Abstract for the general public

Over 300 million people are suffering from depression worldwide (World Health Organization, 2017) with an estimated one out of five individuals affected by major depressive disorder (MDD) which is the most prevalent mood disorder and the leading cause of disability worldwide. Moreover, the prevalence of MDD is two to threefold higher in patients suffering from cardiovascular diseases (e.g. heart failure, or stroke), and it is related to an increased risk of morbidity and mortality. Importantly, affective disorders, including MDD, are more frequent in women, who report higher levels of stress in daily life - the main environmental risk factor for developing depression. There is a clear relationship between disturbances induced by stressful stimuli, especially long-lasting stimuli, and cognitive deficits observed both in humans and in animal models.

The BBB is a term used to describe the unique properties of the microvasculature of the central nervous system (CNS). The key structure of the BBB which offers a barrier is the "endothelial tight junction". Endothelial cells line the interior of all blood vessels. In the capillaries that form the BBB, endothelial cells are wedged extremely close to each other, forming so-called tight junctions (TJs). An intact BBB is maintained by TJ proteins and is a paramount determinant of brain homeostasis.

Recently, it was reported that chronic stress induces alterations in the integrity of the blood-brain barrier (BBB), which in turn promotes depression-like behaviors in male mice, indicating a direct link between neurovascular pathology and stress vulnerability. Interestingly, not every individual develops CNS disorders after experiencing stressful life events and is thus thought to be resilient.

Regular physical activity has a positive effect on CNS functions and contributes to an improvement in mood and cognitive abilities (including memory and learning). Regular physical activity brings another important benefit - stress resilience, which is a process of adapting well in the face of adversity, trauma, threats, or significant sources of stress. **Therefore, we formulated the central hypothesis of this proposal that physical exercise would contribute to the brain's resilience to stress throughout BBB signaling pathways.**

This grant application is based on animal studies and will implement a widely accepted chronic stress model and voluntary wheel running. Experiments will be performed on both sexes of mice. Interdisciplinary analyses will include the assessment of endothelial cell biology, BBB formation, and inflammatory reactions in the fraction of endothelial cells, brain structures, and brain capillaries isolated from mouse brains. We will use a variety of state-of-the-art molecular methods and visualization after staining for specific cell markers.

The ability to cope with stress is crucial for mental health and for maintaining a well-balanced response to physical and social environments. Physical activity has been proposed as an effective and low-cost intervention to prevent CNS disorders, especially those related to long-lasting stress. The neurobiology of different stress responses remains understudied, especially in the context of understanding the role of gender and individual differences in BBB properties as potentially involved in stress resilience vs. vulnerability.

Therefore, the completion of the proposed study promises to establish new therapeutic targets based on natural activity to induce stress-resilience phenotype, making this proposal highly significant for the improvement of public health.