ITALIAN STRESS NETWORK

1st Meeting of the Italian Stress Network

STRESS, BRAIN AND BEHAVIOR: ADVANCES IN TRANSLATIONAL NEUROSCIENCE

Rome – 12,13 February 2026

Sapienza University of Rome

Dept. of Physiology and Pharmacology "V. Erspamer"

Room A Pharmacology Building CU024

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Patrizia Campolongo
Sapienza University of Rome

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Sapienza University of Rome

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SAPIENZA UNIVERSITÀ DI ROMA

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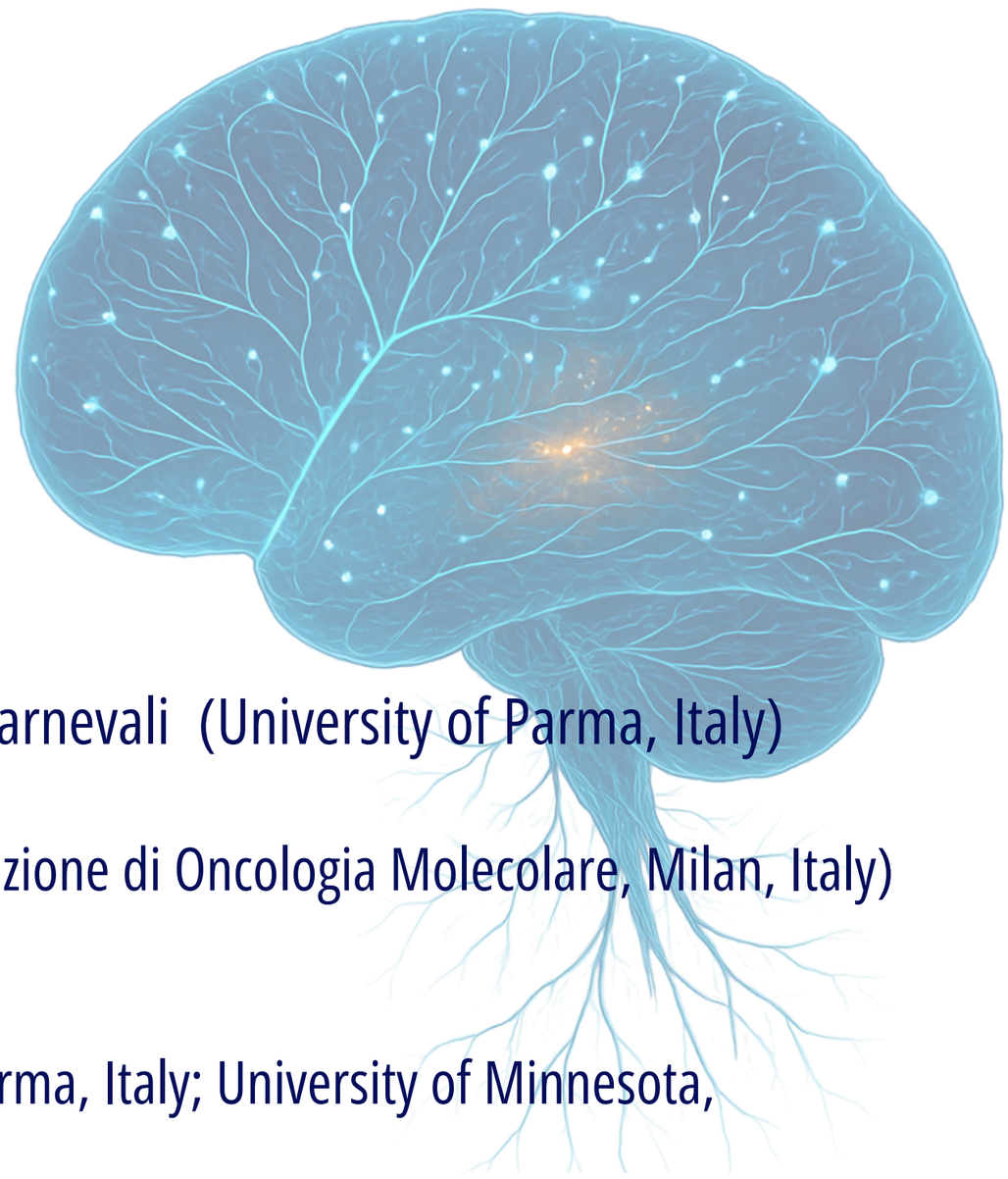
Program



February 12th, 2026

12:30 - 13:45 **Registration**

13:45 - 14:00 **Opening and Welcome Remarks**

14:00 - 15:30 **Session 1 - *Stress Drives Aging***

Chairs: Alessandro Bartolomucci and Luca Carnevali (University of Parma, Italy)

- Fabrizio d’Adda di Fagagna (Istituto Fondazione di Oncologia Molecolare, Milan, Italy)

Telomere biology in aging and disease

- Alessandro Bartolomucci (University of Parma, Italy; University of Minnesota, Minneapolis, USA)

Mechanisms of Stress-induced Acceleration of Aging

- Alessandra Berry (Istituto Superiore di Sanità, Rome, Italy)

Early Life Stress, Nutrition and Aging

- Margherita Barbetti (University of Parma, Italy)

Social stress as an early driver of cardiovascular aging: a sex-specific perspective

15:30 - 16:15 **Round Table - *From Lab to Life: How Stress Shapes Society and Health***

Moderators: Marco Andrea Riva and Patrizia Campolongo

- Filippo Caraci (University of Catania, Italy)
- Raül Andero Galí (ICREA, Universitat Autònoma de Barcelona, Spain)
- Simone Macrì (Istituto Superiore di Sanità, Rome, Italy)
- Miriam Melis (University of Cagliari, Italy)
- Caterina Scuderi (Sapienza University of Rome, Italy)

16:15 -16:45 **Coffee Break**

16:45 - 17:45 **Data Blitz Presentations**

Moderators: Marco Andrea Riva and Patrizia Campolongo

- Lidia Diolosà (University of Catania, Italy)

Sex-dependent effects of NMDA receptor antagonism on stress-induced spatial memory deficits

- Giulia Chiacchierini (Sapienza University of Rome, Italy)

Trauma-evoked increased neural activity in the basolateral amygdala drives susceptibility to PTSD

- Giuseppe Costantino (IRCCS Oasi di Troina, Italy)

Identify new mechanisms underlying PTSD vulnerability and resilience in rats: the role of TGF-β1 pathway

- Alessia Marchesin (University of Milan, Italy)

Sex-specific neuroprotective effects of ketogenic diet in a rodent model of early-life stress

- Jessica Mingardi (University of Milan, Italy)

Sex-dependent prosocial effects of psilocybin in mice exposed to early-life stress

- Valeria Buzzelli (Roma Tre University, Italy)

Early Life Social Isolation Dysregulates Social Reward Processing, BDNF Signaling, and Intracellular Vesicular Sorting in the Nucleus Accumbens of Male and Female Rats

- Vladyslav Sikora (University of Foggia, Italy)

Impact of prenatal stress on emotional and cognitive behaviors in adolescent male and female rats

- Silvia Pascarella (University of Napoli Federico II, Italy)

Effect of maternal separation on the opioid response in mouse cerebellum

- Roberta Facchinetti (Sapienza University of Rome, Italy)

Molecular signatures of astrocytes and microglia maladaptive response to acute stress are rescued by a single administration of ketamine in a rodent model of PTSD

- Giovanni Signorini (Sapienza University of Rome, Italy)

Acute Immune Stress Modulates Hippocampal Plasticity and Kynurenine Pathway Metabolism in a Sex- and Region-Dependent Manner: The Role of CX3CL1–CX3CR1 Signaling

- Edoardo Pisa (Istituto Superiore di Sanità, Rome, Italy)

An antidote for chronic stress may root in chicory roots

- Roberta Lizio (Sapienza University of Rome, Italy)

Home telemonitoring SmartMe&You program reveals that heart rate 24-hour dynamics are associated with cognitive status, sedentariness, and vigilance regulation in older people

- Lluís Miquel Rio (IIBB – CSIC, Barcelona, Spain)

Epigenetic profile of stress-related disorders: sex-specific miRNAs in the MDD dlPFC and their modulation in plasma by psychotherapy

- Aurelia Viglione (Istituto Superiore di Sanità, Rome, Italy)

A Network-Based Approach to Anticipate Time to Recovery in Major Depression Reveals a Plasticity by Context Interplay

17:45 - 18:45 **Keynote Lecture**

Introduced by Patrizia Campolongo

Carmen Sandi (Swiss Federal Institute of Technology Lausanne, EPFL, Switzerland)

Navigating a Stressful World: Insights into Individual Differences and Underlying Mechanisms

19:45 - 00:00 **Tiber Cruise and Social Dinner**

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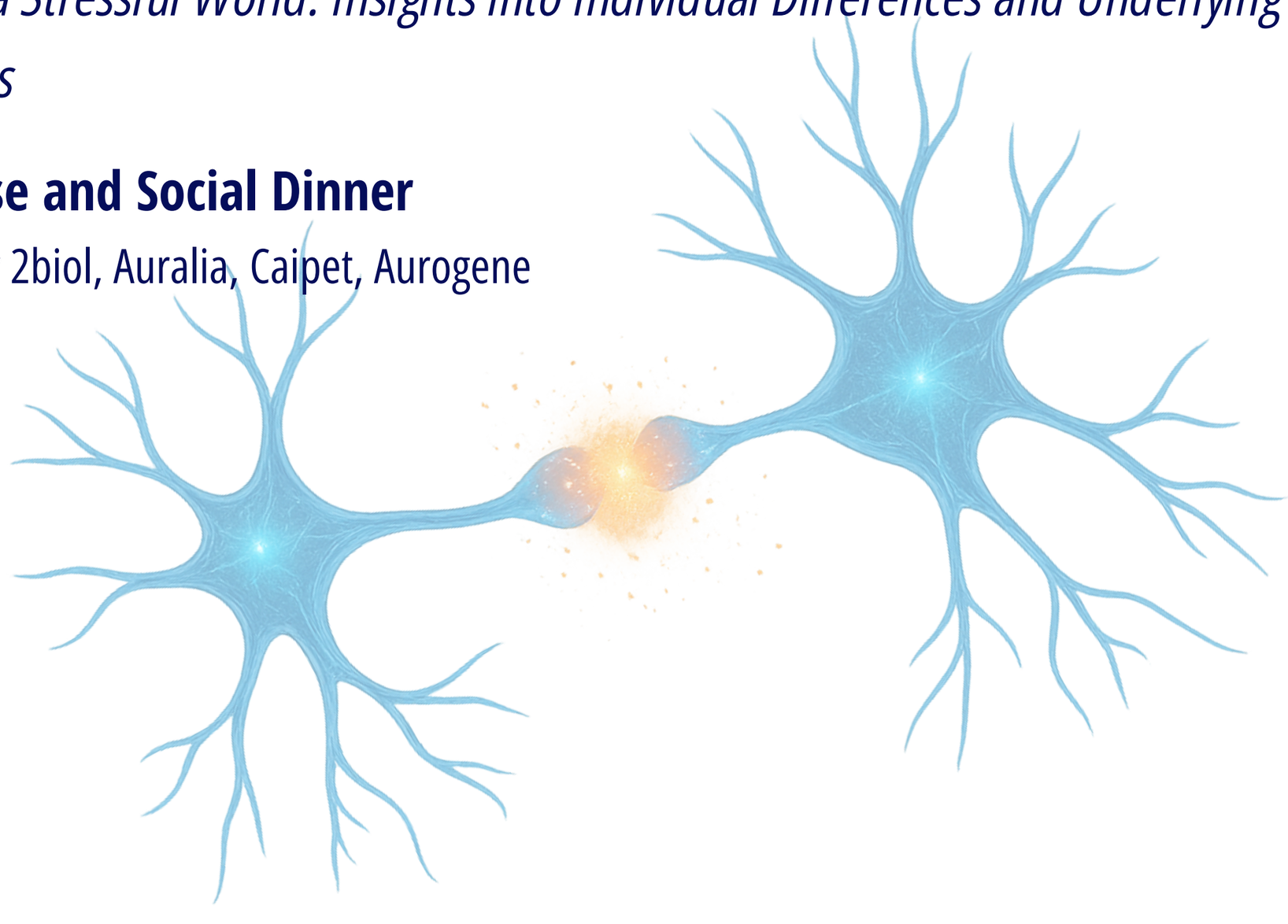

ITALIAN STRESS NETWORK

February 13th, 2026

9:00 - 10:30 **Session 2 - *Pharmacological Modulation of Stress Response***
Chair: Simona Scheggi (University of Siena, Italy)

- Marco Bortolato (University of Florida, Gainesville, USA)

Neurosteroids as Novel Therapeutic Agents for Depression: Role of the Enzyme 5-alpha Reductase 2 in Sex-dimorphic Responses to Stress

- Danilo De Gregorio (IRCCS San Raffaele Hospital, Milan, Italy)

The Additive Effect of Ketamine to the Electroconvulsive Stimulation in a Model of Chronic Social Defeat Stress

- Vittoria Borgonetti (University of Siena, Italy; The Scripps Research Institute, La Jolla, USA)

Targeting IL-18 Signaling in the Central Amygdala in a Rat Model of Comorbid PTSD and Alcohol Use Disorder

- Federico Brandalise (University of Cagliari, Italy)

Stress on the Powerhouse: Sex-specific Subcellular Mechanisms Compromise VTA Circuits Upon Prenatal Cannabis Exposure

10:30 - 11:00 **Coffee Break**

11:00 - 12:30 **Session 3 - *Trauma, Resilience and Psychiatric Vulnerability***
Chair: Gian Marco Leggio (University of Catania, Italy)

- Laura Musazzi (University of Milano Bicocca, Italy)

Hippocampal Multiomic Signature of Stress Vulnerability and Ketamine Antidepressant Response in the Rat Chronic Mild Stress Model

- Gian Marco Leggio (University of Catania, Italy)

Unmasking the neurobiology of PTSD: How the AIS model predicts resilience and susceptibility across sexes

- Giulia Federica Mancini (Sapienza University of Rome, Italy)

From Trauma to PTSD: Dissecting Vulnerability and Resilience in a Rat Model

- Anna Monai (Italian Institute of Technology, Genova, Italy)

Negative Events Influence Behavior through Prefrontal Cortex CRF Mechanisms

12:30 - 13:30 **Lunch**

13:30 - 15:00 **Poster Session**

15:00 - 16:30 **Session 4 - *Psychopathological Implications of Stress During Development***

Chair: Francesca Cirulli (Istituto Superiore di Sanità, Rome, Italy)

- Juliet Richetto (University of Zurich-Vetsuisse, Zurich, Switzerland)

Preconception Social Stress: From Placental Adaptations to Lifelong Behavioral Outcomes

- Annamaria Cattaneo (University of Milan, Italy)

From Mother to Child: Biological Mechanisms Linking Depression in Pregnancy to Offspring Outcomes

- Chiara Musillo (Istituto Superiore di Sanità, Rome, Italy)

Stress and Nutrition During Pregnancy Share Common Mechanisms and Have Sex-specific Effects on Brain Development

- Livio Provenzi (University of Pavia, Italy)

Exploring Mechanisms of Brain-to-brain Attunement Across Socio-emotional Stress Regulation: EEG Hyperscanning in the Parent-infant Dyad

16:30 - 17:00 **Awards and Closing Cerimony**

Moderators: Marco Andrea Riva and Patrizia Campolongo

The two best poster presentations will receive prizes funded by Caipet and Associazione Valentina De Castro

