

Title: Genetic Selection for Methamphetamine Intake Rewires Brain Transcriptional Networks

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Abstract

Purpose: The use of selective breeding in animal models can facilitate the study of the genetics of methamphetamine (MA) addiction. While strong candidate genes such as *Taar1* and *Oprm1* have been identified (Phillips and Shabani, 2015, *Front Neurosci* 9:327), the effects of genetic selection on brain structure are likely to be extensive. Transcriptional analysis offers access to a rich set of endophenotypes and can generate a mechanistic understanding of the links between causal polymorphisms and the behavioral effects.

Methods: To address these issues we examine the transcriptional differences between two mouse populations selectively bred for high or low voluntary MA intake, focusing on the nucleus accumbens, one key region within the “addiction circuitry” (Koob et al., 2010, *Neuropsychopharmacol* 35:217-238).

Results: A network-based analysis strategy identified 28 modules (groups of highly coexpressed genes). We detect extensive transcriptional differences involving six of the modules. A module denoted as “blue” contains 55 affected hubs (highly coexpressed genes) and is enriched in translation initiation Gene Ontology (GO) categories. Additional GO terms associated with the rewired modules include membrane and transmembrane receptor genes, as well as myelin sheath related genes. Within these modules we identify a total of 162 gene hubs that are strongly affected by selection. This group includes *Eif1a*, *Eif2s2*, *Eif3m* and *Eif4e*, several of which have been previously associated with transcriptional effects of MA (Cadet et al., 2015, *Molec Neurobiol* 51:696-717). *Cox6b1*, a member of the proinflammatory oxidases with likely roles in addiction (Crews, 2012, *Alcohol Res: Current Rev* 34:355-361), is also among the affected hubs.

Conclusions: Our results illustrate how network analysis allows prioritization of widespread transcriptional changes based on relative gene importance as quantified by network connectivity/hubness. Affected network hubs emerge as key potential targets for molecular manipulations.

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