TITOLO E ABSTRACT TEMA DI RICERCA DOTTORANDI DEL CORSO DI DOTTORATO DI RICERCA IN NEUROSCIENZE

XL ciclo (A.A. 2024/25)

Carlo Maria Bellanca

Tema di ricerca: *Exploring the complex interplay between substance use disorders and neuropsychiatric conditions: would preventing drug-drug interactions and implementing pharmacogenomic approaches lead to a personalised medicine?*

Abstract: Substance Use Disorders (SUDs) frequently co-occur with neuropsychiatric conditions such as depression, anxiety, and schizophrenia spectrum disorders. Such comorbidity represents a major clinical challenge, as it significantly complicates both diagnosis and treatment planning. The therapeutic management of patients with dual diagnosis often involves complex pharmacological regimens, increasing the risk of drug-drug interactions (DDIs), adverse drug reactions (ADRs), treatment resistance, and poor adherence. This picture is further complicated by the fact that compounds resulting from the use of certain substances can themselves affect xenobiotic metabolism. As an example, nicotine and polycyclic aromatic hydrocarbons (PAHs) are among the most well-documented compounds found in tobacco products. More than five hundred different PAHs have been identified in tobacco smoke compounds consisting of two or more benzenoid rings, reported as carcinogenic and mutagenic agents.

PAHs primarily influence metabolism by inducing the activity of hepatic cytochrome P450 (CYP450) enzymes, a family of haemoproteins involved in phase I reactions of drug biotransformation and xenobiotic detoxification. Additionally, uridine diphosphate (UDP)-glucuronosyltransferases (UGTs), enzymes responsible for phase II reactions with special regard to glucuronidation, can also be affected by PAHs. Specific CYP450 isoenzymes, such as CYP1A1, 1A2, 1B1, and 2E1, may be implied. As PAHs increase the activity of CYPs, drugs metabolised by these enzymes are cleared more rapidly, resulting in decreased blood concentrations. This would require careful therapeutic monitoring and potential dose adjustment.

It is worth noting that psychiatric conditions, together with genes that are involved in regulating brain chemical systems; neurobiological mechanisms, such as cross-tolerance and cross-sensitization to substances; conditioning mechanisms, in which craving are elicited by certain environmental cues may contribute to concurrent use of substances.

Clearly, this complex clinical scenario requires integrated pharmacological management. However, current therapeutic strategies often neglect the interplay between pharmacotherapies for SUDs and psychiatric medications.
Based on these premises, the research project aims to explore the pharmacokinetic and pharmacodynamic interactions between medications used for SUDs, psychiatric disorders, and the potential influence of genetic factors that may affect treatment outcomes.
Pharmacotherapies for SUDs – including varenicline, cytisine, bupropion, nicotine replacement therapy (NRT), methadone, naltrexone, nalmefene, acamprosate, disulfiram, topiramate – act on overlapping neurobiological circuits, primarily involving dopaminergic, serotonergic, glutamatergic, GABAergic, and opioidergic systems. Varenicline, a α4β2 nicotinic receptors partial agonist, has been observed to reduce alcohol craving in some individuals; however, it has also been associated with adverse neuropsychiatric effects. Bupropion, a norepinephrine-dopamine reuptake inhibitor, has been found to be effective in treating across different substance use profiles, although it increases the risk of seizures when combined with alcohol. Naltrexone, a μ-opioid receptor antagonist, may attenuate craving, particularly in individuals carrying μ-Opioid Receptor Gene (OPRM1) polymorphisms, but is contraindicated in patients with opioid use disorder (OUD). Acamprosate, a N-methyl-D-aspartate (NMDA) receptor antagonist, aids the restoration of normal glutaminergic neuron activity, appearing safe in liver-impaired patients and having potential cross-benefits for nicotine use. These medications often interact with antidepressants, antipsychotics, and mood stabilizers, leading to either attenuation or potentiation of therapeutic effects, as well as increased risk of ADRs.
In this field, emerging evidence highlights the role of genes in modulating addiction vulnerability and pharmacological response. Therefore, genetic profiling may offer new avenues for personalised treatment. A deeper understanding of how medications for SUDs interact with psychiatric pharmacotherapies is essential for improving outcomes in this highly vulnerable population.
In conclusion, this project would emphasize the need for a multidimensional and individualised approach in managing SUDs in patients with psychiatric comorbidities. Indeed, a better understanding of DDIs and genetic factors is crucial for optimising therapeutic outcomes and reducing the burden of these disorders.