The best U38 speaker will receive a prize funded by Caipet

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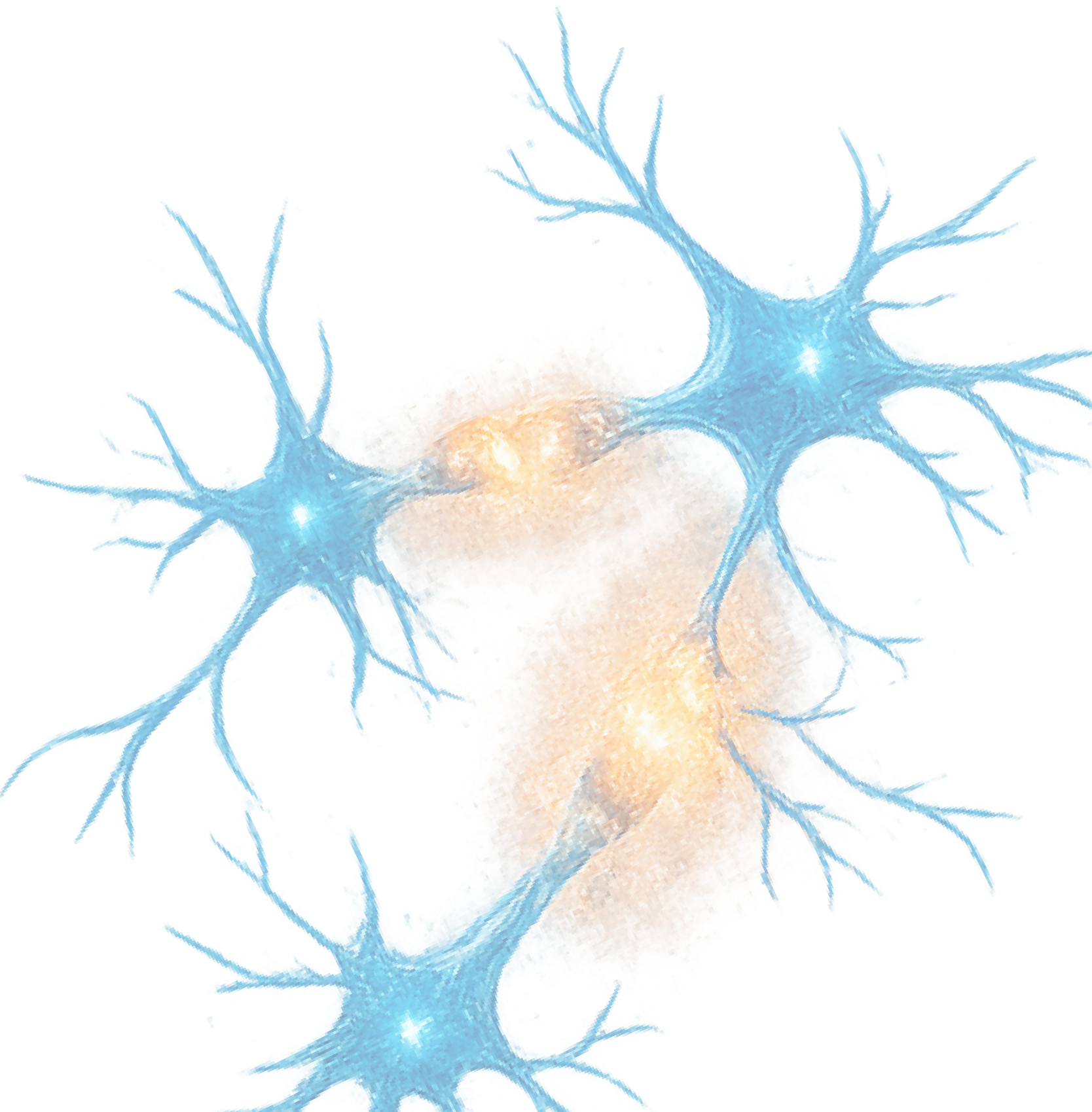
Symposia Abstracts



Session 1 – *Stress Drives Aging*

Chairs: Alessandro Bartolomucci[1,2] and Luca Carnevali[2].

[1] Department of Integrative Biology and Physiology, University of Minnesota, Minneapolis, MN;

[2] University of Parma, Parma, Italy.

Telomere biology in aging and disease

Fabrizio d'Adda di Fagagna[1,2].

[1] IFOM ETS, Milan, Italy;

[2] IGM-CNR, Pavia, Italy.

Telomere shortening was the first demonstrated cause of cell aging, also known as cellular senescence. The causative engagement of telomeres was later extended to long but damaged telomeres. It is now well established that short and/or damaged telomeres are associated, often causatively, with several age-related diseases and aging itself. We recently develop novel innovative RNA therapy-based tools able to reduce the consequences of telomere dysfunction (that is: DNA damage response (DDR) activation at telomeres). This allowed us to determine the contribution of telomere dysfunction in a number of animal models of human diseases. We will demonstrate how selective DDR inhibition at telomeres represent an effective therapy in animal models of telomere-biology diseases, including evidence of lifespan extension in wild-type animals. In addition, we will discuss how telomere clocks talk, or not, to other clocks measuring aging, including those based on DNA methylation changes.

Mechanisms of Stress-induced Acceleration of Aging

Alessandro Bartolomucci[1,2].

[1] Department of Integrative Biology and Physiology, University of Minnesota, Minneapolis, MN;

[2] Department of Medicine and Surgery, University of Parma, Parma, Italy.

A strong overlap exists between stress-associated and aging-associated diseases in both humans, and animal models, suggesting a shared biology. Consistently, exposure to stressors can accelerate the biological age of an individual. Yet, the mechanism of this phenomenon remains poorly understood. In this presentation I will: 1) discuss the validity of animal models for stress-induced aging phenotypes; 2) provide correlational and experimental evidences on the contribution of life stress – particularly stress derived from adverse social environments – to trigger hallmarks of aging; 3) discuss mechanistic evidences linking stress exposure to aging via cellular senescence, sterile inflammation, DNA damage, and epigenetic changes. I will also highlight major gaps of knowledge, and future perspectives for translational geroscience.

Early Life Stress, Nutrition and Aging

Alessandra Berry[1], Giona Letizia[1,2], Collacchi Barbara[1], Musillo Chiara[1], Samà Marianna[1] and Cirulli Francesca[1].

[1] Center for Behavioral Sciences and Mental Health, Istituto Superiore di Sanità, Rome Italy;

[2] PhD program in Science of Nutrition, Metabolism, Ageing and Gender-Related Diseases, Faculty of Medicine and Surgery, Catholic University of the Sacred Heart, Rome, Italy.

Background. The exposure to a high-fat diet during pregnancy (mHFD), by increasing glucocorticoid hormones, inflammation, and oxidative stress (OS) in the womb, may represent a powerful stress for the foetus [1]. Thus, deranging developmental trajectories, mHFD might increase the vulnerability to later-life non-communicable diseases, setting the stage for unhealthy aging [2]. P66Shc is a mitochondrial protein that amplifies insulin signalling and promotes fat storage by increasing OS [3]. We have previously shown that the lack of this gene in mice protects the offspring from the negative sequelae of mHFD at adulthood, including abnormal stress reactivity [4]. Here, we provide evidence for such effects to extend to senescence, promoting healthspan.

Methods. Wild-type (WT) and p66Shc-/- (KO) C57Bl/6 females were fed HFD starting before breeding and until delivery.

Results. The offspring, that was characterized at 18-months of age (aging) showed preserved cognitive abilities, reduced emotionality and better glucose homeostasis. The effects were sex-dependent and associated with increased brain plasticity.

Conclusions. Our results point to redox balance as a key environmental condition affecting brain and metabolic health from early life stages until senescence. They also suggest that lifestyle or nutraceutical intervention buffering OS should be exploited as reliable and cost-effective strategies to prevent or counteract the negative sequelae of metabolic stress [5,6].

References:

[1] Musillo et al. 2022, doi: 10.1016/j.neubiorev.2022.104624.

[2] Iozzo et al. 2014, doi: 10.1159/000362656.

[3] Berry et al. 2013, doi: 10.1016/j.neubiorev.2013.03.005.

[4] Bellisario et al., 2014, doi: 10.3389/fnbeh.2014.00285.

[5] Giona et al., 2024, 10.1016/j.clnu.2024.08.012.

[6] Musillo et al., 2025, 10.1038/s41398-025-03530-0.

Social stress as an early driver of cardiovascular aging: a sex-specific perspective

Barbetti Margherita[1], Ielpo Donald[2], Andolina Diego[2], Lo Iacono Luisa[2], Sgoifo Andrea [1], Savi Monia[1], Carnevali Luca[1].

[1] Department of Chemistry, Life Sciences and Environmental Sustainability, University of Parma;

[2] Department of Psychology, Sapienza University.

Background. Chronic psychosocial stress has been associated with an earlier onset of common aging-related diseases, such as those impacting the cardiovascular system [1]. Sex disparities in this association have been reported [2], yet the extent to which social stress impacts cardiovascular function in a sex specific manner remains unclear. The objectives of this study were to investigate sex differences in the electromechanical remodeling of the heart of socially stressed rats, and to explore potential epigenetic mechanisms (cardiac microRNAs) that may accelerate aging-related cardiovascular processes.

Methods. Adult rats of both sexes vicariously experienced the social defeat bout between two males for nine consecutive days ("witness stress" (WS)) or were exposed to a control condition. After repeated WS exposure, arrhythmic vulnerability was evaluated via beta-adrenergic stimulation with isoproterenol, while cardiac contractile properties were assessed via hemodynamic analyses. Hearts were collected to measure expression levels of several microRNAs (including miR-22 and miR-34a) and their molecular targets (e.g., SIRT1) involved in the regulation of cardiac electromechanical function.

Results. An increased vulnerability to isoproterenol-induced arrhythmias was found in male, but not female, WS rats. Signs of contractile dysfunction were found in both sexes after WS, but to a greater extent in males. In addition, only male WS rats exhibited a significantly higher cardiac expression of miR-34a and miR-22, which were associated with a reduced expression of their common molecular target (SIRT-1), a potential mediator of age-related cardiovascular diseases [3].

Conclusions. These findings suggest a sex-dependent epigenetic mechanism that may predispose the male adult heart to aging-related processes under psychosocial stress conditions.

References:

[1] Polsky LR, Rentscher KE, Carroll JE. Stress-induced biological aging: A review and guide for research priorities. Brain Behav Immun. 2022. doi: 10.1016/j.bbi.2022.05.016.

[2] Helman TJ, Headrick JP, Stapelberg NJ, Braidy N. The sex-dependent response to psychosocial stress and ischaemic heart disease. Front Cardiovasc Med. 2023. doi: 10.3389/fcvm.2023.1072042.

[3] Ministrini S, Puspitasari YM, Beer G, Liberale L, Montecucco F, Camici GG. Sirtuin 1 in Endothelial Dysfunction and Cardiovascular Aging. Front Physiol. 2021. doi: 10.3389/fphys.2021.733696.

Session 2 – *Pharmacological Modulation of Stress Response*

Chair: Simona Scheggi[1].

[1]Department of Molecular and Developmental Medicine, Univesrity of Siena, Italy.

This symposium brings together leading researchers to explore innovative pharmacological strategies for the treatment of stress-related disorders, with a focus on neurobiological mechanisms and sex-specific factors. Marco Bortolato (University of Florida, USA) will discuss the role of neurosteroids and the enzyme 5-α reductase 2 in mediating sex-dimorphic responses to stress and depression. Danilo De Gregorio (IRCCS San Raffaele Hospital, Milan, Italy) will present findings on the synergistic antidepressant effects of combining ketamine with electroconvulsive stimulation in a chronic social defeat stress model. Vittoria Borgonetti (University of Siena, Italy; The Scripps Research Institute, La Jolla, USA) will address the therapeutic potential of targeting IL-18 signaling within the central amygdala in a rat model of comorbid PTSD and alcohol use disorder. Finally, Federico Brandalise (University of Cagliari, Italy) will examine how prenatal cannabis exposure disrupts ventral tegmental area circuits through sex-specific mechanisms. Together, these presentations highlight cutting-edge approaches that bridge molecular, cellular, and behavioral insights to advance treatment for stress-related psychopathologies.

Neurosteroids as Novel Therapeutic Agents for Depression: Role of the Enzyme 5-αlpha Reductase 2 in Sex-dimorphic Responses to Stress

Bortolato, Marco[1]; Cadeddu, Roberto[2]; Braccagni, Giulia[1]; Branca, Caterina[1]; Corridori, Eleonora[3]; Salviati, Sara[3]; Scheggi, Simona[3].

[1] Department of Cellular and Systems Pharmacology, University of Florida, Gainesville FL, USA;

[2] Department of Pharmacology and Toxicology, University of Utah, Salt Lake City, UT, USA;

[3] Department of Molecular and Developmental Medicine, University of Siena, Siena, Italy.

Background. Allopregnanolone is a neurosteroid with rapid antidepressant and anxiolytic properties, the levels of which increase in response to acute stress. The rate-limiting step in allopregnanolone production is the 5alpha reduction of progesterone, mediated by the isoenzymes 5alpha reductase type 1 and type 2; however, the specific role of each type in stress regulation has not been clearly established.

Methods. Male and female rats were exposed to acute stress and evaluated for behavioral, neuroendocrine and neurosteroid responses after selective knockdown of 5alpha reductase type 2 in the medial prefrontal cortex. Complementary experiments were performed in constitutive 5alpha reductase type 2 knockout rats. Behavioral alterations were tested for reversal by systemic allopregnanolone. Single nucleus RNA sequencing was used to identify cell-type-specific molecular pathways associated with enzyme loss.

Results. Acute stress increased 5alpha reductase type 2 expression in the medial prefrontal cortex of males but not females. Reduction or deletion of this enzyme prevented stress induced allopregnanolone synthesis

and impaired adaptive behavioral responses in males, including coping, exploratory behavior and social interaction, while females were unaffected. Allopregnanolone administration restored normal behavioral function in males. Transcriptomic analyses revealed that 5alpha reductase type 2 is necessary for stress induced activation of protein translation and synaptic remodeling pathways.

Conclusions. These results indicate that 5alpha reductase type 2 supports male specific neurosteroid mediated stress resilience. These findings suggest a mechanistic basis for sex differences in depression vulnerability and highlight neurosteroidogenic pathways as therapeutic targets.

The Additive Effect of Ketamine to the Electroconvulsive Stimulation in a Model of Chronic Social Defeat Stress

Fabio Ruto[1], Ivana Esquivel[1], Danilo De Gregorio[1,2].

[1] Vita Salute San Raffaele University, Milan (MI), Italy;

[2] IRCCS San Raffaele Scientific Institute, Milan (MI), Italy.

Background. Major depressive disorder (MDD) is a debilitating disorder involving dysfunction of key neurocircuits, including the dorsal raphe nucleus (DRN). In humans, electroconvulsive therapy (ECT) is a highly effective intervention for treatment-resistant depression, although cognitive side effects remain a concern. In rodents, the equivalent procedure is electroconvulsive stimulation (ECS). Ketamine, an anaesthetic used during ECT procedures, exerts rapid antidepressant effects at sub-anaesthetic doses and has been proposed as a potential adjunct to enhance therapeutic outcomes [1,2]. However, evidence supporting the combined effects of ketamine and ECS, as well as mechanistic insight into stress-related serotonergic dysfunction, remains limited [2,3].

Methods. Eight-week-old male C57BL/6 mice were exposed to a 10-day chronic social defeat stress (CSD) protocol to induce affective-like behavioural alterations. Control mice remained undisturbed. After CSD, mice received a single intraperitoneal injection of ketamine (10 mg/kg) or saline, followed by ECS (15 mA, 100 Hz, 1 s) or sham, three times per week for three weeks. Behavioural outcomes were assessed 24 h after the last ECS session using the open field test (OFT) and forced swim test (FST). Cognitive performance was evaluated using the novel object recognition (NOR) test. To investigate serotonergic mechanisms, in vivo electrophysiological recordings were performed in the dorsal raphe nucleus (DRN) to quantify firing rate activity of putative serotonergic neurons following chronic stress and ECS.

Results. ECS reversed anxiety- and depressive-like phenotypes induced by CSD, as detected in the OFT ($p<0.05$) and FST ($p<0.01$). Notably, ketamine potentiated the behavioural effects of ECS in both paradigms (OFT: $p<0.05$; FST: $p<0.01$). In contrast, no significant differences across treatment groups were detected in NOR performance ($p=0.47$, n.s.). Electrophysiological analyses revealed that CSD significantly reduced the firing rate of serotonergic DRN neurons ($p<0.01$), whereas ECS restored serotonergic neuronal activity to control-like levels ($p<0.05$).

Conclusions. These findings indicate that ECS robustly counteracted stress-induced anxiety- and depressive-like behaviours, and that ketamine enhanced ECS efficacy without altering recognition memory performance. Moreover, restoration of serotonergic DRN firing suggests that ECS reverses chronic stress-induced impairments in serotonergic transmission, supporting a circuit-based mechanism potentially relevant to ECT antidepressant efficacy [2,3].

References:

[1] Berman RM et al. Antidepressant effects of ketamine in depressed patients. Biol Psychiatry. 2000.

[2] UK ECT Review Group. Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis. Lancet. 2003.

[3] Duman RS et al. Ketamine and rapid-acting antidepressants: synaptic plasticity and circuits. Nat Rev Neurosci. 2016.

Targeting IL-18 Signaling in the Central Amygdala in a Rat Model of Comorbid PTSD and Alcohol Use Disorder

Borgonetti Vittoria[1,4], Cruz Bryan[1], Vozella Valentina[1], Steinman Michael Q.[1], Oleata Christopher S.[1], Vlkolinsky Roman[1], Bajo Michal[1], Zorrilla Eric P.[1], Kirson Dean[1,3], Roberto Marisa[1].

