PROJECT

Supervisor:	FRANCESCO BENEDETTI
Title*:*	Lifetime sex effects on white matter microstructure and its relationship with biological factors affecting genetic and immuno-inflammatory setpoints in mood disorders
Curriculum:	Cognitive and Behavioural Sciences
Link to the personal page of the University or relevant hospital site website:	https://www.unisr.it/docenti/b/benedetti-francesco https://research.hsr.it/en/divisions/neuroscience/psychiatry-and-clinical-psychobiology/index.html

Description of the Project (max 3,000 characters including spaces) 2776

Background/gap of knowledge

Epidemiology affirms a 3:1 F:M ratio in the prevalence of Major Depressive Disorder (MDD), beginning in early adolescence and through the postmenopausal period, and a 1.1:1 ratio for Bipolar Disorder (BD). Alterations in white matter (WM) microstructure are a major underpinning of diagnosis and its outcomes, and associate with brain metabolism and function, gene-environment interaction, immuno-inflammatory setpoints.

Sparse evidence suggests that sex-based differences in lifetime dynamics of immune system and brain immune surveillance contribute to divergent trajectories of neuroinflammation in response to pathogens, autoimmunity, psychosocial stressors. Sex-based differences in WM microstructure are driven by sex hormone exposure and not by karyotype, but there is a lack of studies exploring these dynamics with a lifetime cross-sectional perspective. In particular, the understanding of sex-specific mechanisms has been limited by the paucity of sex-stratified clinical analyses and by the underrepresentation of females in preclinical models.

Rationale and hypothesis

Depression in females results in worse outcomes compared to males, with higher rates of chronic, severe, and recurrent episodes, particularly during hormonal changes. Females experience increased disability, higher suicide attempt rates, and metabolic issues (weight gain/appetite increase), along with higher comorbidities like cardiovascular disease. It is surmised that sex-specific associations between biological factors affecting genetic and immuno-inflammatory setpoints and their effects on the brain would change as a function of biological, genetically influenced, and endocrine-driven baseline levels across the reproductive age for females, conferring a specific risk for mood disorders and their consequences on brain structure and function.

Objectives and specific aims

To test these relationships in a cross-sectional design, stratifying samples according to sex and age classes, in order to identify specific profiles for the lifetime sex effects of biological dynamics on risk and outcomes of mood disorders.

Expected outcomes

The molecular neurobiology of mood disorders is highly complex, and current models point toward a still elusive multifactorial etiology including genetic, environmental, biological, psychosocial factors, and impacting whole-body homeostasis across the lifespan. Intertwined signaling pathways trigger and shape the phenotype of the disorder: hence the need of continuous research on pathogenetic mechanisms to address the clinical need of most precisely targeted treatments. Here we will identify sex-specific patterns of biological interaction, to serve as biomarkers of sex-specific risk, and potential targets for treatment.

Skills that the student should acquire (max. 600 characters including spaces): 591

"Imaging genetics": the use of anatomical or physiological imaging technologies as phenotypic assays to evaluate genetic variation

MRI analyses to explore functional & structural networks: for WM, Tract-Based Spatial Statistics (TBSS; FSL) also using NODDI; and BOLD fMRI (SPM12), VBM, subcortical volumes and

cortical thickness (CAT12), and connectivity and graph metrics, local homogeneity, intrinsic connectivity, centrality, etc., on rs-fMRI (CONN and AFNI).

How to use, as regressors on the above, Polygenic Scores; Bio-Plex Multiplex Assays; PBMC gene expression; FACS immunophenotyping.

References (max. 15)

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