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N⁶-methyladenosine and Epitranscriptomic Regulation of Learning and Responses to Cocaine

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N⁶-methyladenosine (m⁶A) profoundly regulates mRNA metabolism and translation. Recent data suggest that m⁶A deficiency within the adult brain have significant functional consequences on synaptic plasticity and learning. We deleted *Mettl14*, an essential component of the m⁶A methyltransferase complex, in two brain regions, dorsal striatum and nucleus accumbens, and in two related yet discrete mouse neuronal populations: striatonigral and striatopallidal. We have also generated or obtained mice with genetic deletion of various m⁶A reader proteins (RNA binding proteins that recognize m⁶A and mediate downstream functional consequences). *Mettl14* deletion reduced striatal m⁶A levels without altering cell numbers or morphology. Transcriptome-wide profiling of m⁶A-modified mRNAs in *Mettl14*-deleted striatum revealed downregulation of similar striatal mRNAs encoding neuron- and synapse-specific proteins in both neuronal types, but striatonigral and striatopallidal identity genes were uniquely downregulated in each respective manipulation. Upregulated mRNA species encoded non-neuron-specific proteins. These changes increased neuronal excitability, reduced spike frequency adaptation and profoundly impaired striatal-mediated behaviors. In the dorsal striatum, they severely impaired motor learning whereas in the nucleus accumbens they severely impaired appetitive Pavlovian learning without affecting motor learning. m⁶A deficiency also severely altered behavioral responses to cocaine and dopamine D1 agonist. We are currently assessing different m⁶A reader proteins in affecting protein synthesis, synaptic plasticity, appetitive Pavlovian learning, motivation and drug addiction in mouse models.