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Signatures of DNA Damage and Epigenetic Erosion in Opioid Use Disorder

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The heterogeneity of brain brain tissue presents difficulties in the studying molecular effects of opioid use disorder (OUD). Using single nuclei RNA-sequencing in OUD subjects and controls, we identified both canonical (e.g., dopamine receptor subtype) and less abundant cell populations (e.g., interneurons) in human dorsal striatum. Pathways related to neurodegeneration, interferon response, and DNA damage were significantly enriched in striatal neurons of individuals with OUD. Increased levels of DNA damage over time can cause an 'epigenetic erosion' or a breakdown in the epigenetic state of cells. To test whether this process is occurring in the brains of subjects with OUD, we analyzed open chromatin data from the striatum of OUD subjects and controls. As expected, we were able to find substantial signatures of epigenetic erosion in OUD subjects. In summary, our results suggest that long term opioid use increases levels of DNA damage that in turn causes broad patterns of epigenetic erosion of neurons in the striatum.