[1] Department of Molecular Medicine, The Scripps Research Institute, La Jolla, CA 92073, USA;
[2] Department of Pharmaceutical Sciences, University of Vienna, Josef-Holaubek-Platz 2, 1090 Vienna, Austria;
[3] Department of Pharmacology, Addiction Science, and Toxicology, The University of Tennessee Health Science Center, Memphis, TN 38163, USA;
[4] Department of Molecular and Developmental Medicine, University of Siena, Siena, Italy.

Background. Alcohol use disorder (AUD) and stress disorders are frequently comorbid and share dysregulated neuroimmune pathways [1]. Interleukin 18 (IL-18) is a key mediator of central immune signaling [2], but its role in the central amygdala (CeA) in comorbid PTSD/AUD models remains unclear.

Methods. Male and female rats were exposed to novel (NOV) or familiar (FAM) shock stress, or remained unstressed controls (CTL), followed by voluntary alcohol drinking and assessments of PTSD-related behaviors. All animals received renewed access to alcohol prior to experiments. Expression of Il18, Il18bp, and Il18r1 in the CeA was assessed using in situ hybridization. IL-18 modulation of synaptic transmission was evaluated via ex vivo electrophysiology of GABAA-mediated mIPSCs.

Results. FAM male rats showed higher ethanol intake and preference than CTL males, whereas female rats exhibited similar intake across groups, with FAM females showing increased alcohol preference compared to CTL females. Il18 mRNA-positive CeA cells increased, while Il18bp decreased. Il18r1 expression was unchanged across groups. In CTL animals, IL-18 reduced mIPSC frequency, indicating decreased presynaptic GABA release. This presynaptic effect persisted in NOV and FAM females. Additionally, IL-18 reduced mIPSC amplitude in CTL females, suggesting postsynaptic effects.

Conclusions. Stress in alcohol-exposed rats alters CeA IL-18 system expression and the ability of IL-18 to modulate GABAergic transmission, in a sex-dependent manner. These findings highlight a critical interaction

between neuroimmune signaling, stress, and sex in regulating amygdala synaptic function.

References:

[1] Koob G.F. Front. Psychiatry. 2013;4:72. doi: 10.3389/fpsyt.2013.00072.

[2] Gracie J.A J. Clin. Investig. 1999;104:1393–1401. doi: 10.1172/JCI7317.

Stress on the Powerhouse: Sex-specific Subcellular Mechanisms Compromise VTA Circuits Upon Prenatal Cannabis Exposure

Brandalise, Federico [1]; Leone, Roberta [1]; Pagano Zottola, Antonio [2]; Bellocchio, Luigi [2]; Marsicano, Giovanni [2]; Melis, Miriam [1].

[1] Department of Biomedical Sciences, University of Cagliari, Cittadella Universitaria di Monserrato, Monserrato, 09042 Cagliari, Italy;

[2] Endocannabinoids and Neuroadaptation U1215 NeuroCentre Magendie, INSERM, Bordeaux, France; University of Bordeaux, Bordeaux, France.

Background. Prenatal cannabis exposure (PCE) confers a sex-dependent hyperdopaminergic phenotype, a key substrate of vulnerability to acute stress [1,2]. The endocannabinoid system (ECS) regulates stress coping by activating type-1 cannabinoid receptors (CB1) and shaping cellular bioenergetics [3]. Here, we probed the potential role of mitochondrial CB1 (mtCB1) receptors in PCE-induced sex-dichotomic dopaminergic reactivity.

Methods. In a rat PCE model, we combined ex vivo electrophysiology with ion imaging, pharmacology and chemogenetics to bidirectionally tune mitochondrial activity. Sex was an a priori factor.

Results. PCE male, but not female, dopamine neurons showed altered cytosolic Ca^{2+} dynamics. Chemogenetic stimulation of mitochondrial activity [4] partially restored Ca^{2+} homeostasis and counteracted dopamine cell hyperexcitability. These effects align with a model in which mtCB1-coupled bioenergetics shapes stress-sensitive dopamine output.

Conclusions. Our data point to a sex-specific mitochondrial bottleneck in PCE that biases VTA networks toward aberrant stress-reactivity. Restoring bioenergetics might be a strategy to buffer stress susceptibility and to normalize dopamine-dependent behaviors after PCE.

References:

[1] Serra, Valeria, et al. "Sex-specific maladaptive responses to acute stress upon in utero THC exposure are mediated by dopamine." Pharmacological research 210 (2024): 107536.

[2] Frau, Roberto, et al. "Prenatal THC exposure produces a hyperdopaminergic phenotype rescued by pregnenolone." Nature neuroscience 22.12 (2019): 1975-1985.

[3] Martínez-Torres, Ari Misael, et al. "Implications of the mitochondrial CB1 receptor in the brain: from mitochondrial dysfunction to neuroprotection." Reviews in the Neurosciences 0 (2025).

[4] Pagano Zottola, Antonio C., et al. "Potentiation of mitochondrial function by mitoDREADD-Gs reverses pharmacological and neurodegenerative cognitive impairment in mice." Nature Neuroscience 28.9 (2025): 1844-1857.

Session 3 – *Trauma, Resilience and Psychiatric Vulnerability*

Chair: Gian Marco Leggio[1].

[1]Dept of Biomedical and Biotechnological Sciences, University of Catania, Italy.

Hippocampal Multiomic Signature of Stress Vulnerability and Ketamine Antidepressant Response in the Rat Chronic Mild Stress Model

Musazzi, Laura[1,2]; Mingardi, Jessica[1,3]; Magri, Chiara[4]; Misztak, Paulina[1]; Chinello, Clizia[1]; Pagani, Lisa[1]; Piga, Isabella[1]; Giovenzana, Mattia[1,5]; Nicosia, Noemi[1,5]; Magni, Fulvio[1]; Barbon, Alessandro[4]; Martini, Paolo[4].

[1] School of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy;

[2] Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy;

[3] Department of Medical Biotechnology and Translational Medicine, University of Milan, Milan, Italy;

[4] Department of Molecular and Translational Medicine, University of Brescia, Brescia, Italy;

[5] PhD Program in Neuroscience, School of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy.

Background. Depression is a multifactorial disorder in which environmental stress plays a key etiopathogenetic role [1]. In this study, we used the Chronic Mild Stress (CMS) rat model of depression to identify hippocampal molecular signatures of stress resilience/susceptibility and response/non-response to the rapid-acting antidepressant ketamine by applying an integrative multiomic approach.

Methods. CMS was applied for 5 weeks on male rats, the sucrose preference test was used to assess the anhedonic phenotype, and acute ketamine (10 mg/kg) was intraperitoneally injected to stress susceptible animals 24 h before sacrifice [2]. Left/right hippocampi (HPC) were randomly assigned to DNA/RNA extraction or protein purification. Transcriptional changes were evaluated by RNA-seq followed by bioinformatic enrichment analysis using WebGestaltR v.4.0.3 and the Gene Set Enrichment Analysis (GSEA) method. The DNA methylation profile was assessed by Enzymatic Methyl-seq. LC-MS/MS was applied on total and synaptic HPC protein fractions, followed by differential protein expression analysis (DeqMS v. 1.12.1) and enrichment with WebGestaltR v.4.0.3 and GSEA.

Results. We found that acute ketamine induced antidepressant-like behavior in approximately 60% of stress-susceptible animals, while the others remained anhedonic and were considered non-responders. RNA-seq revealed hundreds of genes differently regulated among the groups. Proteomic analysis highlighted minor changes in the total extract but multiple differentially expressed proteins at synaptic level. Enrichment analysis showed differences among groups in the enrichment of genes and proteins sets involved in neuronal development, synaptic signaling/organization, and neuronal metabolism.

Conclusions. Our multiomic approach showed that the rapid antidepressant effect of ketamine involves pathways associated to neuroplasticity and synaptic function.

References:

[1] Sanacora, G., 2022. The stressed synapse 2.0: pathophysiological mechanisms in stress-related neuropsychiatric disorders. Nat Rev Neurosci, 23:86–103, DOI: 10.1038/s41583-021-00540-x.

[2] Derosa, S., Misztak, P., 2024. Changes in neurotrophic signaling pathways in brain areas of the chronic mild stress rat model of depression as a signature of ketamine fast antidepressant response/non-response. Prog Neuropsychopharmacol Biol Psychiatry, 128, 110871, DOI: 10.1016/j.pnpbp.2023.110871.

Unmasking the neurobiology of PTSD: How the AIS model predicts resilience and susceptibility across sexes

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Post-traumatic stress disorder (PTSD) remains poorly understood, and translational animal models are crucial to unravel its neurobiology. We developed an arousal-based individual screening (AIS) model, coupling a 24-hour restraint trauma in C57BL/6J mice with post-trauma changes in startle reactivity to distinguish susceptible and resilient individuals. The AIS model reproduces key PTSD features, including persistent hyperarousal, exaggerated fear, avoidance, and cognitive and social impairments, as well as HPA axis dysfunction and altered hippocampal plasticity. Extending this model to both sexes revealed higher trauma susceptibility in females and sex-dependent hippocampal alterations at electrophysiological, structural, and molecular levels. Overall, the AIS model captures core and sex-specific PTSD phenotypes, offering a translational platform to investigate pathophysiological mechanisms and guide sex-tailored therapeutic strategies.

From Trauma to PTSD: Dissecting Vulnerability and Resilience in a Rat Model

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Background. After a traumatic event, dysfunctional stress coping can lead to psychiatric disorders such as post-traumatic stress disorder (PTSD). However, only a subset of trauma-exposed individual develops PTSD, and the factors driving vulnerability or resilience remain largely unknown.

Methods. We have previously developed a rat model that allows early post-trauma behavioral differentiation between susceptible (SUS) and resilient (RES) PTSD-like phenotypes in both sexes [1,2], and through selective breeding, we have established two distinct SUS and RES PTSD-like rat lines. Here, we assessed the behavioral profiles of these SUS and RES rats, and performed bulk RNA sequencing in PTSD-related brain

regions under basal condition to identify markers of susceptibility and resilience.

Results. Our results showed a clear phenotypic distinction, with SUS rats exhibiting fear memory deficits (i.e., enhanced traumatic memory consolidation, recall, and impaired extinction) and socio-emotional alterations compared to RES rats. Transcriptomic profiling revealed marked baseline differences between the two phenotypes, with a greater number of differentially expressed genes in females. Gene ontology enrichment analysis highlighted sex- and brain region- specific alterations in pathways related to stress and memory.

Conclusions. These findings provide novel insights into the molecular basis of PTSD vulnerability/resilience and support the use of these SUS/RES rat lines as a translational model for identifying preventive or therapeutic targets for trauma-related disorders.

References:

[1] Colucci et al., 2020. Transl Psychiatry. 10(1):243.

[2] Chiacchierini et al., 2025. J Neurosci Methods. 416:110380.

Negative events influence behaviour through prefrontal cortex CRF mechanisms

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Background. Emotion recognition is essential for social interaction but can be differentially shaped by prior negative emotional experiences ("negative self-experience") [1,2,3]. Such experiences may impair emotion recognition through self-oriented distress[3] or enhance it by increasing its accuracy [4]. Rodents, like humans, recognize emotional states in conspecifics and display complex behaviors including contagion, helping, and prosocial or selfish choices [5,6,7,8]. Coping with stress is a critical factor, and the corticotropin-releasing factor (CRF) system is a central regulator [9,10]. However, it remains unclear whether self-experience modulates these processes, and how CRF neurons within the medial prefrontal cortex (mPFC) contribute to emotion recognition [9,10,11,12].

Methods. Emotion Recognition Task; Viral Injections; Optogenetics; In vivo fiber photometry recordings and recordings calcium imaging; Cfos; Immunohistochemistry.

Results. Stress self-experience lead to inter-individual and sex hormone–dependent differences in approach behavior toward conspecifics, but only when observers encountered demonstrators in the same negative state. Silencing corticotropin-releasing factor (CRF) mRNA in the medial prefrontal cortex (mPFC) revealed

that CRF signaling mediates the modulatory role of stress self-experience in emotion recognition. In vivo micro-endoscopic calcium imaging showed that mPFC CRF neurons display distinct activation patterns toward stressed or neutral demonstrators depending on prior experience. Furthermore, optogenetic manipulations demonstrated that reduced CRF neuron activity promotes social preference, whereas increased activity drives avoidance, selectively in stress-experienced mice.

Conclusions. Our results demonstrate that sharing the same stressful experience influences social approach to others in stress and that the CRF in the mPFC modulates these social responses.

References:

[1] Adolphs, R. Neural systems for recognizing emotion. Curr. Opin. Neurobiol. 12, 169–177 (2002).

[2] Preston, S. D. & de Waal, F. B. Empathy: its ultimate and proximate bases. Behav. Brain Sci. 25, 20–71 (2002).

[3] Israelashvili, J., Sauter, D. A. & Fischer, A. H. Different faces of empathy: feelings of similarity disrupt recognition of negative emotions. J. Exp. Soc. Psychol. 87, 103912 (2020).

[4] Zaki, J. Empathy: a motivated account. Psychol. Bull. 140, 1608–1647 (2014).

[5] Ferretti, V. & Papaleo, F. Understanding others: emotion recognition in humans and other animals. Genes Brain Behav. 18, e12544 (2019).

[6] Ben-Ami Bartal, I., Decety, J. & Mason, P. Empathy and pro-social behavior in rats. Science 334, 1427–1430 (2011).

[7] Burkett, J. P. et al. Oxytocin-dependent consolation behavior in rodents. Science 351, 375–378 (2016).

[8] Jeon, D. et al. Observational fear learning involves affective pain system and Cav1.2 Ca2+ channels in ACC. Nat. Neurosci. 13, 482–488 (2010).

[9] Deussing, J. M. & Chen, A. The corticotropin-releasing factor family: physiology of the stress response. Physiol. Rev. 98, 2225–2286 (2018).

[10] Sterley, T. L. et al. Social transmission and buffering of synaptic changes after stress. Nat. Neurosci. 21, 393–403 (2018).

[11] Chen, P. et al. Prefrontal cortex corticotropin-releasing factor neurons control behavioral style selection under challenging situations. Neuron 106, 301–315 (2020).

[12] Yuen, E. Y. et al. Acute stress enhances glutamatergic transmission in prefrontal cortex and facilitates working memory. Proc. Natl Acad. Sci. USA 106, 14075–14079 (2009).

Session 4 – *Psychopathological Implications of Stress During Development*

Chair: Francesca Cirulli[1].

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Preconception Social Stress: From Placental Adaptations to Lifelong Behavioral Outcomes

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Background. Maternal depression and psychosocial stress before and during pregnancy are increasingly recognized as risk factors for adverse neurodevelopmental trajectories in offspring. These conditions can precipitate enduring alterations in maternal physiology and behavior, thereby modifying the intrauterine environment even prior to conception. The placenta, serving as the principal interface between mother and fetus, is particularly sensitive to such maternal influences and may mediate their effects on fetal growth and brain development. Nevertheless, the molecular and cellular mechanisms through which preconception stress modifies placental function remain insufficiently understood.

Methods. To model preconception stress, female mice were exposed to social isolation rearing (SIR) prior to mating, inducing a depressive-like phenotype that persisted throughout gestation. Placentas and fetal brains were collected at gestational day 17 and subjected to RNA sequencing, whole-genome bisulfite sequencing and cytokine profiling. Bioinformatic pathway and upstream regulator analyses were performed to identify core signaling networks affected by SIR.

Results. SIR produced extensive transcriptional and epigenetic remodeling in the placenta, with more than 1,000 genes differentially expressed. Enriched pathways included those governing immune regulation, trophoblast differentiation, nutrient transport, and metabolic homeostasis. Selected cytokines were modestly elevated in both placenta and fetal brain, suggesting coordinated maternal–fetal signaling adaptations.

Conclusions. Preconception social stress induces sustained modifications in placental gene regulation and functional pathways, potentially altering fetal developmental trajectories and behavioral outcomes. These findings underscore the placenta's central role as a mediator of maternal experience and as a biological substrate for intergenerational transmission of risk.

