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A multipronged approach unravels the spectrum of variants and transcriptomic signatures in distinct stages of substance use and addiction

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Background: Substance use disorders are long-lasting neuropathological conditions centered on persistent craving, pleasure, and reward, ultimately progressing to addiction. In the brain, dorsolateral prefrontal cortex (DLPFC) controls craving, decision making, and tolerance traits whereas midbrain controls hunger, reward, and pleasure traits. Understanding these complex and dynamic events requires systematic dissection of mutational and transcriptomic signatures at each stage. **Objective:** The goals of the current study were to; a) identify causal variants influencing substance use and addiction in substance users; b) asses concordant and discordant gene expression in DLPFC (*n=160*) and midbrain (*n=50*) regions of substance users; c) parse out expression differences following an overdose as opposed to chronic use. **Methods:** Using a multi-pronged strategy involving variant filtering, classification and transcriptome clustering led us to identify protein-function altering gene variants and transcriptomic alterations affecting distinct stages. **Results and Discussion:** Distinct mutational spectrum in genes CCKAR, NPAS4, TACR1, TENM2, EGF, GRM4 and NPY2R were identified for each stage of substance use to addiction. CCKAR and EGF were found exclusive to midbrain, while CCKAR, NPAS4, TACR1, TENM2, GRM4, and NPY2R were restricted to DLPFC. DLPFC region showed transcript alterations with gene clusters enriched for cocaine, alcohol and nicotine addiction besides other pathways, while midbrain showed enrichment with dopaminergic, GABAergic, and cholinergic synapses, endocannabinoid signaling, besides cocaine and nicotine addiction pathways. By unraveling the mutations and transcriptomic signatures between DLPFC and midbrain, our study advances the understanding of the biology of substance use and its progression towards addiction providing potential stage specific testable targets.