TLR4, being recognized as an exogenous substance and leading to neuroinflammation. However, the role of microglia activation and TLR4 in cocaine induced behavioral abnormalities is still poorly understood. METHODS:Mice were treated with microglial depletor PLX3397 and subjected to behavioral sensitization induced by cocaine . Thereafter, their brains were removed for analysis of number and morphology of microglia cells, as well as quantification of CX3CL1 and BDNF levels. In addition, mice were treated with the TLR4 receptor biased agonist MPLA or TLR4-/- mice were submitted to behavioral sensitization, and to microglia phenotypic analysis by flow cytometry. All procedures were approved under the protocol CEUA 325/2022. RESULTS: PLX3397 treatment reduced Iba-1+ cells and attenuated behavioral sensitization. In the partial depletion group, the drug also increased activation of remaining microglia cells. Animals treated with PLX3397 + cocaine showed altered CX3CL1 in the striatum, hippocampus and in the PFC, as well as BDNF, in comparison with the animals treated with only cocaine. Besides, CX3CL1 and BDNF levels presented a correlation among the cocaine-induced behavioral sensitization. Moreover, MPLA treatment reduced cocaine-induced hyperlocomotion, while TLR4-/- mice showed an increase in cocaine-induced locomotor activity compared to WT animals. Finally, there are different microglia populations between saline, cocaine and cocaine + MPLA and cocaine + TLR4-/-treated animals, with differences in the expression of CX3CR1, CD62L, CD11b, CD44, CD11c, Single H and P2RY12. In addition, cocaine increased monocyte number and activation (Ly6C+), increased lymphocytes TCD8+ and TCD4+ central memory, but not effector memory, which was prevented by MPLA. Cocaine also decreased the dendritic spine in the brain, which was also prevented by MPLA CONCLUSION: Considering this data, we suggest that disruption in the immune homeostasis may be involved in the neural alterations that occur in neurobiology of cocaine addiction.

Keywords. Microglia, Cocaine, Neuroinflammation

P.1.60 - Effect of isolation and binge alcohol drinking in decision-making behaviour rats: study of the sex and age differences

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Social isolation is a significant stressor that impacts emotional regulation and decision-making, and consequently these cognitive alterations could enhance both the development and relapse of alcohol use disorders. Increasing our knowledge of the interaction between these factors and neural basis governing these processes is necessary to develop targeted interventions. The aim of the present study is to examine the effects of alcohol consumption on decision-making process in rats subjected to social isolation. Toward this end we used the Iowa Gambling Task (IGT) adapted to rats in combination with light dark box, isolation and drinking in the dark procedures including sex (male and female) and age (young and adult) variables in the analysis (n=15/group). Our findings indicate that alcohol consumption exacerbates sex differences in decision-making, with males displaying significantly poorer choices. Furthermore, isolation intensifies the negative impact of alcohol, particularly in adult males, who show a greater impairment compared to younger counterparts. Importantly, in isolated males, poor decision-making predicts significantly higher alcohol intake. These results suggest that social isolation impacts the relationship between decision-making abilities and alcohol consumption. Ongoing analysis of the anxiety-like behaviour and the brain tissue will further improve our knowledge on the relationship between isolation, decision-making and alcohol drinking behaviour. Understanding these mechanisms may contribute to developing targeted interventions for individuals at higher risk of alcohol use disorders due to social isolation.

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Keywords. Social isolation, Decision-making, Iowa Gambling Task, Alcohol consumption, Anxiety-like behaviour

P.1.61 - A senotherapeutic approach alleviate alcohol-induce cellular damage and reduce compulsive like alcohol consumption in mice

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Exposure to drugs of abuse exacerbates oxidative stress, induces DNA damage, and triggers inflammatory responses in multiple cell types. This phenomenon, intimately linked to the pathophysiology of substance use disorders (SUDs), leads to cellular damage and contributes to the premature aging observed in individuals with SUDs. A critical yet understudied mechanism connecting these effects is cellular senescence (CeSe), a stress-induced state of stable cell cycle arrest traditionally associated with aging and age-related diseases. Previous studies have identified alcohol-induced CeSe in peripheral organs and the brain; however, its role in alcohol-related damage and alcohol use disorder (AUD) remains unclear. This study investigates the role of CeSe during withdrawal in mouse models of binge alcohol exposure and evaluates senolytic treatments (Dasatinib + Quercetin) as potential therapeutic strategies. Using mouse models of both, passive and voluntary alcohol administration, we characterized CeSe kinetics and identified a persistent increase in CeSe markers (including p21+ cells, Plin2, and senescence-associated β-galactosidase activity) across various brain regions during alcohol withdrawal. Notably, CeSe accumulation was observed in the ependymal layer and choroid plexus, suggesting neuroinflammation and disrupted brain-CSF barrier function. Dasatinib + Quercetin during alcohol withdrawal reduced CeSe marker expression in multiple cell types and reversed frailty and persistent anhedonic phenotypes. Remarkably, Dasatinib + Quercetin mitigated compulsive-like alcohol consumption and preference in previously exposed subjects. Other behavioural changes observed (sucrose preference, anxiety, and social novelty preference) were consistent with the compulsive-like alcohol consumption phenotype. This study provides pioneering evidence of CeSe's role in AUD pathophysiology and highlight a novel therapeutic target for reducing alcohol-induced systemic damage and addiction-related consequences.

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Keywords. Alcohol Use Disorder, Cellular Senescence, Senolytic Therapy

P.1.62 - Therapeutic potential of an ibogaine analog for polydrug opioid and alcohol misuse

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Although alcohol is frequently co-used in individuals with opioid use disorder (OUD), animal models that mimic this polydrug comorbidity are lacking. Additionally, there is a growing body of evidence (both preclinical and clinical) supporting the potential anti-addiction effects of psychedelics and psychedelic-like compounds. Specifically, the ibogaine analog tabernanthalog (TBG) lacks the hallucinogenic and cardiotoxic side effects of ibogaine while reducing alcohol binge drinking and heroin relapse in rodent, single-substance models of addiction. Here, we developed a polydrug model in which rats co-self-administered alcohol and heroin over several weeks of operant training. Progressive ratio tests, wherein the operant requirement for a single reward is gradually increased throughout the session, were used to assess animals' motivation for heroin and alcohol. Rats consistently exhibit higher motivation for heroin than for alcohol, and pre-treatment with TBG (30 mg/kg) acutely reduced heroin motivation, reflected by reduced breakpoints for heroin on the progressive ratio test compared to vehicle rats. Co-administration of the 5-HT2A receptor antagonist MDL 100,907 (0.3 mg/kg) occluded the effect of TBG on heroin breakpoint. However, co-administration of the 5-HT2C receptor antagonist SB-242084 (0.5 mg/kg) did not occlude the therapeutic effect of TBG on heroin motivation. None of these treatments impacted alcohol motivation, which was already low. These findings suggest that TBG may be a promising therapeutic for OUD with comorbid alcohol use, with its efficacy likely mediated by its agonist activity at the serotonin 5-HT2A receptor.

Funding. R01DA056660 and R01DA058951

Keywords. Alcohol, heroin, polydrug use, 5-HT2A, 5-HT2C, psychedelic

P.1.63 - Effects of age of onset of voluntary alcohol consumption on reward sensitivity, impulsivity, and cognitive flexibility in rats

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Alcohol use disorder (AUD) is a major global health concern, affecting approximately 400 million people worldwide. AUD is characterised by recurrent relapses and profound alterations in motivational pathways. Particularly concerning is the increasing prevalence of AUD among youth, as adolescent-onset addiction is often associated with worse long-term outcomes compared to adult-onset. However, the heightened plasticity of the adolescent brain may also provide a greater potential for recovery. To better understand the age-dependent effects of alcohol exposure, this study investigates how the age of first exposure influences reward sensitivity, impulsivity and cognitive flexibility. Adolescent and adult rats are given intermittent access to alcohol using a two-bottle choice paradigm. Following exposure, the animals were tested on three behavioural tasks: the Pavlovian Approach Task, the Delayed Reward Task, and the Probabilistic Reversal Learning Task. This study aims to determine whether these cognitive and motivational processes are differentially affected by adolescent versus adult-onset alcohol exposure.

Funding. European Research Council (ERC)

Keywords. Alcohol, addiction, age, development, behaviour, animal

P.1.64 - Long-term effects of adolescent THC:CBD vapor exposure on alcohol-related behaviour: Evidence from schedule-induced polydipsia and self-administration paradigms

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Objective:Adolescent cannabinoid exposure (ACE), particularly to ∆9-tetrahydrocannabinol (THC), may disrupt the regulatory role of the endocannabinoid system (eCBs) during brain maturation, increasing vulnerability to alcohol use disorders. This study investigated whether adolescent cannabinoid exposure (ACE) facilitates compulsive alcohol drinking and alters coping strategies using two complementary models: operant self-administration and schedule-induced polydipsia (SIP).Methodology:Male and female rats were exposed to vaporised THC, THC:CBD (33:1), THC:CBD (1:33), or vehicle on alternate days from postnatal day (PND) 28–44. In adulthood, ethanol self-administration was assessed under acquisition, progressive ratio, and punished-seeking conditions. Plasma cannabinoid levels and hypothermia were evaluated post-exposure. In a second experiment, the SIP procedure (PND 100) included water (20 sessions), ethanol (20), and quinine-adulterated ethanol (6). Based on their drinking profiles, rats were classified as Water Copers or Alcohol Copers to assess coping strategies.Results and conclusions:ACE did not alter overall alcohol intake, but sex differences emerged during acquisition, with females displaying higher levels of unpunished and punished alcohol self-administration, indicating increased compulsivity. During the SIP procedure, males exposed to THC or THC:CBD exhibited reduced water intake but increased alcohol consumption as a coping strategies (AC). When alcohol was adulterated with quinine, these animals (AC) decreased intake, indicating sensitivity to reward devaluation. Conversely, WC maintained high intake despite quinine adulteration. A chi-square test revealed that males treated with THC and THC:CBD were significantly overrepresented in the AC subgroup compared to the WC. These results suggest sex-specific distribution, long-term effects of ACE on compulsive and coping-related drinking behaviours.

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Keywords. Keywords: Alcohol use disorder; Cannabinoids; Compulsivity, Sex difference; Schedule-induced polydipsia

P.1.65 - Satiety-related treatments on alcohol motivation and choice

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Fibroblast growth factor 21 (FGF21) is a liver-secreted endocrine peptide that classically regulates macronutrient preference, but has shown promise in reducing alcohol consumption. Relatedly, glucagon-like peptide 1 (GLP-1) a satiety-related peptide has shown powerful complementary effects with FGF21 on metabolism, weight loss and liver function whilst also reducing a broad range of alcohol-meditated behaviours in its own right. We assessed whether these agents and their combination 1) Impact motivation for alcohol reward 2) Impact alcohol choice 3) involve choice-related dopaminergic mechanisms in the nucleus accumbens shell (AcbSh). In Experiment 1 animals were trained to respond on a single lever for 15% v/v alcohol reward and underwent a progressive ratio reinforcement schedule under treatment. We found that 10 mg/kg doses of PF-05231023 but not 3 mg/kg reduced the breakpoint and number of lever presses and that combination with 2.4 ug/kg of EX-4 further reduced the number of lever presses. In Experiment 2 animals instrumentally responded for 20% w/v sucrose and underwent a progressive ratio reinforcement schedule under treatment. Interestingly, 10mg/kg PF-05231023 had no impact on the breakpoint or number of lever presses for sucrose rewards suggesting its effects are specific to alcohol motivation. In Experiment 3 animals responded in a discrete trials procedure using two levers, one for grain and one 15% v/v alcohol. This allowed us to measure choices made and latency to respond. Dopamine binding in the AcbSh was also measured using GrabDA biosensor fiber photometry. 10 mg/kg of PF-05231023 reduced alcohol choice and increased choice latency suggesting changes in the value of alcohol. We did not detect an enhancement of the PF-05231023 effect under combination with EX-4 nor any impact of EX-4 alone. These findings show that FGF21 containing treatments can attenuate motivation for alcohol rewards and reduce voluntary alcohol choices possibly by selectively reducing the value of alcohol relative to other rewards.

Keywords. FGF21, GLP-1, Alcohol, Choice, Dopamine

P.1.66 - Voluntary ethanol consumption disrupts circadian rhythm in female mice: preliminary observations exploring the utility of automated home cage monitoring

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The disrupting effects of alcohol on sleep and circadian rhythm are well-established: ethanol consumption is for example known to break the normal sleep structure and increase the number of breaks during sleep both in humans and in rodents. However, in rodent studies these changes can usually be manifested only by forced alcohol consumption decreasing the face validity of the models. While studying a pharmacological intervention on alcohol seeking behaviour after withdrawal in an Intellicage automated homecage-based model, we noticed that the group-housed female mice showed circadian rhythm-related behavioural changes during the 10-day alcohol training phase. During this period, the mice had a free access to both water and 12-% sweetened ethanol throughout the day, and towards the end of the training phase, the mice increased their light time activity, breaking the previously uniform, wave-like diurnal activity pattern. Also, the light-time drinking of alcohol increased almost two-fold while the dark-time drinking dropped almost to a half during the period, implicating changes in the drinking behaviour in addition to overall activity. As opposed to the commonly used models in the literature, our setup could show alcohol-induced circadian disruptions without forced ethanol intake, and additionally the 24-h automated measurement of the drinking behaviour could include a relevant behavioural outcome measure lacking in purely locomotion-based models. While further studies are warranted, the Intellicage homecage monitoring system could provide a powerful new tool for preclinical alcohol research.

Funding. Finnish Foundation for Alcohol Studies

Keywords. homecage, alcohol, circadian, mouse

P.1.67 - Assessing the utility of zuranolone to modify alcohol-related behaviours

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Background:Alcohol is the leading cause of death globally for people aged 15-49 years. Rates of alcohol use disorder (AUD) are rising, especially in women, with an 80% increase in the last 15 years compared to 35% in men. Emerging research suggests sex differences in treatment response, but this remains poorly understood as historical research has focused solely on males. Neurosteroids, are promising treatments for neuropsychiatric disorders; zuranolone, a synthetic form of the neurosteroid allopregnanolone, was recently FDA-approved for postpartum depression. Successful preclinical studies could therefore fast-track zuranolone's repurposing for AUD treatment, offering a novel therapeutic intervention; however, its safety and efficacy remain unknown. Here, we investigate zuranolone's efficacy and safety on alcohol-related behaviours in preclinical rodent models. Methods:Male and female C57BL/6J mice underwent a drinking-in-the-dark binge drinking protocol (n=12/sex). Zuranolone's effect on locomotor behaviour within activity chambers was also evaluated in an alcohol-naive cohort of mice (n=8/sex). Mice received vehicle or zuranolone (0.3, 1, 3 mg/kg; i.p) 30 minutes prior to testing. Data were analysed using two-way repeat- or mixed-measures ANOVA with Bonferroni post-hocanalysis where appropriate. Results:Zuranolone (3 mg/kg) initially decreased binge drinking in male ($p<0.05$), but not female mice; however, no effect on total alcohol consumption was observed in either sex. Zuranolone increased locomotor activity in a dose-related manner in both males ($p<0.0001$) and females ($p<0.01$), with males more sensitive to locomotor effects ($p<0.01$). Conclusions:Zuranolone demonstrates sex-dependent effects on binge drinking and locomotor activity. Future research should explore potential benefits of neurosteroid treatments for AUD and their mechanism(s) of action, which may accelerate development of sex-specific treatments.

Keywords. Alcohol use disorder, sex differences, neurosteroids

P.1.68 - PKC-δ neurons in the Central Amygdala promote compulsive alcohol use

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Alcohol use disorder (AUD) develops in a significant minority of alcohol users. It is characterised i.a. by choice of alcohol over healthy rewards and continued alcohol use despite negative consequences ("compulsivity"). This can be modelled in preclinical studies, where a minority of rats chooses alcohol over valuable alternatives and shows compulsive alcohol self-administration (SA). Compulsivity is operationalised here as continuation to lever press for alcohol rewards despite a mild electric foot-shock. Our previous work shows that activity of central amygdala (CeA) neurons is necessary for compulsive alcohol SA. Compulsive alcohol SA preferentially activated CeA neurons expressing protein kinase-C delta (PKC-δ). To gain access to this neuronal population, we developed a Prkcd::cre ratline using Crispr-Cas9 technology. Here, we employed chemogenetics to investigate whether activation of CeA PKC-δ neurons is sufficient to specifically promote compulsive alcohol seeking. Adult male Prkcd::cre rats were trained to lever press for an alcohol reward on a fixed-ratio (FR)1 and then FR2 schedule. Subsequently, animals were trained on compulsive alcohol SA by pairing reward delivery with increasing foot-shock punishments (0.1-0.25mA). Animals received bilateral microinjections of cre-dependent DREADD hM3Dq or mCherry control targeted at the CeA. Before test sessions, all animals received a systemic injection of DREADD actuator deschloroclozapine. Chemogenetic activation of PKC-δ neurons in the CeA significantly increased compulsive alcohol SA, while DCZ injection did not affect responding in the control group. Importantly, shock sensitivity was not affected. In an independent group of animals, we observed that activation of CeA PKC-δ neurons did not affect regular (i.e.non-punished) alcohol SA. This preliminary study shows that activation of PKC-δ neurons in the CeA specifically enhances compulsive alcohol SA, and may therefore be an interesting target for the development of novel therapeutic strategies in AUD.

Keywords. Alcohol, compulsivity, chemogenetics, amygdala

P.1.69 - Effect of ventral tegmental area dopamine neuron inhibition on stress-induced reinstatement

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Stress is a major contributor to relapse in alcohol use disorder, which can occur even after long periods of abstinence. Ventral tegmental area (VTA) Dopamine (DA) neurons have been shown to mediate various forms of relapse to drug-seeking including stress-induced reinstatement. Yet, the role of VTA DA neurons in stress-induced reinstatement of alcohol-seeking remains unclear. Therefore, here we examined the impact of inhibiting VTA DA neurons on alcohol self-administration and footshock stress-evoked reinstatement using a chemogenetic approach in TH-Cre transgenic Long Evans rats. Following 3 weeks of homecage alcohol exposure, rats (n=12, 6 female) underwent self-administration training. During training, active lever presses resulted in the delivery of 15% EtOH paired with a visual and auditory cue, while inactive lever presses had no consequences. Following training, rats (n=8, 3 female) underwent surgery for cre-dependent expression of hM4Di virus or mCherry control. Counterbalanced DREADD ligand DCZ (0.1 mg/kg) or vehicle injections were given prior to testing under extinction conditions, stress-induced reinstatement, and self-administration. No significant effects of VTA DA neuron inhibition during extinction learning were observed, but we saw a trend towards a decrease in lever pressing following DCZ injections in hM4Di rats during self-administration. Surprisingly, we did not observe a significant increase in alcohol seeking in the footshock stress reinstatement test; if anything, alcohol seeking decreased, suggesting that stress in our paradigm may be too high. During this test (when footshock stress suppressed alcohol seeking) we observed a trend towards an increase in alcohol seeking after DCZ injection in hM4Di rats. Overall, our data suggests that the impact of inhibiting VTA DA neurons may depend on the level of basal alcohol seeking and the current stress state of the animal. Future work is needed to assess the role of VTA DA neurons following exposure to a stressor that increases alcohol seeking by testing different levels of stress to achieve adequate reinstatement, and to fully power this experiment for robust statistical analysis.

Keywords. Dopamine, Relapse, Stress, Alcohol

P.1.70 - A role for social status and social status loss in alcohol-related behaviors in Wistar male and female rats

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Psychosocial factors play a major role in shaping the vulnerability to develop alcohol use disorders in humans. However, how social environments contribute to this vulnerability is not well known. In this study, we investigated the role of social status and social status loss in alcohol-related behaviors using a rat model of operant self-administration. Firstly, we screened male and female Wistar rats in a confrontation tube test to assess their social status based on their winning phenotype. We then trained the animals for alcohol self-administration and screened them in a battery of addiction-like behavior, including motivation to seek alcohol and punishment-resistant responding. Finally, through a modification of the tube test protocol, we switched the animals' winning phenotypes by making "dominant" rats lose against their subordinates and tested the effects of the social status loss in the alcohol-related behaviors. We found that dominant and subordinate rats in both sexes showed a robust and stable separation of their winning phenotype in the tube test. Dominant and subordinate rats of both sexes consumed comparable amounts of alcohol, but males showed higher motivation for alcohol than females whilst females showed higher punishment-resistant responding than males, regardless of their social status. Despite being able to stably lower the social status of both male and female dominant rats, the social status loss did not affect any of the addiction-like behavior in either males or females. Future studies will be needed to address this question, perhaps using different strategies for screening social status in rats.

Keywords. social status, alcohol self-administration, tube test, sex differences

P.1.71 - Exploring the relationship between early-life trauma, circulating endocannabinoids, and problematic cannabis use among young adults

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Cannabis is a commonly used substance, particularly among young adults. Of those who use cannabis, it is estimated that 1 in 5 users will go on to develop a cannabis use disorder (CUD). Early-life trauma (ELT) is a significant predictor of problematic cannabis use, linked to dysregulation of the endocannabinoid (eCB) system. The current study aimed to explore the relationship between ELT, current stress, and cannabis use, and whether a unique eCB profile may underlie the relationship between ELT and problematic cannabis use. Male and female university students (N=90; ages 18-29) with a range of cannabis use responded to a series of questionnaires assessing ELT, current stress, mental health, and cannabis use. Blood was collected for later analysis of eCBs in plasma, and saliva was collected for the analysis of diurnal cortisol. Behavioural data revealed a significant relationship between ELT and problematic cannabis use, above and beyond age of initiation. Current perceived stress mediated the relationship between ELT and problematic cannabis use. Pending analysis of blood and saliva samples, circulating eCBs and diurnal cortisol data will also be discussed. Exploring the relationship between ELT and problematic cannabis use among young adults will not only facilitate more informed use within this population, but also holds the potential for informing targeted therapeutic interventions and clinical strategies.