From Mother to Child: Biological Mechanisms Linking Depression in Pregnancy to Offspring Outcomes

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Perinatal mental health disorders, particularly depression and anxiety, represent a significant public health concern, affecting about 15% of women in the perinatal period. These disorders have profound implications not only for maternal well-being but also for offspring development, increasing their risk of adverse neurodevelopmental, behavioral, and psychiatric outcomes. I will discuss how exposure to adverse and stressful events during pregnancy can affect maternal biology and behavior, as well as offspring behavioural outcomes, showing data from clinical cohorts and preclinical models. In the PRESeNT cohort, pregnant women with depressive symptoms, or at high risk of developing them, showed higher levels of state, trait, and pregnancy-related anxiety, perceived stress, and exposure to recent stressful life events compared with controls. In addition, both depressed and at-risk women exhibited a marked upregulation of immune system activity, though more pronounced in depressed women, along with increased levels of cortisol and estradiol. To better dissect the biology underlying the consequences of exposure to an adverse prenatal environment, we used an animal model in which pregnant dams were exposed to a Prenatal Stress Paradigm (PNS) and exhibited significant dysregulation of the HPA axis, heightened peripheral and central inflammation, and metabolic changes. Interestingly, these effects persisted into the postpartum period, during which stressed dams also showed impaired caregiving behaviors, potentially mediating negative outcomes for the offspring. PNS exposure was indeed associated with the onset of a vulnerable phenotype in about 30–40% of adolescent and adult male and female animals; however, vulnerability status was associated with dysregulation of stress-related and metabolic markers in the periphery and in the ventral hippocampus mainly in males. In contrast, female animals did not exhibit these changes, suggesting that specific metabolic and inflammatory alterations underlie, in a sex-specific manner, the onset of a vulnerable phenotype. These findings suggest that exposure to adversities during the prenatal period is associated with biological changes in mothers and, with a sex-specific effect, also in offspring, influencing the onset of a vulnerable phenotype. We therefore highlight the importance of targeting these biological features to reduce the burden associated with exposure to an adverse prenatal environment, minimizing also the consequences for future generations.

Stress and Nutrition During Pregnancy Share Common Mechanisms and Have Sex-specific Effects on Brain Development

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Background. Adverse maternal conditions during pregnancy result in an increased risk for neuropsychiatric disorders in the offspring, which manifest in a sex-specific manner, although the underlying mechanisms are still not well understood. We hypothesized that maternal high-fat diet (mHFD) consumption during pregnancy may trigger fetal responses similar to those induced by psychological stress thereby disrupting neurodevelopment and increasing the risk of mental health disorders in adulthood. Although these stressors differ in nature, we propose that both psychological and metabolic stress may act through shared mechanisms.

Methods. We have used mouse models of prenatal stress (PNS) and mHFD to study changes related to oxidative stress and inflammation in the placenta and fetal brain and to test the protective effects of the antioxidant N-acetyl-cysteine (NAC), adopting a multi-disciplinary approach combining molecular, histological and proteomic analysis.

Results. Results indicate comparable, but sex-specific, responses to the two maternal stressors, with NAC administration acting as a buffer. The placental function was disrupted in males, with signalling pathways of cardio-metabolic risk emerging in this sex. By contrast, the fetal brain was affected in females, with an increased expression of genes related to inflammation and oxidative stress.

Conclusions. We have provided evidence for an early origin of sex-dependent embedding of prenatal adverse experiences in different organs which might explain differential susceptibility to later disease trajectories.

Exploring Mechanisms of Brain-to-brain Attunement Across Socio-emotional Stress Regulation: EEG Hyperscanning in the Parent-infant Dyad

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Background. Biobehavioral co-regulation processes with the caregiver shapes infants' socio-cognitive and emotional development. Parents and infants are believed to co-regulate their neural activity during social interactions, a phenomenon known as interpersonal neural synchrony (INS). While INS is expected to be predominantly of the mutual kind, we hypothesize that an interactive perturbation might change the structure of the dyadic INS, leading it to become directed/sequential.

Methods. A sample of 48 parent-infant dyads (infant mean age 9 months) engaged in an adapted Face-to-Face Still-Face (FFSF) procedure while their brain activity was recorded via the electroencephalograph (EEG) hyperscanning paradigm. Partial directed coherence (PDC) in the alpha and theta bands was measured both in the infant-to-parent (I->P) and parent-to-infant (P->I) directions. Infant negative emotionality and gaze aversion were coded and quantified as percentage of time across the FFSF, as well as percentage of maternal affective touch during Play and Reunion.

Results. Alpha PDC was predominantly infant-led during both Play and Reunion; however, a significant reduction in the number of I->P connections was observed in the subgroup of dyads with high infant negative emotionality. Theta PDC was also predominantly infant-led during Play, while in the Reunion, dyads displaying high infant gaze aversion or high maternal affective touch displayed a significant increase in the number of P->I-dominated inter-neural connections.

Conclusions. Our results suggest that the INS in the caregiver-infant dyad is sensitive to interactive ruptures, so that direction of reciprocal influence is shaped as the dual dynamic system is engaged in regulating perturbations of expected contingencies.

ITALIAN STRESS NETWORK

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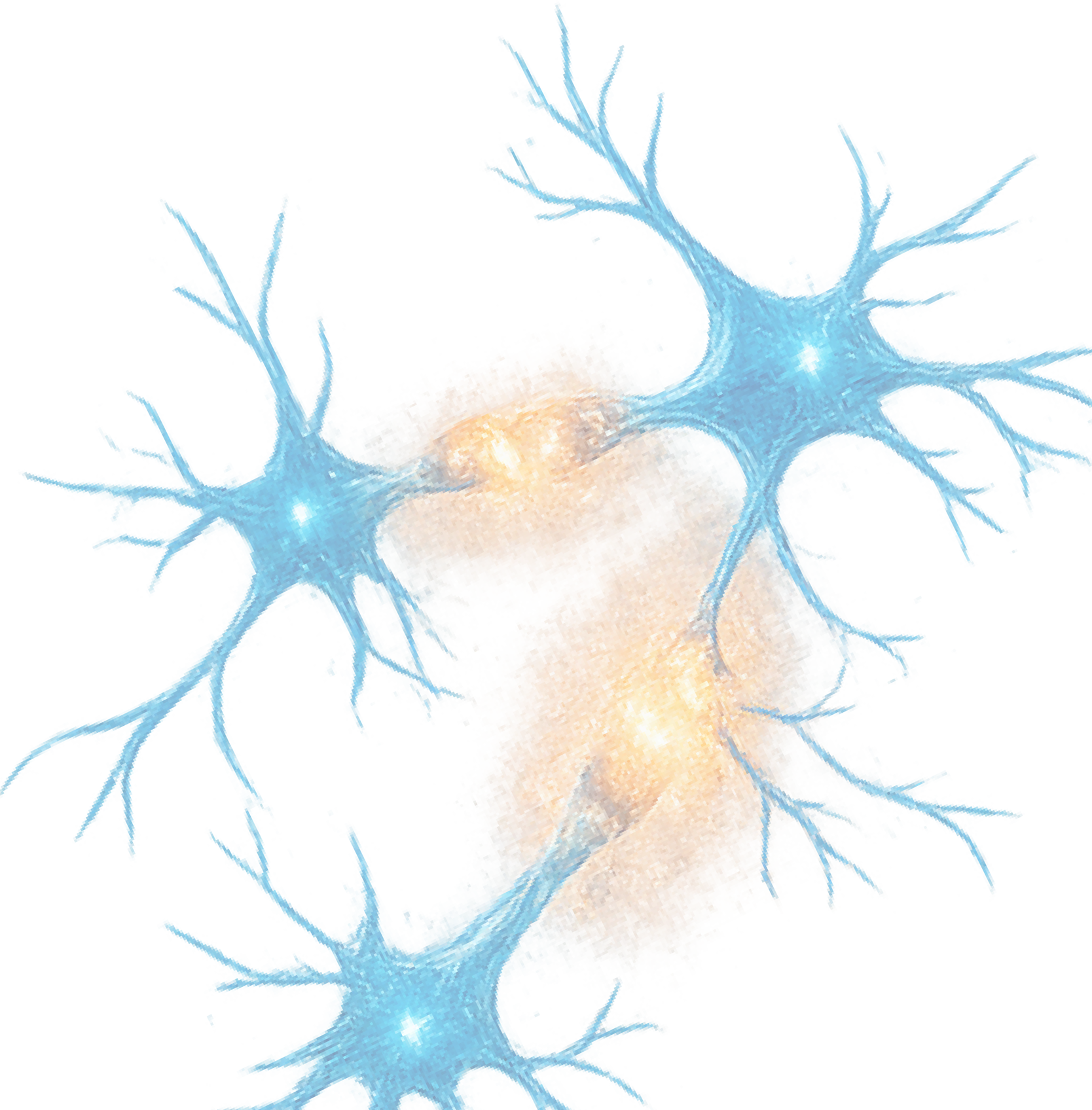
Poster Abstracts



Poster n.1

Chronic social defeat stress disrupts core psychopathological domains of motivation and sociability in rats: reversal by lurasidone

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Background. Chronic stress is a major risk factor for psychiatric disorders, contributing to core symptoms such as anhedonia and social withdrawal. This study investigated the potential of the antipsychotic drug lurasidone in reversing motivational and sociability deficits in rats exposed to social defeat stress (SDS).

Methods. Male Sprague-Dawley rats underwent a 7-week SDS paradigm. Starting from day 21, they were chronically treated with lurasidone (1 or 3mg/kg) or vehicle. Motivational anhedonia was assessed via sucrose self-administration in fixed-ratio (FR1, FR5) and progressive ratio (PR) schedules. Sociability was assessed through direct and indirect interaction with unfamiliar conspecific. At the end of the paradigm, a subgroup of rats was exposed to a social stimulus (SI) after 72 hours of isolation and sacrificed. Transcriptional changes were evaluated at the level of the prefrontal cortex (PFC), amygdala (AMY), nucleus accumbens (NAc) and ventral hippocampus (VH).

Results. Rats exposed to SDS exhibited impaired performance across all motivational tasks and showed reduced social interaction. Chronic treatment with lurasidone at the higher dose (3 mg/kg) significantly ameliorated motivational anhedonia, whereas both tested doses effectively improved sociability. Analysis of activity-dependent genes expression revealed that SDS disrupted PFC-NAc connectivity, while lurasidone at 1mg/kg restored network integration and elicited robust VH and NAc activation after SI. Moreover, we observed brain region–specific changes in SI-induced glucocorticoid-dependent transcription after SD, which were dynamically modulated by lurasidone administration.

Conclusions. These results highlight lurasidone's potential to restore behavioral and neurobiological alterations induced by chronic stress, supporting its relevance for treating motivation and social dysfunction in psychiatric disorders.

References:

[1] Luoni A, et al. Intl. J.Neuropsychopharmacol.18(4):pyu061, 2015.

[2] Begni V. et al. Eur. Neuropsychopharmacol., 61:78-90, 2022.

[3] Corridori E. et al. Neuropharmacology, 267:110302, 2025.

Poster n.2

Sex-specific effects of N-Acetylcysteine administration on emotional behaviour and neuroendocrine dysfunctions induced by two-hit stress exposure in rats

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Background. Individuals exposed to early life stress appear to be more vulnerable to develop psychiatric conditions, particularly when combined with further stressful events later in life [1]. Since oxidative stress has been proposed has a shared mechanism for both pre- and post-natal insults [2,3], antioxidant treatments, aiming at counteracting redox imbalance, could represent a promising therapeutic tool.

Methods. Here, we investigated the effects of the antioxidant compound N-Acetylcysteine (NAC) on a two-hitstress exposure paradigm, i.e. rat prenatal stress (PNS) exposure, through maternal restraint (first hit), combined with social isolation in the adolescent male and female offspring (second hit), thus evaluating emotional dysfunctions, redox and hypothalamic-pituitary-adrenal (HPA) axis parameters, as well as oxytocin content.

Results. Emotional behaviour dysfunctions in PNS male and female rats, independently of social isolation during adolescence, were only partially reverted by NAC treatment. Levels of HPA axis parameters and ROS production were increased in both male and female animals exposed to the two-hit stress paradigm, with a reduction in the amount of those biomarkers following NAC treatment only in male animals. Plasmatic oxytocin levels, decreased in both sexes when exposed to the two-hit stress, were restored only in females, showing a sex-specific antioxidant response.

Conclusions. Our data showed that PNS heightened the vulnerability to a second stress during adolescence, thus strengthening the necessity of an accurate early-life fetal programming. Moreover, by revealing different sex responses following NAC treatment, we highlighted the importance of the development of sex-tailored therapies targeting stress-induced behavioural and biomolecular dysfunctions.

References:

[1] doi: 10.1016/j.bbi.2023.01.004

[2] doi: 10.1192/j.eurpsy.2023.294

[3] doi: 10.1016/j.biopha.2022.112820

Poster n.3

Sex-dependent effects of NMDA receptor antagonism on stress-induced spatial memory deficits

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Background. The neural mechanisms through which acute stress affects spatial memory remain poorly understood. Despite extensive evidence from clinical studies indicating sex differences in spatial memory performance, most preclinical research has relied predominantly on male rodents. Our previous findings revealed that, although acute stress induces comparable long-term spatial memory impairments in both sexes, a marked increase in the mRNA expression of N-methyl-D-aspartate (NMDA) receptor subunits occurs exclusively in the dorsal hippocampus of stressed female mice [1].

Methods. In the present study, we tested the hypothesis that pharmacological manipulation of NMDA receptors can prevent the detrimental effects of acute stress on spatial memory consolidation in a sex-dependent manner. For this purpose, male and female C57BL/6J mice received intraperitoneal injections of the selective non-competitive NMDA antagonists MK-801 (0.1 mg/kg) or Memantine (5 mg/Kg). Then they were exposed to 2 hours of restraint stress immediately after the training session of the novel object location task.

Results. Both MK-801 and Memantine counteracted acute stress-induced spatial memory deficits in a sex-dependent manner. While vehicle-injected stressed animals of both sexes, as well as MK-801-treated stressed females and Memantine-treated stressed males, exhibited spatial memory deficits, MK-801-treated stressed males and Memantine-treated stressed females showed preserved spatial memory comparable to that of control mice.

Conclusions. These findings suggest that the functionality of NMDA receptors under stress conditions is modulated by sex- dependent mechanisms. The investigation of sex-specific processes in this context may lead to more targeted pharmacological treatments for cognitive deficits associated with neuropsychiatric and neurological disorders.

References:

[1] Torrisi et al., 2023. Neurobiol Stress. 25:100545.

Poster n.4

Brain miRNA profile in a corticosterone-induced mouse model of stress and its reversal by ketamine

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Background. Major depressive disorder (MDD) is the most prevalent mental illness worldwide and a leading cause of suicide. Its molecular basis involves genetic, epigenetic, and environmental factors converging in emotion-regulating brain circuits. MicroRNAs (miRNAs), short non-coding RNA transcripts, are key post-transcriptional regulators of gene expression, modulating physiological processes linked to MDD and mediating cellular responses to stress. Ketamine, a fast-acting antidepressant, has also been shown to change miRNA expression in the brain.

Methods. We examined miRNA regulation in the medial prefrontal cortex (mPFC), caudate putamen (CPu), and hippocampus (HPC) of a corticosterone-induced depression-like mouse model treated with ketamine. After behavioral assessment, brain regions were collected for miRNA sequencing (mPFC and HPC), followed by qPCR validation and target prediction of significantly altered miRNAs. Over-representation analyses (ORA) with KEGG and GO pathways were used to identify biological processes regulated by the changed miRNAs.

Results. Ketamine reversed the behavioral depressive-like phenotype. miRNAseq revealed alterations in miRNA expression in the mPFC and HPC of both corticosterone- and ketamine-treated mice relative to controls, which were subsequently validated by qPCR and extended to the CPu. KEGG-based ORA showed enrichment in pathways related to neuronal function and MDD pathogenesis, including neurotrophin and chemokine signaling, neuroinflammation, and synaptic plasticity.

Conclusions. Overall, we identified changes in miRNA expression in the mPFC, CPu, and HPC of a corticosterone-induced depression-like mouse model, some of them reversed by ketamine. The enrichment of neuronal and MDD-related pathways highlights the potential of miRNAs as biomarkers and therapeutic targets for depression and suicide.

References:

[1] Fries, G. R., Saldana, V. A., Finnstein, J., & Rein, T. (2023). Molecular pathways of major depressive disorder converge on the synapse. Molecular psychiatry, 28(1), 284–297.

[2] Rio, L. M., Yanes, C., Haro, E., Jericó, J., Sarriés-Serrano, U., Meana. J. J., et al. (2024). miRNA-seq analyses in human dorsolateral prefrontal cortex reveal sex-specific differences in miRNAs regulating depression and suicide-related pathways. Neurosci Appl, 3:104569.

[3] Roy, B., & Dwivedi, Y. (2023). An insight into the sprawling microverse of microRNAs in depression pathophysiology and treatment response. Neuroscience and biobehavioral reviews, 146, 105040.