Camilla Coraddu

Tema di ricerca: *Ruolo del sistema endocannabinoide nello sviluppo del sistema dopaminergico mesolimbico del ratto*

Abstract (ITA): Il sistema endocannabinoide (ECB) svolge un ruolo cruciale nel funzionamento del sistema nervoso centrale (SNC) e nel suo sviluppo. Durante la vita prenatale, questo sistema è infatti coinvolto nell'ontogenesi, nella proliferazione e differenziamento cellulare, nella migrazione, nella potatura e nella formazione delle reti neuronali.

Anche il sistema dopaminergico esercita un ruolo importante nello sviluppo del SNC. Alterazioni di entrambi i sistemi sono state riscontrate in alcuni disturbi del neurosviluppo, come il disturbo da deficit dell'attenzione e iperattività (ADHD) e quello dello spettro autistico (ASD). Ad oggi, tuttavia, non è del tutto noto come l'interazione tra questi sistemi, se modificata durante la vita prenatale, possa contribuire alla manifestazione di questi disturbi. Le attuali evidenze scientifiche suggeriscono che le alterazioni del segnale ECB, in seguito all'attivazione diretta dei recettori dei cannabinoidi di tipo 1 da parte di alcuni agonisti esogeni (e.g., principi attivi contenuti nella cannabis), durante la vita prenatale siano in grado di modificare le funzioni dopaminergiche. Tuttavia, non è chiaro se altri tipi di modulazione del sistema ECB durante il neurosviluppo prenatale possano influenzare lo sviluppo del sistema dopaminergico del nascituro. Lo scopo del mio progetto di ricerca è di cercare di colmare questa lacuna, investigando il ruolo che il sistema ECB ha sullo sviluppo del sistema dopaminergico mesolimbico del ratto. A tal fine intendo modulare indirettamente il segnale ECB durante la vita prenatale tramite un trattamento farmacologico delle ratte gravide, a partire dal sedicesimo giorno di gravidanza fino al settimo giorno dopo il parto. Questa scelta è di tipo traslazionale perché nell'uomo questo periodo coincide con il secondo e il terzo trimestre di gravidanza. Durante questa finestra temporale, nelle ratte gravide, si procederà con la modulazione dei livelli degli ECB mediante l'inibizione farmacologica o del loro trasportatore o dell'enzima di degradazione. Per valutare i potenziali effetti dannosi di un alterato segnale ECB prenatale sul sistema dopaminergico, gli esperimenti verranno condotti sulla prole in età preadolescenziale (tra il quattordicesimo e il ventottesimo giorno di vita), in quanto questa rappresenta una finestra del neurosviluppo estremamente vulnerabile, perché caratterizzata da un'elevata plasticità cerebrale. Gli esperimenti verranno effettuati in soggetti di entrambi i sessi per capire se il fattore sesso gioca un ruolo nella manifestazione o prevenzione di questi disturbi. Sugli animali verranno effettuati test comportamentali per svelare un potenziale deterioramento del comportamento sociale, un eventuale comportamento ripetitivo e/o possibili mutamenti della funzione sensorimotoria. Saranno inoltre condotte analisi di immunoistochimica e biologia molecolare per analizzare l'espressione della proteina Netrina-1 e del suo recettore DCC (deleted in colorectal cancer), che sono implicati nella migrazione e nell'organizzazione spaziale e funzionale del sistema dopaminergico mesolimbico. Infine, verranno effettuate delle registrazioni elettrofisiologiche dai neuroni dopaminergici mesolimbici ex vivo per valutare la loro attività spontanea. Questo studio si propone di migliorare le conoscenze riguardo le interazioni tra il sistema ECB e dopaminergico durante lo sviluppo prenatale e potrebbe svelare nuovi punti chiave per comprendere meglio la causa e la manifestazione di disturbi del neurosviluppo, cruciali per potere identificare nuove strategie terapeutiche.

Abstract (ENG): The endocannabinoid system (ECB) plays a crucial role in the functioning and the development of the central nervous system (CNS). During the prenatal life, this system is involved in ontogenesis, as well as in cell proliferation and differentiation, migration, pruning, and formation of neural networks. The dopaminergic system also plays an important role in the development of the CNS. Alterations of both ECB and dopaminergic systems have been observed in neurodevelopmental disorders, such as Attention Deficit Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD).

