Clinical studies clearly show that stressful and traumatic events occurring early in life i.e., early-life stress (ELS) increase the risk of mental disorders (e.g., depression, anxiety, addiction). Presumably, ELS interferes with brain development and maturation; however the primary mechanisms engaged in its action are poorly understood. It has been hypothesized that ELS-induced processes of cellular stress may underlie aberration in brain maturation. Cellular stress is triggered by a disturbance in cellular homeostasis, induced by e.g., hypoxia, abnormal calcium and glucose levels or by accumulation of unfolded/misfolded proteins. It leads to the activation of repair processes, such as the endoplasmic reticulum (ER) stress and unfolded-protein response (UPR). Thanks to ER stress and UPR, the synthesis of specific proteins is activated. These proteins are responsible for proper folding of defective proteins or their elimination. These actions increase the chances of cell survival. However, when cellular stress exceeds the pro-survival capabilities of UPR, ER activates UPR paths associated with cell death. Recent data have suggested that above-mentioned processes are involved in the development of various diseases, including neurodegenerative diseases (e.g., Parkinson's disease and Alzheimer's disease), diabetes, atherosclerosis and autoimmune diseases. Moreover, the latest data have shown that ER stress can be also associated with mental disorders, such as depression and bipolar disorder. Aberrant expression of genes and proteins related to ER stress has been revealed in leukocytes and the temporal cortex of patients suffering from these diseases. However, the knowledge about the role of ER stress and UPR in development and progression of mental disorders is poor. Surprisingly, there are also no data showing the effects of ELS on ER stress and UPR processes, although ELS is well-known factor in the etiology of mood and anxiety disorders. All above facts and arguments has prompted us to undertake a study aimed to determine whether ELS activates ER stress in the medial prefrontal cortex (mPFC), i.e., in a brain region strongly associated with the development of mood and anxiety disorders. In particular, we are planning to examine whether ELS by activating ER stress and UPR processes during early-postnatal period, critical for mPFC maturation: (a) affects the survival and the numbers of neurons and glial cells, (b) changes UPR processes for the rest of the lifespan, (c) triggers depressive- and anxiety-like behaviors. What is more, we want to examine whether ER stress and UPR responses might be the targets for early-postnatal therapeutic intervention of antidepressant fluoxetine.

To model ELS we will use the procedure of separation of rat pups from their mothers (maternal separation paradigm) carried out in the first two weeks of life, i.e., during critical period for brain maturation. We are planning a comprehensive study in all stages of postnatal development, i.e., in juvenile, adolescent and adult animals. Activation of ER stress and UPR will be assessed by analyzing the expression of genes and proteins involved in these processes. We will also examine cell death processes, proliferation and how they influence the final numbers of cells in the mPFC. We are also planning to examine whether early-postnatal fluoxetine treatment reverses ELS-induced disturbances in the mPFC and animal behavior and how it generally affects mPFC maturation.

Our study and findings may expand the current knowledge about the mechanisms engaged in ELS-induced mPFC dysfunction. Moreover, the results may bring us closer to understanding the pathophysiology of mood and anxiety disorders. Mood and anxiety disorders are big medical, social and economic worldwide problems. They affect also children and adolescents. One of the few drugs registered and approved to treat depression and anxiety in children and adolescents is fluoxetine. Therefore, our result may also broaden the knowledge about mechanisms of action, effectiveness and safety of fluoxetine treatment in young subjects. The development of non-invasive neuroimaging techniques makes the identification of mPFC dysfunctions possible. Thus, our findings may prompt to introduce preventive mPFC neuroimaging in subjects with a history of early-life adversity and contribute to early diagnosis of future mental problems. Prevention of ELS-associated diseases may have very important social and economic impacts. Moreover, taking into account that ELS programs brain functions for the entire life, we also hope that our research will increase social awareness and sensitivity to the problem of child abuse and neglect.