

Orthogonal Transcriptional Programs Distinguish Compulsive from Hedonic Alcohol Drinking: Implications for Addiction Neurobiology

Substance use disorders are often conceptualized along a severity continuum, where compulsive drug seeking represents an escalation of reward-driven use. However, whether compulsive drug use reflects quantitative amplification of hedonic mechanisms or recruitment of a distinct biological program remains unclear.

Using alcohol as a tractable experimental model of addiction-relevant behavior, we compared transcriptional profiles associated with (i) voluntary, hedonic alcohol intake and (ii) punishment-resistant, compulsive-like drinking in mice. Transcriptomic analyses of dorsomedial striatal neuronal populations revealed a striking dissociation between these states. Rather than observing concordant scaling of gene expression changes, effect-size comparisons between intake-driven and compulsive phenotypes revealed an orthogonal structure: genes most strongly associated with compulsive drinking were largely independent from those tracking consumption magnitude. This relationship indicates that compulsivity engages a partially distinct transcriptional axis rather than representing an extreme of reward-driven intake.

Pathway-level analyses further supported this separation, with compulsive drinking preferentially engaging programs related to synaptic remodeling, intracellular signaling reorganization, and stress-responsive transcriptional regulation, whereas hedonic intake was enriched for canonical reward and metabolic processes. Importantly, shared gene-level overlap between the two phenotypes was limited, suggesting convergence at systems-level functions rather than identical molecular effectors.

Although alcohol was used as the experimental model, these findings have broader implications for addiction neuroscience. The dissociation between reward-driven and compulsion-associated transcriptional programs suggests that compulsivity may represent a transdiagnostic biological state across substances. Alcohol offers a uniquely scalable system in which voluntary and punishment-resistant phenotypes can be experimentally dissociated, providing a powerful platform to define the molecular architecture of compulsive drug use.

These results support a conceptual shift in addiction research: compulsive drug seeking may not simply reflect “more reward,” but instead the engagement of an orthogonal, systems-level transcriptional program. Defining this axis across substances may uncover convergent molecular mechanisms that transcend drug class and inform targeted therapeutic development.

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