However, to date, it is not entirely clear how the interaction between these systems, if altered during prenatal life, may contribute to the manifestation of these disorders. Scientific evidence suggests that alterations of ECB signaling upon direct activation of type 1 cannabinoid receptors by exogenous agonists (e.g., active compounds of cannabis), during prenatal life, affect dopaminergic functions. However, it is not known whether other potential modulations of the ECB system during prenatal neurodevelopment might influence the development of dopaminergic system of the offspring. The aim of my research project is to fill this gap by investigating the role of ECB in the development of the mesolimbic dopaminergic system. To this purpose, I will indirectly modulate ECB signaling during prenatal life through a pharmacological treatment of rat dams, starting from the gestational day sixteen (GD16) until the postnatal day seven (PND7). The choice of this regimen is translational, because this period coincides with the second and third trimesters of pregnancy in humans. During this time window, rat dams will be administered with either a pharmacological inhibitor of the transporter or of ECB degrading enzyme. To evaluate the potential detrimental effects of altered prenatal ECB signaling on dopaminergic system, experiments will be carried out on the offspring at preadolescence (PND14-28), as this represents a sensitive window of neurodevelopment, characterized by high plasticity. Experiments will be conducted in both sexes to determine whether sex plays a role in the manifestation or prevention of these disorders. Behavioral tests will be performed on the offspring to reveal potential impairments of social behavior, repetitive behavior, and/or changes in sensorimotor gating function. Furthermore, immunohistochemistry and molecular biology analysis will be conducted to examine the expression of Netrin-1 and its receptor DCC (deleted in colorectal cancer), which are involved in the migration and the temporal and functional organization of mesolimbic dopaminergic system. Finally, to evaluate the spontaneous activity of mesolimbic dopaminergic neurons electrophysiological recordings will be performed ex vivo. This study aims to improve our understanding of the interactions between the ECB and dopaminergic system during prenatal development, and could reveal new insights to better discern the causes and the manifestations of neurodevelopmental disorders, which are crucial for pinpoint novel therapeutic strategies.

Giorgia Ferniani

Tema di ricerca: *Disease-modifying therapies in a preclinical model of Parkinson's Disease based on alpha-synuclein overexpression*

Abstract: Parkinson's Disease (PD) is a progressive neurodegenerative disorder characterized by motor dysfunction and accumulation of misfolded alpha-synuclein (α-syn) protein within Lewy bodies, particularly along the nigrostriatal dopaminergic pathway. Preclinical models based on α-syn overexpression (via adeno-associated viral vectors) effectively replicate key pathological features of human PD, including α-syn aggregation, dopaminergic neurodegeneration in the substantia nigra, and neuroinflammation, thereby providing a reliable tool for studying the pathogenesis of the disease and evaluating potential disease-modifying therapies.

Our research is currently focused on two main lines of investigation. The first explores the role of neurosteroids in the context of PD, aiming at elucidating their involvement in neurodegeneration and assessing their potential as therapeutic targets for neuroprotection. The second line examines the effects of D-serine —an endogenous modulator that acts as a co-agonist on the NR1 subunit of NMDA receptors— on the NMDA receptor function, aiming at clarifying its effect on glutamatergic neurotransmission and synaptic alterations associated with the disease, as well as its impact on neuroinflammation and neurodegeneration.

Elisa Meloni

Tema di ricerca: *Evaluation of novel NKCC1 inhibitors for the treatment of ADHD and comorbid neuropsychiatric disorders*

Abstract: This project aims to characterize selective and potent inhibitors of the chloride transporter NKCC1 through a series of highly innovative preclinical and translational assays targeting the core symptom triad of ADHD: attention deficits, impulsivity, and hyperactivity. These neurobehavioral domains will be investigated using the Spontaneously Hypertensive Rat (SHR), the animal model with the highest face, construct, and predictive validity for ADHD, providing a robust platform for evaluating therapeutic efficacy of NKCC1 modulators. Behavioral assessments will be complemented by a series of molecular analyses to elucidate the mechanisms through which these compounds mitigate ADHD-like phenotypes. Given the multifactorial aetiology of ADHD—which encompasses both genetic predispositions and environmental risk factors—the study will also assess the efficacy of these drugs in environmentally induced models that replicate the onset and progression of symptoms observed in patients, such as those based on chronic stress and sleep deprivation exposures. Behavioral experiments will be carried out at the Guy Everett Laboratories of the University of Cagliari (UNICA), while pharmacokinetic and post-mortem molecular analyses will be conducted at the laboratories of IAMA Therapeutics.

Siwac Ankit

Tema di ricerca: *Effects of environmental pollutants on brain and behavior: focus on micro/nanoplastics*

Abstract (ENG): Over the past 20 years, there has been an increase in mental illnesses and neurological conditions in the countries bordering the Mediterranean Sea, one of the seas most affected by marine pollutants of anthropogenic origin in the world. According to the Horizon2020 Mediterranean Report, many human activities are degrading the Mediterranean Sea, contributing to the accumulation and diffusion of anthropogenic pollutants in the entire region, as recently described for microplastic hotspots.