Keywords. Cannabis, Young adult, Addictions, Trauma, Endocannabinoids, Cortisol

P.1.72 - Effect of nicotine dose and dose expectancy on puff- and bout-level analysis of smoking topography

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Puff topography is often measured in tobacco regulatory science as an indicator of addiction risk. However, analyses typically focus on experimentally controlled puffing procedures and do not consider in-depth analysis of micro-level behavior under ad libitum conditions. Here, we evaluate puff- and bout-level metrics that may prove useful in the analysis of smoking behavior with promising applications to clinical research and tobacco cessation outcomes. People with daily cigarette use (N=21; 9 female) completed one practice and four experimental sessions in which nicotine dose expectancy (labelled “average” versus “very low” nicotine) and nicotine dose (0.80 mg versus 0.03 mg yield) were manipulated. Participants smoked cigarettes in the laboratory under ad libitum conditions and puff topography data were collected. Topography was investigated using puff-level measures (e.g., overall puff volume, total time, total number of puffs) and a novel rolling topography window that separated smoking bursts by 1-second intervals from 1 to 30 seconds. Analyses evaluated main and interactive effects of expectancy and nicotine dose on overall puff topography as well as the rolling window, demonstrating unique utility and predictive of the latter method of analyzing data. Analyses demonstrated that low dose nicotine, but not low dose expectancy, resulted in reduced number of bouts ($p = .006$), increased puffs/bout ($p = .013$), and more rapid smoking timecourse (p’s $< .005$). These data demonstrate the utility of puff- and bout-level analyses for evaluating pharmacological and contextual moderators of smoking behavior as well as the flexibility of within-session topography by examining multiple smoking timeframes.

Funding. R03DA054098; T32DA07209; Study cigarettes were provided by the NIDA Drug Supply Program.

Keywords. Topography, cigarettes, nicotine, smoking

P.1.73 - The impact of childhood maltreatment on the endocannabinoid system and the processing of socially relevant information in healthy humans

Abigail R. Lunge, Gavin N. Petrie, Matthew N. Hill, Leah M. Mayo

Background: Childhood Maltreatment (CM), exposure to neglect or physical, sexual, and emotional abuse, is a highly prevalent public health concern. Exposure to CM is associated with altered stress responses and threat-related social processing, contributing to vulnerability to developing psychopathologies, including anxiety disorders. The endocannabinoid (eCB) system, a critical neuromodulator of stress and social processing, may mediate the neuropsychological consequences of CM. To date, the relationship between CM exposure and eCB signalling and its impact on stress and social processing beyond threat-related has been poorly investigated. Thus, the present study examined the impact of CM severity on eCB contributions to various modalities of social processing, elucidating potential eCB-related therapeutic targets for related psychiatric conditions in CM populations. Aims: Aim 1: Does CM severity predict alterations in basal eCB levels. Aim 2: Does CM severity predicted alterations in processing socially relevant information, including social evaluation. Methods: Participants completed 2 in-person sessions. During the baseline session, CM severity was retroactively assessed with the Childhood Trauma Questionnaire (CTQ). At the onset of the experimental session, hair and blood samples were collected for eCB and cortisol analysis. Participants performed social processing tasks while measures of stress and arousal, including facial electromyography, were recorded. Preliminary Results: 69 participants completed the study, with 54.2% of participants reporting exposure to CM on the CTQ. Analyses of blood samples indicate that baseline cortisol levels were not significantly impacted by CM severity. Analysis of eCBs in blood and hair samples and their contributions to social processing are ongoing.

Funding. I currently hold the Cumming School of Medicine Graduate Scholarship.

Keywords. Developmental neuroscience, endocannabinoids, stress, psychiatric disorders

P.1.74 - Longitudinal changes in endocannabinoids and clinical course in adolescents with non-suicidal self-injury

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Non-suicidal self-injury (NSSI) in adolescents has previously been linked to alterations in the endocannabinoid system. While increasing evidence supports endocannabinoid levels as a biomarker in psychiatric disorders, little is known about their longitudinal trajectories over the course of treatment or in predicting clinical symptoms. This is the first study to investigate endocannabinoids in a longitudinal cohort of patients with NSSI, exploring associations with their clinical course. Plasma endocannabinoids were assessed in n=46 female adolescents with NSSI at baseline and after one year of treatment (follow-up). Associations between endocannabinoids and clinical symptoms over time were analyzed. Anandamide (AEA) significantly decreased from baseline to follow-up, and this decrease was associated with improvement of NSSI frequency. Furthermore, AEA at baseline predicted the change in NSSI frequency and trajectories of AEA differed between responders and non-responders concerning depressive symptoms. Findings suggest that plasma AEA may predict and indicate treatment response in adolescents with NSSI.

Keywords. Endocannabinoid System, Non-Suicidal Self-Injury, Childhood Trauma, Adolescents

P.1.75 - Longitudinal changes in apolipoproteins correlate with alterations in cognitive decline in alcohol use disorder: a prospective cohort study

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Introduction. Alcohol Use Disorder (AUD) is associated with cognitive impairment, which may persist despite long abstinence. This study explores the relationship between apolipoproteins and cognitive recovery in patients with AUD during early abstinence (1-3 months) and their progression over 6-month (t=1) and 12-month (t=2) follow-ups. Understanding these biological mechanisms is key to improving therapeutic interventions. Materials and Methods. 33 abstinent AUD patients from an outpatient alcoholism program at Hospital 12 de Octubre in Madrid and 34 controls were assessed at t=0, t=1 and t=2 using the "Test for the Detection of Cognitive Impairment in Alcoholism (TEDCA)", which evaluates general cognitive function (GCF). Biological evaluations included plasma biomarkers (LPS, LBP) and multiple apolipoproteins (APOAI, APOAII, APOB, APOCII, APOE, APOJ, APOM).Results. AUD patients who maintained prolonged abstinence exhibited significant cognitive improvements, reaching performance levels similar to controls by t=2. Biomarker levels normalized to those of controls by t=1. Notably, APOAI and APOM displayed opposing trends over time, with APOAI decreasing and APOM increasing. These apolipoproteins were previously identified as contrasting biomarkers for AUD diagnosis. Furthermore, the duration of abstinence was a strong predictor of cognitive improvement (mixed models analysis). However, elevated LPS levels were associated with cognitive decline, as increases in this biomarker predicted lower GCF scores in AUD patients (mixed models).Conclusion. These findings emphasize the importance of sustained clinical intervention and adherence to abstinence programs. Monitoring abstinence and addressing underlying pathology is essential, as it contributes to the normalization of apolipoproteins, reduces peripheral inflammation, and supports cognitive recovery in AUD patients.

Keywords. Alcohol Use Disorder (AUD), cognitive impairment, abstinence, apolipoproteins, cognitive recovery, inflammatory biomarkers

P.1.76 - Exploring access to psychedelics among canadian veterans: pathways, barriers, and experiences

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Psychedelic-assisted therapies have recently gained attention as potential novel treatments for various mental health conditions. In Canada, there has been particular interest from the veteran communities regarding the potential therapeutic impact of psychedelics. However, legal access remains limited in Canada, leading some veterans to explore alternative pathways. This study examines how Canadian military veterans learn about and access psychedelics for mental health treatment. Using a retrospective survey-based design in collaboration with the registered Canadian charity, Heroic Hearts Canada, we collected data from 30 veterans on their mental health history, prior treatments, information sources, and methods of access. Our findings indicate that while some veterans accessed psychedelics through legal pathways, most sought them underground options, including self-directed and guided experiences. Veterans primarily relied on peers and media for information rather than healthcare providers. Those who avoided discussions with their healthcare providers cited concerns about stigma, while those who did consult healthcare providers often found them to lack knowledge on psychedelic treatments. These findings highlight gaps in access, and education surrounding psychedelic therapies for veterans. We propose that addressing these barriers through improved clinician training and education, policy reform, and safer legal pathways is essential to ensuring informed and effective care for those seeking alternative mental health treatments, such as psychedelics. Moreover, these efforts will contribute to broader harm reduction strategies by equipping clinicians with the knowledge and tools to support individuals who may continue to access these substances outside legal frameworks.

Keywords. Psychedelic-assisted therapy, Veteran mental health, Access barriers

P.1.77 - Neurofunctional mechanisms of behavioural inhibition in ADHD and OCD: A comparative study using the stop-signal task and resting-state functional connectivity

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Behavioural inhibition (BI) is a core executive function crucial for self-regulation, impulse control, and adaptive decision-making. Both attention-deficit/hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD) are associated with BI deficits, but each presents distinct phenotypic and neurofunctional profiles. The stop-signal task (SST) is commonly used to assess motor inhibition via stop-signal reaction time (SSRT); however, its diagnostic utility is limited due to overlapping impairments across conditions. This study aimed to examine multiple SST-derived variables and their relationship with resting-state functional connectivity (rsFC) in the frontoparietal network (FPN) to better understand inhibitory control mechanisms in both disorders. A total of 155 adults (59 with ADHD, 42 with OCD, and 54 healthy controls) participated. Inhibitory performance was assessed using an adaptive version of the SST, and fNIRS-based rsFC was used to explore connectivity within the FPN. OCD participants exhibited slower reaction times in Go trials and greater post-error slowing compared to both ADHD and control groups, consistent with a hypercontrolled, punishment-sensitive profile. In contrast, ADHD participants showed shorter Go reaction times, faster post-error responses, and lower success rates on stop trials, reflecting impulsivity, attentional dysregulation, and insensitivity to negative feedback. Additionally, the ADHD group committed more commission errors, while OCD participants exhibited more omission errors, reinforcing distinct inhibitory control profiles. Notably, we found that FPN connectivity predicted behavioural performance, highlighting the relationship between neural dynamics and inhibitory control. These results reveal dissociable cognitive and behavioural profiles of BI in ADHD and OCD, offering insights into the underlying mechanisms of inhibition and their neural correlates.

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Keywords. attention-deficit/hyperactivity disorder, obsessive-compulsive disorder, behavioural inhibition, stop-signal task, functional connectivity

P.1.78 - Co-prescription of anticholinergics and benzodiazepines in chronic pain patients treated with opioids: a population-based case-control study

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Given the potential risks associated with the co-prescription of opioids, benzodiazepines, and anticholinergics and the few studies in literature, the aim of this study was to investigate their combined impact on the patient's quality of life. This exploratory, cross-sectional, single-center study was conducted over 12 months utilizing ALUMBRA® system data while ensuring patient confidentiality and ethical compliance. The study included adult patients with chronic non-cancer pain (CNCP), diagnosed using ICD-10, requiring opioid treatment for over three months to avoid a bias. Patients with only neuropathic pain or insufficient clinical data were excluded. Key demographic variables analyzed included age, sex, and health status, were classified using Clinical Risk Groups (CRG). Healthcare utilization was assessed through primary care visits, outpatient visits, and hospital admissions. Treatment-related variables included opioid, benzodiazepine, and anticholinergic use, were categorized according to the WHO ATC Classification System. Additional factors such as dosage schedules, polypharmacy, concomitant treatments, and prescribing physician category were examined. The ALUMBRA® database initially contained 72735 records, narrowing to 3103 patients after applying inclusion criteria, and further to 1154 patients afterfiltering as mentioned before. The mean age was 69.9 years, with women (70.4%) outnumbering men (29.6%). Patients were divided into Opioid group (Control G) (n=520), Benzodiazepines (BZD G) (n=459), Anticholinergics (ATC G) (n=86), and BZD-ACT G (n=89) groups. Age distribution was homogeneous, but gender significantly influenced treatment allocation, with women being overrepresented in BZD and BZD-ATC groups. Morbidity was higher in BZD and BZD-ATC groups, suggesting potential health risks. These findings align with the hypothesis that pharmacological treatment decisions may be influenced by underlying comorbidities and that the use of BZD G and ATC G are associated with increased cognitive impairment, falls, and hospitalizations in elderly populations.

Funding. This research was funded by Alicante Institute for Health and Biomedical Research, code ISABIAL: 2021-0458

Keywords. Opioid, Benzodiazepine, Anticholinergics, Interaction Drug, Patients, Quality of life

P.1.79 - Action-sequence learning, habits and automaticity in obsessive-compulsive disorder: implications for treatment

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The goal/habit imbalance theory of obsessive-compulsive disorder (OCD) proposes that compulsions arise from heightened habit formation, greater behavioral automaticity, and difficulties in shifting between goal-directed and habitual actions. This study sought to investigate these interconnected components within a unified framework using a set of innovative behavioral tasks. Thirty-two individuals with OCD and thirty-five healthy controls were trained daily for one month using a custom-designed smartphone application to perform chunked sequences of finger movements (similar to a piano-based app; see accompanying video for task design). Contrary to our hypotheses, both groups exhibited comparable procedural learning and attainment of automatic performance. After the training phase, participants completed an arbitration task assessing the ability to switch between previously learned/habitual sequences and newly introduced goal-directed actions. No significant group differences in arbitration were observed when outcomes were tied to monetary feedback. Nonetheless, a subset of patients with OCD showed a stronger preference for the previously learned habitual sequence in other contexts, possibly reflecting an increased intrinsic valuation of familiar actions. Notably, these individuals also demonstrated higher levels of compulsivity and habitual tendencies, engaged more extensively with the training app, and reported symptom relief after the experiment. This tendency to assign intrinsic value to familiar actions may be the key mechanism in the transition to compulsive behavior. Our findings further emphasize the potential of smartphone-based motor habit training as a scalable tool for habit reversal therapy in OCD. A recent clinical trial has provided evidence supporting the positive impact of the app on symptom improvement.

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Keywords. goal/habit, skill, automaticity, motor sequence learning, OCD, psychiatry, cognitive neuroscience

P.1.80 - Repurposing antidepressants for diabetic neuropathic pain: in combination or alone?

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Diabetes Mellitus (DM) is a chronic metabolic disorder marked by high blood glucose levels, often leading to diabetic peripheral neuropathy (DPN), which affects up to 50% of people with DM. DPN frequently results in neuropathic pain (DPNP), characterized by burning, tingling, electric shocks, and numbness, significantly reducing quality of life.International guidelines recommend treatments with antidepressants as amitriptyline, duloxetine or the gabapentinoids as pregabalin and gabapentin for DPNP, but fewer than half of patients experience significant relief, often due to side effects at higher doses.In order to assess the efficacy of antidrepressants for DPNP, a systematic review was conducted using the PRISMA methodology across PubMed and Web of Science, identifying 388 records. After screening, only 6 studies from the past 10 years met inclusion criteria.A total of 388 records were identified with both databases. After initial screening 347 records were excluded based on: publication date older than 10 years (n = 142) or inadequate study design (n = 91). A total of 51 full-text articles were assessed for eligibility. 45 were excluded for not focusing on the primary aim of the review resulting in 6 studies included in the final review.Findings were conflicting. The COMBO-DN trial found similar efficacy between combination (duloxetine with pregabalin) and high-dose monotherapy. The OPTION-DM trial supported combination therapy when monotherapy is insufficient. A recent study showed potential for amitriptyline with liraglutide, a GLP-1 receptor agonist, in managing DPNP.However, current guidelines do not support combination therapy due to limited robust evidence highlighting the need for further research.

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Keywords. diabetic neuropathy, antidepressants, drug repurposing

P.1.81 - The effects of Ayahuasca on inter-brain synchrony during the ritual in the Amazon – a field study

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Background. One of the key elements that can influence the course of a psychedelic experience is the setting in which the substance is used. In contrast to an experimental or clinical setting, a typical ritual setting is in a group arrangement and accompanied by ritual chants - icaros. In order to understand the role of the setting, our main aim was to study the ayahuasca ritual in Amazonia itself. We chose high-density EEG as a tool that would allow us to quantify the dynamics of changes in participants' brains during the ceremony, and to make synchronised recordings at the same time. Methods: We used 64-channel ANT Neuro amplifiers with gel-based caps and collected synchronised continuous EEG from seven subjects during two ayahuasca ceremonies. The EEG amplifiers were synchronised with video from an IR camera and audio from icaros. Pre-processing of the EEG and alignment with events describing major artefacts and the beginning and end of chanting was performed in BrainVision Analyzer using standard pipelines. The pre-processed data were exported to Matlab for further analysis, where inter-brain synchrony was calculated using alpha (8-12 Hz) envelope correlation. The analyses also considered the spatial arrangement of the subjects during the ceremony. Results: The EEG after ayahuasca ingestion showed a spectral profile typical of all psychedelics with an overall reduction in alpha activity. Hyperscanning revealed an increase in interbrain synchrony during the peak of the ceremony/ayahuasca effect. The singing of Icarus, however, resulted in lower synchrony compared to the periods where there was no singing. Discussion: Practical experience from this type of field study is crucial for conducting controlled studies with ayahuasca or other psychedelics in a ritual context. These studies can provide important insights into understanding the influence of ritual setting and group dynamics during work with psychedelics.

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Keywords. psychedelics; ayahuasca; EEG; hyperscanning; field study

P.1.82 - The effect of caffeine consumption and acute withdrawal on mood, cognition, and resting state brain activity

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Caffeine is the most widely consumed psychoactive substance globally, yet few studies have investigated how habitual consumption and acute withdrawal impacts resting-state brain activity. Notably, prior research lacks adequate control for deprivation state, despite evidence that caffeine reinforcement occurs primarily by alleviating withdrawal. This study used a between-participants design to assess mood, cognition, and resting-state brain activity in three groups: (1) moderate consumers (200-500mg/day) tested after overnight abstinence (caffeine withdrawn, CW); (2) moderate consumers (200-500mg/day) tested after overnight abstinence followed by 100mg of caffeine (caffeine not-withdrawn, CNW); and (3) non-consumers of caffeine (< 50mg). Sixty healthy human volunteers, aged 18-45 (n = 20 per group) completed the Bond-lader mood battery, a rapid visual information processing task and a resting-state fMRI scan. While no significant group differences emerged for mood and cognition, seed-voxel analysis found significant differences in brain activity. Specifically non-consumers of caffeine had significantly higher connectivity from the nucleus accumbens to the primary visual cortex and lower connectivity to the lingual and occipital fusiform gyrus compared to the CW group. In addition, non-consumers had significantly lower connectivity from the anterior insula to the precuneus cortex compared to the CNW group. In conclusion, these findings suggest that deprivation state alters resting-state brain activity in the nucleus accumbens, a region traditionally associated with reward. Additionally, increased interior insula connectivity in the CNW group supports caffeine's role in attention. Subsequent independent component analysis is planned to investigate whole-brain differences.

Keywords. Caffeine, resting-state, fMRI, reward, withdrawal

POSTER SESSION 2

P.2.1 - Investigating the role of the alpha-7 nicotinic acetylcholine receptor during a signal detection task: pharmacological modulation and molecular analysis

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Cholinergic dysfunction contributes to attentional deficits in various neuropsychiatric disorders. Cortical cholinergic inputs are fundamentally linked to attention and phasic acetylcholine (ACh) release mediates performance in tasks involving cue-directed responding. An expanding body of both clinical and preclinical data has identified the alpha-7 nicotinic Ach receptor (α7nAChR) as a promising target for pro-cognitive interventions. This experiment will investigate role of α7nAChRs in attentional performance by applying systemic manipulations in adult male and female Sprague-Dawley rats (n = 32) during the Signal Detection Task (SDT). In the SDT, subjects detect and respond to the absence or presence of visual light to obtain food reward. Outcome measures include accuracy (%), response latencies (s), sensitivity, and response bias. To fully characterise the role of α7nAChRs in attentional performance, this experiment will utilise four α7-targeting compounds: a selective full agonist (EVP-6124), a partial agonist (SSR-18071), an allosteric modulator (CCMI), and a selective antagonist (MLA). Dose-dependency will be established using a Latin square design with a 48-hour washout between each compound. We will also examine the relationships between individual differences in cortical α7nAChR expression and both task performance and drug response, using western immunoblotting. Data will be analysed using linear mixed-effects regressions, as appropriate.Our findings will inform the future development of cholinergic interventions for cognitive and attentional impairments, providing strong evidence to either support or discourage the use of α7nAChR-targeting compounds as potential treatment strategies. Molecular analyses will yield valuable insights into the mechanisms by which α7nAChRs confer pro-cognitive benefits.

Funding. UK Medical Research Council iCASE Studentship; Boehringer Ingelheim Pharma GmbH & Co KG

Keywords. Acetylcholine, Attention, Signal Detection, Behavioural Pharmacology, Molecular Analysis

P.2.2 - GlyT1 inhibitor, Bitopertin redistributes the excitatory and inhibitory network connectivity in mouse medial Prefrontal Cortex

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Cognitive impairments linked to schizophrenia are believed to originate from a disruption in the balance of excitation and inhibition (E/I) within the medial prefrontal cortex (mPFC). This imbalance is thought to arise from dysfunctions in N-methyl-D-aspartate receptors (NMDAR) and compromised GABAergic neurotransmission. Our prior research has shown that bitopertin, an inhibitor of the glycine transporter 1 (GlyT1), can correct this E/I imbalance. Despite these findings, the precise mechanisms by which bitopertin acts remain elusive. In our current study, we employed channel rhodopsin-assisted circuit mapping (CRACM), two-photon ex vivo functional imaging, and electrophysiological recordings within the mouse medial prefrontal cortex (mPFC) to delve deeper into bitopertin's mechanism of action. Our findings indicate that bitopertin primarily acts postsynaptically, modulating NMDAR-mediated currents in a cell-type-specific manner. It enhances NMDAR-dependent connectivity between pyramidal cells and both parvalbumin (PV) and somatostatin (SST) interneurons, while diminishing connectivity to vasoactive intestinal peptide (VIP) interneurons. Furthermore, we detected significant increase in excitatory transmission to PV neurons, which may lead to decreased excitability of pyramidal neurons, offering a plausible mechanism for bitopertin's efficacy in correcting the E/I imbalance. This aims to provide a clearer understanding of bitopertin's therapeutic potential in mitigating cognitive deficits in schizophrenia through its nuanced modulation of neural circuitry within the mPFC. In summary, our research provides comprehensive insights into the effects of GlyT1 inhibition on local neural circuitry and its potential mechanisms. This knowledge paves the way for developing more effective therapies for cognitive impairments associated with E/I imbalance.

