EARLY-LIFE STRESS CAUSES MICROGLIA DYSFUNCTION AND BEHAVIOR CHANGES IN THE PRE-FRONTAL CORTEX OF JUVENILE AND ADOLESCENT MICE

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Background: Exposure to early-life stress (ELS), such as that caused by maternal separation in the post-natal period, can induce maladaptive behaviors and increase the vulnerability to neurodevelopmental and neuropsychiatric 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 how ELS contributes to microglia dysfunction and interferes with key microglia features, such as neurogenesis, synaptogenesis synaptic pruning and neuronal elimination, which occur during the first post-natal weeks and which are crucial for correct circuit wiring.

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, allowing to study the behavior consequences of ELS, as well as its impact on microglia number, morphology and gene expression profile. We have focused our evaluation in the medial pre-frontal cortex (mPFC), a brain region highly implicated in social behaviors and impulse control, which presents a delayed maturation profile and, thus, is more susceptible to stress exposure during the post-natal period.

Results: We have observed that exposure to MSUS causes changes in social interaction and impulsivity, as well as an increase in submissive behaviors in male mice, but no significant behavior changes in females. Exposure to ELS also leads to morphological and gene expression changes in male microglia that are compatible with activation towards a classical M1-like activation phenotype during the early life period and that are only partly reversed during the juvenile period. Juvenile male mice exposed to MSUS also present changes in myelination-related genes, an increase in the number of PV+ inhibitory neurons in the mPFC, as well as deficits in social interaction and a tendency to display increased anxiety, while female MSUS mice appear to be less susceptible to ELS-driven changes, despite showing early changes in microglia morphology and gene expression.

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 stronger response of male microglia to this type of stress.

Keywords: Microglia, Early life stress, Neuroinflammation, Maternal neglect

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