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Neuronal Kmt2a/Mll1 histone methyltransferase is essential for prefrontal synaptic plasticity, anxiety-like behavior and working memory

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Neuronal histone H3-lysine 4 methylation landscapes are defined by sharp peaks at gene promoters and other cis-regulatory sequences, but molecular and cellular phenotypes after neuron-specific deletion of H3K4 methyl-regulators remain largely unexplored. We report that neuronal ablation of the H3K4-specific methyltransferase, Kmt2a/Mixed-lineage leukemia 1 (Mll1), in mouse postnatal forebrain and adult prefrontal cortex (PFC) is associated with increased anxiety and robust cognitive deficits without locomotor dysfunction. In contrast, only mild behavioral phenotypes were observed after ablation of the Mll1 ortholog Kmt2b/Mll2 in PFC. Impaired working memory after Kmt2a/Mll1 ablation in PFC neurons was associated with loss of training-induced transient waves of Arc immediate early gene expression critical for synaptic plasticity. Medial prefrontal layer V pyramidal neurons, a major output relay of the cortex, demonstrated severely impaired synaptic facilitation and temporal summation, two forms of short-term plasticity essential for working memory. Chromatin immunoprecipitation followed by deep sequencing in Mll1-deficient cortical neurons revealed downregulated expression and loss of the transcriptional mark, trimethyl-H3K4, at <50 loci, including the homeodomain transcription factor Meis2. Small RNA-mediated Meis2 knockdown in PFC was associated with working memory defects similar to those elicited by Mll1 deletion. Therefore, mature prefrontal neurons critically depend on maintenance of Mll1-regulated H3K4 methylation at a subset of genes with an essential role in cognition and emotion.

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