Keywords. Bitopertin, Glyt1 inhibitor, E/I imbalance, schizophrenia, prefrontal cortex network, PV neurons

P.2.3 - Behavioral and molecular effects of CBD in a peripartum depression mouse model

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Peripartum depression (PPD) is a subtype of major depressive disorder affecting about 20% of new mothers each year. PPD's symptomatology is characterized by deficient maternal care, potentially impacting mother-infant bonding and offspring development. The recent use of allopregnanolone-based treatments has highlighted the role of reproductive hormones and GABAergic transmission in the pathophysiology of PPD. Still, many factors participate in the neurobiology of depressive conditions. In this regard, the endocannabinoid system (ECS) plays a crucial role in the neurobiology of psychiatric disorders, as it modulates stress and anxiety responses. The present study explores the use of cannabidiol (CBD) in ameliorating the depressive-like phenotype present in PPD by targeting the ECS. Thus, a well-established PPD mouse model combining 15 days of maternal separation and early weaning (MSEW) at postnatal day 17, was implemented and compared to a standard nest (SN) condition. CBD or vehicle was administered during the maternal separation period. Subsequently, RNA expression assessment (OpenArray) and behavioral tests were performed to evaluate the effects of this compound on our model. OpenArray analyses conducted on limbic and cortical areas revealed differential expression of genes related to mood, behavior, and reward processing in untreated MSEW mice compared to the SN group. Accordingly, behavioral results showed a negative affect state in untreated MSEW dams compared to the SN group, which was absent in MSEW CBD-treated mice, suggesting CBD's involvement in restoring the SN phenotype. Altogether, these findings support the importance of the ECS in PPD's neurobiology, opening new possibilities for its pharmacological management.

Keywords. Peripartum depression (PPD), endocannabinoid system (ECS), cannabidiol (CBD), maternal separation

P.2.4 - Brain CB2 receptor: A new target in medication development for treating opioid use disorder in rodents

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Opioid use disorder (OUD) is a major public health crisis in the U.S., underscoring the need for safe, non-opioid pharmacotherapies. Emerging evidence suggests that the cannabinoid CB2 receptor (CB2R) may serve as a therapeutic target for chronic pain and neuropsychiatric disorders without psychoactive side effects. However, its role in opioid use and relapse remains unclear. Here, we report that MRI-2594, a novel highly selective CB2R agonist, dose-dependently inhibited heroin self-administration and heroin-induced reinstatement of drug-seeking behavior in rats. Notably, MRI-2594 produced mild analgesic effects without reducing opioid analgesia or causing sedation or locomotor impairment. Intracranial administration of MRI-2594 into the ventral tegmental area (VTA) or nucleus accumbens (NAc) dose-dependently suppressed heroin self-administration. Furthermore, optogenetic activation of midbrain dopamine (DA) neurons was rewarding, an effect inhibited by MRI-2594. To confirm CB2R's role in these effects, we developed a CB2R-knockout and enhanced green fluorescent protein (eGFP) reporter mouse line (CB2-KO-eGFP), in which the CB2R-coding region was replaced with the eGFP gene. Immunocytochemistry revealed eGFP expression in tyrosine hydroxylase (TH)-positive DA neurons in the VTA and in NAc cells of CB2-KO-eGFP mice, but not wild-type mice. Lastly, systemic administration of MRI-2594 dose-dependently inhibited heroin self-administration in wild-type but not CB2-KO-eGFP mice. These findings suggest that brain CB2R is a promising therapeutic target for OUD, and MRI-2594 warrants further investigation as a potential treatment.

Keywords. Opioid, heroin, MRI-2594, dopamine, CB2 receptor, CB2-KO mice, CB2-eGFP reporter mice, self-administration

P.2.5 - To flee or not to flee: the role of the endocannabinoid system

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Survival requires the selection of appropriate behaviors in response to threats. Dysregulated defensive reactions may trigger maladaptive coping underlying several neuropsychiatric conditions. Threat-evoked behaviors, including freezing (passive) and fleeing (active), are controlled by multiple neuronal circuits. However, the mechanisms controlling the active-passive trade-off (APT) in defensive responses have only been scantly investigated. The endocannabinoid system, and particularly cannabinoid type-1 (CB1) receptors in striatal direct and indirect pathways, has been proposed to participate in this effect, but the neuronal basis of this interaction has not been addressed. Using a combination of semi-naturalistic behavioral paradigms, computational behavior tracking, pharmacogenetics and viral approaches, the contribution of different striatal subpopulations of CB1 receptors in orchestrating APT was assessed during different tasks. While striatonigral CB1 receptors are not involved in regulating defensive responses, escape behaviors require the activation of CB1 receptors specifically located at striatopallidal terminals (indirect pathway). Threat presentation increases dorsostriatal Adora2a+ neuron activity in wild-type animals, an effect that quickly resolves thereafter but persists in animals lacking striatopallidal CB1 receptors. This is concomitant with a significant increase in the number of cFos+ cells in dorsomedial Adora2a+ populations after imminent, but not remote, threat presentation. Functional manipulations revealed that specific targeting of striatopallidal CB1 neurons is sufficient to reinstate the ability to cope with threatful stimuli. These findings indicate a new mechanism by which striatopallidal CB1 receptors regulate threat response and offer insights into a local circuit critically involved in defensive behaviors. Overall, this work may provide potential therapeutic avenues for disorders characterized by maladapting coping.

P.2.6 - Endocannabinoid modulation of cortical dopamine release

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The anterior cingulate cortex (ACC) is involved in motivational aspects of learning and contributes to motor functions via projections to subcortical motor systems. Endocannabinoids (eCBs) and dopamine (DA) are important neuromodulators involved in many aspects of these behaviors. Although DA release regulation by eCBs has been documented in other brain regions such as the striatum, their role in cortical regions, such as the ACC, that express less dense DA innervation, has not been well investigated. The eCBs, anandamide and 2-arachidonoylglycerol (2-AG) are the primary endogenous ligands of CB1 receptors. Recently, the development of new genetically encoded biosensors for eCBs and DA, like GRAB2-AG and GRABDA, has allowed for the to study these neuromodulators in brain regions, like the ACC, where such measurements were previously not feasible. Here we used photometry in mouse brain slice experiments to pharmacologically characterize the interaction of both systems. We found that DA and 2-AG can be measured in ACC. While photometric DA signals are smaller in this area compared to striatum, 2-AG responses are similar to those observed in striatal regions. We also found that WIN 55212-2 a CB1 receptor agonist decreases the release of DA in ACC, an effect blocked by CB1 receptor antagonist AM251. This is a provocative finding due to earlier findings suggesting DA terminals lack CB1receptors. We have also find that 2-AG release is modulated by adrenergic alpha-2 receptor antagonist idazoxan, introducing a possible synergistic role for the endocannabinoid and noradrenergic systems in the regulation of DA release in cingulate cortex.

Funding. ZIA AA000407/ NIH Intramural/ HHS

Keywords. cannabinoids; dopamine; photometry; cingulate cortex

P.2.7 - Is there a role for extended amygdala dynorphin/κ-opioid receptor in opioid addiction-like behaviors?

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Opioid use disorder (OUD) is a chronic relapsing disorder characterized by compulsive drug taking and seeking. Drug use is motivated by drug reward and the avoidance/alleviation of withdrawal symptoms (e.g., pain, dysphoria, irritability, etc.) after chronic use. Repeated opioid exposure alters stress circuitries, including regions of the extended amygdala. However, the specific role of the dynorphin/κ-opioid receptor (KOR) system in opioid withdrawal-related behaviors remains unclear. To address this, we injected drug-naïve dynorphin-Cre Long Evans rats with the Cre-dependent adeno-associated virus rAAV2/EF1a-DIO-hCHR2-eYFP into the central amygdala (CeA). We then assessed the role of dynorphin/KOR in opioid dependent behaviors. Male and female dynorphin-cre rats were tested for baseline mechanical sensitivity using von Frey and assigned to either saline or fentanyl groups. Fentanyl (0.02-0.06 mg/kg, SC) or saline (1 mg/ml, SC) was administered daily, 5 days per week for 2 weeks to induce dependence. Spontaneous withdrawal-induced hyperalgesia was characterized using the electronic von Frey 2, 4, 8, 24, 48, and 72 h after injections. To test the role of KORs, the KOR antagonist aticaprant or vehicle was administered one hour before peak withdrawal. In a separate cohort, we performed stereological assessment of prodynorphin (pDyn) expression in CeA and BNST subregions of fentanyl-dependent and control rats. We identified a strong dynorphin projection from CeA to BNST. We will present a time course of spontaneous fentanyl withdrawal and results of pDyn expression mapping in opioid dependence. These data will provide key information on how this circuitry modulates opioid withdrawal-related behaviors that could motivate opioid taking.

Keywords. opioid addiction, dynorphin, kappa opioid receptor, central amygdala, bed nucleus of the stria terminalis, hyperalgesia

P.2.8 - Exploring behavioural interactions between methamphetamine and psilocybin in mouse models of methamphetamine sensitization and head twitch response

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Psilocybin shows promise for the treatment of substance use disorders, although its interactions with methamphetamine are relatively unstudied. Importantly, methamphetamine-induced psychosis is prevalent in 37-43% of users and is an exclusion criterion for psilocybin clinical trials, which may be related to methamphetamine-induced changes to expression of psilocybin's primary neural target, the cortical 5HT2A receptor. These interactions need to be understood to inform safety and accessibility of psilocybin-assisted therapy. Therefore, our study addresses two questions: 1)Does withdrawal from chronic methamphetamine alter the potency of psilocybin for inducing hallucinogenic-like behaviour? 2)Does psilocybin administered throughout withdrawal alter the development of sensitization to methamphetamine? Mice were administered methamphetamine (2mg/kg, i.p.) or saline daily for 8 days, and were then withdrawn for 14 days. On withdrawal day 14, mice were challenged with methamphetamine. Mice were allocated to receive saline or a dose of psilocybin (0.3, 1, 3 mg/kg), administered at different periods during withdrawal: acute (WD1), protracted (WD13), or a combination (WD1&7). The head-twitch-response to psilocybin was assessed using custom software. Locomotor activity was recorded following methamphetamine injection on days 1, 8, and challenge day 22. This experiment is underway; however, we have several hypotheses. We anticipate that chronic methamphetamine administration will alter the potency for inducing HTR (ED50) and efficacy (maximum HTR at any dose), and that this will interact with withdrawal stage. Similarly, we anticipate that psilocybin treatment in early, but not late withdrawal from methamphetamine will reduce the development of methamphetamine sensitization. Our findings will help clarify methamphetamine-psilocybin interactions relevant to clinical trial design. The head-twitch assay will assess psilocybin's potential to exacerbate psychosis in chronic methamphetamine users, informing treatment eligibility. Locomotor sensitization findings will guide optimal timing and dosing of psilocybin relative to methamphetamine use, shedding light on its therapeutic mechanism and timing.

Funding. NHMRC, CRC-P, National Industry PhD Program

Keywords. Psilocybin, Methamphetamine, Addiction, Psychedelics, Neuroplasticity

P.2.9 - Effects of the 5-HT2A agonist DOI on compulsivity and reversal learning in preclinical models

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Compulsivity is a central symptom in several psychiatric disorders, and identifying the neurochemical pathways underlying this behavior is essential for effective therapeutic development. The 5-HT2A receptor is of particular interest due to its involvement in cognitive processes, mood regulation, and compulsive behaviors, making serotonergic psychedelics potential modulators of compulsivity. Our study aimed to assess the effects of the psychedelic drug DOI (2,5-dimethoxy-4-iodoamphetamine), a potent 5-HT2A agonist, on compulsive behaviors using a preclinical model known as Schedule-Induced Polydipsia (SIP). We employed 48 male Wistar rats, categorized according to their compulsive water drinking behavior as high drinkers (HD) or low drinkers (LD). Rats were divided into three groups (n=16 per group), receiving either DOI at doses of 2 mg/kg or 8 mg/kg, or a vehicle control. Treatments were administered intraperitoneally (i.p.). After drug administration, rats were retested under the SIP paradigm to evaluate changes in compulsive drinking behavior. Results indicated no significant behavioral alterations at the evaluated doses of DOI in either HD or LD rats. Given these findings, further behavioral assessments using the probabilistic reversal learning paradigm are planned, employing lower DOI doses (0.5 mg/kg and 2 mg/kg) to investigate potential cognitive and behavioral effects. This subsequent evaluation has yet to be performed, with an expected total sample of n=48 subjects.

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Keywords. Compulsive Behavior, Receptors, Serotonin, 5-HT2A, Hallucinogens, Polydipsia, Rats, Wistar

P.2.10 - Characterizing the antidepressant-like effects of psilocybin in adolescent rats of both sexes

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Adolescent depression is a significant public health concern, yet treatment options remain limited, particularly due to age- and sex-related differences in antidepressant efficacy. This study explored the potential antidepressant-like response of psilocybin in adolescent rats, examining acute and repeated effects while incorporating sex as a biological variable. Adolescent Sprague-Dawley rats were treated with psilocybin (0.3 and 1 mg/kg/day, n=10 per dose/sex) or vehicle (saline, 1 ml/kg/day, n=10 per sex) for 7 days (oral gavage). Acute and repeated antidepressant-like responses were measured under the stress of the forced-swim test. Statistical evaluations were done through two-way ANOVAs (independent variables: Sex and Treatment). The main results proved that all doses tested of acute psilocybin produced rapid antidepressant-like effects in rats of both sexes as measured 30 minutes post-treatment, demonstrated by reduced immobility in the forced swim test. However, sex differences were observed in the long-term antidepressant effectiveness following repeated administration. Specifically, a sustained antidepressant-like effect was observed in male rats exposed to repeated psilocybin, still lasting up to 15 days post-treatment. In contrast, this response persisted only for up to 8 days in adolescent female rats, and only with the highest psilocybin dose tested. These findings underscore the potential beneficial effects of psilocybin during adolescence, with proved rapid and long-lasting effects, while suggesting the critical need to consider sex as key factor in developing effective, personalized therapeutic strategies for adolescent depression. Additionally, given psilocybin's psychoactive nature and current regulatory restrictions, any potential safety issues might be detected prior to its use in adolescence.

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Keywords. Adolescence, Psilocybin, Antidepressant, Sex differences

P.2.11 - Transcriptomic and metabolomic signatures of ibogaine treatment: preclinical and clinical investigation

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Opioid dependence is a global public health issue with limited therapeutic alternatives. Methadone maintenance programs remain one of the most commonly used approaches. However, methadone itself lead to dependence and tolerance. Ibogaine (IBO), a natural alkaloid, has demonstrated potential in treating substance dependence and mitigating withdrawal symptoms, but its mechanism of action remains not fully understood. This study evaluates the effects of IBO on gene expression in C57BL/6 mice and on the metabolic profile of patients undergoing methadone treatment. On the one hand, adult male and female mice were administered by a single oral dose of either 0 or 60 mg/kg of IBO by gavage. Four hours post-administration, frontal cortex samples were collected from three animals of each sex and treatment for transcriptomic analysis. On the other hand, blood samples were collected from patients enrolled in methadone maintenance programs one week prior to IBO administration and 24 hours after receiving 100 mg of IBO. Transcriptomic analysis revealed that IBO increased the expression of genes related to oxytocin, vasopressin and synaptic plasticity, while genes associated with apoptosis and endosomal transport were reduced. Gender differences were observed, with up to 28 genes up-or downregulates in females and eight in males. Metabolomic changes in patients showed that IBO administration resulted in a reduction of plasma levels of lactate, regardless of the methadone dosage, suggesting that IBO improve energy metabolism. This study expands our understanding of IBO opening the possibility to study new specific targets and metabolic pathways.

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Keywords. Ibogaine, Transcriptomics, Substance Use Disorder, Metabolomics

P.2.12 - Ketamine prevented the anxiety- and depression-like symptoms and the enhanced sensitivity to cocaine induced by social defeat in mice

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Stress has been identified as a significant trigger for the development of mental and drug use disorders. In previous studies we observed that adolescent male mice exposed to intermittent social defeat (ISD) exhibited anxiety- and depression-like symptoms as well as heightened sensitivity to cocaine reward in adulthood. Since there are no approved pharmacotherapies for the cocaine use disorder, it is important to identify treatments that can prevent the stress-induced vulnerability to cocaine. The objective of the present study was to evaluate the effectiveness of ketamine in reversing the effects of ISD in male mice. To this end, four groups of male mice were used. A control group of mice was treated with saline and not exposed to stress (SAL+NS) while three groups of mice received saline or ketamine (10 and 30 mg/kg) before each episode of social defeat in an encounter with an aggressive opponent on postnatal days (PND) 47, 50, 53, 56 (groups SAL+ISD, K10+ISD and K30+ISD, respectively). All mice performed the elevated plus maze and the social interaction test to evaluate the presence of anxiety- and depression-like symptoms (PND 57) and the conditioned place preference (CPP) procedure to evaluate the sensitivity to the rewarding effects of 1 mg/kg of cocaine (PND 77). Mice of the SAL+ISD group demonstrated a decrease in the percentage of time spent in the open arms of the elevated plus maze and a reduction in social interaction when compared to the control group. Administration of the high dose of ketamine reversed both effects of ISD. Furthermore, only the group of mice treated with saline and exposed to ISD acquired cocaine CPP. Consequently, treatment with ketamine prevented the ISD-induced potentiation of the rewarding effects of cocaine. These results suggested that ketamine may have therapeutic potential in increasing resilience to the short- and long-term adverse consequences of social stress, including the development of anxiety- and depression-like symptoms as well as the enhanced vulnerability to cocaine.

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Keywords. Anxiety, cocaine, depression, ketamine, mice, stress

P.2.13 - Acute and enduring effects of psilocybin on EEG power spectra and sleep architecture in mice

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Psilocybin shows promising, transdiagnostic therapeutic potential across a diverse range of psychiatric conditions. However, despite increasing clinical and preclinical research, its acute impact on EEG spectral activity and longer-term alterations in sleep architecture are inconsistent, and comprehensive preclinical characterisation is lacking. As EEG and sleep measures offer sensitive, translational indices of population-level neural activity, clarifying these signatures will refine our understanding of psilocybin's neurophysiological profile and potentially inform dose-selection and treatment optimisation. These outcomes may aid in identifying biomarkers relevant to early-phase clinical research and strengthen translation between animal and human research. Hence, the aim of this study is to characterise the acute and enduring, dose-dependent effects of psilocybin on the EEG power spectrum and sleep architecture in mice.Male and female C57BL/6J mice will be implanted with prefabricated headmounts for qEEG/EMG recording. After a 7-day recovery and 2-day habituation period, baseline brain activity and sleep architecture will be recorded over 22 hours. Mice will then receive psilocybin (0.3, 1.0, or 1.5 mg/kg, i.p.) or saline (1 ml/kg) in a counterbalanced order, followed by immediate 22-hour qEEG/EMG recordings to assess acute effects on the power spectrum and vigilance states. Recording periods will be followed by a washout period of at least 10 days. Following this acute phase, mice will receive an additional injection of psilocybin (dose dependent on acute findings) and the enduring effects on sleep architecture will be assessed at 1-, 3-, and 7-days post-treatment.

Funding. NHMRC, CRC-P

Keywords. Psilocybin, sleep, biomarker, psychedelics, qEEG

P.2.14 - Exploring the prosocial impact of psilocybin in male and female adult mice

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Disruptions in social interaction are a hallmark of stress-related disorders, profoundlyimpacting well-being. Despite their significance, effective treatments remain limited dueto an incomplete understanding of the neural mechanisms underlying social behaviors.Psychedelics like psilocybin have emerged as potential therapies to restore socialconnection by modulating neural circuits that govern social behavior, leveraging theirprosocial and anti-inflammatory properties to foster resilience and mitigating stressinducedsocial withdrawal. In this context, this study investigated the potential prosocialeffects of psilocybin in adult C57BL/6 mice, assessing both acute and repeatedadministration while considering sex differences. Mice received psilocybin (0.3 or 1mg/kg, n=11-8 per dose/sex) or vehicle (0.9% NaCl, n=9-8 per sex) via oral gavage (5ml/kg), for seven days. Social interactions were evaluated using a reciprocal socialinteraction test, in which mice were exposed to a novel mouse of the same age and sex.Social behaviors included anogenital sniffing, nose-body, and nose-nose interactions.Statistical analyses were conducted using two-way ANOVAs (Sex and Treatment asindependent variables). Results indicate that 1 mg/kg of psilocybin acutely increasedsociability in males 30 minutes post-administration, evidenced by more anogenitalsniffing and nose-nose interactions. After repeated administration, this dose increasedsocial interactions in both sexes one day post-treatment. Males showed more anogenitalsniffing and nose-nose interactions, while females exhibited increased nose-body andnose-nose interactions. These findings suggest psilocybin enhances prosocial behavior,with rapid effects in males and sustained improvements in both sexes, supporting itspotential as a therapeutic strategy for social dysfunction in stress-related disorders.

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Keywords. Psilocybin, Social Behavior, Sex differences

P.2.15 - BDNF/TrkB signalling in tolerance development to diazepam in mice

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Background:Benzodiazepines continue to be routinely used as rapidly acting, short-term therapy for status epilepticus, anxiety, panic attacks and insomnia. Yet, tolerance development, leading to escalating doses and a heightened risk of dependence, hampers their clinical usage. Here, we aimed to further explore the poorly understood mechanisms leading to tolerance. We focused on the brain-derived neurotrophic factor (BDNF) and its tropomyosin-related kinase receptor (TrkB) which have previously been reported to be modulated by benzodiazepines, both acutely and after repeated administration, in the rodent cortex, striatum and hippocampus.More specifically, we aimed to explore the interplay between the BDNF/TrkB system and the long-term actions of diazepam and identify underlying cell-type and brain region-specific TrkB signalling mechanisms.Methods:Adult heterozygous BDNF knockout mice (BDNF+/−), heterozygous TrkB knockout mice specifically in somatostatin-positive (SST+) (SST-TrkB-hetCKO) and parvalbumin-positive (PV+) interneurons (PV-TrkB-hetCKO) were used. Mouse line-specific wild-type (WT) littermates served as controls. Mice were injected with either diazepam (morning 10 mg/kg, evening 5 mg/kg, i.p.) or vehicle twice a day for three days. Tolerance development to motor-impairing effects of diazepam was assessed using the rotarod performance and elevated beam walking tests 30 minutes after morning drug administration.Results and conclusions:Upon repeated administration of diazepam, BDNF+/- mice displayed a strong deceleration in tolerance development to diazepam in the rotarod ($p<0.001$) and beam walking test ($p<0.001$) compared to WT mice. Next, we sought to define through which cell types this tolerance-preventing effect is exerted. Interneurons, including SST+ and PV+ neurons, have been shown as main cell targets of diazepam action, and exert a crucial role in fine-tuning local networks and regulating brain plasticity and learning. Interestingly, we found a similar decrease in tolerance development in SST-TrkB-hetCKO mice (rotarod: $p<0.01$, beam walking: $p<0.01$), while PV-TrkB-hetCKO mice showed no difference compared to WT mice. The reduced tolerance development in BDNF+/- and SST-TrkB-hetCKO mice was not connected to an increased sensitivity to diazepam.Altogether, our data suggest a novel role for the BDNF-TrkB system in the chronic sedative effect of diazepam, which is at least partly driven through SST+ interneurons.

