PROGETTO

Supervisore:	Colnaghi Luca
Titolo/*Title*:	Transcriptomic profiling of subjects with major depressive disorder as a new clinical tool
Curriculum:	Neuroscienze e Neurologia Sperimentale
Link alla pagina personale del sito web di Ateneo o del polo ospedaliero di riferimento:	https://research.hsr.it/en/divisions/neuroscience/luca-colnaghi.html

Descrizione del progetto (max 3.000 caratteri spazi inclusi)

Background/gap of knowledge

Major Depressive Disorder (MDD) is a chronic and debilitating medical condition affecting over 320 million individuals, making it one of the leading causes of disability globally (1). Despite advancements in psychopharmacology, only 30% of patients experience symptom remission with their initial antidepressant treatment (2). The current approach to selecting antidepressants remains trial-and-error, often requiring multiple attempts. Treatment-resistant depression is a multifaceted phenomenon influenced by various factors, including depressive subtypes, psychiatric comorbidities, adjunctive polypharmacotherapy, and concurrent medical conditions (3). Emerging evidence suggests a role for aberrant inflammatory processes in MDD pathogenesis and antidepressant response mechanisms (4).

Rationale and hypothesis

For years, researchers have explored the involvement of the immune system in the development and progression of depression. Elevated levels of proinflammatory cytokines can result from various factors such as pathogenic infections, autoimmune reactions, inflammation, and chronic, unpredictable, and maladaptive psychophysiological stress (5). The presence of increased peripheral concentrations of proinflammatory cytokines in the blood of depressed patients consistently supports the notion of immune-related mechanisms playing a role in depression. However, a clear role of the immune system is still unclear in MDD. We hypothesize, however, that a better understanding of the molecular underpinnings of the role of the immune system in MDD subjects has the potential to improve the diagnosis of the condition, suggesting more reliable biomarkers and suggesting new therapeutic avenues.

Therefore, starting from the bulk RNA-seq of 170 blood samples of MDD subjects and controls, this project plans to shed new light on how the immune system may facilitate MDD.

Objectives and specific aims

In this study, the Ph.D. candidate will commence by analyzing recent transcriptomic data derived from bulk RNA sequencing of blood samples obtained from approximately 170 individuals diagnosed with depression, recruited from the Unit of Psychiatry and Clinical Psychobiology at San Raffaele Turro. The analysis will encompass gene expression studies and pathway analysis aimed at investigating inflammatory or related pathways. This cohort is already extensively phenotyped, including multimodal neuroimaging, genetic data, and assessments of peripheral inflammation. All this will allow the candidate to integrate the new gene expression findings into multimodal models, combining gene expression with brain imaging, genetic data, and inflammatory markers.

Expected outcomes

Altogether, this computational approach, based on new and still unpublished evidence, may allow the Identification of a novel gene expression signature of the disorder, that may inform new therapeutic avenues and also research strategies.

Competenze che deve acquisire lo studente (Max 600 caratteri spazi inclusi):

Programming Languages: Python, R, and Perl.

RNA Sequencing Analysis: methods for analyzing RNA-Seq data: differential gene expression analysis, alternative splicing detection, and isoform quantification.

Statistical Analysis: hypothesis testing, regression analysis, and machine learning techniques.

Machine Learning: supervised and unsupervised learning methods, feature selection, and model evaluation for RNA sequence analysis.

Data Integration: Ability to integrate RNA translation data with other types of data.

Collaboration and Communication: Strong communication and collaboration skills.

Bibliografia (max. 15)

1. Otte, C., Gold, S. M., Penninx, B. W., Pariante, C. M., Etkin, A., Fava, M., Mohr, D. C., & Schatzberg, A. F. (2016). Major depressive disorder. Nature reviews. Disease primers, 2, 16065. https://doi.org/10.1038/nrdp.2016.65
2. Souery, D., Oswald, P., Massat, I., Bailer, U., Bollen, J., Demyttenaere, K., Kasper, S., Lecrubier, Y., Montgomery, S., Serretti, A., Zohar, J., Mendlewicz, J., & Group for the Study of Resistant Depression (2007). Clinical factors associated with treatment resistance in major depressive disorder: results from a European multicenter study. The Journal of clinical psychiatry, 68(7), 1062–1070. https://doi.org/10.4088/jcp.v68n0713
3. Bornhoff, A., Davis, E. B., Yousey, J., Kimball, C. N., Stier, E., & Wang, E. (2024). Patient and Provider Perspectives on the Phenomenon and Effective Treatment of Treatment-Resistant Depression: A Grounded Theory. Journal of Affective Disorders Reports, 100779
4. Miller, A. H., & Raison, C. L. (2016). The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nature reviews immunology, 16(1), 22-34.

6. Kim, Y. K., Na, K. S., Myint, A. M., & Leonard, B. E. (2016). The role of pro-inflammatory cytokines in neuroinflammation, neurogenesis and the neuroendocrine system in major depression. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 64, 277-284.