PROJECT

Supervisor:	Dr Raffaella Zanardi
Title:	Integrating Immuno-metabolic dysregulation and cognitive dysfunction in Major Depressive Disorder
Curriculum:	Cognitive and Behavioural Sciences
Link to the personal page of the University or relevant hospital site website:	https://www.hsr.it/dottori/raffaella-zanardi

Description of the Project (max 3,000 characters including spaces)

Background / gap of knowledge

Major Depressive Disorder (MDD) ranks among the leading causes of disability worldwide, with a progressively increasing disease burden. Despite extensive research, the pathophysiological mechanisms underlying MDD remain incompletely understood.

Systemic low-grade inflammation, characterized by increased circulating pro-inflammatory cytokines and dysregulation of T-cell–mediated immune responses, has emerged as a key contributor to MDD. Peripheral inflammation appears linked to brain alterations and neuroinflammatory responses that may influence mood and cognitive disturbances that are closely associated with illness severity, functional impairment, and treatment resistance..

Recent studies also suggest that metabolic alterations may play an important role in MDD pathophysiology. Metabolomic approaches allow a comprehensive characterization of systemic metabolic profiles reflecting immune activation, cellular metabolism, and neurobiological functioning. However, few studies have jointly examined immune dysregulation, metabolic alterations, brain changes, and their relationship with cognitive and psychopathological manifestations of MD. This represents an important gap in knowledge and highlights the need for integrative multidimensional research.

Rationale and hypothesis

Immune dysregulation, metabolic alterations, and brain changes are likely interconnected through multiple biological pathways and may contribute synergistically to the pathophysiology of mood disorders. Metabolic pathways are closely linked to immune_function and neural

activity, influencing cellular signaling, energy balance, and neurochemical processes involved in cognition and emotional regulation.

Metabolomic profiling can capture global metabolic signatures associated with disease states. When integrated with immune markers and neuroimaging data, metabolomic information may help identify biological patterns underlying cognitive and psychopathological variability in MDD.

Objectives and specific aims

Recent models emphasize the dynamic interaction between peripheral biological processes and central nervous system functioning. Inflammatory mediators can cross the blood-brain barrier and influence brain morphology and signaling pathways.

This study will integrate multidimensional data including: T-cell subpopulation profiles, plasma cytokine levels, metabolomic profiling of peripheral blood samples, and multimodal brain MRI. These biological measures will be combined with clinical, cognitive, and psychopathological assessments.

The aim is to characterize, through innovative computational approaches, interactions between immune dysregulation, metabolic alterations, brain changes, and cognitive-psychopathological features in MDD, identifying integrated biological and cognitive profiles that may support patient stratification and personalized treatment approaches.

Expected outcomes

The project aims to clarify how immune dysregulation, metabolic alterations, and brain changes interact in MDD and how these mechanisms relate to cognitive dysfunction and clinical features.

By integrating metabolomic, immunological, neuroimaging, and cognitive data, the study may identify biomarkers associated with illness severity and treatment response, and TRD. These findings could help define biologically informed subtypes of MDD and contribute to the development of more targeted and personalized therapeutic strategies.

Skills that the student should acquire (max. 600 characters including spaces):

Statistics: General and Generalized Linear Model, Structural equation modeling; Machine learning tools (PCA, K-means), Matlab, R, Python, Stata, OS: Linux;

• Cellular Analysis: Flow cytometry (FACS), Seahorse Cell Metabolism Technology, fluorescence techniques and probe-based approaches, PBMCs isolation.

• Drafting and publishing papers;

• MRI analyses: VBM, subcortical volumes and cortical thickness; Tract-Based Spatial Statistics and tractography; seed-to-voxel, ROI-to-ROI connectivity, ICA networks for fMRI.

References (max. 15)

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7. Milaneschi, Y, et al.. Depression Heterogeneity and Its Biological Underpinnings: Toward Immunometabolic Depression. Biol Psychiatry, 2020 Sep 1;88(5):369-380.

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13. Haroon, E., A.H. Miller, and G. Sanacora, Inflammation, Glutamate, and Glia: A Trio of Trouble in Mood Disorders. Neuropsychopharmacology, 2017. 42(1): p. 193-215.