BACKGROUND: It is established that SUDs and Parkinson’s Disease (PD) among many other neuropsychiatric disorders are dopamine (DA)-related brain disorders with strong heritability. However, it is unclear whether DA-associated genetic risks share commonality across these disorders.

AIM: Determine whether these neuropsychiatric disorders have common risks in DA-associated genes, including DA synthesis (2 genes), metabolism (2 genes), receptors (DRs, 5 genes), monoamine transporters (5 genes), an uptake modulator (alpha-synuclein: SNCA), and transcription factors (7 genes).

MATERIALS & METHODS: This study utilizes the dbGaP GWAS from 6,500+ subjects for each disease, and analyzes case-control-based epistasis among these 22 DAergic genes.

RESULTS: Extensive and significant epistasis signals were uncovered between gene variants and SUDs or, to less extent, PD. For SUDs, the strongest significant interaction was SNCA with the developmentally expressed vesicular monoamine transporter 1 gene SLC18A1 and our recently discovered TFs. The largest number of significant interactions was between the DA transporter gene SLC6A3 and 21 of the 22 genes including two DR genes, DRD3 and DRD5. For PD, DRD3 interacted with the tyrosine hydroxylase gene TH and the dopa-decarboxylase gene DDC; SLC6A3 interacted with 6 of the 22 target genes. Interestingly, the interaction between DRD3 and the NET gene (SLC6A2) was implicated in both diseases.

CONCLUSIONS: DA pathways are significantly implicated in the genetic etiology of both SUDs and PD but much more in the former. Epistatic effects may represent a major portion of missing heritability observed in current main effect-oriented GWAS analyses.