Poster n.5

GABAergic microRNA-34a in the dorsal raphe nuclei contributes to stress-induced circulating microRNA-34a levels

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Background. Circulating microRNAs (c-miRs) are increasingly recognized as peripheral biomarkers of stress-related disorders, with predictive and diagnostic potential. Understanding the mechanisms underlying their transport from brain to periphery is therefore crucial. Although brain microRNAs (miRs) are expressed in a cell type–specific manner, only limited evidence directly links specific neuronal populations or brain regions to circulating miR levels [1]. Among these, in the dorsal raphe nucleus (DRN) miR-34a is highly and selectively expressed in GABAergic neurons, where it regulates serotonergic neurotransmission and stress-related behaviors [2-4]. Furthermore, miR-34a expression in the DRN is enhanced by repeated stress [4] and chronic SSRI administration [5]. Here, we examined whether plasma miR-34a levels reflect its expression in the DRN.

Methods and Results. In mice exposed to repeated social defeat stress or chronic SSRI treatment, plasma miR-34a levels increased, suggesting that DRN homeostatic adaptations are mirrored in the periphery. To identify the source of circulating miR-34a, we used a genetic strategy to selectively delete miR-34a in GABAergic neurons. This manipulation reduced miR-34a in both DRN and plasma, but not in other brain regions, demonstrating that DRN GABAergic neurons are the primary contributors to circulating miR-34a. Similarly, intra-DRN infusion of AntagomiR-34a decreased miR-34a levels in both DRN and plasma, confirming this region as a key source. Remarkably, the same manipulation reduced miR-34a expression in ependymal cells of the choroid plexus, pointing to a possible brain-to-periphery route.

Conclusions. These findings demonstrate that plasma miR-34a faithfully reflects miR-34a expression in DRN GABAergic neurons and can serve as a peripheral indicator of stress-related neuronal adaptations.

References:

[1] Torres-Berrío A, Nouel D, Cuesta S, et al (2020) MiR-218: a molecular switch and potential biomarker of susceptibility to stress. Mol Psychiatry 25:. https://doi.org/10.1038/s41380-019-0421-5.

[2] Ielpo D, Guzzo SM, Porcheddu GF, et al (2023) GABAergic miR-34a regulates Dorsal Raphè inhibitory transmission in response to aversive, but

not rewarding, stimuli. Proc Natl Acad Sci U S A 120:. https://doi.org/10.1073/pnas.2301730120.

[3] Lo Iacono L, Ielpo D, Accoto A, et al (2020) MicroRNA-34a Regulates the Depression-like Behavior in Mice by Modulating the Expression of Target Genes in the Dorsal Raphè. Mol Neurobiol 57:. https://doi.org/10.1007/s12035-019-01750-2.

[4] Andolina D, Savi M, Ielpo D, et al (2021) Elevated miR-34a expression and altered transcriptional profile are associated with adverse electromechanical remodeling in the heart of male rats exposed to social stress. Stress 24: https://doi.org/10.1080/10253890.2021.1942830.

[5] Lo Iacono L, Ielpo D, Parisi C, et al (2021) MicroRNA-34a regulates 5-HT2C expression in dorsal raphe and contributes to the anti-depressant-like effect of fluoxetine. Neuropharmacology 190:. https://doi.org/10.1016/j.neuropharm.2021.108559.

Poster n.6

Epigenetic profile of stress-related disorders: sex-specific miRNAs in the MDD dlPFC and their modulation in plasma by psychotherapy

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Background. Major depressive disorder (MDD) is a leading cause of suicide and disability worldwide. Its mechanisms involve complex epigenetic interactions, with microRNAs (miRNAs) as critical regulators of gene expression within emotion-controlling circuits, such as dorsolateral prefrontal cortex (dlPFC). This study aimed to characterise sex-specific miRNA profiles in the dlPFC of MDD/suicide subjects and assess their translational modulation in plasma following psychotherapy in MDD patients.

Methods. Total RNA-seq, qPCR validation, and integrated miRNA-mRNA network analyses were conducted on post-mortem dlPFC samples (N=62, male/female). KEGG/GO functional analysis was performed to identify miRNA-regulated relevant pathways. To integrate miRNA and transcriptome data, validated mRNA targets of differentially expressed (DE) miRNAs were cross-referenced with altered mRNAs identified in the RNA-seq. Second, a panel of miRNAs (selected based on dlPFC dysregulation) was analysed by qPCR in plasma from MDD patients before and after psychotherapy.

Results. In the dlPFC, qPCR validation confirmed 14 (males) and 11 (females) DE miRNAs, functionally linked to MDD-related pathways (e.g., synaptic plasticity). Parallel transcriptome analysis identified 1057 DE mRNAs in males and 1152 in females. Subsequent data integration showed 272 (males) and 157 (females) of these mRNAs were validated targets of the confirmed DE miRNAs. Plasma analysis revealed psychotherapy significantly modulated circulating miRNA levels, with increases in seven (e.g., miR-129-5p, miR-451a) and decreases in two (e.g., miR-34c-5p) post-intervention.

Conclusions. This study identifies distinct, sex-specific miRNA-mRNA regulatory networks in the dlPFC of MDD/suicide individuals, highlighting their role in MDD pathophysiology. Their modulation in plasma post-psychotherapy suggests potential as translational biomarkers for therapeutic response.

Poster n.7

miRNA expression in the hippocampus and pre-frontal cortex of male and female mice exposed to unpredictable chronic mild stress

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Background. Due to the prominent influence of stress in triggering major depression, the unpredictable chronic mild stress (UCMS) model is particularly suitable for gaining insight into the neurobiological correlates of the disease, with the ultimate aim of identifying new pharmacological targets. miRNAs are small, non-coding RNAs regulating gene expression significantly involved in the pathogenesis of many diseases, including depression. The aim of this study was to assess miRNA levels in mice exposed to UCMS.

Methods. Male and female C57Bl/6 mice were exposed to mild stresses in an unpredictable fashion for 9 weeks. Weight and grooming behaviours were evaluated weekly. miRNA levels were compared between control and stressed groups in hippocampus (HIP) and pre-frontal cortex (PFCx) by qPCR.

Results. UCMS exposure caused reduced weight gain specifically in males. Both males and females displayed significantly impaired self-care behaviours. In the HIP of stressed mice, miR-30e-5p and miR-181a-5p were significantly upregulated in females, while miR-124-3p and miR-182-5p were increased in males. In PFCx, miR-182-5p, miR-7116-3p, miR-137-5p, and miR-206-3p showed higher levels in UCMS, whereas no significant changes were detected in males.

Conclusions. The results support a major role for miRNA in the regulation of stress responses, in association with the development of depressive-like behaviours. Remarkably, miRNA levels differed in males and females, possibly contributing to the molecular substrates supporting the heterogeneity of behavioural responses between sexes. These findings underscore the importance of performing studies in both sexes, especially in consideration of the fact that women are twice as likely to experience major depression.

Poster n.8

Cortisol-Driven Dysregulation in Human Hippocampal Progenitor Cells: Insights into the Protective Role of Exercise-Derived Factors

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Background. Depression is the most prevalent mood disorder and a major cause of disability worldwide. Its pathogenesis is multifactorial, with chronic stress and inflammation contributing to hippocampal dysfunction. Excessive glucocorticoid signaling impairs neurogenesis and induces stress-related molecular alterations [1]. Exercise exerts protective effects partly through the release of myokines such as adiponectin and irisin, which display neurotrophic and anti-inflammatory properties [2]. This study investigates how cortisol-induced stress alters molecular pathways and neurogenic processes in human hippocampal precursor cells and explores the potential of exercise-derived myokines to restore these impairments.

Methods. Human hippocampal precursor cells (HIP-009) were exposed to 100 µM cortisol for 3 days to mimic mild stress. Neurogenesis and gene expression were assessed after proliferation and 21-day differentiation. To define non-cytotoxic doses, cells were treated with increasing concentrations of adiponectin (5–25 ng/mL) and irisin (20–100 ng/mL), mimicking physiological brain ranges.

Results. Cortisol exposure significantly upregulated SGK1 ($p<0.001$), GR ($p<0.001$), and FKBP5 ($p< 0.0001$) during proliferation, with effects persisting after differentiation. Neurogenic markers were impaired, as shown by reduced BDNF and BDNF VIb expression ($p<0.05$) and decreased $Ki67^+$, $MAP2^+$, and $GFAP^+$ cells. Dose-response analysis identified physiological concentrations of adiponectin and irisin that maintained viability and prevented cytotoxicity. Preliminary data suggest these factors may attenuate cortisol-induced molecular and cellular alterations.

Conclusions. Cortisol induces stress-related transcriptional and neurogenic impairments in human hippocampal precursor cells. Exercise-associated myokines such as adiponectin and irisin may counteract these effects. Further studies should clarify the mechanisms underlying their protective actions against stress-induced dysfunction.

References:

[1] Park C, Rosenblat JD, Brietzke E, Pan Z, Lee Y, Cao B, Zuckerman H, Kalantarova A, McIntyre RS. Stress, epigenetics and depression: A systematic review. Neurosci Biobehav Rev. 2019 Jul;102:139-152. doi: 10.1016/j.neubiorev.2019.04.010. Epub 2019 Apr 18. PMID: 31005627.

[2] Wang N, Zhu S, Chen S, Zou J, Zeng P, Tan S. Neurological mechanism-based analysis of the role and characteristics of physical activity in the improvement of depressive symptoms. Rev Neurosci. 2025 Jan 21;36(5):455-478. doi: 10.1515/revneuro-2024-0147. PMID: 39829004.

Poster n.9

Sex and complex PTSD comorbidity affect treatment outcomes in bipolar disorder

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Background. Bipolar disorder (BD) affects men and women at comparable rates, but-sex-related differences are well-known. Trauma-related comorbidities are frequent in BD, and some patients develop complex PTSD (cPTSD), a novel diagnosis that combines core PTSD symptoms with persistent disturbances in emotion regulation, self-concept, and relationships [1]. This study examined the influence of sex and cPTSD on BD features and pharmacological treatment response.

Methods. A cohort of 343 BD patients with comorbid PTSD (177 females, 166 males) was followed over three years. Clinical characteristics were recorded, comorbid PTSD/cPTSD were assessed using the International Trauma Questionnaire and treatment response to mood stabilizers with the Alda Scale.

Results. Significant sex differences emerged in BD patients. Comorbidity with the complex form of PTSD increased BD severity and suicidality. Treatment response was significantly poorer in cPTSD patients. While males generally responded better than females, cPTSD comorbidity strongly reduced response to treatment, especially among men [2].

Conclusions. Sex differences and cPTSD comorbidity significantly shape the clinical course of BD and response to mood stabilizers. Tailored approaches that address trauma-related symptoms are needed, as standard treatments may be insufficient for certain patient subgroups.

References:

[1] WHO International Classification of Diseases (ICD-11) 2022.

[2] Steardo L et al, 2025. PMID:40097134.

Poster n.10

A Network-Based Approach to Anticipate Time to Recovery in Major Depression Reveals a Plasticity by Context Interplay

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Background. Predicting disease trajectories in patients with major depressive disorder (MDD) can allow designing personalized therapeutic strategies. In this study, we aimed to show that measuring patients' plasticity – that is the susceptibility to modify the mental state – identifies at baseline who will recover, anticipating the time to transition to wellbeing [1-2].

Methods. We conducted a secondary analysis in two randomized clinical trials, STAR*D and CO-MED. Symptom severity was assessed using the Quick Inventory of Depressive Symptomatology while the context was measured at enrollment with the Quality-of-Life Enjoyment and Satisfaction Questionnaire. Patients were retrospectively grouped based on both their time to response or remission and their plasticity levels at baseline assessed through a network-based mathematical approach that operationalizes plasticity as the inverse of the symptom network connectivity strength [3].

Results. The results show that plasticity levels at baseline anticipate time to response and time to remission. Connectivity strength among symptoms is significantly lower -- and thus plasticity higher -- in patients experiencing a fast recovery. When the interplay between plasticity and context is considered, plasticity levels are predictive of disease trajectories only in subjects experiencing a favorable context, confirming that plasticity magnifies the influence of the context on mood.

Conclusions. In conclusion, the assessment of plasticity levels at baseline holds promise for predicting MDD trajectories, potentially informing the design of personalized treatments and interventions. The combination of high plasticity and the experience of a favorable context emerge as critical to achieve recovery.

References:

[1] Branchi I. Plasticity in mental health: A network theory. Neurosci Biobehav Rev 2022; 138: 104691.

[2] Price RB, Duman R. Neuroplasticity in cognitive and psychological mechanisms of depression: an integrative model. Mol Psychiatry 2020; 25(3): 530-43.

[3] Branchi I. A mathematical formula of plasticity: Measuring susceptibility to change in mental health and data science. Neurosci Biobehav Rev 2023; 152: 105272.

Poster n.11

Long-Term Behavioral and Molecular Consequences of a Perinatal Stress Model in Mice

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Background. The perinatal period represents a critical window for both mother and offspring, during which exposure to stress and the consequent emergence of maternal depressive-like features can exert long-lasting effects on offspring development. Establishing robust and translationally relevant preclinical models capable of reproducing these phenomena is therefore essential. To this end, we developed the prenatal and early postnatal stress (PNS/LBN) model, designed to mimic depression-like features arising during late gestation and extending into the postpartum period, ultimately leading to behavioural and molecular alterations in the offspring.

Methods. Pregnant mice were subjected to repeated restraint stress during the last week of gestation (PNS), followed by rearing in an impoverished environment with limited nesting and bedding materials (LBN) from postnatal day 2 to 9. Offspring was assessed during adolescence or adulthood for behaviours. Peripheral blood samples were analysed for HPA-related and inflammatory markers.

Results. Adolescent females showed transient cognitive deficits that resolved by adulthood, whereas social, anxiety-like, and depressive-like impairments appeared later. Male offspring exhibited behavioural disinhibition in adolescence, which did not persist into adulthood. Moreover, IL-6 levels were selectively increased in PNS/LBN-exposed adolescent females, suggesting a sex-specific inflammatory response.

Conclusions. Exposure to perinatal stress produced a range of mild effects that were strongly modulated by sex and developmental stage.

Poster n.12

From Womb to Well-Being: Sex-Specific Impacts of Prenatal Stress

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Background. Exposure to stress early in life is a well-established risk factor for the development of psychiatric disorders later in life. The placenta plays a central role in mediating these effects, acting as a crucial interface between the maternal and fetal environments. It translates maternal experiences—such as stress—into molecular signals that can influence fetal brain development and long-term neurobehavioral outcomes. Using a validated mouse model of prenatal stress (PNS), we investigated how gestational stress affects placental structure and function, as well as transcriptional profiles in fetal brains.

Methods. Pregnant C57BL/6 dams were exposed to restraint stress under bright light from gestational day (GD) 12 to GD17. On GD18, placentas and fetal brains were collected and subjected to gene expression analysis.

Results. Transcriptomic profiling of the placenta revealed pronounced sex-specific effects, with a greater number of differentially expressed genes in males compared with females. Similarly, in fetal brains from PNS pregnancies, we observed marked sex differences both in the number of differentially expressed transcripts and in the biological pathways they regulate.

Conclusions. Our findings underscore the placenta as a key mediator of prenatal stress, translating maternal experiences into sex-specific molecular changes also in fetal brains. The pronounced differences observed between male and female offspring suggest that sex critically shapes the fetal response to maternal stress, influencing both gene expression patterns and the biological pathways engaged.

Poster n.13

Prenatal stress alters maternal homeostasis and induces sex-specific placental and fetal brain dysregulation

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Background. Pregnancy involves profound metabolic, neuroendocrine, and immune adaptations that support fetal development while preserving maternal homeostasis. These include changes in glucose and lipid metabolism, insulin sensitivity, and energy expenditure. Prenatal stress (PNS) can disrupt these processes, altering maternal physiology and placental function, thereby increasing offspring susceptibility to metabolic and psychiatric disorders. To investigate how gestational stress affects maternal metabolism and inflammation, and modulates placental and fetal metabolic profiles, revealing mechanisms that may increase offspring susceptibility to metabolic and psychiatric disorders.

Methods. Pregnant rats were exposed to restraint stress from gestational day (GD) 14–21. On GD21, maternal samples (plasma and hippocampi), placentas, and fetal brains were collected. Maternal plasma corticosterone and oxytocin were measured by ELISA, and pro-inflammatory cytokines (TNFα, IL6, IL1β) by Luminex. Real-time PCR assessed mitochondrial and metabolic gene expression in maternal hippocampi, placentas, and fetal brains, with sex-specific analyses.

Results. PNS increased maternal corticosterone, reduced oxytocin ($p < 0.05$), and elevated TNFα, IL6, and IL1β ($p < 0.01$). In the dorsal hippocampus, leptin receptor expression increased and adiponectin receptor decreased ($p < 0.05$); ventral hippocampus was unaffected. Placental effects were sex-specific: in males, NFE2L2 decreased, while NQO1 and leptin receptor decreased; in females, insulin receptor was elevated. Fetal brains showed sex-dependent mitochondrial and metabolic alterations, including increased insulin expression in males.

