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Mapping Cell Types in the Human Putamen from Cocaine Abusers

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The human putamen, as part of the dorsal striatum, integrates dopaminergic inputs from the midbrain and glutamatergic inputs from the cortex. Consequently, this brain region expresses high levels of dopamine signaling components. Specifically, the dopamine transporter (DAT), as the primary target of cocaine's action, exhibits intense binding of radiolabeled cocaine in PET imaging studies. Furthermore, dopamine signaling in the putamen, as measured by dopamine D2 receptor occupancy with radiolabeled raclopride, is significantly associated with cue-evoked cravings in human subjects addicted to cocaine. This convergence of human data strongly implicates the putamen in cocaine addiction, and its association with cravings makes it an ideal region for targeting anti-addiction therapies. However, translating preclinical rodent findings to humans is challenging, since the gross anatomy of the rodent striatum differs significantly from the human striatum, as rodents lack distinction between the caudate and putamen. To address this challenge, we have mapped cell types in human postmortem putamen tissues from individuals that overdosed on cocaine and matched controls using single nuclear RNA sequencing (snRNAseq). Notably, we recognize distinct populations of dopamine D1 vs. D2 receptor-expressing neurons and large numbers of apparent oligodendrocytes. We also see scant expression of DAT, suggesting the labeling of this target in human PET studies likely results from expression on presynaptic innervating midbrain dopaminergic neurons. This is consistent with near-complete loss of DAT in the putamen of individuals with Parkinson's disease. Additional studies are necessary to identify robust changes in gene expression across cell types in cocaine abusers versus controls.