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Abstract

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Identifying structural endophenotypes in a rat model of schizophrenia-like behavior

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Animal models reflecting cognitive manifestations of mental disorders are widely used to shed light on the neurobiology behind specific behavioral phenotypes. The Roman rat strains are a neurobehavioral animal model derived from selective breeding into an inbred Roman Low- (RLA-I) and Roman High-Avoidance (RHA-I) strain, based on their performance in the two-way active avoidance task in the shuttle box. The RHA-I strain presents behavioral phenotypes associated with schizophrenia and schizophrenia risk, making it an ideal model for investigating the underlying neurobiology behind these behavioral traits. The prefrontal cortex (PFC) is a central player in cognitive processes, which are known to be impaired in schizophrenia. Interestingly, the RHA-I strain, when compared to the RLA-I, show enhanced expression of pre- and postsynaptic components and increased number of immature dendritic spines in this region. The aim of this study is to investigate whether this is accompanied by differences in number of astrocytes and microglia, as these cells are involved in regulating synaptic pruning.

Coronally cut brain sections from male RHA-I ($n = 5$) and RLA-I ($n = 5$) rats were stained for GFAP and Iba1 for identification of astroglia and microglia respectively, using colorimetric immunohistochemistry. The optical fractionator sampling design was used to estimate the total numbers of astrocytes and microglia in mPFC, and a point-counting method based on Cavalieri's principle in combination with systematic random sampling was used to estimate the reference volume of mPFC.

RHA-I rats had a significantly higher number of astrocytes in their mPFC than their RLA-I counterparts ($P \leq 0.01$). The number of microglia in mPFC did not differ between the two groups, neither did the volume of the mPFC.

The finding that astrocyte numbers in mPFC is increased in RHA-I rats is in line with findings from other studies of animal models of schizophrenia and psychosis, as well as in schizophrenic patients, where changes in astrocyte numbers have been

observed in different brain regions. The astrocytes might therefore be involved in the synaptic alterations and cognitive deficits observed in the RHA-I rats.