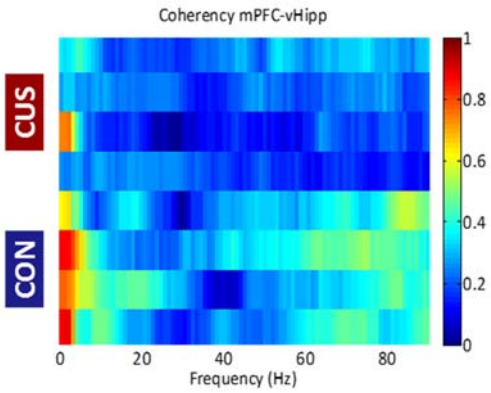
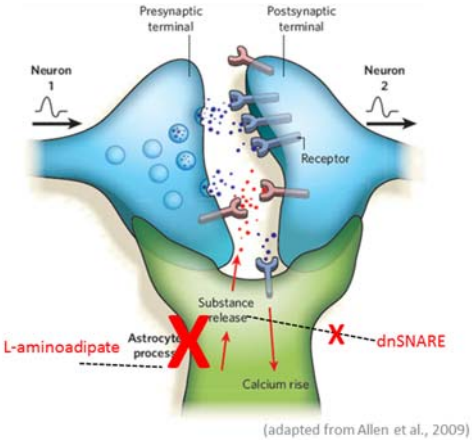
THE STRESSED SOCIETY

Life in modern societies is vibrant and very demanding. People face daily a number of challenges that present different levels of stress that appear at unpredictable paces and intensities. Stress exposure sets primarily a response to restore physiological homeostasis and promote behavioural adaptation. However, prolonged stressful experience may trigger maladaptive responses that lead to severe manifestations such as depressive-like behaviour, learning and memory deficits. Indeed, one of the major hallmarks of modern life is the high prevalence of psychiatric disorders as consequence of chronic exposure to stress, such as major depression disorder (MDD). This disorder affects nowadays over 120 million people worldwide, represents a huge burden for the society and health systems, and is projected to be one of the leading causes of death by 2030.

HOW MAY ASTROCYTES HELP?



The identification of the mechanisms triggered by stress is essential to disclose and design therapeutic approaches to restore cognitive function in psychiatric patients. Indeed, advances in neurobiology reported clear morphological deficits in neurons of both hippocampus and prefrontal cortex (PFC) after chronic-stress exposure. However, the classical paradigm that brain information processing is exclusively a neuronal process has been challenged by an emerging body of evidence. In fact, astrocytes, the most numerous glial cell type, were recently described to establish important cross-talk with neurons, modulating their function. Of notice is that the neuroglial networks are severely affected in brain regions such as the prefrontal cortex and the hippocampus, as indicated by our measures of coherency between these two regions after stress exposure (Figure above). The idea under this project was to use a novel approach to test the importance of astrocytes in pathophysiology of stress disorders. For that we established in the lab two animal models (figure below): (1) the astrocyte toxin L-aminoadipate was injected in the medial prefrontal cortex to induce astrocyte loss in this region critically affected by stress; (2) the dnSNARE mouse model was implemented in the lab to block exocytotic release of substances specifically by astrocytes. A detailed analysis of the networks function by behaviour,



(adapted from Allen et al., 2009)

electrophysiological and molecular tools was performed. The better understanding of the role of astrocytes in these disorders will surely guide to novel therapeutic possibilities.

WHAT DID WE LEARN FROM ASTROCYTES?

To model astrocyte pathology observed after chronic stress exposure we injected animals with the astrocyte specific toxin L-aminoadipate (L-AA) in the medial prefrontal cortex (mPFC); a behavioral and structural characterization two and six-days after the injection was performed. Behavioral data shows that the astrocyte pathology in the mPFC affects the attentional set-shifting, the working memory and the reversal learning functions. Histological analysis of brain sections of the L-AA-injected animals revealed a pronounced loss of astrocytes in the targeted region. Interestingly, analysis of neurons in the lesion sites showed a progressive neuronal loss that was accompanied with dendritic atrophy in the surviving neurons. These results suggest that the L-aminoadipate-induced astrocytic loss in the mPFC triggers subsequent neuronal damage leading to cognitive impairment in tasks depending on the integrity of this brain region. These findings mimic the symptoms and in psychiatric disorders related with chronic stress exposure. They are of relevance to better understand the pathophysiological mechanisms underlying such disorders that involve astrocytic loss/dysfunction in the PFC. This study was cover of the Molecular Psychiatry Journal of NPG, the most relevant journal of psychiatric disorders worldwide (above). The dnSNARE model presents a dysfunction that was confirmed to specifically affect astrocytes. The dysfunction alone was not enough to trigger chronic stress-related behaviors such as anhedonia, learned helplessness, anxious like-behaviour. However, some levels of cognitive impairment are observed. Curiously, after chronic stress exposure the astrocytic dysfunction triggers an anxiolytic behavior. These behavior observations are supported by in vivo electrophysiological measurements that provide a complementary measure of neuroglial network function. Notably, it seems that the network is much more affected in terms of lack of synchrony between brain regions, which appears to be compensated by the recruitment of additional regions.

These results provide interesting insights into mechanisms by which astrocytes interact with neurons to produce behavior outputs. The affection of astrocytes by stress may trigger deleterious consequences in neurons. If we learn how to protect astrocytes and use them to protect neurons, we will possibly disclose novel therapeutic avenues for the treatment of chronic stress-related disorders such as depression.