Funding. Finnish Foundation for Alcohol Studies, Finnish Cultural Foundation, Society for Drug Research, Finnish Pharmacological Society

Keywords. benzodiazepine, tolerance, plasticity

P.2.16 - Cognitive and emotional consequences of new psychoactive substances chronic use: investigation with Alkyl Nitrites (Poppers)

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Background: Alkyl nitrites, more commonly referred to as "poppers," emerged as new psychoactive substances (NPS) with recreational uses. They are very volatile and commonly used by inhalation associated with sexual practices due to their vasodilatory effect and sensation of euphoria. However, their neurotoxic effects remain poorly understood. While some studies have linked poppers to maculopathies and cardiovascular effects, little is known about their impact on the central nervous system and behavior. Objective: This study aimed to evaluate the effects of chronic exposure to two common alkyl nitrites, isoamyl nitrite and isobutyl nitrite, on cognitive and emotional behavior, neuroinflammation, and potential retinal toxicity on animal models. Methods: Male ICR mice were administered daily intraperitoneal injections of either isoamyl nitrite (50 mg/kg), isobutyl nitrite (50 mg/kg) or saline solution for 12 days. Memory, anxiety, depressive-like behavior and motivation were measured by analyzing performance in the Morris Water Maze, Elevated Plus Maze, Forced Swimming Test, and Saccharin Preference Test. Results: The behavioral tests showed that mice exposed to alkyl nitrites, compared to control group, exhibited significant memory impairment, increased anxiety-like behaviors and depressive-like symptoms and induce alterations in the preference for sweet solutions. Conclusion: Chronic exposure to alkyl nitrites leads to behavioral alterations, including cognitive impairment and emotional disturbances. These findings highlight the need for further research into the long-term consequences of poppers use and their implications for public health.

Keywords. Poppers, NPS, new psychoactive substances

P.2.17 - Comparative effects of serotonergic and glutamatergic modulators to remediate behavioral alterations in anhedonia, anxiety and compulsivity in preclinical models

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Glutamatergic modulators act on various glutamate receptors and play a key role in long-term potentiation and synaptic plasticity. Their dysregulation has been linked to several psychological and neurological disorders. On the other hand, serotonergic modulators, particularly psychedelics, have shown promising neuroplastic and neurogenic effects, promoting structural and functional plasticity in brain circuits essential for healthy brain function. This study aimed to compare the therapeutic potential of serotonergic and glutamatergic modulators to remediate behavioral alterations in anhedonia, anxiety and compulsivity in preclinical models. Three 5-HT_2A receptor agonists were tested: 2,5-Dimethoxy-4-iodoamphetamine (DOI), Ibogaine (IBO), and Tabernanthalog (TBG). Additionally, three glutamatergic modulators acting on NMDA receptors were evaluated: D-serine (DS), an agonist at the glycine site of the GluN1 subunit; L-serine (LS), a precursor of D-serine with neuroprotective properties; and D-cycloserine (DCS), a partial agonist at the same site. Two experimental procedures were conducted using male Wistar rats. In the first, 18 rats were divided into control and treatment groups receiving IBO or TBG, followed by behavioral testing. In the second procedure, an additional 18 rats received a single dose of DOI, LS, DS, DCS, or vehicle (saline), following a Latin square design. All rats underwent a behavioral test including the Marble Burying Test (MBT), Sucrose Preference Test (SPT), Elevated Plus Maze (EPM), and Open Field Test (OFT) to assess compulsivity, anhedonia, anxiety, and locomotion. The results will be discussed in terms of the underlying mechanisms of serotonergic and glutamatergic modulators action to reduce compulsive behavior, anxiety, and anhedonia without impairing locomotor activity.

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Keywords. Serotonergic modulators, Glutamatergic modulators, Neuroplasticity, Anxiety and Compulsivity

P.2.18 - Reinforcing effects of nicotine in the hypothalamic supramammillary region involve activation of glutamatergic projections to the medial septum

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Nicotine administration directly into the supramammillary region (SuM) of the posterior hypothalamus produces reinforcing effects. Rats will self-administer nicotine into this region, indicating its role in reward-related behavior. Furthermore, selective activation of SuM glutamatergic (Glu) neurons that project to the medial septum (MS) is reinforcing and leads to dopamine release in the nucleus accumbens. However, the mechanisms by which nicotine produces reinforcement in the SuM remain unclear.

To address this, we investigated whether SuM Glu neurons express nicotinic acetylcholine receptors (nAChRs) and whether systemic nicotine activates these neurons. We used retrograde tracing with cholera toxin subunit B (CTB) injected into the MS to label SuM→MS projection neurons in mice. RNAscope HiPlex in situ hybridization was performed on SuM sections to detect mRNA for nAChR subunits (α3, α4, α7, β2, β4) as well as markers for glutamatergic (VGluT2) and GABAergic (VGAT, GAD) neurons. Approximately 95% of CTB-labeled neurons expressed the β2 nAChR subunit, with other subunits detected in 20–30% of these cells.

To determine if systemically administered nicotine activates SuM Glu neurons, we implanted jugular catheters for intravenous (IV) nicotine delivery and expressed GCaMP in these neurons of mice. Fiber photometry recordings revealed that both experimenter-administered and self-administered IV nicotine elicited time-locked increases in calcium activity in SuM Glu neurons. Mice acquired nicotine self-administration behavior, and each IV infusion of nicotine was associated with robust, time-locked GCaMP responses.

These findings suggest that β2-containing nAChRs on SuM Glu neurons mediate nicotine's reinforcing effects via activation of the SuM→MS circuit.

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P.2.19 - Amphetamine selectively reduces dopamine transients in the nucleus accumbens core during decision-making and distraction in a visual signal detection task

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The indirect dopamine (DA) agonist d-amphetamine (AMPH) is widely known to influence executive functions such as attention and working memory. However, few studies have investigated time-resolved changes in DA release in animals treated with AMPH during executive task performance. We used a dLight sensor transfected in the nucleus accumbens core to assess trial-by-trial fluctuations in DA release during performance of rats on a visual Signal Detection Task (SDT which required sustained visual attention whilst ignoring visual distractors to earn food reward. Following task acquisition, rats were infused with a viral vector encoding dLight1.3b and implanted with an optic fibre in the nucleus accumbens core to allow for in vivo fibre photometry recordings (n = 12). Subjects received systemic administration of d-amphetamine (0.1; 0.2; 0.4 mg/kg) and a vehicle prior to DA-recordings and behaviour. Low-dose AMPH improved attention during the standard trials, but impaired performance when a blinking visual distractor (1Hz) was presented during blocks of 20 trials interspersed among non-distractor blocks. The distractor specific modulation of AMPH for attentional performance was not be related to nucleus accumbens DA release. However, AMPH selectively reduced DA-signalling during trial-initiation and decision-making, but not during reward or reward omission. These findings suggest an AMPH-induced suppression in phasic DA in response to specific behaviourally relevant events. This disruption in DA signalling may be partially mediated by an altered ratio of tonic to phasic DA release in the nucleus accumbens. The results imply that the drug may be more effective at enhancing attentional processes of target detection than selection, possibly relevant to its clinical actions in ADHD.

Keywords. dopamine, fibre photometry, decision-making, amphetamine

P.2.20 - Psychedelics, stimulants, and habituation: behavioral effects of DOI and amphetamine in the earthworm *dendrobaena veneta*

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The use of invertebrate animals as research models in psychology has aroused great interest in recent years. A first task is to study and characterize the psychophysical and cognitive abilities and then to investigate the psychopharmacological effects on learning and behavior of the organism. We present preliminary data on the effects of some drugs on behavior and learning in the earthworm, Dendrobaena veneta. First, we evaluated the effect on the retraction reflex elicited by tactile stimulation with different doses of DOI (1 and 10 µM) and amphetamine (1 and 10 µM). A significant decrease in the frequency of responses under the effect of DOI was observed, with a statistically significant difference in the highest dose (10 µM) at 20 min after exposure to the substance, compared to the control group. In the case of methamphetamine, both concentrations showed a statistically significant decrease in the earthworm response at 10 and 20 min after exposure to the substance. ..... Second, we evaluated the habituation response of the withdrawal response under the effects of amphetamine and DOI.

Our findings reveal distinct and substance-specific alterations in sensory processing and behavioral patterns, suggesting that D. veneta may serve as a useful model for studying the fundamental neurobehavioral mechanisms affected by psychoactive compounds. The results contribute to the emerging field of invertebrate neuropharmacology and offer insights into the evolutionary conservation of neuromodulatory pathways.

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Keywords. Dendrobaena veneta, Drugs, Methamphetamine, 2,5-dimethoxy-4-iodoamphetamine, DOI, Tactile stimulation, Effect of retraction, Habituation, Contextual specific

P.2.21 - Inflammatory cytokine profile in plasma and brain during chronic pain progression

M. Zelai Garçon-Poca, Nadja Kulesza, Amelie Essmann, Jordi Bonaventura

Chronic pain and mood disorders are among the leading causes of disability worldwide. It is now thought that between 32 and 56% of people experiencing it are at risk of developing a mood disorder. In the recent years, increasing evidence has linked inflammatory cytokines with mood disorders. Cytokines are commonly known as immune regulators, but they have also been shown to influence brain development, neurogenesis and diverse neuroendocrine functions.In our study male mice received 30 mL of Complete Freund's Adjuvant (CFA) inflammatory agent or saline in the hind paw. We sacrificed the animals at different time points day 4, day 7 and day 14 post-injection, to collect plasma and brain samples. The samples were analyzed using the Proteome Profiler Mouse Cytokine Array Kit (Bio-techne) aiming to identify relative changes in the cytokine levels.We compared the cytokine profile from the saline and CFA-injected mice at all time points. Later, by immunohistochemistry, we identified those present in limbic areas that hold the potential to modulate neurotransmitter release there. In parallel, we also studied dopamine dynamics at the different time points in the Nucleus Accumbens using fiber photometry and adeno-associated virus encoding for the dopamine sensor DLight1.3.Our results show an increase in pro-inflammatory cytokines in the CFA-exposed mice, with distinct expression patterns in plasma versus brain samples and specific profiles at the different time points studied. These findings highlight the relationship between peripheral and central inflammation over time, reflecting how chronic inflammatory pain may contribute to mood disorders through cytokine regulation.

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Keywords. Chronic pain, Mood disorders, Complete Freund's Adjuvant (CFA), Inflammation, Cytokine profile, Depression

P.2.22 - Maternal immune activation and vulnerability to develop adjunctive behaviours in adulthood: an exploratory study.

Natalia de las Heras-Martínez, Jairo S. Acosta-Vargas, Marcos Ucha-Tortuero, Alejandro Higuera-Matas

The role of viral infections in addictive disorders is still largely unexplored. On this point, animal models offer us an opportunity to study the long-term consequences of these infections. Maternal immune activation (MIA) during pregnancy has been linked to long-term behavioural and neurochemical alterations in offspring which may lead to increased compulsive behaviours. In the present work, we aimed to explore the relationship between MIA and the development of long-term compulsive drinking strategies, reflected in patterns of adjunctive drinking behaviour, compared to non-exposed controls. To test this, pregnant Sprague-Dawley rats received an intraperitoneal injection of viral analogue polyinosinic:polycytidylic acid (Poly I:C) or saline solution on gestational day 15. Effective maternal immune activation was studied examining changes in body temperature. The adult offspring (both sexes) was assessed using a schedule-induced polydipsia (SIP) procedure. Furthermore, to evaluate coping profiles, animals were classified into subpopulations based on their drinking strategies (High drinkers, low drinkers, alcohol copers and water copers). Our preliminary results revealed interesting sex-specific modulations exercised by poly I:C, pointing to a possible link between viral analogue infection and long-term alterations in the development of compulsive strategies. Preclinical models of maternal immune activation could be of vital importance for understanding the long-term effects of viral infections on the complex psychological mechanisms underlying addictive disorders.

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Keywords. Maternal immune activation, addictive disorders, SIP

P.2.23 - Dysregulation of the oxytocin system and disruption of social reward processing in a rat model of gaming disorder

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In 2018, the International Classification of Diseases (ICD-11) recognized Gaming Disorder (GD) as a mental disorder, predominantly affecting adolescents. Individuals with GD develop an addiction to gaming, leading to anxiety, social isolation, depression, and attention deficits. While studies on humans are numerous, many have limitations such as short exposure durations, observation periods, and gender differences. To overcome these limitations, we proposed a new animal model to better understand the neurobiological mechanisms involved in GD.Our results showed that rats subjected to the GD protocol, compared to the control group (CON), exhibited a significant increase in gaming frequency, duration, and distance traveled in front of the screen. This attachment to gaming altered social behavior, with GD rats preferring gaming over social stimuli. Furthermore, the reduced positive effect of social reward on attachment behaviors was linked to a decrease in oxytocin-expressing neurons in the Paraventricular and Supraoptic Nuclei of GD rats.The loss of control over gaming, along with anxiety and hyperactivity observed in the GD rats, supports the translational validity of the model. The reduced social interaction and its effect on compulsive gaming behaviors suggest the involvement of the oxytocinergic system in GD. Oxytocin, a neuroendocrine hormone, is linked to various pathologies, including mental disorders and addictions. Alterations in this system may contribute to compulsive behaviors seen in addiction, potentially predisposing adolescents to GD.

Keywords. Gaming Disorder (GD), compulsive behavior, social behavior, Oxytocin system, animal model, mental disorder

P.2.24 - An efficient raw pixel approach for machine learning-based annotation of novel object recognition videos

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Automatic systems to score animal behavior from videos have gained increasing attention in recent years. Compared to manual scoring, automatic scoring is faster, less liable to bias, and it improves reproducibility. Existing machine learning pipelines for behavioral annotationof neuroscience videos fall into two categories: 1) pose estimation and 2) raw pixel analysis. Pose estimation involves tracking animal body parts, followed by feature extraction from poses and behavior classification. In contrast, raw pixel analysis directly classifies behaviors from video frames, eventually incorporating temporal information. While effective, both approaches can be computationally demanding.A computation-efficient raw pixel approach where a 2D convolutional neural network (2D-CNN) annotates individual frames of novel object recognition videos was recently published (EXPLORE, Ibañez et al., 2023), This method has demonstrated high accuracy in predicting object exploration times and strong correlations with human annotations. However, this method, not allowing temporal integration, offers limited possibilities to explore metrics sensitive to temporal context such as the number of exploration episodes, their average length or bouts between episodes. Here we evaluated the ability of EXPLORE to predict bout statistics by training it on a custom dataset using rats.Our findings indicate that, while the model effectively estimates total exploration times, it overestimates the number of bouts and underestimates their durations. This suggests that frame-level analysis alone is insufficient for accurate bout prediction. We then decided to modify the original EXPLORE model to accept as input multiple frames as separate channels in the original 2D-CNN, to evaluate whether this approach could lead to improved bout statistics. Results demonstrated that even by incorporating a time-window, accuracy of the model does not improve. Further work includes the use of a time-series model such as a long-short term memory network on top of the original model. This approach allows one to integrate a short temporal context with lower computational overhead compared to existing models. Such a pipeline would reduce time for annotation, improve reproducibility of results and allow for fast collection of advanced data such as bout statistics.

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Keywords. Animal Behavior, Machine Learning, Novel Object Recognition, Convolutional Neural Network

P.2.25 - A systematic review focused on micro-/nano-plastic developmental neurotoxicity. in search for common biological target across different models

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In 2024 and 2025 The Guardian and Nature News published several notices where is explained that microplastics were detected in every semen sample and in every brain analyzed. However, apart from the research performed in reproductive and metabolic impact of different plastic size, few evidence available links micro- or nano-plastics (MNPs) with neurodevelopmental disorders. Also, no specific effect of MNPs on neural system has been elucidated. Due to the absence of clear evidence, we decided to conduct the present systematic review. To do so, a comprehensive search within PUBMED and Scopus database was performed following PRISMA guidelines with the classical used models in neurotoxicology (C.Elgans, Rattus norvegicus, Mus musculus, Danio rerio, In vitro, Drosophila Melanogaster). No specific dates were specified to achieve the most articles published. Eligibility criteria required studies to be published in English, report any outcome related with behavioral, developmental or neural/biochemical outcomes. After screening 869 studies, only 132 articles met the inclusion criteria. We expect to find common neurotoxicological targets after MNPs exposure. Specifically, we expect to find in all the models an increase of oxidative stress and inflammation. In addition, we expect to detect any relationship between MNPs exposure and behavioral alterations, mediated by any impact on the Nervous System. We also expected to detect the specific neurotransmission system involved in potential effects of MNPs exposure.

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Keywords. Micro-/Nano-plastics, Neurodevelopment, Biological Target, Research Models, Neurotoxicology, Systematic Review

P.2.26 - Dissecting the role of lateral septum PKCδ neurons

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The lateral septum (LS) is a GABAergic brain region that serves as a hub for a wide reservoir of behaviors and biological functions, including reward, anxiety, fear, sociability, learning and memory, and drug addiction. This area is characterized by considerable heterogeneity, comprising distinct neuronal populations that modulate different aspects of its functions. Protein kinase C delta type (PKCδ) is discretely expressed in a few brain regions, including the central amygdala (CeA), the bed nucleus of the stria terminalis (BNST), and the LS itself. While extensive work has thoroughly characterized the behavioral function of CeA and BNST PKCδ-expressing neurons, the role of LS PKCδ neurons remain unexplored. To address this gap, we first evaluated the co-expression with known LS neuronal markers and their connectivity. Fos analysis and fiber photometry recordings showed that LSPKCδ neurons are activated by a wide range of aversive stimuli. Accordingly, their artificial stimulation promotes aversion and is anxiogenic. Collectively, our data provides insights on the functional significance of this previously undescribed LS neuronal population.

Keywords. Lateral Septum; Aversion; PKCδ

P.2.27 - Genotype-dependent corticolimbic network differences in cue-induced fear responses: A data-driven c-Fos-based analysis

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BACKGROUND: The core feature of Post-Traumatic Stress Disorder (PTSD) is the strong reactivity to trauma-related cues triggering the retrieval of aversive memories. However, regional neural changes linked to this vary across individuals. This variability is common in psychiatric disorders, with neuroimaging studies revealing widespread brain changes associated with specific pathological behaviors. Despite regional differences, the circuits embedding these regions are common across individuals, suggesting that circuit-level analysis can explain neural heterogeneity under phenotypic similarities. Comparisons between C57BL/6J (C57) and DBA/2J (DBA) inbred mice strains have provided insights into how neural differences underlie similar behaviors in response to appetitive cues. Using this model, this study aims to identify genotype-dependent differences in cortico-limbic structures at both regional and circuit levels, focusing on the incubation of cue-induced fear responses, which replicate the core PTSD-like symptom.METHODS: C57 and DBA mice underwent a single training in which a tone (CS) was paired with a foot-shock. Their freezing responses to the CS were tested 1 day or 14 days later. One hour after re-exposure, c-Fos expression was quantified in 19 corticolimbic regions and analyzed for regional and inter-regional connectivity using correlation-based hierarchical clustering and network analysis.RESULTS: Although C57 and DBA mice exhibit similar behavioral responses, our study reveals significant genotype-dependent differences in corticolimbic circuits organization, affecting regional recruitment and network dynamics underlying cue-induced fear.CONCLUSION: These findings highlight the importance of considering both regional and circuit-level brain dynamics to understand neural variability across individuals in psychiatric conditions, as it may provide a personalized understanding of how distinct neural circuits contribute to similar behaviors.

Keywords. Post-Traumatic Stress Disorder (PTSD), Fear Conditioning, Network Analysis, Hierarchical Clustering Analysis, Individual Differences, Inbred mouse strains

P.2.28 - Cognitive Impairments in the RHA vs RLA rats: insights into schizophrenia-related deficits

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Research using animal models is essential for advancing our currently limited understanding of the neurobiological mechanisms underlying schizophrenia and for developing more effective treatments. One promising model is the inbred Roman rat strains, selectively bred for their high (RHA) or low (RLA) ability to acquire the two-way active avoidance task. Compared to Roman Low-Avoidance (RLA) rats, Roman High-Avoidance (RHA) rats exhibit increased mesolimbic dopamine function, social behavior deficits,sensorimotor and attentional impairments, and deficits in learning/memory and cognitive flexibility—phenotypes relevant to schizophrenia.This study investigated working and long-term memory in the Roman rat strains using the Object Recognition Test (ORT), a non-spatial declarative memory task that assesses object memory encoding, consolidation, and retrieval. Additionally, spatial working memory differences were evaluated using a delayed-matching-to-position (DMTP) task in the Morris water maze. Results indicated that RHA rats exhibited deficits in both working and long-term memory compared to RLA rats in the ORT. Notably, prolonged habituation to the testing context significantly improved long-term memory performance in RHA rats. Similarly, RHA rats demonstrated impaired spatial working memory in the DMTP task.These memory deficits align with the known schizophrenia-like alterations in the hippocampus and prefrontal cortex of RHA rats. Furthermore, the finding that extended habituation mitigates long-term memory impairment suggests that attentional deficits contribute to this cognitive dysfunction. Overall, our findings lend support to the utility of the RHA rat strain as a genetic model for investigating cognitive symptoms associated with schizophrenia.

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Keywords. Schizophrenia, Roman rat strains, Cognitive deficits, Memory impairment, Object Recognition Test (ORT)

P.2.29 - Neonatal handling enhances exploratory and social behaviour, and neuroplasticity in a genetic rat model of schizophrenia-relevant traits

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Neonatal handling (NH) is an early-life environmental intervention involving brief maternal separation, isolation and tactile stimulation. NH has been shown to induce long-lasting reductions in anxiety and stress-related behaviours and hormonal responses, as well as cognitive improvements in laboratory rodents. However, its effects on schizophrenia-like negative symptoms, such as reduced motivation for social interaction (SI), remain underexplored.This study investigated the long-term effects of NH on SI and the expression of brain-derived neurotrophic factor (BDNF), its tyrosine kinase receptor (trkB), and c-Fos in the prefrontal cortex (PFC) and amygdala—brain regions implicated in social behaviour and schizophrenia. Male Roman high-avoidance (RHA) and low-avoidance (RLA) rats, a validated genetic model for schizophrenia-related traits, were assigned to NH or control groups and tested in three conditions: home cage (HC), test setup context exposure (CTX), and SI exposure.NH increased social behaviour and preference, particularly in RHA rats (which are the model of schizophrenia-like symptoms). Moreover, NH specifically increased c-Fos expression in the infralimbic cortex and medial posterodorsal amygdala of RHA rats exposed to SI. Additionally, NH enhanced BDNF and trkB expression in the PFC exclusively in RHA rats tested for SI.These findings suggest strain-dependent effects of NH on neural activation in SI-related brain regions. The NH-induced increases in c-Fos, BDNF, and trkB expression in RHA rats may reflect enhanced neuroplasticity, highlighting NH as a potential intervention for negative-like symptoms of schizophrenia.

