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Long-access heroin self-administration induces region specific reduction of grey matter volume and microglia reactivity in NIH Heterogeneous Stock rats.

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Reduced grey matter volume (GMV) has been associated with opioid use disorder (OUD). Whether this is the consequence of prolonged exposure to opioids or a factor predisposing to OUD remains unclear. To investigate this, we conducted a structural MRI longitudinal study in NIH Heterogeneous Stock (HS) rats exposed to prolonged long access heroin self-administration and yoked heroin-naïve controls. We chose the HS for their large genetic heterogeneity to closer mimic the human population.
Heroin self-administration resulted in escalation of drug intake and in reduced cortical and sub-cortical GMV, while no changes were observed in drug-naïve controls. Notably, the degree of GMV reduction in the medial prefrontal cortex (mPFC) and insula positively correlated with the amount and the escalation of heroin consumption. Next, by an RNAseq analysis in the mPFC, we identified a large set of genes altered by heroin, among which we found several transcripts linked to neuroinflammation. This prompted us to hypothesize a link between changes in microglia homeostasis and loss of GMV. Thus, we analyzed the morphology of microglia in the mPFC and insula. The primary motor cortex, where no GMV change was observed, was used as negative control. In the same regions where reduced GMV was detected, we observed a shift towards a rounder microglia shape and size reduction, suggestive of their homeostatic change towards a reactive state. Altogether these findings suggest that escalation of heroin intake correlates with loss of GMV in specific brain regions and that this phenomenon is linked to changes in microglial morphology.