Exposure to pollutants, in turn, threatens the health and well-being of people living along the coast, among which the incidence of psychiatric illnesses is recently increased. Numerous studies indicate adverse associations between pollution and mental illnesses; yet the biological mechanistic pathways responsible remain elusive. However, pollutants are persistent sources of neuroinflammation and reactive oxygen species production, two processes that are strongly related to the pathogenesis of brain diseases. We hypothesize that pollutants present in the Mediterranean Sea, like pesticides (e.g., glyphosate) and microplastics, expose nearby populations to an increased risk of brain dysfunctions and maladaptive behaviors. By using both drosophila and rodent models, the project aims to investigate whether exposure to micro/nanoplastics contributes to variations in brain functions and behavior by interfering with synaptic processes, causing neuroinflammation, and disrupting neurotransmission systems.

Abstract (ITA): Negli ultimi 20 anni, si è registrato un aumento delle malattie mentali e delle patologie neurologiche nei paesi che si affacciano sul Mar Mediterraneo, uno dei mari più colpiti al mondo dagli inquinanti marini di origine antropica. Secondo il Rapporto Horizon 2020 sul Mediterraneo, numerose attività umane stanno degradando il Mar Mediterraneo, contribuendo all'accumulo e alla diffusione di inquinanti antropici nell'intera regione, come recentemente descritto per gli hotspot di microplastiche. L'esposizione agli inquinanti, a sua volta, minaccia la salute e il benessere delle persone che vivono lungo la costa, tra le quali l'incidenza di malattie psichiatriche è recentemente aumentata. Numerosi studi indicano associazioni negative tra inquinamento e malattie mentali; tuttavia, i sottostanti meccanismi biologici responsabili rimangono poco chiari. Tuttavia, gli inquinanti sono fonti persistenti di neuroinfiammazione e produzione di specie reattive dell'ossigeno, due processi fortemente correlati alla patogenesi delle malattie cerebrali. Ipotizziamo che gli inquinanti presenti nel Mar Mediterraneo, come i pesticidi (ad esempio il glifosato) e le microplastiche, espongano le popolazioni vicine ad un aumentato rischio di disfunzioni cerebrali e comportamenti disadattivi. Utilizzando modelli sia di drosofila che di roditori, il progetto mira a indagare se l'esposizione a micro/nanoplastiche contribuisca a variazioni nelle funzioni cerebrali e nel comportamento interferendo con i processi sinaptici, causando neuroinfiammazione e disturbando i sistemi di neurotrasmissione.

XXXIX ciclo (A.A. 2023/24)

Khosro Aminzadeh

Tema di ricerca: *Research theme: Targeting Neuroinflammation and Microglial Modulation in neurodegeneration*

Abstract: Parkinson's disease (PD) is a progressive neurodegenerative disorder primarily affecting individuals in later life. It is clinically characterized by bradykinesia, resting tremor and muscular rigidity. In addition to motor impairments, PD is associated with a range of non-motor features, including hyposmia (loss of smell), sleep disturbances (REM sleep

behavior disorder), mood disorders, sialorrhea, constipation, and excessive periodic limb movements during sleep.
Epidemiological data suggest that PD affects approximately 1% of the population over the age of 60. Neuropathologically, the disease is marked by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and the accumulation of intraneuronal protein aggregates known as Lewy bodies, primarily composed of misfolded α-synuclein. Although neurodegenerative diseases such as PD exhibit distinct pathogenic mechanisms—including differing protein aggregates and genetic factors—they commonly share a hallmark of sustained, chronic neuroinflammation.
The overarching goal of our research is to advance the understanding of the neuropathological mechanisms underlying PD, with a particular focus on identifying molecular targets for neuroprotective interventions. Our work centers on elucidating the role of microglia, the resident immune effector cells of the central nervous system, in PD pathogenesis. While microglia are known to contribute to neuronal degeneration through the adoption of pro-inflammatory phenotypes, we aim to investigate whether their function can be pharmacologically modulated to promote neuroprotective responses.
To this end, we are exploring the therapeutic potential of Immunomodulatory Imide Drugs (IMiDs), a class of compounds with emerging evidence of beneficial effects in preclinical models of neurodegenerative diseases. We propose IMiDs as a novel therapeutic strategy capable of modulating microglial function to attenuate neuroinflammation and support neuronal survival in PD.
Our experimental approach integrates pharmacological intervention with a comprehensive methodological framework, including behavioral assessments and immunohistochemical analyses. These techniques are applied in a well-established preclinical model of PD, which involves the stereotaxic infusion of toxic preformed oligomers of human α-synuclein (H-αSynOs) into the SNpc to induce progressive dopaminergic neurodegeneration and recapitulate key pathological features of the disease.