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Keywords. Neonatal handling, Roman Rat Model, Social interaction, Schizophrenia-like symptoms, BDNF, Prefrontal cortex and amygdala

P.2.30 - Anodal tDCS improves anxiety-like behavior in rats with ischemic stroke

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Introduction. Stroke is a major cause of death and disability worldwide. Emotional and behavioral disorders frequently occur in stroke patients, impacting their quality of life. Transcranial direct current stimulation (tDCS) is a non-invasive neuromodulation technique with potential benefits for post-stroke neurological impairments. However, the most effective stimulation protocols remain unclear. Objective. To evaluate the efficacy of anodal tDCS and cathodal tDCS in improving emotional behaviors (anhedonia, anxiety, and learned helplessness) in an ischemic stroke rat model. Methods. Ischemic stroke was induced in Wistar rats using endothelin injections into the prefrontal cortex via stereotaxic surgery. Rats were assigned to four groups (n=10/group): stroke control, healthy control, anodal tDCS, and cathodal tDCS. The anodal and cathodal groups received five tDCS sessions while control groups received sham stimulation. Anxiety was evaluated using the elevated plus maze, anhedonia with the sucrose preference test, and learned helplessness with the forced swim test at post-stroke days 18, 19, and 36, respectively. Results. Anodal tDCS improved anxiety-like behavior (38% time in closed arms, 22 seconds latency) compared to the stroke control group (56% and 4 seconds). However, neither stimulation protocol significantly improved learned helplessness behavior (48%, 40% and 39% immobile time in stroke control, anodal tDCS and cathodal tDCS groups respectively). No anhedonia was observed in stroke rats (79% sucrose intake) compared to healthy control group (71%). Discussion. Our results suggest that anodal tDCS has an anxiolytic effect in stroke-affected rats, consistent with clinical findings on tDCS and emotional regulation (Zheng et al., 2024). However, learned helplessness-like behaviors were not improved, indicating different recovery mechanisms for anxiety and learned helplessness. This study highlights the pivotal role of anodal tDCS in post-stroke emotional rehabilitation.

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Keywords. stroke, tDCS, emotional behavior

P.2.31 - Sex chromosomes and sex hormones differently shape microglial properties during normal physiological conditions in the adult mouse hippocampus

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The brain presents structural and functional sex differences based on genetic, epigenetic, metabolic, and hormonal factors. While biological sex is determined by sex chromosomes and sex hormones, little is known about how these two factors interact. Sex differences affect the brain's resident immune cell, microglia, which actively survey the parenchyma and perform physiological functions. However, possible differences in microglial properties during normal adulthood are largely unknown. We investigated microglial density, morphology and ultrastructure at steady-state using the Four Core Genotypes (FCG) model, allowing for independent assessment of gonadal hormones and sex chromosomal effects in four conditions: FCG XX and Tg XY- (both ovaries); Tg XXSry and Tg XYSry (both testes). We also compared these mice with XX and XY wild-type (WT) mice. We investigated the ventral hippocampus layers: CA1 stratum radiatum(Rad), CA1 stratum lacunosum-moleculare (LMol), and the dentate gyrus polymorphic layer (PoDG). Iba1 and TMEM119 immunostaining revealed that microglial density is influenced by both sex chromosomes and sex hormones. In the Rad and LMol, microglia were denser in FCG XX compared to Tg XYSry, yet microglia were densest in WT XX mice. In the PoDG, ovarian animals had increased microglial density compared to testes animals. Microglial morphology showed a complex interaction between hormones and chromosomes, affecting cellular soma and arborization. Microglia in WT animals also made more contacts with pre- and post-synaptic elements than in FCG animals. Lastly, microglial markers of cellular stress, including mitochondrion elongation and dilation of the endoplasmic reticulum and Golgi apparatus, were mostly chromosomally driven.

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Keywords. Four core genotypes, Sex differences, Microglia, Hippocampus, Morphology, Scanning Electron Microscopy

P.2.32 - In search of molecular signatures preceding full symptoms appearance: towards early interventions for Rett syndrome

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Rett syndrome (RTT) is a rare and incurable neurologic disorder affecting mainly females carrying de novomutations in the epigenetic factor methyl-CpG-binding protein 2 (MECP2). The clinical phenotype is usually mutation-dependent, and is mainly characterized by intellectual disability, inability to speak and walk, autistic-like behavior and motor stereotypies, which appear around 18 months of age, after a period of apparent normal development. Mounting evidence suggests that mild phenotypical alterations are already present before the overt symptoms appearance, arguing for the presence of precocious disruptions at the brain level. However, the patterns of molecular alterations in RTT brain at prodromal stages have been barely addressed. By exploiting extensively validated mouse models carrying different RTT-causing mutations, we aimed at dissecting the neuromolecular underpinnings of early abnormalities and uncover alterations in signaling pathways that may constitute novel targets for precocious interventions. To this end, cortical tissue from mouse pups from four MeCP2-mutant colonies and wild type siblings were collected during the first two postnatal weeks, and nanoflow reversed-phase liquid chromatography tandem mass spectrometry was performed to analyze the proteome. Classical statistical approaches did not reveal consistent molecular alterations, suggesting substantial heterogeneity across different MeCP2 mutations. While machine learning strategies confirmed mutation-dependent variability, they also uncovered age-dependent patterns of molecular alteration that were relatively consistent across RTT models. The present results reveal early, transient disruptions in the RTT brain proteome, and highlight novel pathways that could be targeted to redirect neurodevelopmental trajectories and mitigate the accumulation of alterations that ultimately trigger full symptoms manifestation.

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Keywords. mouse model, proteomics, machine learning, neurodevelopment

P.2.33 - Influence of ingestion of live microalgae rich in omega-3 acids on biochemistry, behaviour and gut microbiota in mice

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The presence of n-3 PUFAs in the body, particularly in our liver and brain, is crucial for optimal brain function. These n-3 PUFAs have the potential to provide neuroprotection through a variety of mechanisms, including neurogenesis, modulation of cell signalling pathways and inhibition of inflammation. The potential of n-3 PUFAs to prevent and inhibit the progression of several central nervous system (CNS) disorders has been demonstrated. The aim of this project is to study the fatty acid profile, behavioural profile and gut microbiota of the consumption of two types of algae, Scenedesmus obliquus(SO) and Isochrysis galbana(IG), both are rich in omega-3, although the last one in higher levels. After a 10-day acclimatization period, saline alone or algae suspension was administered orally to male C57BL/6J mice at a dose of 1ml/100g body weight for 30 consecutive days. Our results show that the administration of microalgae, particularly IG, resulted in increased PUFA content in the tissues examined, including the brain. Behavioural parameters such as anxiety, depression and memory were assessed. There were no significant differences between the three groups. There was no statistically significant difference in alpha and beta diversity between the groups in terms of OTU richness. 16s sequencing revealed a decrease in the IG group in both Actinobacteriaand Bacteroidetesand in their genera Enterorhabdusand Muribaculaceaerespectively. Enterorhabdushas been reported to be involved in the pathogenesis of CNS diseases. The increase in these bacteria has been linked to Alzheimer's disease and autism. Our findings underline the efficacy of IG and SO in enriching tissue fatty acid profiles and highlight their potential role in reducing inflammation and supporting neurological health.

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Keywords. n-3 PUFAs, gut microbiota, inflammation, microalgae

P.2.34 - Sex-specific effects of gut microbial depletion on adult hippocampal neurogenesis and spatial and contextual memory

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Growing evidence links gut microbiota to brain function with most studies done in males. However, limited research has examined whether gut microbial depletion affects adult hippocampal neurogenesis (AHN) and associated behaviours, particularly in females. Therefore, this study investigated the effects of antibiotic-induced gut microbiota depletion on cognitive, anxiety- and antidepressant-like behaviours, and AHN in male and female rats.Male and female Sprague Dawley rats (PND70) received antibiotic-supplemented (ampicillin, vancomycin, imipenem) drinking water or normal drinking water for the experiment duration. After 6 weeks of antibiotic administration, rats underwent a battery of behavioural tests. Doublecortin-positive cells in the hippocampus were counted as a measure of AHN. Data were analysed using student's T-test or Mann-Whitney t-test.In males, antibiotics decreased AHN in the dorsal hippocampus, impaired contextual memory in the novel object in context test, induced a mild anxiogenic effect in the open-field test, improved spatial memory in the Morris water maze (MWM) and had no effect in the forced swim test or on locomotor activity. Conversely, in females, antibiotics did not impact AHN, contextual memory, or anxiety behaviour. In females, antibiotics induced a trend (p=0.07) of reduced immobility in the forced swim test, and a mild spatial memory impairment in the MWM but this effect may have been confounded by antibiotic-induced reductions in locomotor activity.These findings suggest sex-specific effects of gut microbiota depletion on AHN and hippocampus- associated behaviours and highlight the importance of including biological sex as an experimental variable. Future studies are required to determine the mechanisms underlying these sex differences.

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Keywords. microbiota gut-brain-axis, adult hippocampal neurogenesis, sex differences, memory, anxiety, depression

P.2.35 - Brain metabolomic alterations in compulsive rats selected by schedule-induced polydipsia

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Introduction: Compulsions are repetitive and stereotyped behaviors that follow rigid rules and aim to minimize harm. They are observed in several pathological conditions, such as obsessive-compulsive disorder, depression, and schizophrenia, where metabolic changes have been identified as potential biomarkers for early detection.Objective: This study explored individual differences in the metabolomic profile of rats selected based on their compulsive drinking behavior.Methods: We used schedule-induced polydipsia (SIP) to classify male Wistar rats into high drinkers (HDs) or low drinkers (LDs). Metabolomic analysis of the frontal cortex, hippocampus, and cerebellum was conducted using nuclear magnetic resonance spectroscopy. Four experimental groups were established based on exposure conditions: LD without re-exposure (LD-NRE), LD with re-exposure (LD-RE), HD without re-exposure (HD-NRE), and HD with re-exposure (HD-RE).Results: In the frontal cortex, succinate levels were higher in HD-RE than in LD-RE. In the cerebellum, formate levels decreased, while sterols increased in HD-NRE compared to LD-NRE. In the hippocampus, alanine levels were increased in HD-RE compared to LD-RE, whereas formate increased; and amino acids and derivatives such as uracil, tyrosine, histidine, pyroglutamate, and isoleucine levels were lower in HD-NRE compared to LD-NRE.Conclusions: These findings highlight metabolomic screening as a promising approach for identifying diagnostic and treatment-monitoring biomarkers in compulsive disorders.

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Keywords. compulsive behavior, schedule-induced polydipsia, nuclear magnetic resonance spectroscopy, metabolomic profile, frontal cortex, cerebellum

P.2.36 - Effects of deep brain stimulation on BDNF-ERK-CREB signaling pathway in animal model of treatment-resistant depression

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To develop effective strategies for therapy of the treatment-resistant depression (TRD), which affects more than one-third of people with depression, it is essential to understand the mechanisms of non-response to antidepressants. In this study, we investigate effects of deep brain stimulation (DBS) in left medial prefrontal cortex (mPFC) in the Wistar Kyoto rats exposed to 4 weeks of a chronic mild stress (CMS) model. This version of the CMS procedure has been previously validated as an animal model of TRD (Willner et al. 2019). The effectiveness of chronic stress was evaluated by a weekly sucrose consumption tests (a measure of anhedonia), and elevated plus maze, novel object recognition and social interaction tests, conducted at the end of the study, were used to assess anxiety, cognitive functions and social skills in stressed animals. Before each of the above tests the animals received an acute session with DBS. 24 hr after the final session animals were decapitated and protein levels of BDNF, TRKB, ERK, CREB and PSD95 were measured in mPFC and ventral hippocampus (vHPC).As in our previous studies, the CMS caused anhedonia, enhanced anxiety, as well as cognitive and social deficits. These effects were effectively reversed by DBS in mPFC. Stress also increased pERK and tCREB and decreased TRKB protein levels in the mPFC. These effects were antagonized by DBS. In vHPC, stress reduced mBDNF, tCREB and PSD95 protein levels and these effects were also normalized by DBS.This study confirms that DBS in mPFC is effective against the behavioural deficits observed in this animal model of TRD. The fact that DBS can also normalize the CMS-induced changes in the levels of TRKB, ERK, CREB and PSD95 suggest that this intracellular signaling pathway in mPFC and vHPC play a pivotal role not only in the long-lasting and transcription-dependent neuroadaptations that are critical for depression but may also be engaged in the mechanisms of resistance to traditional antidepressants.References: Willner P, Gruca P, Lason M, Tota-Glowczyk K, Litwa E, Niemczyk M, Papp M. Validation of chronic mild stress in the Wistar-Kyoto rat as an animal model of treatment-resistant depression. Behav Pharmacol. 2019 Apr;30 (2 and 3-Spec Issue):239-250. doi: 10.1097/FBP.0000000000000431.

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Keywords. deep brain stimulation, chronic mild stress, model of TRD, medial prefrontal cortex, behaviour, protein level

P.2.37 - The D3 receptor knock-out mutation in dopamine deficient aphakia mice reverses activational impairments: impact on the cerebral dopamine neurotrophic factor

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Pitx3 is a transcription factor essential for the survival of dopaminergic neurons. Aphakia mice (Ak) have a mutation in Pitx3, which leads to a high reduction in dorsal-striatal dopaminergic innervation. However, dopamine (DA) levels in the ventral striatum (nucleus accumbens, Nacb), are less affected. Ak mice show behavioral activational deficiencies compared to WT mice. The present study investigates how deletion of dopamine D3 receptors (D3R) in Ak mice (Ak-D3KO) affects spontaneous behavioral activation, including exploration of different types of environments or vigorous running in a running wheel (RW). Thus different measures of locomotion and exploration were evaluated in an open field, social interaction chamber, dark-light box, elevated plus maze and RW. We also assessed the effects of cariprazine, a D3-partial agonist, and L-DOPA (DA precursor) in the RW. Finally, the cerebral dopamine neurotrophic factor (CDNF), which plays a critical role in the survival of dopaminergic neurons, was evaluated in the Nacb.The deletion of the D3 receptors in Ak mice led to higher spontaneous exploration in all the paradigms; they showed significantly higher total distance travelled, average speed, number of rearings and crosses between compartments with different types of stimuli, compared to Ak mice. However, in the RW, both groups had the same level of performance. L-DOPA significantly increased while cariprazine reduced activity equally in both groups of mice. Ak-D3 mice show more CDNF immunoreactivity in the Nacb core. Thus, in animals with low levels of DA (Ak mice), the lack of D3 receptors improves anergic patterns.

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Keywords. Aphakia (Ak) mice, dopamine, D3 receptors, CDNF, nucleus accumbens, pitx3

P.2.38 - Validating a preclinical model of PMDD in female Sprague-Dawley rats

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Premenstrual dysphoric disorder (PMDD) is a severe mood condition affecting 3-10% of reproductive-age women, characterized by emotional and physical symptoms that negatively impact daily life, including depression, irritability, and anxiety. Since current treatments are often insufficient, there is a need to explore novel therapeutic approaches. In this context, we aimed at validating a preclinical model of PMDD in female Sprague-Dawley rats in which to later evaluate potential treatment options. To do so, a total of 31 adult female Sprague-Dawley rats were treated (i.p.) with progesterone (500 mg, 1 ml/kg) for 5 (n=10) or 10 (n=12) days (1 dose/day) or vehicle (1 ml/kg DMSO, n=9), and later exposed to forced withdrawal, to mimic the abrupt progesterone decline hypothesized to underlie the negative symptomatology of PMDD. Rats were scored through a battery of consecutive tests during withdrawal to capture the emergence of different manifestations of affective-like responses (i.e., forced-swim, open-field, and sucrose preference). Data were analyzed through one-way ANOVAs, and solely found a significant effect for the sucrose preference test ($F_{2,27}$= 3.73, p=0.037). In particular, Dunnett's post-hoccomparisons revealed dose-dependent decreases in sucrose preference in rats treated with progesterone (5 days: -18 ± 13%, p=0.285, ns; 10-days: -35 ± 13%, *p=0.020 vs. vehicle-treated rats), which is an indicative of anhedonic-like responses. Therefore, the treatment paradigm of 500 mg of progesterone for 10 days followed by forced-withdrawal represents a valid preclinical PMDD model in which to evaluate how novel potential treatment options might improve anhedonia. Ongoing studies aim to further characterize this model using ovariectomized rats to dissect the role of sex hormones in PMDD pathophysiology.

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Keywords. PMDD, progesterone, mood disorders, animal model

P.2.39 - Conditioned place aversion induced by electrical stimulation of the Lateral Parabrachial area is blocked by selective mu-opioid antagonists

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The Parabrachial Complex of the brainstem, which processes visceral and sensory information, has been associated with several “motivated behaviors”. The external lateral subnucleus (LPBe), located at the most lateral end of this area, seems to be part of different brain circuits involved in processes of both reinforcing and aversive nature. This structure has indeed been associated with the emotional, autonomic and visceral processing of negative events, and is considered as a relay for the nociceptive spino-trigeminal-parabrachial-hypothalamic system. Previous studies using electrophysiological techniques such as intracerebral electrical stimulation, carried out by our team, have shown that activation of this area can induce consistent preferences or aversions towards gustatory and spatial stimuli with which it is associated, with a preference for the latter. Since the identification of μ and κ opioid receptors in this region, some authors have suggested that μ receptors might be involved in positive reinforcement processes, whereas κ receptors might be related to the processing of aversive information. Preliminary results from our current research, in which animals received an injection of CTOP (a μ-receptor-specific antagonist), have shown that this drug can block aversion to spatial cues associated with electrical stimulation of the LPBe in the negative subgroup of male and female rats. These results will be discussed in relation to the role of the parabrachial area in the processing of stimuli with positive and negative valence.

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Keywords. Electrical Brain Stimulation, Mu-opioid receptors, external lateral parabrachial area (LPBe), Spino(trigemino)-Parabraquial-circuit, conditioned place aversion, rats

P.2.40 - Habits study network in experimental psychology

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Living beings develop a broad set of habits, given their high adaptive value. Habits endure in our evolutionary history as they are behaviours that save us a high cognitive effort. However, sometimes these habits become pathological when they are carried out despite having undesirable consequences. We are pleased to introduce a network of collaborative research groups focused on habit, an initiative aimed at fostering interdisciplinary cooperation, academic exchange, and the advancement of knowledge with a traslational perspective. This network brings together a diverse community of researchers affiliated with multiple institutions in Spain, each contributing their expertise to address complex global challenges through joint projects, knowledge sharing, and collaborative innovation. Our mission is to understand the mechanisms of acquisition and maintenance of normal and pathological habits from a multi-disciplinary approach at a behavioural and neuroscientific level. In addition, we intend to work with a translational approach implementing measures in clinical and preclinical models of habitual behaviours, and transdiagnostic by studying normal individuals and individuals with pathologies in which persistent and inappropriate habits are present.

Keywords. habit, compulsive behavior, addiction, decision-making

P.2.41 - Time-based diminishing returns task: Effects of d-amphetamine on decision-making strategies under multiple schedules

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This study examines impulsivity and self-control using the Time-Diminishing Returns task (DIM), a paradigm that offers greater ecological validity than classical delay discounting tasks by simulating better complex decision-making scenarios. In the DIM task, under reset conditions, selecting an initially disadvantageous alternative may yield long-term benefits, whereas consistently choosing the less delayed option leads to a lower overall reinforcement rate. A multiple food-reinforcement schedule procedure was employed with 10 Wistar Han rats exposed to two conditions: reset and no-reset. In the reset condition, rats could choose between a lever associated with a progressive delay (PD) and a lever associated with a fixed delay (FD). The delay associated with PD increased progressively with each response, but presses on the FD lever reset the PD delay to its minimal value. In the no-reset condition, PD increased following the same progression as in the reset procedure, but pressing the FD lever did not reset the PD delay. The values of PD and FD levers varied across blocks of sessions, with PD values set at 1, 2, or 3 seconds and FD values set at 10 or 20 seconds, resulting in different combinations. The same value combinations were employed for both reset and no-reset conditions. In the reset condition, the optimal strategy involves pressing PD and waiting for a larger delay before resetting PD well before reaching the equality point. In contrast, under the no-reset condition, the optimal strategy is to press PD until it matches the value of FD and then continue choosing FD. Additionally, the effect of d-amphetamine was assessed in both components, considering its potential influence on behavioral perseveration.

Keywords. diminishing returns, d-amphetamine, choice, decision-making, impulsivity

P.2.42 - Enhancing impulsivity assessment in mice: validation of the variable delay-to-signal task

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Assessing impulsivity in animal models is crucial for understanding neuropsychiatric disorders; however, traditional methods, such as the five-choice serial reaction time task (5-CSRTT), are labor-intensive and subject animals to prolonged stress. To address this, we propose the Variable Delay-to-Signal (VDS) task as an efficient alternative for evaluating motor and choice impulsivity in mice with reduced training demands. This study aimed to validate the VDS task by assessing its ability to differentiate low-impulsivity (LI) and high-impulsivity (HI) phenotypes, while also investigating genotype and sex differences. Homozygous humanized ApoE3- and ApoE4-target replacement mice underwent the VDS task, which included habituation, training, and test phases. During training, mice initiated trials and responded to a light stimulus after a delay, receiving rewards for correct responses and timeouts in darkness for premature or omitted responses. The test phase incorporated variable delays to assess choice impulsivity and delay intolerance. Results demonstrated successful task acquisition, with stabilization over time in the number of completed trials, correct responses, and omissions. Motor impulsivity, measured by premature responses during training, distinguished statistically validated LI and HI groups. ApoE3 mice exhibited higher motor impulsivity than ApoE4 mice. Choice impulsivity was higher in males than in females at longer delays to stimulus presentation, as well as in HI mice. While LI mice showed better delay tolerance, HI mice exhibited greater delay intolerance, though the difference was not statistically significant. In conclusion, the VDS task is a robust and efficient tool for preclinical impulsivity research, reliably identifying impulsivity phenotypes and detecting genotype- and sex-related differences with reduced training requirements compared to the 5-CSRTT.

