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The RNA-binding Protein YTHDF1 Mediates Translational Control by m6A mRNA Methylation in Learning

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Animals adapt in learning with long-term changes at the behavioral, circuit, and cellular levels which often require new protein synthesis. For translational control, reversible m6A modifications of mRNA add an important layer of post-transcriptional regulation with better spatial and temporal resolution than transcriptional level regulation. Using cell-type specific gene deletion in dopamine D1 or D2 receptor expressing neurons, we found that deficiency of either the m6A methyltransferase METTL14 or the m6A reader protein YTHDF1 blunted adaptation at the behavioral, cellular, and molecular levels. In three behavioral paradigms, gene deletion in D1 and D2 neurons impaired D1 and D2-dependent learning respectively; and modulation of D1 and D2 neuron firing was blunted. Ythdf1 deletion resembled learning impairment caused by Mettl14 deletion in a cell type-specific manner, suggesting that YTHDF1 is the main mediator of m6A function in learning. Striatal neurons from control but not Ythdf1 knockout mice responded to elevated cAMP by increasing new protein synthesis. Cocaine drastically increased YTHDF1 binding to many mRNA targets in the striatum, especially those that encode structural proteins. The impaired adaptive responses in mutant mice also allowed us to dissociate the opposing yet cooperative roles of D1 and D2 striatal neurons in learning.