Enrico Ginelli

Tema di ricerca: *Biomarcatori neurobiologici e psicologici nei disturbi psichiatrici*

Abstract (ITA): La ricerca sui disturbi psichiatrici rappresenta una priorità emergente, considerata l'elevata prevalenza, l'impatto sociale e il carico di disabilità associati a queste condizioni. Il mio progetto di dottorato si inserisce nell'ambito della ricerca traslazionale in psichiatria, con l'obiettivo di indagare il ruolo di biomarcatori neurobiologici (come fattori neurotrofici e marcatori infiammatori) e psicologici (tra cui tratti di personalità e profili cognitivi) nell'ambito dei disturbi psichiatrici maggiori. Durante il primo anno ho contribuito a uno studio clinico sull'efficacia della stimolazione magnetica transcranica (TMS) nei pazienti con depressione resistente, esplorando in particolare la relazione tra BDNF e risposta clinica. Attualmente, sto conducendo un progetto presso l'Università di Graz (Austria) focalizzato sul disturbo bipolare, volto ad analizzare l'interazione tra profili temperamentali e marcatori infiammatori nella modulazione del rischio e della risposta al

trattamento. L'obiettivo finale è contribuire alla definizione di modelli integrati di comprensione e stratificazione dei pazienti psichiatrici, utili per lo sviluppo di approcci personalizzati.

Abstract (ENG): Research on psychiatric disorders is an emerging priority, given their high prevalence, social impact, and substantial burden of disability. My PhD project is part of a translational research approach in psychiatry, aimed at exploring the role of neurobiological (e.g., neurotrophic and inflammatory markers) and psychological (e.g., personality traits and cognitive profiles) biomarkers in major psychiatric disorders. During my first year, I contributed to a clinical study on the efficacy of transcranial magnetic stimulation (TMS) in treatment-resistant depression, with a specific focus on the association between BDNF and clinical response. I am currently conducting a research project at the University of Graz (Austria) focused on bipolar disorder, investigating the interplay between affective temperament and inflammatory markers in shaping risk and treatment outcomes. The ultimate goal is to contribute to the development of integrated models for understanding and stratifying psychiatric patients, in support of precision psychiatry.

Daniele Pala

Tema di ricerca: *Ruolo del Sistema Endocannabinoide nella Risposta al Trattamento con Anticorpi Monoclonali anti-CGRP nei Disturbi Emicranici*

Abstract (ITA): Il progetto di ricerca del dottorando è incentrato sull'esplorazione degli effetti farmacodinamici degli anticorpi monoclonali contro il peptide correlato al gene della calcitonina (CGRP) nel trattamento dell'emicrania, con particolare attenzione alla loro interazione con il sistema endocannabinoide (ECS). Sebbene i mAbs anti-CGRP abbiano rappresentato un importante progresso nella terapia preventiva dell'emicrania, i loro effetti biologici più ampi, in particolare sul sistema dei neuromodulatori endogeni, non sono ancora del tutto chiariti. Considerata la documentata implicazione dell'ECS nella modulazione del dolore e nella fisiopatologia dell'emicrania, il progetto mira a valutare se il trattamento con mAbs anti-CGRP possa indurre modificazioni nei livelli plasmatici di endocannabinoidi e mediatori lipidici strutturalmente correlati.
Lo studio viene condotto nell'ambito di una coorte clinica prospettica in condizioni di real-life, reclutando pazienti affetti da emicrania episodica ad alta frequenza (HFEM), emicrania cronica (CM) e cefalea da uso eccessivo di farmaci (MOH). I campioni ematici vengono raccolti al basale (prima dell'inizio del trattamento) e dopo 3 e 6 mesi di terapia con anticorpi monoclonali (erenumab, fremanezumab o galcanezumab). Oltre agli esiti clinici (giorni di emicrania, intensità del dolore, scale di disabilità come MIDAS e HIT-6, uso di farmaci), viene effettuata un'analisi quantitativa dei livelli plasmatici di endocannabinoidi chiave (come l'anandamide, AEA) e di altri mediatori lipidici non cannabinoidi tramite cromatografia liquida ultra-performante accoppiata alla spettrometria di massa tandem (UPLC-MS/MS).
I risultati preliminari mostrano una riduzione dei livelli circolanti di endocannabinoidi dopo il trattamento con mAbs, suggerendo un adattamento compensatorio del sistema endocannabinoide.

