Title: Human Transcriptome Analysis of Cocaine Abuse Identifies Genes Associated with Adult Striatal Neurogenesis

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Background: Drug addiction involves transitions from initial voluntary drug use to habitual and compulsive use with a shift from reward mechanisms in the ventral striatum to activation of circuits in the dorsal caudate. Chronic cocaine administration induces neuroplastic changes in rodent models within corticostriatal systems regulating emotions and cognitive control. New research demonstrates that adult striatal neurogenesis only occurs in humans and may derive from local cells within the parenchyma of the caudate, in addition to those deriving from the neurogenic niche of the subventricular zone. We report here RNA-Seq data mining and network analysis of the human caudate from cocaine abusers, which identifies transcripts associated with adult striatal neurogenesis.

Methods: We used RNA-Seq to quantify transcript changes and analyzed global gene expression in well-characterized cohorts to identify candidate gene markers that are regulated by cocaine abuse in striatal dopamine pathways. The dorsal caudate was sampled postmortem from individuals who were chronic cocaine abusers (N=25) and from age-matched unaffected control subjects who died suddenly without a history of drug or alcohol abuse (N= 25). The RNA-Seq read alignment and differential analyses were done using TopHat and Cufflinks packages. For the initial analysis, cutoffs were set as FDR < 5%, fold change >1.2 and RPKM > 1 for cocaine cases and control groups. HTSeq-DESeq2 and Cufflinks-SAMr pipelines were used to identify differentially expressed genes and transcripts, respectively.

Results: In the caudate, cocaine-mediated changes in DE genes and transcripts were associated with neurophysiological processes, including axon transport and glutamate regulation of dopamine D1 receptor signaling, Wnt signaling in development and degradation of beta-catenin, protein folding and maturation, cadherin-mediated cell adhesion, and cell cycle regulation of G1/S transition. Based on the pathway analysis, 10 DE genes from the caudate were validated using qPCR and NanoString

Technologies nCounter Analysis System. Wnt signaling molecules (Sox11, NeuroD1 and MSX1) and the regulator of dopamine