Conclusions. Prenatal stress disrupts maternal metabolic–inflammatory homeostasis and induces sex-specific alterations in placental and fetal brain metabolism, suggesting impaired maternal–fetal interactions that may increase offspring susceptibility to metabolic and psychiatric disorders.

Poster n.14

Impact of prenatal stress on emotional and cognitive behaviors in adolescent male and female rats

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Background. Prenatal stress (PNS) represents a risk factor negatively impacting on neurodevelopment that may predispose to life-long adverse outcomes [1,2]. In particular, PNS is associated to a broad spectrum of neuropsychiatric disorders, which often manifest or intensify during adolescence, making this life phase particularly vulnerable [3,4]. However, so far, underpinning pathogenetic mechanisms still remain unclear. Here, we investigated the impact of PNS, obtained by maternal restraint, on the development of emotional and cognitive dysfunctions in adolescent male and female offspring.

Methods. Pregnant rats were exposed to the restraint procedure during the last gestational week [4]. Offspring of both sexes were tested at postnatal day 35 using the following behavioral battery: sucrose preference (SP), novel object recognition (NOR), elevated plus maze (EPM), and forced swimming (FS) tests.

Results. PNS significantly increased sucrose preference in both sexes compared to the corresponding controls, showing increased hedonic sensitivity. No differences were observed in the discrimination index of the NOR among experimental groups, suggesting the absence of cognitive impairment. PNS-exposed males, but not females, spent less time in the open arms of the elevated maze than control males, denoting a sex-specific anxiety-like behavior. In FST, immobility and swimming frequencies did not significantly differ among groups. Nevertheless, PNS-exposed females exhibited a reduced frequency of struggling compared to controls.

Conclusions. These findings demonstrated that PNS can impair emotional behaviour during adolescence, finally resulting in the development of stress-induced neuropsychiatric conditions, thus identifying this life phase as a critical period for both preventive and therapeutic strategies.

References:

[1] https://doi.org/10.1007/S12038-021-00153-7.

[2] https://doi.org/10.3389/fnins.2020.573107.

[3] https://doi.org/10.1016/j.psyneuen.2023.106725.

[4] https://doi.org/10.3389/fphar.2022.1075746.

Poster n.15

Biological mechanisms linking childhood trauma to anxiety: the interplay between emotion regulation and inflammatory signatures

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Background. Childhood trauma (CT) is a well-known risk factor for anxiety and mood disorders, with lasting effects on neurodevelopment [1]. CT is associated with emotional dysregulation, poor coping, and immune dysfunction, which may contribute to adult anxiety [2]. This study explores the long-term impact of CT on anxiety, focusing on inflammatory biomarkers as potential mediators.

Methods. The study included four groups: individuals with CT and anxiety symptoms (n = 34); with CT but no anxiety (n = 48); without CT but with anxiety (n = 23); and without CT and anxiety (n = 47). CT was assessed using the Childhood Trauma Questionnaire, anxiety with the State-Trait Anxiety Inventory, and emotional functioning and depressive symptoms with validated questionnaires. Inflammatory markers were analysed using bead-based multiplex immunoassay (Luminex xMAP). Statistical analyses included one-way ANOVA or Kruskal-Wallis tests ($p < 0.05$).

Results. Clinical findings revealed that individuals exposed to CT demonstrated significantly lower emotion regulation, higher alexithymia, poorer coping abilities, and higher levels of depressive symptoms compared to those not exposed to CT. Cytokine analyses revealed higher IL-12p70 ($p = 0.048$) and IL-17A ($p = 0.035$) levels in individuals with both CT and anxiety compared to subjects with CT but without anxiety. Conversely, IL-4 ($p = 0.031$) was higher in participants without CT and anxiety compared to those without CT but with anxiety symptoms.

Conclusions. CT impacts both emotional and immune functioning, potentially increasing vulnerability to anxiety symptoms. These findings highlight the need for early interventions targeting both psychological and immunological profiles.

References:

[1] Agorastos A, Pervanidou P, Chrousos GP, Baker DG. Developmental Trajectories of Early Life Stress and Trauma: A Narrative Review on Neurobiological Aspects Beyond Stress System Dysregulation. Front Psychiatry. 2019 Mar 11;10:118. doi: 10.3389/fpsyt.2019.00118. PMID: 30914979; PMCID: PMC6421311.

[2] Mathur A, Li JC, Lipitz SR, Graham-Engeland JE. Emotion Regulation as a Pathway Connecting Early Life Adversity and Inflammation in Adulthood: a Conceptual Framework. Advers Resil Sci. 2022;3(1):1-19. doi: 10.1007/s42844-022-00051-3. Epub 2022 Feb 23. PMID: 35224511; PMCID: PMC8863511.

Poster n.16

Early Life Social Isolation Dysregulates Social Reward Processing, BDNF Signaling, and Intracellular Vesicular Sorting in the Nucleus Accumbens of Male and Female Rats

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Background. Early- life social deprivation negatively impacts brain development and behavior, increasing susceptibility to neuropsychiatric disorders (Chandan et al. 2019; Brandt et al. 2022). In social species such as rats, interactions with the mother and conspecifics are crucial for offspring survival and proper neurobehavioral maturation (Keller et al. 2019). However, the mechanisms underlying sex- dependent vulnerability to early- life social stressors, such as social isolation, remain unclear. This study aimed to (1) investigate the effects of early- life social isolation (ESI) on social and depressive- like behaviors in female and male rats during adolescence and adulthood and (2) explore the molecular mechanisms involved, focusing on the BDNF system in the nucleus accumbens (NAc), a key brain region for social behavior and reward processing.

Methods. To this aim, we implemented an ESI protocol involving brief periods of repeated social isolation from postnatal day (PND) 14–21 to mimic an adverse early social environment, and then we tested female and male rats across development (i.e., during adolescence and adulthood).

Results. ESI impaired social reward processing in male rats, whereas general social and depressive- like behaviors remained unaffected. Furthermore, males exhibited a persistent ESI- induced downregulation of BDNF signaling paralleled by alterations in endocytic- recycling mechanisms mediated by Rab5- Rab11, suggesting increased TrkB sorting and reduced neuroplasticity. Conversely, females showed increased BDNF signaling and enhanced early endosome- recycling mechanisms.

Conclusions. These results suggest that male and female rats rely on distinct neurobiological mechanisms to modulate reward processing in response to early- life stress.

References:

[1] Brandt, L., S. Liu, C. Heim, and A. Heinz. 2022. “The Effects of Social Isolation Stress and Discrimination on Mental Health.” Translational Psychiatry 12: 398.

[2] Chandan, J. S., T. Thomas, K. M. Gokhale, S. Bandyopadhyay, J. Taylor, and K. Nirantharakumar. 2019. “The Burden of Mental Ill Health Associated With Childhood Maltreatment in the UK, Using the Health Improvement Network Database: A Population- Based Retrospective Cohort Study.” Lancet. Psychiatry 6: 926–934.

[3] Keller, M., L. N. Vandenberg, and T. D. Charlier. 2019. “The Parental Brain and Behavior: A Target for Endocrine Disruption.” Frontiers in Neuroendocrinology 54: 100765.

Poster n.17

Stress-related neuroadaptations following adolescent exposure to the synthetic cannabinoid 5F-MDMB-PICA

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Background. Synthetic cannabinoids (SC) constitute the largest group of novel psychoactive substances worldwide and pose significant risks for developmental neurobiology [1]. Among them, 5F-MDMB-PICA is a potent full agonist at CB1/CB2 receptors, previously shown to enhance mesolimbic dopamine (DA) transmission in adolescent but not adult mice [2]. Given the pivotal role of endocannabinoid signaling in regulating the hypothalamic–pituitary–adrenal (HPA) axis and stress responses [3,4], we hypothesized that adolescent self-administration of 5F-MDMB-PICA induces long-term dysregulation of stress reactivity and emotional regulation.

Methods. Adolescent male CD-1 mice underwent intravenous self-administration (IVSA) of 5F-MDMB-PICA. The same animals were later tested in adulthood through the Sucrose Preference (SPT), Resident-Intruder (RIT), and Olfactory Reactivity (ORT) tests. Dopaminergic responses to a predator odor were assessed via brain microdialysis in the medial prefrontal cortex (mPFC), and excitatory neuronal activity was monitored using GCaMP-based fiber photometry.

Results. Adolescent mice acquired intravenous self-administration of 5F-MDMB-PICA, displaying an inverted U-shaped dose–response curve with maximal responding at 2.5 µg/kg/25 µl. In adulthood, previously exposed animals showed increased aggression, reduced social interaction, and anhedonia. Neurochemical analyses revealed a complete loss of the mPFC dopaminergic response to a stressor, while fiber photometry recordings demonstrated reduced calcium activity of excitatory mPFC neurons during exposure to the same aversive stimulus.

Conclusions. Our findings indicate that 5F-MDMB-PICA IVSA is acquired at lower doses compared to the prototypical SCRA JWH-018 (Margiani et al., 2022), pointing to a higher abuse liability. Importantly, the adolescent exposure induced persistent neurobehavioral changes in stress-reactivity circuits, underscoring the adolescent period as a window of vulnerability. These results highlight the need to consider SC exposure not only from a reward/addiction perspective, but critically for its long-term impacts on stress regulation and emotional resilience.

References:

[1] European Monitoring Centre for Drugs and Drug Addiction. European Drug Report 2019: Trends and Developments [Internet]. Luxembourg: Publications Office of the European Union; 2019. Available from: https://www.emcdda.europa.eu/publications/edr/trends-developments/2019_en.

[2] Musa A, Simola N, Piras G, Caria F, Onaivi ES, De Luca MA. Neurochemical and Behavioral Characterization after Acute and Repeated Exposure to Novel Synthetic Cannabinoid Agonist 5-MDMB- PICA. Brain Sci. 2020 Dec 18;10(12):1011. doi: 10.3390/brainsci10121011. PMID: 33353194; PMCID: PMC7766979.

[3] Hillard CJ, Beatka M, Sarvaideo J. Endocannabinoid Signaling and the Hypothalamic-Pituitary-Adrenal Axis. Compr Physiol. 2016 Dec 6;7(1):1-15. doi: 10.1002/cphy.c160005. PMID: 28134998; PMCID: PMC5871916.

[4] Loomba N, Patel S. Circuit mechanisms governing endocannabinoid modulation of affective behaviour and stress adaptation. Nat Rev Neurosci. 2025 Nov;26(11):677-697. doi: 10.1038/s41583-025-00961-y. Epub 2025 Sep 11. PMID: 40935953.

Poster n.18

Sex-specific neuroprotective effects of ketogenic diet in a rodent model of early-life stress

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Background. Early-life stress (ELS) is a major risk factor for psychiatric disorders such as depression, producing long-lasting behavioral and neurobiological alterations, including social deficits and emotional dysregulation. Dietary interventions targeting neuroinflammation, oxidative stress, and HPA axis imbalance show therapeutic potential. The ketogenic diet (KD), a high-fat, low-carbohydrate regimen, shifts metabolism toward ketone bodies and exerts neuroprotective, anti-inflammatory, and antioxidant effects. Preclinical evidence suggests KD enhances mitochondrial function and modulates monoaminergic signaling processes disrupted by ELS. This study examined whether post-weaning KD prevents behavioral and molecular consequences of prenatal stress (PNS) and whether sex influences these effects.

Methods. Pregnant Sprague Dawley rats underwent repeated restraint stress on gestational days 15–21. Offspring were weaned at postnatal day (P)21 and fed control diet (CD) or KD for four weeks. Adolescents (P42–P45) were tested for social interaction and anhedonia (splash test). At P48, prefrontal cortex tissue was analyzed for inflammatory (TNFα, IL-6, C4) and antioxidant (Nrf2, Gclc1, Keap1) gene expression. Group sizes: n = 10–12 per sex/diet. Data were analyzed by two-way ANOVA with Tukey's post hoc tests.

Results. KD reduced weight gain and intake across groups. PNS impaired social interaction in CD-fed rats, an effect prevented by KD. KD also increased grooming, suggesting improved self-care. Behavioral vulnerability to PNS was reduced from ~50% in CD-fed animals to 22% in KD males and 12% in KD females. KD downregulated C4 in both sexes and suppressed TNFα and IL-6 in males, while upregulating Nrf2 and Gclc1 and normalizing Keap1 in females.

Conclusions. Post-weaning KD prevents PNS-induced social deficits with sex-specific mechanisms: anti-inflammatory in males, antioxidant in females. KD thus represents a promising, sex-sensitive dietary approach against stress-related psychopathology.

Poster n.19

Sex-dependent prosocial effects of psilocybin in mice exposed to early-life stress

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Background. Early-life stress can cause sex-dependent changes in mood and social behavior and is recognized as a main risk for neurodevelopmental and psychiatric disorders [1,2]. Interestingly, psychedelic drugs, due to their rapid neuroplastic and prosocial effects, are gaining attention for treating neuropsychiatric conditions [3]. Here, we studied sex differences in the long-term behavioral, social, and neurobiological consequences of Maternal Separation (MS) in mice, as well as the modulatory effects of a single administration of the psychedelic drug psilocybin.

Methods. C57BL/6 male and female pups were exposed to maternal separation (3 h/day; PND2-14). Behavior was assessed at PND 25, 37 and 50 using the home-cage monitoring system Phenotyper2 with the video-tracking software Ethovision XT (Noldus), allowing in-depth and automatized behavioral phenotyping. 1 week before the last recording and sacrifice, some mice received a single dose of psilocybin (1 mg/kg i.p.).

Results. At PND50, we found sex-dependent effects of stress, particularly regarding social behavior. When housed in pairs, MS male mice spent more time in the shelter and tend to reduce the time spent in proximity to the other animal, while MS females engaged less in social interactions (reduced movements towards peers). Importantly, acute psilocybin induced no obvious behavioral changes in unstressed animals but reversed social alterations in both sexes.

Conclusions. Our data show that psilocybin has a therapeutic potential in reversing social dysfunctions induced by stress in early life. Ongoing spatial transcriptomic analyses will provide insights into the putative molecular determinants of early-life stress and psilocybin behavioral readouts.

References:

[1] Sanacora, G., Yan, Z., & Popoli, M. (2022). The stressed synapse 2.0: pathophysiological mechanisms in stress-related neuropsychiatric disorders. Nature reviews. Neuroscience, 23(2), 86–103. https://doi.org/10.1038/s41583-021-00540-x.

[2] Sandi, C., Haller, J. Stress and the social brain: behavioural effects and neurobiological mechanisms. Nat Rev Neurosci 16, 290–304 (2015). https://doi.org/10.1038/nrn3918.

[3] Melani, A., Bonaso, M., Biso, L., Zucchini, B., Conversano, C., & Scarselli, M. (2025). Uncovering Psychedelics: From Neural Circuits to Therapeutic Applications. Pharmaceuticals, 18(1), 130. https://doi.org/10.3390/ph18010130.

Poster n.20

Effect of maternal separation on the opioid response in mouse cerebellum

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Background. Substance abuse results from various risk factors, with early life stress (ELS) emerging as a key contributor to increased vulnerability [1]. Maternal separation (MS) in early life induces lasting changes in the opioid systems [2,3]. Animals exposed to MS show increased sensitivity to morphine and altered opioid levels in brain regions involved in reward and emotional regulation [4]. Although the cerebellum is the brain region with a high density of μ-opiod receptors (MOR) [5], little is known about the functional role of the cerebellar opioid system at the cellular level and its involvement in the neurobiological changes associated with ELS. This study investigates the impact of MS on opioid responsiveness and MOR distribution in the cerebellum, using electrophysiological and molecular approaches.

Methods. CD1 pups were separated from the mother from postnatal day P2 to P18, for 4 h per day. Patch-clamp recordings, immunofluorescence (IF), and Western Blot (WB) analysis were performed on cerebellar samples of MS and control mice at P20.

Results. Electrophysiological recordings showed that the MOR agonist DAMGO reduced synaptic transmission at parallel fiber-Purkine cell synapse in control mice but not in MS mice. Both groups responded similarly to the KOR agonist U50488. WB and IF analyses showed reduced levels of phosphorylated MOR in the cerebellar cortex of MS mice.

Conclusions. MS alters Purkinje cell responsiveness to MOR activation, likely due to reduced expression of MOR within the cerebellum. These findings suggest that disrupted cerebellar opioid signaling maycontribute to long-term vulnerability to stress-related disorders and addiction.