Questa osservazione è coerente con il meccanismo proposto secondo cui l'AEA, attivando i recettori CB1 sui terminali presinaptici dei neuroni trigeminali, inibisce la trasmissione nocicettiva e il rilascio di CGRP. Neutralizzando farmacologicamente il CGRP, i mAbs potrebbero ridurre la necessità di un'inibizione endogena da parte dell'ECS, modulando così l'omeostasi del segnale lipidico.
Nel complesso, il progetto mira a chiarire una nuova dimensione del profilo farmacologico delle terapie anti-CGRP, con l'obiettivo di identificare nuovi biomarcatori di risposta e approfondire la comprensione degli adattamenti neurochimici che accompagnano il trattamento dell'emicrania cronica.
Abstract (ENG): The PhD candidate's research focuses on exploring the pharmacodynamic effects of calcitonin gene-related peptide (CGRP) monoclonal antibodies (mAbs) in the treatment of migraine, with a specific emphasis on their interaction with the endocannabinoid system (ECS). While anti-CGRP mAbs have significantly advanced preventive therapy for migraine, their broader biological impact, particularly on endogenous neuromodulatory systems, remains incompletely understood. Given the well-documented involvement of the ECS in the modulation of pain and migraine pathophysiology, this project investigates whether anti-CGRP mAb treatment alters circulating levels of endocannabinoids and structurally related lipid mediators.
The research is conducted within a real-world, prospective clinical framework, enrolling patients diagnosed with high-frequency episodic migraine (HFEM), chronic migraine (CM), and medication overuse headache (MOH). Blood samples are collected at baseline (prior to treatment), and at 3 and 6 months after initiating anti-CGRP mAb therapy (erenumab, fremanezumab, or galcanezumab). Clinical outcomes, including migraine days, pain intensity, disability scores (MIDAS, HIT-6), and medication use, are assessed alongside quantitative analysis of plasma levels of key endocannabinoids (such as anandamide, AEA) and other non-cannabinoid lipid signaling molecules using ultra-performance liquid chromatography–tandem mass spectrometry (UPLC-MS/MS).
Preliminary findings indicate a reduction in circulating endocannabinoid levels following anti-CGRP treatment, suggesting a compensatory adaptation of the ECS. This is interpreted in light of the proposed mechanism by which AEA, via activation of CB1 receptors on presynaptic terminals of trigeminal neurons, inhibits nociceptive transmission and CGRP release. By pharmacologically neutralizing CGRP, mAbs may reduce the need for endogenous inhibition by the ECS, thus modulating lipid signaling homeostasis.
Overall, the project aims to elucidate a novel dimension of the pharmacological profile of anti-CGRP therapies, potentially uncovering new biomarkers of response and furthering our understanding of the complex neurochemical adaptations underlying chronic migraine treatment.

Francesco Salis

Tema di ricerca: *Trattamento farmacologico del disturbo da uso di alcol, medicina di genere e valutazione psicogeriatrica in diversi modelli di invecchiamento*

Abstract (ITA): La mia attività di ricerca è dedicata a due principali filoni tematici nel campo delle neuroscienze: il disturbo da uso di alcol (DUA) e la psicogeriatria in vari modelli di invecchiamento, con particolare attenzione alla medicina di genere.
Il filone relativo al DUA si pone l'obiettivo di valutare l'efficacia dei trattamenti disponibili per tale patologia e di esplorare tematiche di salute pubblica, quali differenze di genere, strategie dedicate al management delle donne affette, e consapevolezza dell'alcol come fattore di rischio oncologico. In particolare, lo studio del trattamento combinato farmacologico e non farmacologico nel DUA è stato svolto attraverso un approccio di revisione sistematica della letteratura e metanalisi, che dimostra l'efficacia e la sicurezza di tale combinazione rispetto ai singoli trattamenti. Studi cross-sectional hanno indagato potenziali differenze di genere in soggetti affetti da DUA, dimostrando la maggior prevalenza di comorbilità psichiatriche nei soggetti di sesso femminile, ed esaminato la limitata disponibilità, nel territorio nazionale, di strategie dedicate alla gestione di donne con DUA.
Il tema dell'alcol come fattore di rischio per malattie neoplastiche è stato affrontato attraverso un trial clinico, che ha dimostrato l'efficacia di un sito web appositamente sviluppato nell'aumentare la consapevolezza delle donne in merito al legame tra uso di alcol e carcinoma della mammella. Ulteriori progetti sono in corso per approfondire la relazione tra tale neoplasia e uso di alcol, attraverso la valutazione del microbioma e dello stato ossidativo plasmatico.
Il filone relativo alla psicogeriatria mira a ottimizzare strategie di screening, diagnosi e trattamento di patologie neuropsichiatriche in diversi modelli di invecchiamento. In particolare, sono in corso studi cross-sectional sull'applicazione di strumenti di screening cognitivo di primo livello in soggetti anziani e HIV-infetti, i cui risultati preliminari suggeriscono la necessità di disporre di test capaci di indagare differenti domini cognitivi in base alle specifiche eziologie sottostanti il disturbo neuro cognitivo. Essi suggeriscono altresì associazioni tra declino cognitivo, disturbo depressivo e trattamento con antidepressivi. Inoltre, è in corso un'indagine sull'efficacia del trattamento del disturbo depressivo maggiore nell'anziano, attraverso un approccio di revisione sistematica della letteratura e metanalisi.
I due temi succitati si integrano infine in alcuni progetti trasversali, quali un progetto di revisione della letteratura rivolto allo studio di potenziali interazioni alcol-farmaci nella popolazione in età geriatrica, e uno studio clinico volto a indagare l'uso attuale e pregresso di alcol nella popolazione anziana, al fine di determinarne potenziali associazioni con domini di interesse geriatrico quali il deficit cognitivo, la depressione e la fragilità.
Abstract (ENG): My research activity is focused on two primary thematic areas within the field of neuroscience: alcohol use disorder (AUD) and psychogeriatrics across various aging models, with particular attention to gender medicine.
The AUD area aims to evaluate the efficacy of treatments for this psychiatric pathology and to explore public health issues such as gender differences, management strategies for women with AUD, and awareness of alcohol as a carcinogenic risk factor. In detail, we conducted a systematic review of the literature and meta-analysis on combined pharmacological and nonpharmacological interventions for AUD, demonstrating the efficacy and safety of the combination compared to individual treatments alone.

