

**The primary objective of this proposal is to test the hypothesis that the association between the level of exposure to stressful events and the severity of psychopathology is mediated by the allostatic load and brain responses.** This project will be conducted by experts in the field of biological psychiatry from Department of Psychiatry (DP) at Wroclaw Medical University. Resting state functional Magnetic Resonance Imaging (rs-fMRI) will be conducted on a 3 Tesla MR scanner at Department of Radiology and Neuroradiology (DR), Wroclaw Medical University. The unprovoked Russian attacks on Ukraine during February-May 2022 will leave long-lasting devastating effects on millions of innocent victims. Over 7 million people had left Ukraine in the first 3 months of war and nearly 3.5 million of them, mostly women and children, came to Poland. Several studies have shown that anxiety, depression and posttraumatic stress disorder (PTSD) are the main psychopathological symptoms experienced by refugees. Notwithstanding the widely recognized association of stress with disasters such as war-related emigration, relatively little work has been done to incorporate objective measures of physiological stress such as allostatic load (AL) and brain responses in disaster-related health studies. The term “allostasis” refers to biological processes that enable to achieve and maintain homeostasis in response to environmental challenges. It is important to note that the AL concept is not only a theoretical framework providing a comprehensive conceptualization of stress response. Indeed, the AL index, capturing endocrine, immune-inflammatory, metabolic and cardiovascular markers is a useful measure predicting unfavorable stress-related outcomes. Our hypothesis is based on compelling evidence suggesting that the brain is organized into functionally distinct brain networks with high intrinsic connectivity - dubbed intrinsic connectivity networks (ICNs). The triple network model, comprising the default mode network (DMN), salience network (SN) and central executive network (CEN), has been proposed to understand brain disruptions in cognitive and affective disorders, including PTSD. We hypothesize that brain disturbances present among Ukrainian refugees may involve these three critical networks. Our hypothesis is based on marked overlap in studies regarding people with PTSD, depression and anxiety including refugees, which shared neurobiological alterations identified in studies referred to chronically stressed individuals. Namely, both people suffering from PTSD including refugees and people with allostatic overload present overlapping abnormalities in the hippocampus, amygdala, insula and others leading to similar disturbances in ICNs: the CEN and the DMN resulting from insufficient SN modulation between CEN and DMN activity. Additionally, this proposal is based on the following secondary objectives:

**#1: To investigate whether biological and psychopathological responses to war stress are moderated by intrinsic psychological factors such as resilience, attachment styles and coping strategies**

**#2: To indicate neural substrates of elevated AL index among refugees.**

Psychiatric and psychological examination will be carried out on the basis of an outpatient clinic of the Department and Clinic of Psychiatry at Wroclaw Medical University, Poland. Recruitment procedures will be finished after enrollment of **65 refugees from Ukraine** who crossed the Polish-Ukrainian border after the Russian invasion on 24 February, 2022 - aged 18-65 years. Refugees, as well as a **control group of equal numbers**, will undergo a **psychiatric assessment**. The **rs-fMRI** test will be performed among the studied refugees and the control group, and **blood will be taken to determine the AL index**.

Exposure to war stress has repeatedly been shown to trigger a number of unfavorable mental health outcomes. The exact mechanisms underlying this association remain unknown. The AL concept is a useful framework that helps to understand biological consequences of stress exposure in various populations. However, its usefulness in terms of investigating the outcomes of war stress has not been investigated so far. It is also unknown what are the neural substrates of AL in vulnerable populations. The presented study will be an important step towards a better understanding of the biological and psychopathological consequences of the refugee crisis, based on the AL concept.