Exposure to chronic stress contributes to the risk of developing a neuropsychiatric disease such as major depressive disorder (MDD). Although many individuals experience stressful events and are exposed to trauma during life, most do not develop psychiatric illnesses such as MDD, becoming stress-resilient. Stress resilience is the dynamic process of adaptively overcoming stress and adversity while maintaining normal cognitive functioning. However, research aimed at understanding the molecular bases of resilience is sparse. The importance of studying stress resilience has become even more evident in the last years, considering the frequency and variety of stressors that humans have to cope with and the attendant stress-related disorders, and especially now more than ever due to the COVID-19 worldwide crisis and military conflicts in Europe and Middle East.

The overall goal of the proposed project is to assess the molecular mechanisms of neural processes that underlie the phenomenon of resilience and the vulnerability to chronic stress. Our focus will be on the role of post- translational modifications and in particular palmitoylation. Since our data shows that enzymes regulating palmitoylation operate both in a stress- and sex dependent manner, we hypothesize that specific changes in the posttranslational palmitoylation of NMDA receptor subunits are responsible for the behavioural switch between the resilient and depressive-like behaviour during stressful conditions. In this proposal, we will use a well- established animal models of depressive-like behaviours, *in vitro* cell cultures, human induced pluripotent stem cells and human post mortem brain samples collected from Major Depressive Disorder (MDD) patients to: (i) characterize the specific pattern of palmitoylation of NMDA receptor subunit - GluN2B, in anhedonic and resilient mice and examine how this pattern is affected by NMDAR antagonist; (ii) identify specific palmitoyl-acyl transferases (ZDHHCs) that are responsible for S- palmitoylation of specific cysteines in GluN2B; (iii) identify specific regulatory mechanism that control expression of these DHHCs enzymes (iv) evaluate to what extent the level of identified regulators of palmitoylation are dysregulated in the human samples from MDD patients (v) evaluate if changes obtained in the animal models are present in human iPSC-derived neuronal models and whether those changes differ between men and women. Our research will thus provide a novel view on the mechanisms of stress resilience and possibly pave the way for developing treatment strategies for human stress-related disorders and/or improved prevention strategies.