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Keywords. impulsivity, animal models, ApoE, sex differences, behavior, neuropsychiatric disorders

P.2.43 - Where you live matters: air pollution affects cognitive and emotional health along with changes in the inflammatory response during aging

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Cognitive decline refers to the progressive deterioration of brain functions, commonly linked to the aging process, and is a leading cause of disability and dependency among older adults. While variables such as age and educational level have been extensively studied in this context, others, such as place of residence, have received comparatively little attention. The place of residence is closely associated with air quality, particularly with the level of exposure to PM2.5. These fine particulate matter particles can infiltrate the lungs and bloodstream, potentially depositing in various organs, including the brain. This study aims to explore whether place of residence, and consequently exposure to PM2.5 concentrations, isassociated with cognitive decline (including executive and attentional functions) and mood disorders, particularly symptoms of anxiety, depression, and stress.Additionally, by utilizing biochemical markers, the study seeks to identify potential links between these impairments and inflammatory variables. A total of 95 older participants from the regions of Aragón and Castilla-La Mancha (Spain) were included in the study (mean age = 65.39 years; 67% women). Results suggest that factors such as air pollution, place of residence, and levels of inflammation may play a role in predicting cognitive and emotional decline during aging. Participants residing in areas with lower PM2.5 concentrations showed better cognitive and emotional performance. This suggests that cognitive and emotional health may be influenced by PM2.5 exposure in human participants. Our findings indicate that environmental agents could be the key to understanding the susceptibility and variability observed during aging in behavioral symptoms.

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Keywords. air quality, PM2.5, cognitive function, emotional health, inflammation, aging

P.2.44 - MicroRNA-34a as a possible functional marker of the innate freezing defensive response

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Innate defensive behaviors such as freezing and escape are crucial for animal survival. These behavioral responses are mediated by distinct neural circuits conserved across species. However, whether molecular signatures can selectively identify and regulate functional units underlying specific defensive strategies remains largely unexplored. MicroRNAs (miRNAs) are small, conserved, non-coding RNAs with region- and cell-type-specific expression in the brain, making them promising candidates for this role. Among them, miR-34a shows high specificity in a subset of GABAergic neurons in the dorsal raphe nuclei (DRN), modulating inhibitory transmission selectively in response to aversive stimuli.We combined optogenetic, pharmacological, and genetic approaches to investigate whether miR-34a contributes to the modulation of innate defensive responses to distinct visual threats. First, using optogenetics, we demonstrated that GABAergic activity in the DRN is necessary for expressing defensive behaviors in response to ethologically relevant visual stimuli—specifically, a sweeping stimulus that induces freezing and a looming stimulus that triggers shelter-directed escape. Next, we showed that pharmacological inhibition of miR-34a in the DRN selectively impairs the freezing response without affecting escape. Finally, genetic suppression of miR-34a, specifically in DRN GABAergic neurons, confirmed its selective role in modulating the freezing—but not the escape—response to visual threat.These findings suggest miR-34a is a molecular signature of specific neural circuits modulating distinct defensive behavioral outcomes.

Keywords. innate defensive behavior, microRNA, Dorsal Raphe Nuclei

P.2.45 - Sleep deprivation and risky play during early life: implications for cognitive control in rats

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Recent rodent studies have shown that sleep deprivation can impair brain development and our preliminary neonatal data suggest that the amount of sleep in the neonatal intensive care unit (NICU) is correlated with white matter brain development, suggesting that sleep is an important driver of early brain development. Rodent studies have also shown that play is not just fun, but also very important for the development of brain and behaviour. Recently, we showed that providing rats with the opportunity to engage in risky play increases cognitive control over behaviour and enhances GABAergic inhibition in the prefrontal cortex. The aim of this study was to determine whether sleep deprivation would affect cognitive control and whether risky play may alleviate this effect. To address this question, we compared rats with a normal sleep rhythm to rats that were sleep deprived through gentle handling daily for 3 hours from postnatal day (PND) 5 to 21. The control group was handled for just 10 minutes each day. These groups were then subdivided into two subgroups: regular play and risky play. The risky play group was allowed to play in a risky play cage, that was high end equipped with multiple (un)stable ladders, twice a day for 30 minutes from PND 21 to 42. During this period we compared the rats for their tendency to engage in social play behaviour. Once the animals reached early adulthood they were subjected to a behavioural inhibition task to compare their degree of cognitive control. The initial findings suggest that the sleep deprived rats show a similar degree of social play behaviour compared to non-sleep deprived peers. The cognitive control task is yet to be performed.

Keywords. sleep, play, cognition, rats, early life

P.2.46 - Impact of combined prenatal exposure to Chlorpyrifos and particulate matter on early neurodevelopmental outcomes in Wistar rats

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Prenatal exposure to environmental pollutants is increasingly recognized as a risk factor for neurodevelopmental disorders. Particulate matter (PM) is considered the most extended air pollutant present in the environment, consisting of agglomerated soot aggregates, regular and irregular mineral particles, spherical particles, and other complex chemical components. PM can cross the placental barrier, inducing systemic inflammation, oxidative stress, and impairing blood-brain barrier integrity. Furthermore, prenatal CPF exposure has been linked to developmental alterations and autism-like behaviors in preclinical studies. In this study, pregnant Wistar rats were exposed to CPF from gestational day 12.5 to 15.5, and to PM throughout the whole gestation. Neurodevelopmental outcomes in the offspring were assessed through ultrasonic vocalizations (USVs) during social isolation on postnatal day 7 and measurement of body weight. In addition, whole brain hemispheres were analyzed via RTqPCR to assess the expression of genes related to social behavior, vocal communication, GABAergic signaling, and the excitatory/inhibitory balance. We hope that offspring prenatally exposed to both environmental pollutants exhibited marked alterations in USVs and alter brain gene expression of relevant genes for neurodevelopment and autism-like behaviors. These findings may contribute to a better understanding of how combined environmental exposures during pregnancy may disrupt normative brain development and increase the risk of neurodevelopmental disorders.

Keywords. Prenatal, Neurodevelopment, Chlorpyrifos, Particulate Matter, Ultrasonic Vocalizations, Gene Expression

P.2.47 - Long-term effects of prenatal exposure to PM10 and Chlorpyrifos in aging: impact on memory and hippocampal gene expression in offspring

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Environmental exposure during prenatal development can have long-lasting effects on brain health, potentially increasing the risk of neurodegenerative processes later in life. Particulate matter (PM), a major component of air pollution, and chlorpyrifos (CPF), a widely studied organophosphate pesticide, are two common neurotoxicants well-known to impact neurodevelopment. However, the long-term consequences of prenatal exposure to these agents on cognitive decline and hippocampal integrity during aging and its interactions in organisms remain poorly understood. In this study, we aimed to evaluate the effects of prenatal exposure to PM and CPF on late-life neurodegeneration and hippocampus-dependent memory functions in Wistar rats. Pregnant dams were exposed to PM throughout the entire gestational period and/or to CPF from gestational days 12.5 to 15.5. Offspring were assessed in late adulthood for behavioral performance using the Morris Water Maze, and hippocampal gene expression was analyzed via RT-qPCR. Additionally, a functional developmental battery was conducted to evaluate body weight gain, sexual and visual maturation, and motor skill development. This study aims to provide insight into the long-term impact of prenatal exposure to environmental pollutants on cognitive aging and hippocampal function. A better understanding of these effects may inform public health policies to reduce exposure to neurotoxicants during critical windows of development.

Keywords. Particulate Matter, Memory, Chlorpyrifos, Rat, Prenatal, Neurodegeneration

P.2.48 - Aphakia dopamine deficient mice show anergia but not anhedonia: the role of cerebral dopamine neurotrophic factor in dopaminergic terminal areas

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The transcription factor Pitx3 is critical for the functional survival of dopaminergic neurons. Aphakia mice (Ak) have a mutation in Pitx3, which leads to a considerable reduction in dorsal-striatal dopaminergic innervation and results in parkinsonian-like motor alterations. They also show a smaller reduction in ventral-striatal DA, including Nucleus accumbens (Nacb). Since Nacb dopamine (DA) plays a major role in vigorous voluntary locomotion and in the activational component of motivated behaviors, including effort-related decision-making, we evaluated spontaneous behavioral activation in a running wheel (RW), and vigor-based choice in the T-maze-RW task in these Ak mice and their wild type (WT) counterparts. WT mice showed higher vigorous locomotion in the RW compared to Ak. In the T-maze with 3 reinforcers with different activational requirements (a RW, sweet pellets, or a floral odor), WT mice spend most of their time running, and although Ak mice also preferred the RW, they spent less time running, but more time eating compared to WT. Ak mice consumed more palatable pellets under different experimental conditions, but they were not different in consumption or preference of sucrose solutions. Additionally, repeated administration of L-DOPA (a DA precursor) significantly increased voluntary running in the RW in both types of animals, making Ak mice reach basal WT levels of running. However, neither group changed relative preferences in the T-maze task. In parallel to the anergic effects observed in Ak mice, they showed less immunoreactivity of the cerebral DA neurotrophic factor (CDNF) in the Nacb core, compared to WT mice. However, Ak showed higher CDNF levels in Dorsomedial Striatum (DMS), which, nevertheless, may be underlying a potentiation in goal-directed behaviors. These results could have high clinical importance for modeling the psychomotor retardation and the low-effort bias seen in neurological and neurodegenerative diseases, such as PD. Furthermore, the introduction of CDNF as a new therapeutic tool aimed at limiting the advances of PD and specifically the motivational symptoms that are observed in this neurodegenerative disease, remains a promising possibility.

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Keywords. Motivation, dopamine, Nucleus Accumbens, CDNF, pitx3

P.2.49 - A cognitive pathway to maladaptive choice

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Individuals differ in sensitivity to adverse consequences of their actions and these differences have been linked to alcohol and other substance use disorders. The causes of these individual differences remain poorly understood but include a failure to correctly learn about the causal relationship between actions and their negative consequences. The costs of a behaviour can remain hidden to some individuals. Using a well validated human punishment task in 195 participants, we asked whether provision of explicit instruction about the causes of punishment could rescue individuals from punishment insensitivity and asked how the timing of this explicit instruction determined its effectiveness. Explicit instrumental contingency information was provided before or after participants had experienced strong (40%) or weak (10%) punishment contingencies. We found that early instruction was more successful than late instruction in rescuing individuals from persisting in punished behaviour, but that the benefit of this intervention was only observed when punishment was frequent. Notably, punishment insensitivity was due to conscious, goal-directed choices, as all participants were aware of their actions and believed them to be optimal. Together these findings show that even when presented in advance with accurate warning information about the risks/adverse consequences of actions, rare punishment still acted as a significant barrier to successful learning in some people. This lends further support to a cognitive pathway to punishment insensitivity, demonstrating the critical role played by our capacity to correctly recognise and attribute the adverse outcomes of our actions in protecting versus promoting maladaptive choice.

P.2.50 - Outcomes of CADM2 recursive splice site variation on rodent neuroimaging and ADHD-related behaviours

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Background: Attention-Deficit/Hyperactivity Disorder (ADHD) is a highly prevalent neurodevelopmental disorder with a well-established genetic basis. Prior studies link the Cell Adhesion Molecule 2 (CADM2) gene to ADHD-related traits in humans, including externalizing behaviours, hyperactivity, and inhibitory control deficits. Recent research has suggested associations between CADM2 recursive splicing variations and an increased risk for ADHD, but the causal effects of these variations remain unknown. Here, we explore the effects of a novel CADM2 recursive splice site (RS1) deletion on brain connectivity and behaviour in rats. Methods: Cadm2 wild-type (WT, RS1-/-), heterozygous (Het, RS1+/-), and homozygous (Homo, RS1+/+) rats (n = 6-11/sex/genotype) were imaged for functional connectivity (9.4T MRI). Behavioural testing followed, starting with a Pavlovian Conditioned Approach (PCA) task to measure sign-tracking (placing incentive value on cues) and its reversal, extinction, reinstatement and negative automaintenance. Additional tasks included an Open Field Test to assess locomotor activity, Novel Object Recognition for memory, and Pre-Pulse Inhibition for sensorimotor gating. Results: Our behavioural findings show sex effects on several sign-tracking metrics during reversal, reinstatement, and negative automaintenance phases, where males show higher sign-tracking tendencies than females. A main sex*genotype interaction effect was found in acquisition, with female Hets showing higher probabilities to press the unconditioned lever than male Hets ($p = 0.040$). In extinction, a main genotype effect showed that Homo animals pressed the unconditioned lever more often than WT rats ($p = 0.018$). Conclusion: These results suggest that reward-related learning processes differ between sexes. Additionally, the effects of CADM2 RS1 deletion on autoshaping behaviours appear to be limited and difficult to interpret.

Keywords. CADM2, ADHD, genetics, animal model, behaviour, neuroimaging, sign-tracking

P.2.51 - Neural representation of altered reward-seeking behavior following punishment

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Drug abstinence is often motivated by a desire to avoid some aversive consequence of drug seeking. Learning to abstain from reward-seeking behaviors can be modelled in animals via punishment, in which a reward-seeking response now also earns an aversive outcome such as electric shock. Reward-seeking behavior is associated with activity in D1 and D2 receptor expressing neurons in the nucleus accumbens (NAc), however it is unclear how these neurons encode new inhibitory learning about a reward-seeking response during punishment. We recorded in vivo calcium dynamics from D1 and D2 receptor-expressing NAc neurons in rats trained and punished for food-seeking in separate contexts. We then applied machine learning methods to predict relevant behavior outcomes at a trial level, as well as to characterize diffuse response-adjacent behavioral changes during punishment. Punishment altered population-level neural activity immediately following each of four response types: those that earned reward, punishment, both, or neither. A similar trend immediately preceding each response type suggested that neural activity tracked both expectation of outcomes as well as the confirmation/violation of that expectation. We also analyzed behavior videos with DeepLabCut and identified an “abortive” lever approach behavior, as well as altered latency between lever approach and response. These results collectively suggest that D1 and D2 receptor-expressing NAc neurons track the expectation and delivery of both appetitive and aversive outcomes during punishment, and that punishment induces qualitative changes in how animals emit a reward seeking response.

Keywords. punishment, addiction, accumbens, dopamine, calcium

P.2.52 - Cerebellar modulation in cocaine self-administration and drug-seeking behavior

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Substance Use Disorder (SUD) is a chronic condition characterized by compulsive drug consumption despite adverse consequences, high relapse rates, impaired behavioral control, and dysregulated emotional processing. It is associated with neuroadaptations in circuits governing reward, motivation, and memory. While research has traditionally focused on the cortico-striatal-limbic circuit, recent evidence suggests a significant role for the cerebellum in addiction-related behaviors, particularly the posterior cerebellar vermis. Our laboratory previously demonstrated that coordinated activity between the cerebellum and mPFC is necessary for the acquisition of drug-induced Pavlovian memory. However, its role in drug self-administration remains unexplored.Our objective was to investigate the role of the posterior vermis (LVIII) in short-access cocaine self-administration using chemogenetic tools (designer receptor exclusively activated by designer drug, DREADDs). Additionally, we explored the effects of cerebellar manipulations on cFos and perineuronal nets (PNNs) across cerebellum and other regions in the addiction circuitry.Male Sprage Dawley rats underwent an initial catheterization surgery and then after one week, a stereotaxic surgery to express the inhibitory DREADD AAV5-hSyn-hM4D(Gi)-mCherry. DREADD was activated by intraperitoneally (IP) CNO for the last five days of cocaine self-administration. Twenty-four hours later, rats undertook a drug seeking test under extinction. The results demonstrated that AAV5-hSyn-hM4D(Gi)-mCherry selectively inhibited inhibitory interneurons of the granular and molecular layer of lobule VIII. The inhibition of Golgi and molecular interneurons dramatically reduced cocaine intake and decreased drug-seeking behavior in a drug-free test 24 hours following the last cocaine self-administration session.

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Keywords. Addiction, Cerebellum, Cocaine, Self-administration, DREADDs

P.2.53 - Role of progesterone on cue-induced cocaine seeking in rats

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Drug addiction is characterized by long-lasting risk of relapse even after long abstinence periods. Historically, addiction research mainly focused on males, generalizing the findings to females. However, clinical and preclinical studies revealed sex differences in cocaine relapse. Indeed, our previous study revealed a higher cue-induced cocaine seeking in female than male rats, an effect dependent on the hormonal cycle. Females were more vulnerable to cue-induced cocaine seeking during the estrus phase characterized by low progesterone levels, compared to females in non-estrus phase with high progesterone levels. Here, we studied whether endogenous and exogenous progesterone would decrease cue-induced cocaine seeking in rats. Female rats were trained to self-administer cocaine intermittently for 12 days and then underwent a cue-induced cocaine seeking test 29 days after forced abstinence. In the first experiment, blood sampling was performed after the relapse test and progesterone level was measured by ELISA. In the second experiment, the rats received an acute systemic progesterone injection before the relapse test. Then, the future experiment will be to decrease the risk of cocaine relapse in estrus females. We observed that progesterone levels were negatively correlated with the number of active lever presses during relapse. Moreover, in estrus females, progesterone decreased cue-induced cocaine seeking compared to the vehicle group and decreased the number of c-fos+ neurons in the insular cortex. In non-estrus females, progesterone had no effect on cue-induced cocaine relapse and c-fos expression in the insular cortex. Our results demonstrate endogenous progesterone protective effect against cocaine seeking and suggest that exogenous progesterone treatment could prevent cocaine relapse in vulnerable estrus females via insular cortex activity modulation.

Keywords. Cocaine relapse, sex differences, progesterone, insular cortex

P.2.54 - Knock-down of the histone methyltransferase Prdm2 in the dorsomedial Prefrontal Cortex: effect on cocaine-related behaviors in male rats

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Cocaine use is increasing, especially in Europe, yet no therapies are approved for cocaine addiction. A key challenge in addiction research is identifying relevant therapeutic targets. Recent studies have identified specific epigenetic mechanisms involved in compulsive alcohol consumption in rats. Post-dependent male rats show reduced mRNA expression of histone methyltransferase Prdm2in the dorsomedial prefrontal cortex (dmPFC), and Prdm2knock-down (KD) in this area promotes compulsive-like alcohol consumption (Barbier E, et al. 2017). We aimed to determine if Prdm2expression in the dmPFC is also linked to cocaine addiction-like behavior, using a DSM-based addiction model that identifies ~20% of rats as addicted-like after protracted cocaine self-administration (Deroche-Gamonet V, et al. 2004).Brains from addicted-like and non-addicted rats were analyzed. As with alcohol, we found a correlation between cocaine addiction-like behavior and Prdm2expression in the dmPFC, measured by qPCR. Prdm2 expression was lower in addicted-like rats, and the lower the expression the higher the addiction score.To test a causal role for Prdm2, we decreased its expression in the dmPFC using an AAV driving a short hairpin RNA targeting Prdm2. This was done before or after stabilizing cocaine self-administration. In both conditions, Prdm2-KD did not induce addiction-like behavior. However, in rats imitating self-administration with Prdm2-KD, cocaine reinforcing effects were altered. Prdm2-KD rats stabilized self-administration at lower intake levels than controls. The dose-response curve and intake pattern indicated increased sensitivity to reward, which was further confirmed by greater oral sucrose self-administration (10% v/v) in an independent batch of rats.A lower Prdm2expression in the dmPFC may enhance the response to rewards, leading to spaced cocaine use and increased sucrose intake. Ongoing studies are investigating the molecular and circuit mechanisms of these effects in the mesocorticolimbic system. How the decrease of Prdm2expression in cocaine addicted-like rats relate to the observed effects and to their addiction-like behavior remain to be explored.

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Keywords. Cocaine, reward-related behaviors, dorsomedial prefrontal cortex, Prdm2, gene knockdown

P.2.55 - Effects of chemogenetic modulation of the mesocorticolimbic dopamine pathway on cocaine choice

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Rationale: The mesocorticolimbic dopamine pathway is recognized as playing a central role in reward and reinforcement. Pharmacological manipulations targeting dopamine have been shown to modulate drug maintained behavior. However, these manipulations impact dopamine transmission globally and thus lack pathway specificity. The goal of the present studies was to selectively target the mesocorticolimbic pathway using Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) and determine the effects of chronic and acute activation of this pathway on cocaine-maintained responding in rats using a cocaine-vs-food choice procedure that has shown translational utility in modelling clinical aspects of behavioral misallocation between drugs of abuse and alternative nondrug reinforcers. Methods: Two main experiments were conducted using adult male and female TH:Cre Sprague Dawley rats. First, the effect of chronic activation of the mesocorticolimbic dopamine pathway on cocaine-vs-food choice before and after bilateral intra-VTA hM3Dq DREADD expression was determined in rats (n=10) using continuous DCZ treatment (vehicle, 1.0-100 µg/kg/h). Subjects were aseptically implanted with single-lumen catheters and responded under a concurrent “choice” schedule of food (32% liquid food) and cocaine (0-1.0 mg/kg/injection) during daily 2-h sessions. Second, animals (n=15) received acute DCZ pretreatment (vehicle, 1.0-1000 µg/kg) to determine the effect of acute activation of the mesocorticolimbic pathway on cocaine-vs-food choice. Results: Under baseline conditions, cocaine maintained a dose-dependent increase in cocaine-vs-food choice. Chronic and acute DCZ administration before Gq-DREADD expression did not significantly alter cocaine choice. Continuous administration of DCZ post-DREADD expression also did not significantly affect cocaine-maintained behavior. In contrast, acute pretreatment with 100 and 1000 µg/kg DCZ post-DREADD expression significantly increased cocaine choice. Conclusions: Acute and chronic administration of DCZ prior to intra-VTA DREADD expression had no significant effect on cocaine choice behavior demonstrating DCZ behavioral selectivity. Acute DCZ-induced increased in cocaine choice post-DREADD expression suggests VTA activation enhances cocaine reinforcement. The lack of chronic DCZ treatment effects post DREADD expression on cocaine choice suggest potential tolerance to DCZ treatment effects that are dissimilar from chronic d-amphetamine treatment effects on cocaine choice.

