Psychotic-like experiences (PLEs) are highly prevalent and occur in 5 – 8% of the general population. They include hallucination-like and delusion-like experiences that do not meet widely accepted diagnostic criteria of mental disorders4. However, it is widely accepted that they serve as a risk factor for overt psychotic disorders. The exact mechanisms contributing to the development of PLEs and psychotic disorders remain unclear. Nevertheless, recent studies indicate that approaching more complex models may better explain the mechanisms underlying psychotic disorders than those assuming the effects of single insults.

It has been found that various categories of psychosocial stressors increase a risk of PLEs. However, experiencing psychosocial stress is neither necessary nor sufficient to trigger the onset of psychosis. There is evidence that psychosocial stressors increase a risk of PLEs and psychosis through a number of psychological mechanisms. Studies in this field have indicated a role of negative affect, aberrant salience and threat anticipation. Negative affect captures individual tendency to experience negative emotions. In turn, aberrant salience can be defined as the tendency to overattribute meaning to irrelevant environmental exposures. Finally, threat anticipation is the hypervigilance state of anticipating adverse experiences. Studies investigating the association between psychosocial stress and psychosis often neglect one of most important observations, i.e., the fact that PLEs often emerge in the context of routine daily activities and stressors. Therefore, it has been proposed that assessment of real-time functioning by approaching experience sampling methodology (ESM) might provide grounds for better understanding of the association between stress and psychosis. The ESM is based on repeated recordings of daily experiences using modern technologies, such as smartphones.

According to biopsychosocial models of psychosis, psychological processes mediating the association between stress and psychosis should be investigated together with biological mechanisms. Indeed, psychosocial stress activates a number of biological processes that might be relevant to the development of PLEs and psychotic disorders. One of them is related to the activation of the hypothalamic-pituitary-adrenal (HPA) axis that leads to the release of glucocorticoids represented by cortisol. Short-term activation of the HPA axis enables to maintain homeostasis and cope with stress. However, persistent activation or overactivation of the HPA axis may be deleterious. Moreover, it has been reported that the activation of the HPA axis might also increase the release of dopamine in the mesolimbic system. In turn, excessive release of dopamine has been associated with the development of PLEs. Various aspects of the HPA axis dysregulation have been reported in subjects with PLEs and psychosis. However, there is a high interindividual variability in individual HPA axis responses, likely attributable to genetic backgrounds. It has been found that the FK506-binding protein (FKBP5) is one of main regulators of cellular cortisol activity. It protects cells against excessive activity of cortisol. There is evidence that certain variants of the *FKBP5* gene make individuals more prone to develop PLEs in response to various categories of psychosocial stress. However, little is known about the relevance of epigenetic processes, such as DNA methylation and microRNAs (miRNAs) in the regulation of the *FKBP5* expression. Our group was the first to demonstrate that individuals with first-episode psychosis show decreased levels of the *FKBP5* gene methylation, attributable to a history of childhood trauma.

This project will have the following aims: 1) to investigate the role of epigenetic marks at *FKBP5* gene in moderating the association between momentary stress and PLEs by adopting ESM; 2) to explore the moderating effects of epigenetic marks at the *FKBP5* gene on the relationship between momentary stress response and antecedents of PLEs (negative affect, aberrant salience and threat anticipation); 3) to examine the association between epigenetic regulation of the *FKBP5* gene and psychosis proneness and 4) to identify differences in salivary cortisol response to momentary stress between individuals with PLEs and those without PLEs. Out of 3000 general population individuals aged 18 – 35 years and screened for PLEs, we will recruit 100 subjects with PLEs and 100 subjects without PLEs as controls. Next, we will collect blood samples to perform analysis of methylation (at 16 CpG sites) and expression of the *FKBP5* gene as well as miRNAs (32 species) targeting the *FKBP5* gene. All subjects will undergo the ESM protocol (random-sampling protocol, 6 prompts per day on 7 consecutive days). After each prompt, individuals will be asked to collect saliva samples and answer 32 Likert-like questions evaluating the level of psychosocial stress, negative affect, aberrant salience, threat anticipation and PLEs. For the first time, this project will show whether epigenetic marks at the *FKBP5* gene moderate the association between daily stressors and PLEs together with their psychological antecedents and cortisol responses.