Title: Genetic Markers Associated with Brain Structural Abnormalities in Human Cocaine Addiction

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Drug addiction is a heritable and chronically relapsing disease associated with functional deficits in brain regions that underlie reward processing and self-control. These functional deficits are further associated with morphological abnormalities [e.g., gray matter volume (GMV) reductions] in similar or interconnected regions, potentially driven by persistent cellular changes associated with long-term exposure to addictive substances (e.g., cocaine). Importantly, these drug-associated structural alterations are further modulated by genetic factors. Indeed, single nucleotide polymorphisms (SNPs) (e.g., the Dopamine Transporter Gene or the Monoamine Oxidase A gene) have been shown to modulate GMV of the dorsal striatum and orbitofrontal cortex, respectively. Nevertheless, to account for clinically-meaningful genetic variance in complex phenotypes such as GMV abnormalities in addiction, new SNPs need to be discovered and validated. Therefore, in the current study we implemented a genome-wide search for novel SNPs correlating with GMV in human cocaine-addicted individuals as compared with non-addicted controls. Three bilateral, anatomically-defined regions of interest (ROIs) were inspected: caudate, putamen, and pallidum. Selection of these ROIs was based on (1) observed group differences in the current study on GMV between cases and controls in these regions, consistent with prior literature; and (2) a large literature in humans and animals implicating these basal ganglia regions in important addiction-relevant phenotypes (e.g., compulsivity of drug-taking as related to altered dopaminergic neurotransmission). An initial discovery cohort of 133 individuals with cocaine use disorder and 106 healthy controls has been genotyped using the Illumina Multi-Ethnic Genotyping Array (MEGA), which is specifically optimized for GWAS in ancestrally diverse samples. After imputation and quality control, we obtained genome-wide profiling for 11,513,071 total SNPs in our participants. Of this sample, 70 individuals with cocaine use disorder (CUD) and 62 controls also had usable 3T MRI data, and these 132 participants were included in the analyses. Genome-wide association analysis of GMV in our three *a priori* regions of interest was performed using linear regression (additive model) in PLINK (v1.09). Covariates of interest in the models included SNP, Diagnosis, and the SNP × Diagnosis interaction; covariates of no interest included sex and race. Results revealed the following SNP × Diagnosis interactions predicting GMV: rs1801043 in the right caudate (beta=2.6, P=2.8e−09), rs2421616 in the right putamen (beta=−1.5, P=6.3e−09), and rs2421616 in the right pallidum (beta=−1.6, P=7.6e−10). Thus, despite a relatively small sample size, we observed genome-wide significant interactions with SNPs that are within or in proximity to the fibroblast growth factor receptor 2 (*FGFR2*) and protein phosphatase 1, regulatory subunit 3C (*PPP1R3C*) genes. These preliminary results point to the robustness of GMV as an intermediate addiction phenotype versus other available phenotypes (e.g., behavioral impulsivity). Ongoing work is aiming to replicate these associations using a second, independent, and similarly sized cohort of CUD and controls. If replication is successful, future analyses will then aim to (1) establish the possible functional impact of noncoding variants using expression quantitative trait loci derived from human brain

tissue and/or (2) characterize molecular systems associated with addiction through the construction of gene regulatory networks.