Cross-sectional studies examined potential gender differences in individuals with AUD, revealing a higher prevalence of psychiatric comorbidities in women, and the limited availability of gender-specific management strategies within our national healthcare system. The role of alcohol as a risk factor for neoplastic diseases has been studied through a clinical trial, which demonstrated the eWectiveness of a specially developed website in increasing women's awareness of the link between alcohol use and breast cancer. Additional ongoing projects will further investigate the relationship between alcohol and cancer, focusing on microbiome analysis and plasma oxidative status.
The psychogeriatrics area aims to optimize screening, diagnosis, and treatment strategies for neuropsychiatric conditions in various aging models. Ongoing cross-sectional studies are examining the application of first-level cognitive screening tools in people aged 65 years and older, and people living with HIV. Preliminary results suggest the need for tools capable of assessing different cognitive domains based on the specific etiologies underlying neurocognitive disorders. These studies also indicate associations between cognitive deficit, depressive disorders, and antidepressant treatment. Furthermore, a systematic review and meta-analysis are underway to assess the eWectiveness of treatments for major depressive disorder in elderly people.
These two areas are supported by some cross-cutting projects. Specifically, a literature review investigating potential interactions between alcohol and medications in the elderly population, and a clinical study exploring current and past alcohol use among older adults to identify potential associations with geriatric domains such as cognitive impairment, depression, and frailty.

XXXVIII ciclo (A.A. 2022/23)

Jihane Balla

Tema di ricerca: *Exploring Novel Therapeutic Strategies in Neuroblastoma: Synergistic Effects of PPARα Agonists and Type I Interferon*

Abstract: Neuroblastoma (NB) is a pediatric tumor of the sympathetic nervous system, commonly originating from neural crest cells. It is the most frequent extracranial solid tumor in children and accounts for approximately 15% of pediatric cancer-related deaths. Despite advances in conventional therapies, especially for low-risk forms, high-risk NB remains a highly aggressive malignancy with poor therapeutic response and unsatisfactory survival rates. In particular, further investigation is needed to uncover the molecular signaling pathways involved in NB progression and therapy resistance. One emerging area of interest concerns bioactive lipids with high affinity for the nuclear receptor PPARα. Recently, there has been increasing attention on the role of these lipids in malignant tumors; however, their effects on human NB cells have not yet been reported. Additionally, type I interferons (IFN), immunomodulatory cytokines known for their anti-proliferative properties, offer another promising avenue for therapeutic intervention in cancer.

This research project aims to develop an experimental planning tool to evaluate the effects of combining oleoylethanolamide (OEA) or palmitoylethanolamide (PEA) with IFNβ in human NB SH-SY5Y cells. This research project aims to develop an experimental planning tool to evaluate the effects of combining OEA or PEA with IFNβ in human SH-SY5Y cells.
The overarching goal is to contribute meaningfully to the understanding of molecular interactions between bioactive lipids and IFN signals in the context of NB. By uncovering shared or independent pathways modulated by OEA/PEA and IFNβ, this work may pave the way for novel pharmacological strategies aimed at reducing tumor proliferation and promoting apoptosis in the most challenging pediatric malignancies.