References:

[1] Oswald, L. M., Dunn, K. E., Seminowicz, D. A., & Storr, C. L. (2021). Early Life Stress and Risks for Opioid Misuse: Review of Data Supporting Neurobiological Underpinnings. Journal of personalized medicine, 11(4), 315. https://doi.org/10.3390/jpm11040315.

[2] Kalinichev, M., Easterling, K. W., & Holtzman, S. G. (2001). Repeated neonatal maternal separation alters morphine-induced antinociception in male rats. Brain research bulletin, 54(6), 649–654. https://doi.org/10.1016/s0361-9230(01)00485-3.

[3] Nakamoto, K., Taniguchi, A., & Tokuyama, S. (2020). Changes in opioid receptors, opioid peptides and morphine antinociception in mice subjected to early life stress. European journal of pharmacology, 881, 173173. https://doi.org/10.1016/j.ejphar.2020.173173.

[4] Hanson, J. L., Williams, A. V., Bangasser, D. A., & Peña, C. J. (2021). Impact of Early Life Stress on Reward Circuit Function and Regulation. Frontiers in psychiatry, 12, 744690. https://doi.org/10.3389/fpsyt.2021.744690.

[5] Peng, J., Sarkar, S., & Chang, S. L. (2012). Opioid receptor expression in human brain and peripheral tissues using absolute quantitative real-time RT-PCR. Drug and alcohol dependence, 124(3), 223–228. https://doi.org/10.1016/j.drugalcdep.2012.01.013.

Poster n.21

Maternal care and pup ultrasonic vocalizations (USVs) as early markers of PTSD susceptibility in rats

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Background: PTSD is a chronic psychiatric disease that may develop following trauma [1,2]. While only a subset of individuals becomes susceptible to PTSD, most fully recover after the initial acute physiological response [3]. Early-life trauma and the quality of maternal caregiving may contribute to intergenerational transmission of stress vulnerability [4]. We examined early maternal care, and early-life offspring behaviors and ultrasonic vocalizations (USVs) in PTSD susceptible (SUS) rats [5,6].

Methods: PTSD-like SUS [5,6] and control (CTRL) Sprague–Dawley female rats and their offspring were used. On post-natal day (PND) 1, litters were culled to a standardized size (4 females and 4 males). Maternal behavior was evaluated across PND 2-13 [7]. In offspring, USVs (30-70 kHz range) and behavior [8] were assessed on PND 5, 7, 9, 11, 13; a separate cohort underwent the homing test (PND 13), during which both USVs and behavior were analyzed.

Results: Compared with CTRL, SUS dams showed an overall increase in maternal care and reduced non-maternal behaviors across PND 2–13. Moreover, SUS pups emitted more USVs at PND 5 and 7 and displayed different behavioral repertoire, consistent with heightened arousal and altered self-directed and motor patterns. In the homing test, SUS pups produced more and longer USVs, while nest-reaching latency and time spent in the nest were comparable between groups.

Conclusions: PTSD susceptibility is accompanied by early changes in maternal care and offspring emotional reactivity. SUS dams provide more caregiving, yet SUS pups display altered distress-related USVs and behavioral responses.

References:

[1] American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders (DSM-5), 5th ed. American Psychiatric Publishing.

[2] Yehuda et al., 2015. Nat Rev Dis Primers, 1:15057.

[3] Lewis et al., 2019. Lancet Psychiatry, 6(3):247–256.

[4] Klengel et al., 2016. Neuropsychopharmacology, 41(1):219–231.

[5] Berardi et al., 2014. Front Behav Neurosci, 8:142.

[6] Colucci et al., 2020. Transl Psychiatry, 10(1):243.

[7] Colucci et al., 2020. Behav Brain Res, 392:112723.

[8] Branchi et al., 2004. Behav Brain Res, 151(1–2):9–16.

Poster n.22

Sex-specific neuroinflammatory and behavioral effects of early-life stress in MAOA^{Neo} mice

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Background. Antisocial behavior involves aggression, comorbid with psychiatric disorders. A key biosocial risk factor is low MAO-A activity (MAOA-L allele) combined with early-life stress (ES) [1]. ES alters neuronal and glial maturation [2], however the early post-stress neuroimmune mechanisms under MAO-A deficiency remain unclear. These alterations may contribute to increased susceptibility to antisocial behaviors in adults, highlighting a gene-by-environment mechanism [3].

Methods. This study investigated the neuroinflammatory responses in the prefrontal cortex (PFC) of WT and MAOA^{Neo} mice, and their potential relationship with long-term antisocial and antidepressant-like behaviors. Males and females were exposed to ES from PND1 to 7, involving maternal separation and mild physical stress. At PND8, PFC tissue was analyzed for microglial marker IBA-1 and cytokines TNF-α, IL-6, and IL-1β using immunoblotting. At PND30, social interaction and antidepressant-like behavior were assessed.

Results. Data suggest a significant impact of sex-dependent differences in the development of pro-inflammatory responses in the PFC at PND8 after ES in MAOA^{Neo} mice. In male MAOA^{Neo} mice, ES induced an increase in IBA-1 but a modest increase in cytokines. Female MAOA^{Neo} mice exhibited heightened baseline microglial activation and a significant upregulation of IL-6 and TNF-α. IL-1β levels remained unchanged across all experimental groups, suggesting a selective cytokine activation profile. At PND30, a main effect of sex emerged on behavioral outcomes, with differences observed in antisocial tendencies and antidepressant-like behavior.

Conclusions. These findings demonstrate that ES and MAO-A deficiency elicit robust sex-specific neuroinflammatory responses in the PFC along with corresponding sex-dependent behavioral changes in adult mice.

References:

[1] Godar et al., 2016. https://doi.org/10.1016/j.pnpbp.2016.01.001.

[2] Reemst et al.,2022. https://doi.org/10.1038/s41398-022-02265-6.

[3] Bortolato et al., 2011. https://doi.org/10.1038/npp.2011.157.

Poster n.23

Acute Immune Stress Modulates Hippocampal Plasticity and Kynurenine Pathway Metabolism in a Sex- and Region-Dependent Manner: The Role of CX3CL1–CX3CR1 Signaling

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Background. LPS administration is a well-established model of acute immune stress, inducing neuroinflammatory and neuroendocrine responses similar to those triggered by psychological or physical stressors. Different stress paradigms exert region-specific effects on ventral (VH) vs dorsal (DH) hippocampus [1]. Inflammatory challenges can modulate the kynurenine pathway (KP) — key metabolic route integrating immune and stress responses — and the CX3CL1–CX3CR1 axis, a crucial regulator of neuron-microglia communication affecting synaptic function [2]. We investigated whether the CX3CR1 receptor plays a central role in modulating sex- and region-dependent hippocampal plasticity and KP activity.

Methods. A mouse model of acute neuroinflammatory stress was established through lipopolysaccharide (LPS) injection in C57BL/6J (WT) and Cx3cr1-/- (KO) mice lacking the microglial CX3CR1 receptor. Twenty-four hours post-injection, Long-Term Potentiation (LTP) was evaluated by extracellular field recordings, and KP metabolite levels were quantified through High-Performance Liquid Chromatography–Electrospray Ionization–Tandem Mass Spectrometry (HPLC-ESI-MS/MS).

Results. In male C57BL/6J mice, LPS increases LTP in VH, shifting tryptophan metabolism towards the neurotoxic branch in both regions. LPS in C57BL/6J female does not affect LTP, while KP modulation was similar to that observed in males. These effects were attenuated or reversed in Cx3cr1-/-, in both sexes.

Conclusions. LPS induced region- and sex-dependent modulation of hippocampal synaptic plasticity and KP activation. The absence of CX3CR1 alters LTP amplitude and mitigates the neurotoxic shift of the KP induced by LPS, highlighting CX3CR1 signaling as a key modulator of neuroimmune interactions underlying stress-related hippocampal plasticity.

References:

[1] Floriou-Servou, A., von Ziegler, L., Stalder, L., Sturman, O., Privitera, M., Rassi, A., Cremonesi, A., Thöny, B., & Bohacek, J. (2018). Distinct Proteomic, Transcriptomic, and Epigenetic Stress Responses in Dorsal and Ventral Hippocampus. Biological psychiatry, 84(7), 531–541. https://doi.org/10.1016/j.biopsych.2018.02.003.

[2] Bridge, S., Karagiannis, S. N., & Borsini, A. (2024). The complex role of the chemokine CX3CL1/Fractalkine in major depressive disorder: A narrative review of preclinical and clinical studies. Brain, behavior, & immunity - health, 38, 100778. https://doi.org/10.1016/j.bbih.2024.100778.

Poster n.24

Molecular signatures of astrocytes and microglia maladaptive response to acute stress are rescued by a single administration of ketamine in a rodent model of PTSD

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Background. Each individual reacts differently to stress, and the individual level of stress increases the risk of developing neuropsychiatric disorders. Stress alters the architecture and functions of the brain through complex neurobiological mechanisms. Given the numerous homeostatic functions involving astrocytes and microglia, understanding their role in the adaptive or maladaptive response to acute stress is critical for the treatment and prevention of stress-related disorders.

Methods. We exposed Sprague-Dawley rats to footshock stress (FS). Baseline sucrose intake was monitored before stress and compared to sucrose consumption after FS, allowing identification of resilient and vulnerable rats. Morphofunctional alterations affecting astrocytes, microglia, and neurons in the prefrontal cortex were investigated 24 and 48 hours after FS. In addition, we examined the effects of a single subanesthetic dose of ketamine (10 mg/kg, i.p.), a fast-acting antidepressant recently proposed for the treatment of stress-related psychiatric disorders.

Results. Results indicated an activation of the NF-κB pathway after FS. This response persisted in vulnerable rats with the alteration of glial proteins such as S100B, CD11b, and CX43; brain factors such as BDNF, GDNF, and FGF2; and proteins related to synaptic architecture such as MAP2 and PSD95. In contrast, resilient rats showed a pro-reparative response characterized by increased TGF-β levels. Ketamine administration rescued many of the changes observed only in vulnerable rats.

Conclusions. Glial reactivity, alterations in neurotrophic factors, and neuronal damage appear as critical factors characterizing vulnerability to acute stress. Ketamine acts as a pro-resilience agent that may protect against the development of stress-induced psychiatric disorders.

Poster n.25

Identify new mechanisms underlying PTSD vulnerability and resilience in rats: the role of TGF-β1 pathway

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Background. Post-traumatic stress disorder (PTSD) is characterized by cognitive and socio-emotional alterations. Individuals who experience a traumatic event all exhibit an acute response, but only a subset of them (susceptible) will develop chronic PTSD. The neurobiological bases of vulnerability/resilience in PTSD are complex with different factors involved including systemic inflammation and oxidative stress. Recently, dysfunction of TGF-β1 pathway has also been hypothesized.

Methods. Male and female susceptible (SUS) and resilient (RES) PTSD-like rat lines previously obtained [1,2], and their corresponding controls (CTRL), were used. Molecular analyses on TGF-β1 signaling in Amygdala (AMY), Dorsal and Ventral Hippocampus (HP-D and HP-V), Prefrontal Cortex (PFC) were performed by WB Analysis of TGF-β1, pSMAD-2, SMAD-2/7 and TGF-β RI, and by RT-PCR analysis of TGF-β1 and TGF-βRII on basal condition. TGF-β1 plasma levels were assessed by ELISA assay.

Results. We found a significant increase in TGF-β1 expression in PFC only in RES male rats vs. CTRL and SUS groups. Further, we observed a significant increase of TGF-β1 expression in both the HP-D and HP-V of RES female rats vs. the correspondent SUS, whereas an increase of TGF-βRI expression was observed in the HP-V of SUS male rats vs. CTRL. qPCR analyses showed an increase in TGF-βRII gene expression in HP-V of RES male and female rats compared to their CTRLs. We also found increased TGF-β1 plasma levels in male RES rats and female SUS rats vs. their correspondent CTRLs.

Conclusions. These preliminary results suggest a potential role for TGF-β1 in the mechanisms underlying PTSD vulnerability/resilience.

References:

[1] Colucci et al., 2020. Transl Psychiatry. 10(1):243.

[2] Chiacchierini et al., 2025. J Neurosci Methods. 416:110380.

Poster n.26

The brain histaminergic system modulates resilience and vulnerability to psychosocial stress

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Background. Under psychosocial stress, individuals employ coping strategies, which can be adaptive or maladaptive. The distinction between susceptibility and resilience to stress may result in psychopathology or the maintenance of normal psychological functioning. Neuromodulators linked to susceptibility/resilience have been identified [1], but the neural mechanisms explaining why some individuals succumb to stress while others remain unaffected are unclear. Histaminergic neurons of the tuberomamillary nucleus (TMNHA) play a key role in modulating stress responses [2], but their role in resilience vs susceptibility is not fully understood.

Methods. Chronic and subthreshold social defeat stress (SDS) paradigms were used. mRNA levels of HA producing/metabolizing enzymes and HA receptors were analysed in the TMN, hippocampus and frontal cortex of SDS vs control mice. Manipulation of TMNHA was achieved using: (i) chemogenetic activation or inhibition of TMNHA via injection of either AAV8-hSyn-DIO-hM3D(Gq)-mCherry or AAV8-hSyn-DIO-hM4D(Gi)-mCherry constructs; (ii) pharmacological manipulations of histamine H3 receptors using the antagonist pitolisant (10mg/Kg) or the agonist VUF16839 (5mg/Kg); (iii) genetic HA depletion in knock-out mice (Hdc-/-). Mice performance was then evaluated in paradigms relevant to cognitive domains.

Results. SDS upregulated selected HA receptors and enzymes expression in the TMN and downregulated them in the cortex and hippocampus. Manipulation of TMNHA neurons influenced stress-induced phenotypes. Chemogenetic or pharmacological activation of TMNHA promoted resilience to chronic SDS-induced deficits, whereas chemogenetic inhibition or genetic silencing of these neurons, using a short SDS paradigm, triggered susceptibility.

Conclusions. The results suggest that the HA system is affected by stress exposure and highlight the involvement of TMNHA in promoting coping behaviour in response to stress-related dysfunctions.

References:

[1] Sandi C, Haller J (2015): Stress and the social brain: behavioural effects and neurobiological mechanisms. Nat Rev Neurosci. 16:290-304.

[2] Rani, B. et al. Brain histamine and oleoylethanolamide restore behavioral deficits induced by chronic social defeat stress in mice. Neurobiol Stress 14, 100317 (2021).

Poster n.27

Trauma-evoked increased neural activity in the basolateral amygdala drives susceptibility to PTSD

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Background. Trauma-associated stimuli trigger defensive responses, whose unsuccessful extinction is a hallmark of PTSD. Hyperactivation of the basolateral amygdala (BLA) has been associated with maladaptive responses to trauma, together with the impaired top-down control by the medial prefrontal cortex (mPFC) [1]. However, the neural underpinnings of individual vulnerability to PTSD are mostly unknown.

Methods. Adult male control (CTRL) or SUS rats (selectively bred for susceptibility to develop PTSD) were used. They underwent a stereotaxic surgery for the infusion of a genetically encoded Ca2+ indicator (AAV-CaMKII-GCaMP6f) or an opsin (AAV-CaMKII-eArchT3.0-eYFP or AAV- CaMKII-eYFP as control) in the BLA. Fiber photometry recordings in the BLA or optogenetic inhibition of BLA terminals in the mPFC (i.e. infralimbic cortex, IL) were performed during a contextual fear conditioning paradigm [2], consisting of trauma exposure (inescapable foot-shocks + social isolation), spaced extinction sessions, reinstatement of fear and reinstatement test.

Results. SUS rats showed increased freezing behavior during all the extinction sessions and reinstatement test. CTRL and SUS rats did not differ in pre-trauma BLA neural activity. SUS rats showed increased spontaneous and cue-evoked BLA activity during all the extinction sessions (day 7, 10, 13 and 16 after trauma) and during the reinstatement test. Optogenetic inhibition of BLA terminals in the IL fosters extinction in SUS rats.

Conclusions. The BLA is a key correlate for PTSD susceptibility and its projections to the IL contribute to trauma extinction in susceptible individuals.

References:

[1] Bloodgood et al (2018) PMID 29507292.

[2] Colucci et al (2020) PMID 32694545.

Poster n.28

Sex-specific vulnerability to early-life single prolonged stress in rats: behavioral outcomes in adolescence and adulthood in rats

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Background. Early-life adverse experiences are a major risk factor for stress-related psychopathologies, including post-traumatic stress disorder (PTSD) [1]. In rodents, the Single Prolonged Stress (SPS) paradigm is widely used to model core PTSD-like features; however, while extensively characterized in adults [2,3], the effects of SPS exposure during critical developmental periods remain underinvestigated. This study investigated the short- and long- term behavioral effects of early-life SPS, with particular emphasis on sex-specific vulnerability.

