The influence of maternal bonding in neuroimmune synaptic sculpting

ABSTRACT:

Background
Exposure to early-life stress (ELS), such as that caused by maternal separation can induce maladaptive behaviors and increase the vulnerability to neurological disorders later in life. In addition to having a direct impact in neuronal function, stress can also trigger neuroinflammatory events that impact microglia activity.

Aims
With this work, we aim to elucidate what is the acute and long-term impact of ELS exposure and how it interferes with key microglia functions which are crucial for correct circuit wiring during the post-natal period.

Method
Towards this purpose, we have used a paradigm of maternal separation and maternal stress (MSUS), that allows to mimic early life adversity in the form of maternal neglect. We have investigated consequences of ELS to social behavior, as well as its impact on microglia phenotype. We have focused our evaluation in the medial pre-frontal cortex (mPFC), a brain region implicated in social interaction and impulse control that is often implicated in neuropsychiatric disorders.

Results
We have observed that exposure to MSUS causes changes in social interaction, in the form of a reduction in ultravocalizations, as early as P5. In addition, we observed changes in social preference and an increase in submissive behaviors in adolescent and adult male mice, but no significant behavior changes in females. Exposure to ELS also leads to sex-dependent morphological and gene expression changes that are more profound in male microglia and that originate an hyperramified phenotype in adolescent mice. Male MSUS mice also present an increase in the number of PV+ inhibitory neurons in the mPFC, that is not observed in females and that leads to an increase in spontaneous IPSCs in this region.

Conclusions
Taken together, ours results point towards a higher susceptibility of male mice to the negative impacts of ELS exposure. This feature may be directly connected with the different and delayed response of male microglia to this type of stress.

Keywords

Early life stress, Microglia, Neuronal circuits, Maternal bonding, Neuroinflammation

Published Work:

Franco, L. O., Carvalho, M. J., Costa, J., Ferreira, P. A., Guedes, J. R., Sousa, R., ... Peça, J. (2020). Social subordination induced by early life adversity rewires inhibitory control of the prefrontal cortex via enhanced Npy1r signaling. *Neuropsychopharmacology, 45*, 1438-1447. doi: 10.1038/s41386-020-0727-7

Barros-Viegas, A. T., Carmona, V., Ferreiro, E., Guedes, G., Cunha, P., Pereira de Almeida, L., … Cardoso, A. L. (2020). MiRNA-31 improves cognition and abolishes amyloid-ß pathology by targeting APP and BACE1 in an animal model of Alzheimer's disease. *Molecular Therapy - Nucleic Acids, 19*, 1219-1236. doi: 10.1016/j.omtn.2020.01.010

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