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The role for DNA (hydroxy)methylation in epigenetic regulation of different brain cell types

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Brain function depends on the interaction of diverse cell types whose gene expression and identity are defined, in part, by epigenetic mechanisms. DNA methylation (DNAm) marks that are mostly comprised of cytosine methylation (mC) and hydroxymethylation (hmC) are major epigenetic modifications, yet their cell type-specific landscapes and relationship with gene expression are poorly understood. We performed high-resolution (h)mC analyses in three major cell types in human prefrontal cortex (PFC), namely glutamatergic excitatory neurons (Glu), medial ganglionic eminence-derived GABAergic inhibitory neurons, and oligodendrocytes (OLIG)], together with transcriptome and histone modification profiling.

We found that, although all brain cells share general features of epigenomic regulation (such as the negative correlation of mC with gene expression), the quantitative relationship between mC, hmC and RNA expression is significantly different among Glu neurons, GABA neurons and OLIG cells. In particular, we discovered a unique role for hmC in epigenetic regulation of the human GABA neurons. The altered function of these PFC inhibitory interneurons have been previously associated with schizophrenia, major depression disorder, autism spectrum disorders, epilepsy, and drug addiction.

Importantly, the patterns we uncovered could not have been detected either in heterogeneous bulk brain specimens containing multiple cell types or if only total DNAm (tmC=mC+hmC) has been assessed. These approaches, however, have been predominantly used in previous studies of DNAm in the human brain. Thus, our work provides a rich resource for future investigations of the human brain in both health and mental illness, including studies of drug addiction.