

 <p><b>UniSR</b> Università Vita-Salute San Raffaele</p>	<p align="center"><b>APPLICATION TO ACT AS SUPERVISOR AND RESEARCH PROJECT PROPOSAL</b></p>	<p align="center"><b>MO 20-5</b> ed. 02 of 16/01/2026 PO 20 Page 5 of 12</p>
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**PROJECT**

**Supervisor:** Benedetta Vai

**Title:** Depression After Infection: Identifying Biological Subtypes and disorder trajectories with Multimodal Machine Learning

**Curriculum:** Cognitive and Behavioural Sciences

Link to the personal page of the University or relevant hospital site website: <https://research.hsr.it/en/divisions/neuroscience/psychiatry-and-clinical-psychobiology/benedetta-vai.html>

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

**Background/gap of knowledge**

Depression is a complex neuropsychiatric disorder associated with cognitive decline, immunoinflammatory alterations, and increased risk of dementia, cardiovascular disease, and mortality [1,2]. Despite available treatments, therapeutic responses remain suboptimal, with up to 30% of patients not achieving remission [3]. Among emerging factors contributing to the heterogeneity and trajectory of depressive disorders, infectious diseases and immune activation have gained increasing attention. Epidemiological studies show that individuals with a history of severe infections have a higher risk of developing mood disorders and worse clinical outcomes [4,5].

Several biological mechanisms may explain this association. Infection-induced immune activation and chronic inflammation can alter cytokine signalling, neurotransmitter metabolism, neuroplasticity and brain connectivity, thereby contributing to depressive symptoms and cognitive impairment [2,6]. Neuroimaging and biomarker studies further suggest that inflammatory processes affect brain circuits involved in emotion regulation and cognition [7]. Moreover, infection-related inflammation may accelerate cognitive decline and increase vulnerability to comorbid medical conditions and neurodegenerative processes [1,8].

At the same time, depression is biologically heterogeneous. Recent multimodal studies integrating neuroimaging, immune markers and clinical data have identified biologically meaningful subtypes associated with different cognitive and clinical profiles [9,10]. However,



most previous studies examined isolated biological domains, not exploring the role of infections interacting with biological vulnerability to shape depressive trajectories.

### **Rationale and Hypothesis**

This project adopts a computational psychiatry approach integrating multimodal biological and clinical data to investigate infection-related mechanisms in depression.

Hypothesis:

The integration of infection history, genetics, neuroimaging, inflammatory markers and cognitive measures will identify biologically distinct subtypes of depression associated with different cognitive profiles, biological and molecular profiles, clinical trajectories and vulnerability to adverse outcomes.

Objectives

Objective 1: Identify biologically meaningful subgroups of depression associated with infection-related vulnerability using unsupervised machine learning on multimodal datasets.

Objective 2: Characterise the neurobiological, cognitive and clinical signatures of the identified subgroups, including symptom severity, cognitive decline and comorbidities.

Objective 3: Develop predictive models of clinical and cognitive outcomes integrating infection history and biological markers.

### **Expected Outcomes**

The project will develop a multimodal machine learning framework to investigate infection-related mechanisms in depression. It will identify biologically meaningful subgroups associated with different cognitive and clinical trajectories. These findings may improve risk stratification and support personalised monitoring and intervention strategies in depression.

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

- Training in brain imaging: structural MRI (gray matter volumes, cortical thickness, white matter integrity) and resting-state fMRI (connectivity analysis).
- Machine learning: clustering, dimensionality reduction, classification, cross-validation procedures.
- Software: Python, R, MATLAB, FSL, SPM, Freesurfer (Linux).
- Research skills: scientific writing, poster design, conference presentations.

**References** (max. 15)

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