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Keywords. choice; cocaine; deschloroclozapine; DREADD; Th:Cre rats

P.2.56 - Role of Dorsal Raphe glutamatergic neurons in cocaine-seeking behavior

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The dorsal raphe nucleus (DR), though known for containing serotonergic neurons, also contains glutamatergic neurons expressing the vesicular glutamate transporter type 3 (VGluT3). We previously showed that DR-VGluT3 neurons form excitatory monosynaptic connections with a subset of ventral tegmental area (VTA) dopaminergic neurons projecting to the nucleus accumbens. VTA glutamate release from DR-VGluT3 fibers drives dopamine release in the nucleus accumbens and produces rewarding effects. Here, we investigated the extent to which DR-VGluT3 inputs to the VTA play a role in cocaine-seeking behavior using self-administration (SA) and conditioned place preference (CPP) paradigms. We expressed Channelrhodopsin in DR-VGluT3 neurons and used local VTA photostimulation to evoke glutamate release from their terminals. Following extinction of cocaine SA and CPP, photostimulation reinstated cocaine-seeking and preference but not food-seeking, suggesting a drug-specific effect. We next assessed the extent to which DR-VGluT3 glutamate release mediates stress- or cocaine-primed reinstatement. Using Halorhodopsin expression and bilateral VTA photoinhibition, we suppressed DR-VGluT3 glutamate release. Control mice reinstated cocaine-seeking and preference after stress or a cocaine priming injection but not after a saline injection. In contrast, photoinhibition of DR-VGluT3 fibers blocked both stress- and cocaine-induced reinstatement. From these findings, we conclude that glutamate release in the VTA from DR-VGluT3 neurons is both sufficient and necessary for reinstatement of cocaine-seeking behavior and preference.

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Keywords. Dorsal Raphe, VTA, glutamate, cocaine-seeking behavior

P.2.57 - Synaptic zinc and dopamine dynamics in response to cocaine and locomotion

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The striatum integrates dopaminergic input from the ventral tegmental area/substantia nigra and glutamatergic input from the cortex and amygdala to regulate behaviors such as movement, reinforcement, and drug reward. These circuits also play a critical role in addiction. A subset of cortical glutamatergic neurons corelease synaptic Zn2+, a critical modulator of neurophysiological homeostasis. Our previous work showed that striatal Zn2+ modulates cocaine-induced behaviors and dopaminergic transmission. Here, we investigated the molecular profile of Zn2+ -releasing (zincergic) neurons projecting to the striatum and the dynamics of Zn2+ and dopamine during behavior. Using retrobeads and RNAscope, we found that the prelimbic cortex, cingulate cortex, and amygdala send zincergic projections to the dorsal striatum (DS) and nucleus accumbens (NAcc). Molecular analysis revealed that 44–55% of glutamatergic neurons and 2–5% of GABAergic neurons in the cortex, and 51% of glutamatergic and 2% of GABAergic neurons in the amygdala are zincergic. Using fiber photometry with Zn2+ (GRISZ) and dopamine (GRABDA) sensors, we found that Zn2+ and DA release increased in both the DS and NAcc during locomotion but remained low during immobility. Cocaine administration further increased the frequency and duration of Zn2+ and dopamine transients in both regions. These results highlight the activity-dependent release of synaptic Zn2+ and dopamine and suggest zincergic projections play a key role in striatal circuits underlying locomotor and reward-related behaviors.

Funding. NIDA IRP ZIA-DA00069

Keywords. Dopamine, Striatum, Cocaine

P.2.58 - Role of cerebellum projecting neurons to the VTA in cocaine-induced conditioned memory

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Traditionally associated with motor control, the cerebellum has emerged as a key player in cognitive and emotional functions, showing increasing involvement in the regulation of behaviors related to substance use disorder (SUD). Recent evidence indicates that the cerebellum plays a role in the formation of drug-associated memories and in modulating neural activity in drug-related brain regions. A compensatory interaction has been identified between the cerebellum and the infralimbic cortex (IL), suggesting a reciprocal influence in the regulation of drug-conditioned preferences. This interaction is crucial for understanding the neurobiological mechanisms underlying addiction, as well as psychiatric conditions that often co-occur with SUD. Identifying potential mediating structures involved in cerebellum-IL communication such as the ventral tegmental area (VTA) is a key objective that is currently being explored.The present study aims to investigate the role of the deep cerebellar nuclei (DCNs), the main output of the cerebellum, in cocaine-induced conditioned place preference (CPP), as a model to assess drug-context associative learning. We used chemogenetic tools, specifically Designer Receptors Exclusively Activated by Drugs (DREADDs), combined with cre recombinase system, to selectively stimulate or inhibit the activity of the DCNs and the glutamatergic projections to the VTA.Mice used in this study (C57BL76J) underwent initial stereotaxtic surgery to infuse the inhibitory or excitatory Double-Floxed DREADDs (AAV5-hSyn-hM4D(Gi)/hM3D(Gq)-mCherry) into the Interposed /Lateral nuclei together with the retrograde cre virus (AAVrg-pENN-AAV-hSyn-CRE-WPRE-hGH). We activated the DREADDs intraperitoneally using clozapine-N-oxide (CNO) during the 8 days of conditioning. The preference test was performed twenty-four hours after conditioning. Interestingly, inhibiting cerebellar projections to the VTA did not impair cocaine-induced CPP, suggesting these connections may be non-essential for drug-context learning or compensated by other circuits. Current analyses of pathway activation may reveal increased preference, further clarifying the cerebellum’s role in modulating addiction-related behaviors.

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Keywords. Addiction, cerebellum, cocaine, associative memories, DREADDs, transgenic mice

P.2.59 - Impulsivity as a risk factor for alcohol use disorders: development and validation of a go-nogo model of impulsivity

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Impulsivity is a multifaceted behavior characterized by premature, risky, and inappropriateactions that often lead to adverse consequences such as alcohol use disorders. In this project,we developed a rat operant self-administration model of impulsivity to investigate whetherMarchigian Sardinian alcohol-preferring (msP) rats—characterized by a high alcoholpreference associated with elevated anxiety and stress responses—also exhibit impulsive-liketraits, and whether this trait contributes to their alcohol-seeking behavior. We developed two Go/No-Go operant models of impulsivity in non-preferring Wistar rats: abetween-trials Go/No-Go model, in which Go and No-Go signals are presented in separatetrials; and a within-trial Go/No-Go model, in which Go and No-Go signals are presentedwithin the same trial. Rats were required to press a lever during the Go signal or withholdlever pressing during the No-Go signal to obtain a sucrose reward and access a new trial aftera short (5s) inter-trial interval (ITI). In both models, each trial was preceded by a pre-trialperiod during which the rat had to abstain from pressing the lever. Pressing the lever duringeither the No-Go signal or the pre-trial period was punished with a long (20s) ITI. Validation of predictive validity using Atomoxetine confirmed that pressing during the pre-trial and No-Go phases was a measure of impulsivity in both models. When comparing thetwo models, we observed similar performance in pre-trial and No-Go errors, but a higher number of Go-phase errors in the within-trial model—possibly indicating a higher level of inattention induced by this model.A comparison of impulsive behavior between Wistar and msP rats using the within-trialGo/No-Go model revealed that msP rats were more impulsive than Wistars. Finally, to assesswhether impulsivity contributes to the high alcohol preference in msPs, we verified that anti-impulsive doses of Atomoxetine reduced alcohol self-administration (ASA) in these rats. In conclusion, we validated two models of impulsivity, one of which—the within-trialGo/No-Go model—may also reflect inattention. Additionally, we demonstrated that msP ratsexhibit more impulsive-like behaviors than Wistar controls, potentially contributing to theirhigher alcohol preference.

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Keywords. Impulsivity, Alcohol Use Disorder, Atomoxetine

P.2.60 - Inflammatory pain impairs alcohol reward processing without affecting motivation for sucrose or alcohol in female rats

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Chronic pain is a burden for healthcare systems worldwide, affecting 20-30% of people in western countries. During the last years, evidence about psychological comorbidities associated with chronic pain, as anxiety, depression, and addiction. Dynorphinergic system within mesolimbic dopaminergic system has been identified as pivotal connection for pain-induced negative affective states. Therein, we used a sucrose self-administration to test if inflammatory pain, complete Freund adjuvant (CFA) model, produce decrease in sucrose and alcohol motivation in female rats. We did not find alterations for sucrose or alcohol motivation. Furthermore, we explored the kappa opioid receptors (KORs) in different areas of the mesolimbic system. Interestingly, female under pain condition showed an increase in KORs level in CeA, but this was not correlated with the reported behaviors. Finally, we perform a dopamine microdialysis to test if female rats would show the same impairment in alcohol-induced dopamine release in NAc, described before. We found that females in pain did not only show low dopamine release to an ethanol injection, if not DA levels were higher than female controls. Altogether our results provide new insights into the sex-dependent function of dynorphinergic and dopaminergic system in mesolimbic areas pain-induced negative affective states, underlying the need of include both sexes to study properly the neurobiological mechanisms beyond pain-induced negative affective states in a sex-dependent manner.

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Keywords. chronic pain, KOR, dopamine, motivation, sex-dependent

P.2.61 - The role of a positive allosteric modulator of the GABAB receptor (ADX71441) on ethanol vapor dependence-induced compulsive alcohol drinking

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Alcohol use disorders (AUDs) are psychiatric disorders resulting from alcohol use. Prolonged alcohol consumption can induce physical dependence on the drug, associated with negative affective states upon withdrawal, and can shape the vulnerability to develop AUDs later in life. In this study, a population of male Wistar rats (n=64) was trained for oral self-administration of 20% ethanol. Once a stable responding was reached, punished operant self-administration was used to determine individual differences of drinking despite negative consequences (compulsive-like behavior), classifying animals into sensitive, resistant, and intermediate subgroups. After that, to model alcohol dependence, half of the animals were exposed to chronic intermittent ethanol intoxication cycles through inhalation of vaporized alcohol, while an equally sized subgroup was left to a control condition. After treatment, rats were tested for additional unpunished self-administration sessions, showing that the vapor-treated animals escalated their alcohol drinking compared to the control group. Then, rats were screened on punished operant self-administration; no effect of vapor exposure on their individual differences was found. Finally, a synthesized positive allosteric modulator of the GABAB receptor, ADX71441, was tested to see whether it can rescue the compulsive-like behavior. ADX71441 reduced punished alcohol self-administration only at the dose of 3 mg/kg in both dependent and non-dependent rats. In conclusion, our study reports that even though vapor-induced alcohol dependence caused an escalation in alcohol drinking, it did not affect compulsive-like behavior. In addition, ADX71441 successfully attenuated punishment-resistant alcohol responding, regardless of the history of dependence.

Keywords. GABAB receptor, vapor exposure, compulsive-like behavior

P.2.62 - Sexual dimorphism in the behavioural impact of binge drinking during adolescence

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Binge drinking (BD) is a pattern of alcohol abuse characterized by excessive consumption in a short period, which is particularly appealing to adolescents due to its disinhibitory nature. However, its effects, especially across sexes, remain underexplored. This study investigates sex differences during abstinence in adolescent rats exposed to BD. Rats received intermittent intragastric alcohol administration three times daily for four days, following a modified 2-days ON/2-days OFF schedule. Seven-week-old male and female Wistar rats were tested for emotional behaviour using the elevated plus maze (EPM), forced swim test (FST), and saccharin preference test (SPT), as well as cognitive performance through the Morris water maze (MWM) and novel object recognition (NOR). ELISA kits were used to quantify the metabolic enzymes alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH).Under control conditions, females spent less time in the open arms of the EPM and showed longer immobility in the FST than males. Females also performed better in the MWM, while males excelled in the NOR test 24h after the last object exposure.After BD exposure, sexual dimorphism was evident. BD-males showed increased anxiety at 12h abstinence, while BD-females appeared disinhibited versus controls in the EPM. Both sexes showed increased depressive behaviours, especially females, after 27h abstinence. BD-females improved in the NOR test after 12 days of abstinence, whereas BD-males showed impairments. Liver ALDH levels revealed a significant interaction between sex and alcohol exposure.These findings suggest that BD impacts emotional and cognitive behaviours differently in males and females during abstinence, with sex-specific differences in alcohol metabolism, highlighting the need to consider sex as a key variable in alcohol research.

Keywords. Binge drinking, adolescence, sex-differences, animal model, behaviour, anxiety

P.2.63 - Modulation of binge-like consumption of ethanol and other salient reinforcers by acute DHA administration in C56BL/6J mice

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A growing body of research has indicated that omega-3 polyunsaturated fatty acids (n-3 PUFAs), including docosahexaenoic acid (DHA), are effective in the treatment of neuroinflammation-related mental disorders, suggesting their potential benefit in addressing substance abuse. The present study investigated the effect of intragastric administration of DHA-enriched fish oil (700 mg/kg, Brudy Technology, Spain) on binge-like consumption of ethanol and other palatable substances (saccharin and sucrose) in male and female C57BL/6J mice using a drinking-in-the-dark (DID) paradigm. Furthermore, the effects of DHA on locomotor activity and anxiety-like behavior were assessed.The results showed that acute DHA administration significantly reduced binge-like consumption of saccharin, sucrose and ethanol without altering food intake. Finally, DHA-enriched fish oil administration had no effect on locomotor activity or anxiety-like behavior. These findings suggest that acute treatment with omega-3 PUFAs represents a novel approach to mitigating alcohol and palatable substances consumption and their effects.Evidence suggests that neuroinflammation is involved in the development of substance abuse. Given the anti-inflammatory role of n-3 PUFAs in the brain, the findings reported in this study may be attributable to a reduction in the proinflammatory response. However, further studies are needed to elucidate the exact mechanisms through which DHA modulate ethanol and palatable substance consumption

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Keywords. Binge-like consumption, Drinking-in-the-Dark (DID), DHA, Omega-3, Palatable substances

P.2.64 - Decision-making in electric barrier-induced voluntary abstinence

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In alcohol use disorder, individuals consistently choose alcohol consumption over alcohol-free activities, with abstinence being linked to recognition of the adverse consequences of these choices. There has been significant effort to incorporate choice into rodent models of alcohol-seeking and abstinence to understand the mechanisms of these choices. Here we report experiments assessing the nature of choice in an electric barrier-induced voluntary abstinence model of alcohol-seeking. We trained mice to seek and consume alcohol, then we induced voluntary abstinence by introducing an electric barrier. Next, mice received intermittent exposure to alcohol in their home cages before further assessment of voluntary abstinence with the electric barrier. Crucially, across the experiment, we used behavioural microstructure analyses to identify individual choices to approach or abstain from alcohol and we submitted these choices to formal cognitive modelling to deconstruct choice into its latent cognitive mechanisms. Dopamine binding in the AcbSh was also measured using fiber photometry with the GRAB-DA biosensor. Introduction of an electric barrier induced voluntary abstinence in most mice, with high levels of individual variability. Subsequent intermittent exposure to alcohol before re-testing had no effect on decisions to approach alcohol but promoted faster decisions to abstain. This suggests mice became more efficient in abstaining from alcohol. Formal cognitive modelling supported this, showing increased accumulation rates for decisions to abstain from alcohol after intermittent exposure, demonstrating a stronger evidence base for abstaining and aligning with faster abstinence responses. These findings identify a specific decision-making process driving voluntary abstinence and they provide a potential mechanism for the efficacy of approach bias modification tasks used to promote abstinence in human drinkers.

Keywords. Alcohol use disorder, Voluntary abstinence, Electric barrier, Cognitive modelling

P.2.65 - New preclinical research on pathogenesis of fetal alcohol spectrum disorders: The role of myelination and endocannabinoids

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BackgroundFetal Alcohol Spectrum Disorders (FASD), caused by prenatal alcohol exposure (PAE), lead to cognitive deficits, behavioral problems, and alcohol-induced brain changes. Impaired myelination, essential for neural signal transmission, may underlie these deficits and is regulated by the endocannabinoid (eCB) system. The eCB system includes cannabinoid receptors (CB1/CB2), endocannabinoids (anandamide [AEA], 2-arachidonoylglycerol [2-AG]), and enzymes. This study explores how FASD affects the eCB system and myelination in the hippocampus of neonatal rats.Material and MethodsNeonatal rats received ethanol (5 g/kg, i.g.) from postnatal days (PND)4–9, equivalent to the third trimester of human gestation, as an FASD model. Pups were weaned on PND21, sex-separated, and euthanized on PND22. Hippocampi were dissected for eCB level quantification via liquid chromatography-mass spectrometry (LC-MS) and myelin-related changes analyzed using ELISA.ResultsEthanol-exposed females showed increased AEA and decreased 2-AG levels, while males exhibited only reduced 2-AG levels. Ethanol exposure decreased the expression of myelin basic protein (MBP), myelin oligodendrocyte glycoprotein (MOG), myelin and lymphocyte protein (MAL), and 2',3'-cyclic nucleotide 3'-phosphodiesterase (CNPase) in males.ConclusionsPAE disrupts the eCB system and myelination in a sex-specific manner. These findings identify the eCB system as a potential therapeutic target for neurodevelopmental deficits in FASD. Therefore, future studies will investigate how modulating the eCB system with JZL-184, a potent and selective monoacylglycerol lipase (MAGL) inhibitor that blocks the hydrolysis of the endocannabinoid 2-AG, affects myelination and cognitive outcomes in FASD.

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Keywords. Alcohol, FASD, Myelination, eCB, Rats

P.2.66 - Neuroprotective effects of chronic DHA on ethanol intake in a mouse model of adolescent alcohol exposure

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Adolescence is a period of increased risk-taking behavior, including alcohol and drug abuse. In addition to inducing long-lasting changes in the brain at multiple levels, numerous studies have reported a positive correlation between adolescent alcohol exposure and risk of developing an alcohol use disorder (AUD) in adulthood. Given that omega-3 polyunsaturated fatty acids (n-3 PUFAs), including docosahexaenoic acid (DHA), may exert neuroprotective effects by reducing pro-inflammatory activity and oxidative stress. This study aimed to evaluate the impact of an 8-week DHA-enriched fish oil (700 mg/kg, Brudy Technology, Spain) supplementation on voluntary alcohol consumption (10% v/v) in adult C57BL/6J mice with a history of binge alcohol drinking during adolescence. Considering the role of stress and negative emotional states in ethanol consumption, the study also assessed the effects of acute physical stressor (restraint) on alcohol intake.Adolescent mice were exposed to a 4-week Drinking in the Dark (DID) protocol (postnatal days 32–60), which induced robust alcohol intake in both sexes but did not significantly increase alcohol consumption in adulthood (PND118). Interestingly, DHA supplementation resulted in a short-term reduction in voluntary alcohol consumption at 2 and 24 hours in adulthood, although this effect was not sustained over time. Finally, acute stress during adulthood did not influence alcohol intake, nor was this response modulated by adolescent alcohol exposure or DHA treatment. Future studies are needed to elucidate the mechanisms through which chronic exposure to DHA may modulate neurobiological responses to alcohol.

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Keywords. Ethanol consumption, Adolescents, Drinking-in-the-Dark, DHA; Omega-3

P.2.67 - Functional consequences of apolipoprotein AI potentiation in females exposed to intensive alcohol consumption

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Alcohol binge drinking (ABD) is a popular pattern of intensive alcohol consumption (IAC) which has demonstrated to increase plasma apolipoprotein AI (ApoAI) in female rats. This ApoAI, the major protein content of high-density lipoprotein (HDL), is increased in plasma of female animals exposed to IAC and it forms aggregates with lipopolysaccharide (LPS) components in the prefrontal cortex (PFC) of these animals. The functional consequences of this binding are unknown. Here, we indirectly explore the effects of ApoAI potentiation by exogenous administration of HDL and check the effects in alcohol-induced neuroinflammation and neurobehavioral alterations during abstinence.Female Wistar rats (200-225g) received intermittent doses of ethanol (3 g/Kg, i.g.) during 4 days/3 times/day in a 2-day on/2-day off protocol. HDL (20 mg/Kg, i.p.) was injected 15 min before each alcohol gavage. Plasma and brain LPS levels were measured by ELISA; neuroinflammatory parameters in PFC were measured by qPCR. Rats were evaluated in the Open Field Test (OFT), Saccharin Preference test (SPT) and Morris Water Maze (MWM) test during early abstinence.This ABD protocol did not alter plasma LPS levels in females 3h after the last binge, which differs with previous studies in males. However, HDL pre-treatment elevated LPS in both control and ethanol groups. No differences in LPS were found with any treatment or pretreatment in the PFC. We observed increases in CXCL1 in the PFC but no changes in other neuroinflammatory parameters. However, pretreatment with HDL increased TLR4, HMGB1 and CXCL1 (and a trend for TNF-α) both in control and ethanol-treated animals. Females showed anxiety-like behaviour in the OFT, with no behavioural changes in SPT or MWM after IAC. HDL pre-treatment produced anxiety-like behaviour, anhedonia and learning deficits in alcohol-treated females. It also aggravated spatial memory in control females.Our results suggest that the binding of ApoAI to LPS found in the PFC of females exposed to IAC may have negative consequences, since potentiation of ApoAI by a non-specific HDL pre-treatment trigger inflammatory responses in the PFC of both ethanol-exposed and control females, leading to impaired performance in behavioural tasks during abstinence.

Keywords. Apolipoprotein AI, LPS, binge drinking, ApoAI mimetic, neuroinflammation, behaviour

P.2.68 - Combined 5-HT2A receptor agonist and anodal tDCS for modulating compulsive alcohol drinking in a preclinical model

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Clinical research reveals a notable comorbidity between alcohol use disorder and obsessive-compulsive symptomatology, suggesting shared underlying mechanisms. Among these, the 5-HT2A receptor has emerged as a key player in the neurobiology of compulsive spectrum disorders. In line with this, various studies have demonstrated the effectiveness of combining transcranial direct current stimulation (tDCS) with pharmacological treatments such as SSRIs. Based on this, the objective of this study was to evaluate the therapeutic potential of a combined treatment using DOI, 5-HT2A receptor agonist, and anodal tDCS, and to assess treatment-induced changes in genetic biomarkers using RNAscope Hiplex. Male Wistar rats were exposed to alcohol in a preclinical compulsivity model known as Schedule-Induced Polydipsia (SIP) and classified as high drinkers (HD) or low drinkers (LD) based on their alcohol drinking. Two treatment regimens were applied: acute and chronic. Following group formation, animals received DOI (0.5 mg/kg i.p.) or saline, combined with anodal tDCS or sham stimulation on the frontal cortex (20 min, 0.5 mA; chronic treatment over 8 days). In the chronic treatment, behavior was assessed 24 hours after the last session, whereas in the acute regimen, it was measured at 1 and 24 hours post-treatment. Subsequently, gene expression of markers associated with the serotonergic, glutamatergic, and GABAergic systems in the prelimbic and infralimbic areas was analyzed. The results will be discussed regarding the potential of this combined intervention to reduce compulsive alcohol consumption and modulate the neuronal circuits implicated.

