PROGETTO 1/ PROJECT 1

Supervisore/*Supervisor*:	Benedetta Vai
Titolo/*Title*:	Gene-environment interaction in shaping and predicting mood disorders: the inflammatory, neurobiological and cognitive signatures
Corso /*PhD Course*	Cognitive and Behavioral Sciences
Curriculum:	
Link alla pagina personale OSR/UNISR/ *Link to OSR/UniSR personal page*:	https://research.hsr.it/en/divisions/neuroscience/psychiatry-and-clinical-psychobiology/benedetta-vai.html

Descrizione del progetto/Project description (Tra i 2.000 e 3.000 caratteri spazi inclusi/ *Number of characters, including spaces*: 2.000 - 3.000):

Depression is a leading cause of disability worldwide and the burden of mood disorders (major depression, MDD, bipolar disorder, BD) is constantly growing. Around 60% of depressed patients with BD wait 5–10 years for a proper diagnosis, even when diagnosis is correct, one third do not respond to antidepressant treatments, experiencing relapses, general health deterioration, and higher risk of suicide compared to general population [1-4]. BD is highly heritable: genetic influences explain 60–85% of risk, partially shared with MDD [5]. However, approximately 71% of the genetic variance for mania is not shared, identifying an interesting target for differentiating the disorders [6]. On the other hand, the heritability of MDD is lower (40%), suggesting a wider interaction between genetics and environmental factors in contributing to the pathological phenotypes. Among environmental factors, a wide literature supports the detrimental effects of adverse childhood experiences (ACE), associated with early disorders onset, worse illness course and treatment response and higher risk of suicide [7, 8]. Previous studies explored the effect of ACE and genetics over the disorders, while others showed the ability of brain imaging, inflammatory and cognitive markers to predict the differential diagnosis [9-11]. However, no studies explore a gene-environment interaction on multimodal neuroimaging, inflammatory and neuropsychological markers, and its ability to predict the differential diagnosis. In this project, as first aim the PhD candidate will investigate if the main effects and interactions between ACE and Polygenic Risk Scores (PRS) for mood disorders and other conditions on inflammatory, neuropsychological, and multimodal neuroimaging data in a cohort of ~ 360 MDD and BD patients by applying multivariate analysis (e.g. canonical correlation analysis). As secondary aim the PhD will explore if these effects can enable the prediction of a differential diagnosis and suicidal behavior through machine learning techniques.

In the first 12 months, the PhD student will be engaged in pre-analyzing the dataset, obtaining measures of cortical and subcortical volumes on MRI T1-weighted images, indexes of white matter integrity (FA, MD, RD, AD) on DTI images, and functional connectivity and habituation parameters on fMRI data acquired during both resting state condition and an emotional processing task. PRS for different disorders, including bipolar disorder, major depressive disorders, neuroticism, schizophrenia, attention-deficit hyperactivity disorder,

and inflammatory markers (40 and 48 plex Bio-Rad) are already estimated on stocked plasma and blood. In the second year, the candidate will explore interaction of PRS and ACE on neuroimaging and inflammatory markers: data will be harmonized for possible batch effects (e.g. ComBat). The effect will be explored though univariate and multivariate analyses, such as canonical correlation analysis or component analyses, to combine features. The following year, classification and prediction algorithms will be applied to explore the if the previous features can predict the differential diagnosis and clinical outcomes.

Competenze che deve acquisire lo studente/Skills to be acquired by the student (Max 600 caratteri spazi inclusi/ *Number of characters*, *including spaces*: max 600):

- 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.
- Statistics: General and Generalized Linear Model, Structural equation modeling; Machine learning: PCA, ComBat, K-means, support vector machine, multiple kernel learning, Gaussian Processes, Kernel Ridge Regression, Relevance Vector Regression, penalized regressions, Neural-networks, cross-validations procedures, Canonical correlation analyses.
- Matlab, R, Python, FSL, SPM12, Freesurfer, Stata, OS: Linux
- Drafting and publishing papers

Bibliografia/References (max. 15)

1. Hirschfeld, R.M. and L.A. Vornik, Perceptions and impact of bipolar disorder: how far have we really come? Results of the national depressive and manic-depressive association 2000 survey of individuals with bipolar disorder. The Journal of clinical psychiatry, 2003. 64(2): p. 14089.

2. de Almeida, J.R.C. and M.L. Phillips, Distinguishing between unipolar depression and bipolar depression: current and future clinical and neuroimaging perspectives. Biological psychiatry, 2013. 73(2): p. 111-118.

3. Conway, C.R., M.S. George, and H.A. Sackeim, Toward an evidence-based, operational definition of treatment-resistant depression: when enough is enough. JAMA psychiatry, 2017. 74(1): p. 9-10.

4. Stegenga, B.T., et al., The natural course and outcome of major depressive disorder in primary care: the PREDICT-NL study. Social psychiatry and psychiatric epidemiology, 2012. 47(1): p. 87-95.

5. Barnett, J.H. and J.W. Smoller, The genetics of bipolar disorder. Neuroscience, 2009. 164(1): p. 331-43.

6. McGuffin, P., et al., The heritability of bipolar affective disorder and the genetic relationship to unipolar depression. Arch Gen Psychiatry, 2003. 60(5): p. 497-502.

7. Park, Y.-M., T. Shekhtman, and J.R. Kelsoe, Effect of the type and number of adverse childhood experiences and the timing of adverse experiences on clinical outcomes in individuals with bipolar disorder. Brain sciences, 2020. 10(5): p. 254.

8. Daruy-Filho, L., et al., Childhood maltreatment and clinical outcomes of bipolar disorder. Acta Psychiatrica Scandinavica, 2011. 124(6): p. 427-434.

9. Colombo, F., et al., Machine learning approaches for prediction of bipolar disorder based on biological, clinical and neuropsychological markers: a systematic review and meta-analysis. Neuroscience & Biobehavioral Reviews, 2022: p. 104552.

10. Vai, B., et al., Predicting differential diagnosis between bipolar and unipolar depression with multiple kernel learning on multimodal structural neuroimaging. European Neuropsychopharmacology, 2020. 34: p. 28-38.

11. Poletti, S., et al., A peripheral inflammatory signature discriminates bipolar from unipolar depression: A machine learning approach. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 2021. 105: p. 110136.

12. Vai, B., I. Bollettini, and F. Benedetti, Corticolimbic connectivity as a possible biomarker for bipolar disorder. Expert review of neurotherapeutics, 2014. 14(6): p. 631-650.