Longitudinal Assessment of Neuronal 3D Genomes in Mouse Prefrontal Cortex

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ABSTRACT
Neuronal epigenomes, including chromosomal loopings, which bypass the linear genome to move distal cis-regulatory elements into spatial proximity of target genes, could serve as 'molecular bridges' linking present-day-behavior to distant exposures of the past. Longitudinal modeling is challenging, however, because conventional chromosome conformation capture assays essentially provide single snapshots, reflecting genome organization at the time of brain harvest and therefore are non-informative about the past. Here, we introduce 'NeuroDam' to assess past epigenome status in longitudinal context. Short-term expression of the bacterial DNA adenine methyltransferase Dam, tethered to the *Gad1* gene promoter in mouse prefrontal cortex neurons, resulted in long-term tagging of *Gad1*-bound chromosomal contacts bearing the artificial GmethylATC mark. We show by NeuroDam that mice with persistent deficits in cognition and alterations in anxiety-related behaviors, 4 months after pharmacological blockade of NMDA receptor signaling, already were affected by disrupted chromosomal conformations emerging shortly after drug exposure. NeuroDam can be easily modified to retrospectively chart transcription factor occupancies and many other epigenomic determinants that until now remain unexplored in longitudinal context modeling normal and diseased human brain development and aging.

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