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Keywords. Compulsivity, alcohol drinking, 5-HT2A, tDCS, RNAscope Hiplex

P.2.69 - Compulsivity and alcohol abuse: sexual dimorphism and disruption of social interaction in a preclinical model

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Compulsivity is the inability to inhibit repetitive behaviors that are no longer adaptive to the current circumstances. Clinical studies have found a connection between alcohol use disorder and obsessive-compulsive symptoms, resulting in a tendency for compulsive drinking. Consequently, compulsivity might be a vulnerability factor for the development of alcohol use disorder. The aim of the present study was to evaluate compulsive alcohol drinking and its implication as an influential factor in the levels of social interaction in both sexes. Male and female Wistar rats were exposed to a preclinical compulsivity model known as Schedule-Induced Polydipsia (SIP). Initially, the rats were given access to water and subsequently to alcohol, with distinct groups formed based on their levels of water and alcohol intake. Following group formation, a series of variables was recorded to assess sociability and reaction to social novelty using the Crawley sociability test. The results were analyzed taking into account both the sex differences per se and the interaction between clusters and sex. Initially, it was observed that males exhibited an inversion of the typical sociability pattern while females showed greater sociability. However, when examining the interaction between groups and sex, in the groups with high alcohol drinking, the sex differences disappeared, with low social interaction evident in both female and male rats. In conclusion, compulsivity stands out as a vulnerability factor in the development of alcohol use disorder, exhibiting sexual dimorphism. Moreover, alcohol consumption can interfere with normal social interaction patterns.

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Keywords. compulsivity, alcohol drinking, social interaction, sexual dimorphism

P.2.70 - Mapping acute alcohol effects on bodily sensations

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Interoceptive processes may underlie maladaptive patterns of alcohol use. Bodily sensations experienced during alcohol intoxication could therefore reveal distinct mechanistic components relevant for addiction theory and research. Here we apply novel tools to examine how intoxication impacts somatic awareness using bodily maps in relation to objective measures of intoxication. In a double-blind, within-subjects, placebo-controlled study, social drinkers (n=37) were administered 0.4g/kg of alcohol. We measured changes in self-reported bodily sensations during the ascending and descending limbs of the blood-alcohol curves using the emBODY tool. Additionally, we recorded biphasic measures of subjective alcohol effects (sedation and stimulation) and changes in heart rate. Acute alcohol administration altered bodily sensations, reflected by strong sensations in the chest, limbs, and head, with lesser effects in the placebo condition. Linear mixed models examined correlates of bodily sensations across conditions. Intensity of bodily sensations correlated with heart rate changes and breath alcohol content. In the ascending limb, bodily sensations negatively correlated with subjective stimulation and positively with sedation. These findings highlight the value of bodily mapping in psychopharmacology, as interoceptive components of alcohol intoxication may provide a somatic basis for addiction. Bodily sensations of intoxication are derived from alcohol-induced changes in physiological states and drive subjective experiences of intoxication. We interpret our results through low-sensitivity models, suggesting individuals with reduced bodily sensations during intoxication may face elevated risk for alcohol use disorder, a hypothesis that will be examined in future research. We will finally put this research in context with novel bodily mapping approaches to craving.

Keywords. bodily sensations, interoception, alcohol administration, alcohol effects, bodily maps, subjective alcohol effects

P.2.71 - Examining the relationship between drug demand, craving, and withdrawal during a buprenorphine taper among individuals with opioid use disorder

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Hypothetical purchase tasks (HPTs) assess how much drug an individual would purchase at various prices and characterizes drug demand. HPTs are valuable because unlike self-administration paradigms, HPTs capture risk for nonmedical drug use (‘abuse liability’) without exposing individuals in treatment to drugs. This secondary analysis examined how HPT indices relate to other clinically relevant outcomes during a buprenorphine/naloxone taper.Thirty-eight individuals with OUD were randomized to receive 0, 20, or 40 mg of suvorexant during a 4-day buprenorphine/naloxone taper. HPTs for their preferred nonmedical opioid were administered the day before the taper and on the final taper day. Withdrawal was captured using self-report and observer-rated measures and craving was captured daily with a multi-dimensional assessment. Analyses examined whether intensity of demand (amount purchased when drug is free) and elasticity of demand (extent to which drug consumption is sensitive to price increases) correlated with co-occurring and future instances of craving and withdrawal.Regardless of suvorexant condition, intensity of demand decreased and elasticity of demand increased as a function of time. Intensity of demand was significantly correlated with craving ("wanting to use", r = 0.38 and "feeling a lack of control", r = -0.41) but not with withdrawal severity. Baseline demand indices did not predict future craving or withdrawal.Individuals going through a buprenorphine taper experienced decreases in opioid demand. These analyses demonstrates that HPT may be most related to anticipation of positive reinforcement, not withdrawal, and provides insight into how opioid demand functions during an opioid taper.

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Keywords. buprenorphine taper, craving, hypothetical purchase tasks, withdrawal

P.2.72 - Learning contingencies and uncertainty: a modified probabilistic reversal learning task

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The Probabilistic Reversal Learning Task (PRLT) is widely used to investigate contingency-based flexibility, a core component of adaptive behavior. Poor performance on this task may reflect different underlying mechanisms. Given that clinical populations often show altered sensitivity to reinforcement and/or punishment, we present a modified version of the PRLT that manipulates contingencies (positive reinforcement vs. negative punishment) to assess its impact on learning.A total of 121 undergraduate students from the University of Almería (Mage=20.46, 60.33% women) completed the modified PRLT. The task consisted of two phases, each containing four blocks of 40 trials. In phase 1, participants performed one acquisition and one reversal block under low (80%-20%) uncertainty condition, with positive reinforcement and negative punishment. In phase 2, participants performed one acquisition and one reversal block under high (60%-40%) uncertainty conditions with positive reinforcement and negative punishment. The order of reinforcement and punishment blocks was counterbalanced.Generalized Linear Mixed Models were used to analyze performance (correct choices, win-stay, lose-stay proportions) as a function of uncertainty level, contingency type, and counterbalance order. We hypothesized: (1) better learning under punishment in high uncertainty, and (2) no counterbalancing effect. Results showed no main effects of contingency type or order on learning. However, as in previous studies, better learning occurred under low uncertainty. When including sex as a covariate, men showed superior performance under low uncertainty and positive reinforcement conditions. Future studies should extend this paradigm to clinical populations with known differences in reinforcement processing.

Funding. Spanish Ministry of Science and Innovation (PID2023-147063NB-I00/AEI/10.13039/501100011033).

Keywords. probabilistic reversal learning, uncertainty, contingencies, reward, punishment

P.2.73 - Emerging evidence of heterogeneity in the opioid withdrawal syndrome: spontaneous and precipitated withdrawal

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Aims: This study aimed to characterize the heterogeneity of opioid withdrawal by comparing spontaneous and naloxone-precipitated withdrawal symptom profiles in adults with Opioid Use Disorder (OUD). We further explored how these differences might inform clinical management and future research.Methods: A secondary analysis was conducted on de-identified screening data from 86 adults meeting DSM-5 criteria for moderate-to-severe OUD. Participants either presented in spontaneous withdrawal (n=28) or underwent naloxone challenge to precipitate withdrawal (n=58). Trained research personnel assessed withdrawal symptoms using a standardized rating procedure (Wang test). Principal Component Analysis (PCA) of binary symptom data was performed to identify dominant patterns of symptom co-occurrence. Separate PCAs were then conducted for the withdrawal syndrome types to delineate group-specific symptom clusters.Results: In the combined sample, four principal components together accounted for 55.7% of the variance in withdrawal symptoms, with the highest loadings observed on autonomic (e.g., temperature change, sweating) and somatic (e.g., restlessness, yawning) domains. Subgroup analyses revealed distinct symptom-loading patterns: the spontaneous withdrawal group displayed a more pronounced autonomic profile dominated by temperature dysregulation and muscle aching, whereas the precipitated withdrawal group exhibited greater variability, with notable gastrointestinal (vomiting, stomach pain) and somatic features. Across analyses, inter-individual variability was substantial, underscoring the multidimensional nature of opioid withdrawal.Conclusion: These findings suggest that spontaneous and precipitated withdrawal are not interchangeable clinical phenomena. Spontaneous withdrawal presented more gradually and precipitated withdrawal evoked more diverse and acute symptom profiles, though both were heterogeneous. Clinically, this heterogeneity highlights the need for tailored management strategies that address the range of symptom constellations in OUD. Moreover, relying solely on naloxone-challenge paradigms for treatment development may overlook key aspects of “real-world” spontaneous withdrawal, reinforcing the importance of broader experimental models and individualized care approaches. 2316 Characters with Spaces

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Keywords. Opioid Withdrawal, Naloxone Challenge, Spontaneous Withdrawal, Heterogeneity, Symptom Profiles, Interoception

P.2.74 - Mechanisms of Risky Decision-Making in ADHD and OCD: A Transdiagnostic Approach

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Growing evidence demonstrates that traditional diagnostic criteria fail to capture the neuropsychological variability both within and across disorders, including Attention Deficit Hyperactivity Disorder (ADHD) and Obsessive-Compulsive Disorder (OCD). Moreover, both ADHD and OCD are associated with risky choice and neural dysfunction during decision making and reward processing, reflecting underlying impulsive-compulsive behaviours. The present study adopts a transdiagnostic and dimensional perspective to examine risky decision making in adults with ADHD, OCD, and no clinical diagnosis using the Iowa Gambling Task (IGT). A total of 145 adults (aged 18–50 years) completed IGT task along with Probabilistic Reversal Learning Task and Stops Signal Task to assess contingency-based flexibility and inhibitory control, respectively. Resting-state functional connectivity (rsFC) was valued with functional Near-Infrared Spectroscopy (fNIRS), focusing on dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC), and posterior parietal cortex (pPC). Cluster analyses revealed no significant diagnostic group differences in IGT performance, and no robust differences emerged for flexibility. However, we identified three decision-making profiles—learners, explorers, and exploiters—that included participants from all diagnostic categories. Learners showed better inhibitory control than exploiters, while explorers and exploiters differed in rsFC patterns involving the rDLPFC, lOFC, and lpPC, regions central to reward and cognitive control. These results support a dimensional understanding of decision making across clinical conditions. Individual variability in impulsivity and reward sensitivity may be better captured through transdiagnostic, data-driven approaches. Integrating behavioral tasks with rsFC and clustering methods provides novel insights into neurocognitive subgroups and may guide more personalized clinical interventions.

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Keywords. Attention Deficit Hyperactivity Disorder, Obsessive-Compulsive Disorder, Iowa Gambling Task, Stop Signal Task, Probabilistic Reversal Learning Task, Impulsive and Risky Decision-Making Process

P.2.75 - Variability in cognitive reserve across the aging process: structural equation modeling evidence based on rural contexts and sociodemographic determinants

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Aging is a complex and universal phenomenon which may involve cognitive decline in all people. Several sociodemographic variables have been related to the aging process, however, published studies have overlooked the influence of location of residence on the aging process. Furthermore, living in rural or urban places, and its relationship with the aging process, has not been addressed and its influence in the aging process is still unknown. Accordingly, our objectives were to determine whether residential setting affects the cognitive reserve, and consequently, the rate of aging, and analyze the influence of sociodemographic, cognitive, social and emotional variables in a Structural Equation Modelling (SEM) with cognitive reserve. To do so, our sample consisted of seventy-five Spanish elderly people (65-92 years-old) of which 52% lived in rural environments, with a mean of residence in place for 71.44 years. Women comprised 52% of the sample. The SEM analyses predicted an important influence of age, gender, place of residence, impulsivity and daily activities of live on cognitive reserve. Our model showed that age, being a female and less impulsivity measure are protective factors as long as living in a rural area. On the contrary, the kind of daily activities of live are considered a risk factor for worse cognitive reserve according to our model. Our findings suggest that these factors might be useful as indicators of the healthy-aging process. However, further research is needed to better understand how air quality, rural settings, and related variables affect cognitive function in aging.

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Keywords. Rural/urban areas, cognitive reserve, elderly, impulsivity behavior, daily activities, Structural Equation Modelling

P.2.76 - Endogenous opioid modulation of safety learning in humans

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Several chronic conditions including chronic pain, anxiety and post-traumatic stress disorder are characterized by disrupted safety learning and a bias towards threat - where fear- and pain-related information cannot be effectively suppressed in favor of safety information. Preclinical research suggests endogenous opioids underpin core mechanisms facilitating safety learning and inhibition of fear learning, but evidence in humans is limited. Here, we investigate for the first time whether endogenous opioids blockade with naltrexone (50mg) affects human safety learning. The preregistered, randomized, double-blind, between-subject study was conducted over 2 sessions in 80 healthy participants. In session 1, participants underwent fear conditioning (learning to predict a painful stimulus), followed by drug/placebo administration. At drug peak, participants underwent a safety learning phase, where the pain-predictive cue was presented without pain. Participants returned after a 1-week drug washout for session 2 to assess the impact of naltrexone vs. placebo on safety memory retention. Fear-potentiated startle served as the primary outcome measure. With analyses ongoing, we remain blinded to drug conditions but will present full results at EBPS 2025. Preliminary analyses show no significant drug effect during extinction (p=.059), but a significant main effect of drug (p=.01) and a drug*time interaction (p=.005) during retention, consistent with preclinical findings. This effect appears modest, as learning was not entirely disrupted. These results suggest a modest role for endogenous opioids in safety learning, with the direction of the effect pending unblinding. The study provides translational insights into a potential neurochemical mechanism by which fear responses sustain and exacerbate symptoms of chronic conditions.

Funding. Norwegian South-Eastern Health Authorities (2022105)

Keywords. naltrexone, opioids, safety-learning, fear-potentiated startle, translational research

P.2.77 - Differential brain activity between young and older adults associated with performance on a spatial recognition task

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Aging is associated with both anatomical and functional alterations in the brain. Memory, as a cognitive function, is particularly susceptible to age-related changes. To better understand these processes, this study compared the performance of twenty-six young adults (mean age 20; 13 men, 13 women) and twenty-six older adults(mean age 66.5; 12 men, 14 women) on an allocentric spatial recognition taskwhile their event-related brain activity (ERP) was recorded using a 64-active-electrode system. In this task, participants were required to recognize the location or color of three boxes within a virtual room (Encoding Phase), with images presented from various viewpoints. After a pause (Maintenance Phase), a second image appeared (Retrieval phase), and they had to determine whether the displayed box matched one of the previously memorized criteria (Position/Color). Behavioral results indicated that younger adults made significantly fewer errors than older adults during the spatial recognition task, but only in the position criterion. At the electrophysiological level, young adults exhibited greater Late Positive Component (LPC; 300–1500 ms) modulation than older adults during the retrieval phase in centro-parietal and parietal regions. Furthermore, no significant differences in brain activity were observed between men and women. Both sexes exhibited comparable neural activity patterns during the task, suggesting that sex did not significantly influence the neural correlates of spatial recognition. These findings provide valuable insights into how spatial memory processes change with age.

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Keywords. Spatial memory, Allocentric spatial recognition, ERP, LCP

P.2.78 - From clinical trials to real-world impact: introducing a computational framework to detect endpoint bias in opioid use disorder research

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Introduction:Because clinical trial endpoints are determined by a finite sequence of instructions to perform a task (measure treatment effectiveness), they can be understood as algorithms. Consequently, they may exhibit algorithmic bias—their performance can vary across demographic groups, with potential implications for fairness, validity, and subsequent decision-making.Methods:We developed the open-source Detecting Algorithmic Bias (DAB) pipeline in Python to identify endpoint “performance variance” as the proportion of minority and majority participants changes. This pipeline assesses internal performance (on demographically matched test data) and external performance (on a validation set with different demographics). We applied it to representative endpoints from opioid use disorder (OUD) trials.Results:F1 scores remained stable across varying levels of minority representation, suggesting consistent performance despite changes in cohort demographics. Area Under the Receiver Operating Characteristic curve measures were more sensitive: training on homogeneous (largely non-Hispanic white) populations boosted internal performance but compromised external generalizability, particularly for more diverse validation sets. This pattern reveals a trade-off between optimizing performance for a homogeneous population and ensuring broader applicability.Discussion:Endpoints seemingly unbiased within a particular demographic profile may prove unreliable when the population shifts. Increasing minority representation in the training data consistently improved external generalizability, reinforcing the importance of inclusive recruitment in OUD trials.Conclusions:By systematically detecting potential bias, the DAB pipeline helps researchers pinpoint where an endpoint may underperform or misrepresent outcomes. As an open-source tool, it promotes transparent evaluation and guides the selection of OUD endpoints that are empirically robust across diverse populations.

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Keywords. algorithmic bias, performance variance, opioid use disorder, open-source software, demographic parity

P.2.79 - Effects of a multi-strain probiotic on mental and emotional health in older adults: a randomized crossover study

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The increasing proportion of older adults worldwide has brought heightened attention to age-associated cognitive decline. In this context, probiotics targeting the gut-brain axis have gained interest as potential modulators of mental and emotional health. This study investigated the efficacy of a probiotic combination containing Lactobacillus rhamnosusand Bifidobacterium lactisin supporting cognitive function and mood in healthy older adults. A randomized, double-blind, placebo-controlled crossover design was employed. Participants consumed either the probiotic formulation or a placebo daily over a 10-week period, followed by a 4-week washout phase before crossing over to the alternate condition. Cognitive outcomes were evaluated using the Mini-Mental State Examination and a comprehensive set of neuropsychological tests. Emotional status was assessed via the Beck Depression Inventory and the State-Trait Anxiety Inventory. 33 participants, enrolled between July 2020 and April 2022, completed the protocol. The probiotic intervention was associated with statistically significant improvements in global cognitive function, memory performance, and a reduction in depressive symptoms. Enhanced executive functioning was also observed, particularly in areas related to attention control, decision-making, and inhibition. These findings suggest that probiotic supplementation may offer cognitive and emotional benefits in the context of healthy aging.

Keywords. Affective symptoms, aging, gut microbiome, cognitive, probiotics

P.2.80 - Treatment of apathy in stroke patients. A systematic review

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- Introduction:Apathy is a frequent but under-recognized neuropsychiatric syndrome after stroke, often associated with poorer functional and cognitive outcomes. Unlike depression and cognitive impairment, apathy remains insufficiently studied, particularly regarding treatment strategies. This review aims to evaluate the efficacy and safety of current therapeutic options for post-stroke apathy.- Methods:The search strategy follows the PRISMA guidelines and is registered in the PROSPERO database (CRD42022332559). A comprehensive search was conducted in Pubmed, Web of Science, and Scopus for articles published in Spanish or English up to November 2024. Eligible studies included randomized and non-randomized clinical trials assessing treatments for apathy in adult stroke patients, both pharmacological and non-pharmacological. Case series were excluded. The RoB-2 tool was used for quality assessment.- Results:After screening 5,346 results, 10 studies involving 2,359 patients were included. Effective pharmacological treatments included escitalopram, donepezil, and galantamine. Among non-pharmacological interventions, motor relearning therapy (MRT), problem-solving therapy, strategy training, and repetitive transcranial magnetic stimulation (rTMS) demonstrated benefits. Results for nefiracetam and fluoxetine were inconsistent..- Discussion:This review identified several promising pharmacological and non-pharmacological treatments for stroke apathy. However, heterogeneity across study designs and outcomes emphasizes the need for further research to establish definitive treatments for post-stroke apathy.

Keywords. Apathy, depression, stroke, treatment

P.2.81 - The Emergence of ketamine use as an adjunct to physical exercise: a netnographic analysis

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Ketamine has recently garnered interest as a potential adjunct to physical exercise (PE), with anecdotal reports suggesting benefits related to motivation, endurance, and mental well-being. This study aimed to explore the emerging use of ketamine alongside PE by investigating reported effects, side effects, dosing patterns, routes of administration, and purchasing modalities. Due to the scarcity of scientific literature on this topic, a qualitative netnographic analysis was conducted on Reddit from November 2024 to February 2025. Netnography, a methodological approach to studying digital communities and online discourse, offers unique opportunities to examine under-researched behaviors, particularly in the context of drug use. A total of 461 comments were reviewed, with 26 posts meeting the inclusion criteria based on firsthand, anecdotal reports. Ketamine was most frequently used in weightlifting (21.0%), and to a lesser extent, in running, yoga, and snowboarding. Users reported enhanced endurance (23.1%), increased strength (19.2%), and reduced pain (11.5%) as primary benefits. Noted side effects (3.9%) included dehydration, bladder discomfort, cardiovascular strain, and tolerance buildup. Most users insufflated ketamine, with doses ranging from 0.025g to 0.1g. Both pharmaceutical and illicit sources were mentioned, with a preference for legal, pharmaceutical-grade ketamine when accessible.

This study highlights an emerging trend of unsupervised ketamine use to enhance physical performance and psychological resilience during exercise. While some users report subjective benefits, the potential for harm including addiction, cardiovascular risk, and unclear dosing protocols raises significant concerns. Variability in administration methods and sourcing further complicates assessments of safety and efficacy. These findings underscore the urgent need for controlled, quantitative research to better understand the risks and potential therapeutic applications of ketamine in the context of physical exercise.

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Keywords. Ketamine; Exercise; Athletes; Emerging Drug Trend

P.2.82 - Higher smartphone addiction is associated with more impulsive decision-making in young adults

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The rise in smartphone use among young adults has sparked concern about its potential impact on cognitive control and reward-based decision-making. Excessive use of smartphones—especially when it becomes compulsive or addictive—has been linked to reduced attention span, increased impulsivity, and altered self-regulation. However, empirical evidence connecting smartphone addiction to specific cognitive processes such as temporal discounting remains scarce. In this study, we examined the relationship between smartphone addiction and impulsive choice in a sample of 23 university students (mean age = 21 years; 18 women). Participants completed the Smartphone Addiction Scale – Short Version (SAS-SV) and an incentivized computerized Delay Discounting Task (DDT), which measures preferences between smaller immediate and larger delayed rewards. The discounting parameter k, calculated using a hyperbolic model and winsorized to reduce the influence of extreme values, served as an index of impulsivity. Results revealed a positive correlation between SAS-SV scores and k values, indicating that higher levels of smartphone addiction were associated with steeper temporal discounting and more impulsive decision-making. These findings contribute to a growing body of research suggesting that problematic smartphone use may interfere with adaptive reward evaluation and future-oriented behavior.

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Keywords. Smartphone addiction; problematic smartphone use; impulsivity; delay discounting; temporal decision-making

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