Submitter Name: Xiaoxi Zhuang
Submitter email: xzhuang@bsd.uchicago.edu

N^6-methyladenosine and Epitranscriptomic Regulation of Learning and Responses to Cocaine

Meera Patel[1], Zhuoyue Shi[1], Jessica Koranda[1], Chuan He[2], and Xiaoxi Zhuang[1],

[1]Department of Neurobiology and [2]Department of Chemistry, the University of Chicago

N^6-methyladenosine (m^6A) profoundly regulates mRNA metabolism and protein synthesis. Recent data suggest that m^6A deficiency in the brain have significant functional consequences on development, synaptic plasticity and learning. We deleted *Mettl14*, an essential component of the m^6A methyltransferase complex, in different brain regions and cell types. We also generated or obtained mice with constitutive or cell type specific genetic deletion of various m^6A reader proteins (RNA binding proteins that recognize m^6A and mediate downstream functional consequences). *Mettl14* deletion reduced striatal m^6A levels without altering cell numbers or morphology. Transcriptome-wide profiling of m^6A-modified mRNAs in *Mettl14*-deleted striatum revealed downregulation of striatal mRNAs encoding neuron- and synapse-specific proteins in both D1 and D2 neurons, but D1 and D2 neuron identity genes were uniquely downregulated in each respective cell type. 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. *Mettl14* deletion in D1 neurons severely impaired responses to cocaine whereas *Mettl14* deletion in D2 neurons or in dopamine neurons significantly enhanced responses to cocaine. One of the m^6A reader proteins, YTHDF1, seems to mediate many of the above phenotypes. How exactly YTHDF1 responds to challenges, affects downstream targets, cellular properties, circuit functions and behaviors is under investigation.