PROJECT 1

DoS: Prof Francesco Benedetti

Title: Role of immune activation and inflammation in functional and structural brain integrity in bipolar disorder.

Curriculum: Neuroscience and Experimental Neurology

Link to OSR/UniSR personal page:
https://www.hsr.it/ricerca/struttura/divisione-di-neuroscienze/francesco-benedetti/

Project description (Number of characters, including spaces: 2.000 - 3.000):

Across mood states, bipolar disorder (BD) is associated with elevated biomarkers of cell-mediated immune activation and inflammation in the absence of active somatic immune diseases, combined with signs of widespread disruption of white matter (WM) integrity in adult life, which result in a decreased effective connectivity in the frontolimbic network, probably mediating the relationship between biological underpinnings and clinical expression of BD.

Consistent findings in animal models link WM damage in inflammatory diseases of the brain and both, peripheral levels of cytokines and immunophenotyping. According to the inflammation theory of mood disorders, the deregulation of the immune system involves both, elevated peripheral markers of macrophage/monocyte inflammatory activation patterns, and activation of microglia into the brain. Preliminary research by our group showed that inflammatory cytokines influence measures of white matter integrity in BD, and that growth factor that contributes to neurotrophic and immune effects are also involved in the process of remission/recovery from depression, and associate with grey matter volumes and functional responses during bipolar depression.

What we will do is to prospectively study patients with BD, combining: (1) time-lagged MRI scans, to study the changes in brain structure and function during the course of illness, and (2) flow cytometry immunophenotyping, assessment of cytokines and chemokines gene expression, and multiplexed sandwich immunoassays of cytokines concentrations and in peripheral blood. The hypothesis is that current mood states, MRI measures of brain structure and function, and measures of immune activation and inflammation will covariate, with levels of inflammation being higher, and brain integrity lower, than in control healthy subjects.

The candidate will actively participate to all phases of the project, starting from paradigm definition to MR images acquisition and analyses. During the three years of duration, the project will aim at (1) recruiting a sample of patients affected by Bipolar Disorder type I, in charge at our Dept., and assess them with a combination of multimodal MRI (mmMRI) and neuropsychological methods (1st year); (2) follow-up the patients, with two assessments of global functioning & psychopathology and two repeated mmMRI scans, six and twelve months after the first (2nd and 3rd years); complete the endpoint assessment of all patients (1 year after recruitment) and investigate the relationship between mmMRI and the effects of interest (3rd
year). No power calculations are possible for this groundbreaking research approach, but the wide literature generated at our research center in patients with BD allows to declare a sample size of n=50 as sufficient to estimate the level of significance of the effects of interest.

The analyses of peripheral blood markers of immune activation and inflammation will be performed in the Unit of Clinical Neuroimmunology at the Institute of Experimental Neurology (Head of Unit: Roberto Furlan). Based on the above aims, a detailed PhD-student-taylored project will then be defined with the eligible student.

Patients will be recruited in the psychiatric clinical units located at San Raffaele Turro, which strictly collaborate with the research unit in Psychiatry and Clinical Psychobiology (-> refs).

**Skills to be acquired by the student:**

Based on the specific background of the applicant and on the specific proposed project, the PhD student will choose between two technical tracks. Techniques in the project include:

**Brain Imaging track**

- "Imaging genetics": the use of anatomical or physiological imaging technologies as phenotypic assays to evaluate genetic variation, including gene polymorphisms and gene expression
- MRI analyses to explore functional & structural networks: BOLD fMRI (SPM12), VBM, subcortical volumes (Freesurfer) and cortical thickness (CAT12), Tract-Based Spatial Statistics (TBSS; FSL) and tractography analysis of WM tracts, Dynamic Causal Modelling (DCM; SPM12), new fMRI tools for the analysis of seed-to-voxel connectivity maps, ROI-to-ROI connectivity and graph metrics, Independent Components (ICA networks), local homogeneity, intrinsic connectivity, centrality, etc.; resting state fMRI (RestPlus, CONN)

**Clinical Neuroimmunology track**

- FACS immunophenotyping
- Bio-Plex Multiplex Cytokine Assay
- Real-time (RT)-PCR to measure mRNA levels of chemokines, chemokine receptors, cytokines and T-reg markers.

**References** (max. 3)