Martina Mulas

Tema di ricerca: *Cognitive Impairment in Sleep Disorders and Neurodegeneration*

Abstract: REM Sleep Behaviour Disorder (RBD) is widely recognised as a prodromal stage of alpha-synucleinopathies, with a latency from symptom onset to phenoconversion that typically exceeds 10 years. Current research is focused on identifying reliable biomarkers that may indicate early neurodegeneration. Among these, particular emphasis has been placed on the assessment of cognitive functioning in patients diagnosed with idiopathic RBD (iRBD). A large proportion of patients exhibit signs of Mild Cognitive Impairment (MCI) early in the course of the sleep disorder. This is typically characterised by subtle deficits in specific cognitive domains, without significant impact on daily functioning or the presence of other hallmark symptoms of neurodegenerative diseases (e.g., motor signs or hallucinations).
Neuropsychological deficits and MCI have been observed in iRBD cases, with prevalence rates ranging from approximately 33% to 50%, compared to around 8% in the general population. The most commonly impaired cognitive functions include attention, executive functioning, episodic memory, and visuospatial abilities, while praxis, gnosis, and language skills generally remain preserved. Although current data strongly support the presence of a specific cognitive pattern in iRBD patients, several critical issues still remain unresolved.
First, the diagnostic criteria commonly used to define MCI often do not align with the specific cognitive profile observed in this population, potentially delaying recognition and diagnosis. This suggests that cognitive impairment in iRBD may represent an independent feature of the disorder, rather than being solely a consequence of an underlying neurodegenerative condition.
Another major challenge lies in the early identification of individuals who are most likely to undergo phenoconversion. Increasing evidence suggests that the neuropsychological profile could serve as a valuable biomarker for predicting disease progression.
My research aims to characterise the neuropsychological profile of iRBD patients to better understand the nature of the cognitive impairment associated with RBD and to explore its potential utility in forecasting future phenoconversion.

Lala Chaimae Naciri

Tema di ricerca: *L'intelligenza artificiale permette l'automatica definizione della funzione gustativa: implicazioni per la pratica clinica e le valutazioni chemosensoriali.*

Abstract (ITA): I sistemi gustativo, olfattivo e trigeminale sono anatomicamente separati. Tuttavia, interagiscono cognitivamente per dare origine alla percezione orale, che influenza la scelta alimentare e la salute. La riduzione chemosensoriale è associata a disturbi patologici o all'assunzione di farmaci. Metodi psicofisici affidabili sono strumenti essenziali per analizzare la funzione gustativa durante le valutazioni cliniche di routine. Tuttavia, si tratta di metodi soggettivi e spesso richiedono molto tempo. In controlli sani e in pazienti con perdita chemosensoriale, utilizziamo il regressore Random Forest per caratterizzare la combinazione di risposte che meglio posono predire la funzione gustativa nei due gruppi e il regressore CatBoost per predire la sensibilità orale, determinando anche il contributo delle componenti gustative, olfattive e trigeminali. Inoltre, utilizziamo un metodo automatizzato basato su un'architettura di deep learning (U-Net) per la segmentazione delle immagini al fine di identificare in modo accurato e automatico le papille fungiformi. Il nostro studio apporta notevoli progressi nella ricerca sul gusto e sulla nutrizione, offrendo un metodo rapido, preciso ed efficiente per automatizzare l'identificazione delle differenze tra soggetti sani e pazienti con perdita chemosensoriale e l'identificazione delle papille fungiformi.
Abstract (ENG): The gustatory, olfactory, and trigeminal systems are anatomically separated. However, they interact cognitively to give rise to oral perception, which affects food choice and health. Chemosensory reduction is associated with pathological disorders or medications. Reliable psychophysical methods are essential tools for analyzing taste function during routine clinical assessments. However, they are subjective methods and are often time-consuming. In healthy controls and patients with chemosensory loss, we use the Random Forest regressor to characterize the combination of responses that best can predict the taste function of the two groups, and the CatBoost regressor to predict oral sensitivity, also determining the contribution of gustatory, olfactory, and trigeminal components. In addition, we use an automated method based on a deep learning architecture (U-Net) for image segmentation to accurately and automatically identify FPs. Our study provides significant advancements in taste and nutrition research, offering a quick, precise, and efficient method for automating the identification of differences among healthy subjects and patients with chemosensory loss, and FPs identification.

Pasquale Paribello

Tema di ricerca: *Integrating clinical and biological signatures to support prognostic stratification for suicide behavior among individuals with severe mental illnesses*

Abstract: Translational psychiatry is a research field that aims to incorporate the most recent basic science advances in clinical practice. Unfortunately, as with several fields of medicine, an ever-growing gap between research and clinical practice is apparent.

Several lines of research exist that focus on varied outcomes, hoping to identify robust and clinically expendable evidence for translational biomarkers associated with clinically meaningful outcomes. In this context, my research focuses on exploring biomarker candidates' association with neuropsychological patterns that may be associated with a higher frequency of lifetime suicide behaviors. More specifically, my project aims at exploring the possible interplay between biological signatures (e.g., -omics), cognitive performances, psychometric severity and lifetime suicide behaviors (i.e., suicide ideation or attempts) in clinical samples of individuals living with severe mental illness. A more detailed stratification of these high-risk populations may serve to focus preventive efforts and even identify possible targets for therapeutic interventions aiming at thwarting such risks.