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Network Approaches Identify Brain Regions and Gene Hubs Associated with Genetic Predisposition for Methamphetamine Intake

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Methamphetamine (MA) addiction has a strong genetic component, partially explained by the actions of genes, such as *Taar1* and *Oprm1* (Phillips and Shabani, 2015, Front Neurosci 9:327). However, the specific impacts of these and other genes in particular brain regions remain largely unknown. Transcriptional analysis across multiple brain regions, coupled with genotype data, offers access to a rich set of endophenotypes and can generate a mechanistic understanding of the links between causal polymorphisms and behavioral effects. This approach was used to identify and rank genes most central to the genetic and behavioral differences between two mouse populations selectively bred for high or low voluntary MA intake. Transcriptional differences were examined within three "addiction circuitry" regions: the nucleus accumbens (NAC), prefrontal cortex (PFC) and ventral midbrain (VMB). Differential gene expression analysis was supplemented with "differential network" analysis, which identifies and quantifies changes in the correlation structure between genes. In addition to Weighted Gene Co-expression Network Analysis (WGCNA) a novel cosplicing network analysis technique was employed (Iancu et al., 2015, Front Genet 6:174), which identifies genes that change exon inclusion and transcript composition in a coordinated manner. "Differential wiring" of genes and modules between the lines was also examined. Transcriptional effects were moderate in the NAC and PFC but pronounced in the VMB. Network modules were independently detected in each region and network type; however, their structure was largely preserved across brain regions. Differential wiring was more pronounced in VMB. Affected network hubs emerge as key targets for potential molecular manipulations.