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Methamphetamine-induced region-specific transcriptomic and epigenetic changes in the brain of male rats

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Psychostimulant methamphetamine (METH) is neurotoxic to the brain and, therefore, its misuse leads to neurological and psychiatric disorders. The gene regulatory network (GRN) response to neurotoxic METH binge remains unclear in most brain regions. Here we examined the effects of binge METH on the GRN in the nucleus accumbens, dentate gyrus, Ammon's horn, and subventricular zone in male rats. At 24 hours after METH, ~16% of genes displayed altered expression and over a quarter of previously open chromatin regions - parts of the genome where genes are typically active - showed shifts in their accessibility. Intriguingly, most changes were unique to each area studied, and independent regulation between transcriptome and chromatin accessibility was observed. Unexpectedly, METH differentially impacted gene activity and chromatin accessibility within the dentate gyrus and Ammon's horn. Around 70% of the affected chromatin-accessible regions in the rat brain have conserved DNA sequences in the human genome. These regions frequently act as enhancers, ramping up the activity of nearby genes, and contain mutations linked to various neurological conditions. By sketching out the gene regulatory networks associated with binge METH in specific brain regions, our study offers fresh insights into how METH can trigger profound, region-specific molecular shifts.