Methods. Male and female Sprague–Dawley rats were exposed to SPS at postnatal day (PND) 23 or left undisturbed (controls). During adolescence, social behavior, anxious-like behavior, locomotor activity, and fear-associated memory were assessed using the Social Play, Elevated Plus Maze, Open Field, and Auditory Fear Conditioning tests. In adulthood, emotional memory, anxious-like behavior, and emotional reactivity were evaluated using the Inhibitory Avoidance, Light–Dark Box, and Acoustic Startle Response tests.

Results. Early-life SPS reduced social interaction in adolescent rats of both sexes, with more pronounced effects in males. Anxious-like behaviors showed marked sex-specific patterns, with males displaying increased anxiety and behavioral inhibition, whereas females exhibited attenuated responses. Fear learning, extinction, and cognitive performance were not affected in adolescence. In adulthood, males exposed to SPS showed persistent alterations in emotional reactivity, including enhanced startle response and altered risk evaluation, while females largely resembled controls.

Conclusions. Early-life SPS induces sex-specific behavioral alterations in the short- and long- term, primarily affecting social and emotional domains while sparing cognitive function. These findings highlight developmental timing and sex as critical determinants of vulnerability to stress-related psychopathology.

References:

[1] Sherin and Nemeoff (2011). Dialogues in Clinical Neuroscience, 13(3): 263-78.

[2] Mancini et al., (2021). Behavioural Brain Research, 5;401:113096.

[3] Nahvi et al., (2019). Frontiers in Behavioral Neuroscience 13, 17.

Poster n.29

Central and Peripheral Inflammation as Key Mechanisms of Vulnerability in Adult Rats Exposed to Prenatal Stress

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Background. Early-life stress is a major risk factor for psychiatric disorders. In preclinical research, the prenatal stress (PNS) model is widely used to mimic early adversity, inducing long-lasting alterations in brain and behavior. Among these, immune-inflammatory changes and mitochondrial dysfunction have emerged as key mechanisms. Microglia and inflammation are promising therapeutic targets, however, how they contribute to stress vulnerability remains unclear.

Methods. Pregnant rats were exposed to restraint stress during the last week of gestation. In adulthood, male offspring were classified as vulnerable or resilient based on social interaction performance. After behavioral testing, blood, ventral and dorsal hippocampus (VH, DH), and prefrontal cortex (PFC) were collected. Neuroinflammatory markers were analyzed by qRT-PCR and immunofluorescence, while corticosterone and peripheral cytokines were quantified by Luminex and ELISA. Transcriptomic analysis on RNA extracted from blood was performed.

Results. Vulnerable animals displayed reduced sociability and elevated corticosterone levels compared with both control and resilient rats. PNS induced region-specific upregulation of microglial activation and pro-inflammatory cytokines in VH and DH, but not in PFC, correlating with behavioral deficits. Systemically, vulnerable rats exhibited low-grade inflammation, with increased pro-inflammatory and reduced anti-inflammatory cytokines. Blood transcriptomics revealed mitochondrial dysfunction consistent with in situ impairments in VH and DH.

Conclusions. Overall, these findings indicate that region-specific neuroinflammation, systemic immune imbalance, and mitochondrial dysfunction contribute to behavioral vulnerability after prenatal stress, highlighting potential biomarkers and therapeutic targets for early prevention of stress-related psychopathology.

Poster n.30

Neuroplastic mechanisms underlying sex-dependent vulnerability to social reward deficits following social isolation in rats

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Background. In highly social species such as humans and rodents, an adequate social environment is essential for proper neurobehavioral development. The absence or impairment of social stimuli during critical or sensitive developmental stages, such as early life or adolescence, increases susceptibility to neuropsychiatric disorders including anxiety and depression [1,2]. However, the mechanisms underlying sex-dependent vulnerability to early-life social stressors, such as social isolation, remain unclear [3].

Methods. To this aim, we investigated the effects of early-life and adolescent social isolation on social and depressive-like behaviors in female and male rats during adolescence and adulthood and explored the molecular mechanisms involved.

Results. Brief periods of early-life social isolation impaired social reward processing in male rats across development, together with sex-specific molecular changes in limbic brain regions that persist even long after the isolation procedure. While early-life social isolation did not significantly alter general social behavior or induce depressive-like behavior at adulthood, it selectively impaired social reward processing in males and altered the homeostasis of the glutamatergic synapse.

Conclusions. This highlights sex-specific, long-lasting effects of early-life social isolation on social behavior and related molecular pathways, providing insights into differential susceptibility to social adversity.

References:

[1] Orben A, Tomova L, Blakemore SJ. The effects of social deprivation on adolescent development and mental health. Lancet Child Adolesc Health. 2020 Aug;4(8):634-640. doi: 10.1016/S2352-4642(20)30186-3. Epub 2020 Jun 12. PMID: 32540024; PMCID: PMC7292584.

[2] Calado CMSDS, Manhães-de-Castro R, Gouveia HJCB, Nogueira RMTBL, da Silva Souza V, Soares Martins de Lira AV, de Araújo Merencio SM, Lima BMP, Pinto de Oliveira MV, Toscano AE. From the past to the future: The influence of early social deprivation on learning and behavioral development through programming. Brain Res. 2025 Nov 1;1866:149924. doi: 10.1016/j.brainres.2025.149924. Epub 2025 Sep 11. PMID: 40945565.

[3] Beery AK, Zucker I. Sex bias in neuroscience and biomedical research. Neurosci Biobehav Rev. 2011 Jan;35(3):565-72. doi: 10.1016/j.neubiorev.2010.07.002. Epub 2010 Jul 8. PMID: 20620164; PMCID: PMC3008499.

Poster n.31

Modulation of fear extinction under stress: the role of Amygdala-Entorhinal Cortex projections

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Background. Heightened levels of stress disrupt the extinction of traumatic memories1. The amygdala is a primary brain hub activated by stress, which identifies threatening stimuli, and plays a critical role in the regulation of traumatic memory by integrating information with the dorsal hippocampus (dHPC), a fundamental brain structure for contextual learning and fear extinction2,3. The amygdala communicates with the dHPC through indirect projections to the entorhinal cortex (EC)4. This study investigates the impact of stress on fear memory extinction and the role of the amygdala-EC pathway in mediating such effects.

Methods. Male Sprague-Dawley rats underwent a contextual fear conditioning paradigm to associate a context with an aversive experience (i.e. footshocks) and, the following day, exposed to the same context in the absence of the shocks to induce fear extinction (extinction training). To examine the effects of stress, rats were exposed to a swim stress before the extinction training. Optogenetic manipulation was performed under no stress conditions and during swim stress exposure to investigate the role of amygdala-EC projections in driving stress behavioural effects on fear extinction.

Results. Behavioral analyses showed that acute stress impaired fear extinction. Moreover, we found that activation of amygdala–EC projections are sufficient to drive stress-induced fear memory alterations, whereas silencing this circuit prevented the stress-induced impairment of fear extinction.

Conclusions. Our results shed light on the mechanisms underlying stress detrimental effects on fear extinction opening the avenue to investigate new potential tools to treat stress-related psychopathologies.

References:

[1] Maren S & Holmes A et al 2016 NPP 41:58-79.

[2] Roozendaal, B et al 2009 Nat Rev Neurosci 10:423-33.

[3] Milad MR et al 2009 Biol Psychiatry 66:1075-82.

[4] Fyhn M et al 2004 Science 305:1258-64.

Poster n.32

Optogenetic dissection of BLA–IL reciprocal circuits and vCA1 inputs reveals distinct control of trauma memory and extinction in rats

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Background. Traumatic memories are a core feature of post-traumatic stress disorder (PTSD), a condition still lacking fully effective treatments. Key nodes of the rodent fear circuit, the basolateral amygdala (BLA), the infralimbic cortex (IL), and the ventral hippocampus (vHPC), regulate threat detection, emotional responses, and contextual memory. However, the pathway-specific contributions of BLA–IL reciprocal projections and vCA1–IL inputs to trauma memory and its extinction remain unclear.

Methods. Adult male Sprague Dawley rats were exposed to a validated PTSD-like protocol consisting of unpredictable foot-shocks followed by prolonged single-housing. Extinction of trauma-associated memory was evaluated across spaced sessions on days 7, 10, 13, and 16 after trauma. Using pathway-specific optogenetics, in a first experiment we silenced BLA→IL or IL→BLA projections during extinction memory consolidation (immediately after the first three extinction sessions) and in a second one stimulated vCA1→IL projections during extinction learning. Freezing behavior was measured during extinctions as an index of fear memory retention. Fear-related ultrasonic vocalizations (USVs) and social interaction were also assessed, with the latter measured 18 days after trauma.

Results. Optogenetic inhibition of BLA→IL projections reduced freezing and fear-related USVs, whereas inhibition of IL→BLA projections increased freezing. In a separate experiment, stimulation of vCA1→IL projections during extinction learning led to a reduction of both freezing and fear-related USVs.

Conclusions. These findings demonstrate that IL-centered circuits exert pathway-specific control over traumatic memory processing, with IL exerting a top-down control over BLA and vCA1-IL facilitating extinction learning. The study offers mechanistic insight into circuit-level therapeutic strategies for PTSD.

References:

[1] Giustino, T. F. and S. Maren (2015). "The Role of the Medial Prefrontal Cortex in the Conditioning and Extinction of Fear." Front Behav Neurosci 9: 298.

[2] Dixsaut, L. and J. Gräff (2021). "The Medial Prefrontal Cortex and Fear Memory: Dynamics, Connectivity, and Engrams." Int J Mol Sci 22(22).

Poster n.33

Severity of depressive symptoms by perceived stress and gut microbiota composition: A sex-stratified Bayesian approach in a non-clinical sample

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Background. Gut dysbiosis, an imbalance in gut microbiota, is increasingly linked to depression through the microbiota-gut-brain (MGB) axis. Stress is an important risk factor for both gut dysbiosis and depression. Despite evidence of altered gut microbiota composition in patients with depression, little is known about how stress and specific gut microbiota features interact to influence depressive symptoms in healthy individuals.

Methods. This study examined 398 healthy adults (241 women) who provided stool samples and completed validated questionnaires on perceived stress (PSS) and depressive symptoms (CES-D), with a focus on sex differences. In this sample, men and women were characterized by similar gut microbiota composition and diversity.

Results. Women reported higher PSS scores than man, whereas no differences were found in CES-D scores. Using Bayesian analyses, results showed that perceived stress predicted depressive symptoms in both sexes. Notably, in women, the genus Eubacterium moderated this relationship: higher perceived stress combined with lower Eubacterium abundance predicted more severe depressive symptoms. In contrast, no moderations by gut bacteria were found in men.

Conclusions. The current results warrant further sex-specific investigations of the interaction between stress and specific gut microbiota features in influencing depressive symptoms and suggest that strategies for influencing the gut microbiota might consider the genus Eubacterium as a promising microbial target associated with depression, particularly in women under higher stress levels.

References:

[1] Cryan, John F et al. "The Microbiota-Gut-Brain Axis." Physiological reviews vol. 99,4 (2019).

[2] Sanada, K et al. "Gut microbiota and major depressive disorder: A systematic review and meta-analysis". Journal of Affective Disorders, 266, 1–13 (2020).

Poster n.34

An antidote for chronic stress may root in chicory roots

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Background. The gut-brain axis represents a promising target for dietary interventions to preserve cognitive function and motivation under chronic stress conditions[1]. Prebiotics such as fructans can modulate gut microbiota composition and increase short-chain fatty acid (SCFA) production[2,3]. We investigated whether the consumption of chicory taproots - particularly rich in fructans - could contrast cognitive and motivational impairments induced by chronic corticosterone (CORT) administration in mice, the latter mimicking chronic stress.

Methods. Male C57BL/6 mice (n=18/group) received chronic CORT supplementation (35 μg/mL) in drinking water and were fed either a standard diet or a diet enriched with chicory taproots. We assessed cognitive and motivational functions using a test battery including fixed ratio (FR), progressive ratio (PR), attentional set-shifting task (ASST) and Barnes maze test. Gut microbiota composition (16S rRNA sequencing), faecal SCFA concentrations, gene expression of epigenetic regulators (miR-29b/29c, miR-132/212) and target genes (Cnr1, Bdnf) in hippocampus and prefrontal cortex were analysed.

Results. CORT dysregulated HPA axis reactivity to restraint stress (10-15-fold elevated baseline, paradoxical suppression upon restraint). Chicory consumption reduced baseline CORT concentrations ($p<.05$), mitigated CORT-induced deficits in associative learning (FR: $p<.0001$), motivation (PR: $p=.007$), and executive functions (ASST: $p=.016$). Chicory consumption promoted the growth of selective bacteria which elevated SCFA concentrations ($p=.013$). These changes correlated with increased hippocampal miR-29c-3p expression ($p=.007$) and Cnr1 gene expression ($p=.01$).

Conclusions. Our results establish a mechanistic pathway whereby prebiotic-induced microbiota alterations and SCFA elevation restore hippocampal Cnr1 expression and normalise HPA axis dysfunction, effectively reversing chronic stress-induced cognitive and motivational deficits.

References:

[1] PMID:25392516

[2] PMID:28165863

[3] PMID:8813896

Poster n.35

HeartSync: A Validated Platform for Automated Integration of Heart Rate Variability and Ecological Momentary Assessment Data for Stress Research

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Background. We introduce HeartSync, a desktop application that automates the coding of heart rate variability (HRV) for Experience Sampling Method (ESM) studies, representing a valuable alternative to slow, error-prone workflows based on manual file handling and visual inspection.

Methods. The reliability of the software was investigated in a double coding one-day ambulatory study (N = 96; 741 ESM-anchored windows). The same ESM data were coded using standard hand methods, and HeartSync. The software automatically segmented RR intervals relative to questionnaire times and computed standard HRV indices. For benchmarking, we compared HeartSync's HRV outputs with those produced by Kubios HRV using complementary agreement and convergence analyses, including intraclass correlation coefficients (ICC), Pearson correlations at the between-person and within-person levels, Bland–Altman analysis, and multilevel models estimated with identical specifications across outcomes.

Results. Intraclass correlations indicated strong alignment at the level of single measurements (ICC(3,1) = 0.843, 95% CI [0.821, 0.863]) and even higher consistency for averaged values (ICC(3,2) = 0.915, 95% CI [0.902, 0.926]). Correlations showed near-identity in between-person differences ($r = .981$, $p < .001$) and clear correspondence in within-person fluctuations across windows ($r = .502$, $p < .001$). Bland–Altman analysis suggested minimal average difference (bias = 0.19 ms; 95% CI −0.28, 0.66) with most paired observations falling within approximately ±13 ms. Multilevel models reproduced the same pattern of associations with age, BMI, posture, and negative affect when estimated on either set of HRV values.

Conclusions. Taken together, the results indicate that HeartSync provides accurate HRV estimates while greatly streamlining HRV–ESM integration for large-scale, intensive longitudinal studies in stress research.

Poster n.36

Home telemonitoring SmartMe&You program reveals that heart rate 24-hour dynamics are associated with cognitive status, sedentariness, and vigilance regulation in older people

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Background. Chronic stress is a key risk factor for cognitive decline in patients with neurodegenerative diseases. Among other effects, it impairs the autonomic nervous system (ANS) regulation of heart rate (HR) variability and cardiac adaptability. This study examined the relationship between HR dynamics, daily motor activity as a measure of sedentariness, and resting- state EEG (rsEEG) rhythms, as a measure of vigilance regulation systems, and cognitive performance in cognitively unimpaired older (Healthy) people and patients with Alzheimer's (ADCD) and Parkinson's (PDCD) diseases and cognitive deficits.

Methods. Within the eBRAIN-Health, PREDICT-NEURODEGEN, and TELEMAIA projects, supported by Rome Technopole project, 17 Healthy, 39 ADHD, and 45 PDD-NOS participants underwent one week of SmartMe&You home telemonitoring of dementia risk factors. HR and steps were continuously recorded via a Samsung Galaxy Watch 6. Cognitive performance was monitored through seven tablet-based serious videogames. Biomarkers included rsEEG measures.

Results. Compared to the Healthy group, the ADCD and PDCD groups showed lower differences in HR between nighttime and daytime. This effect was associated with lower daily step counts and increased rsEEG delta activity.

Conclusions. Reduced 24-hour HR variability, measured in ADCD and PDCD patients during one- week home telemonitoring, was a clinically relevant variable associated with sedentariness risk and brain dysfunctions of vigilance in quiet wakefulness. The SmartMe&You home telemonitoring platform enables remote, ecologically valid monitoring of dementia risk factors in the aged population.