

Title:**Chromosomal Conformations Affecting Cognition and Behavior in Human and Mouse Brain****Abstract**

Large-scale consortia provide increasingly detailed insights into the genetic and epigenetic risk architectures of common psychiatric disorders and offer vast amounts of molecular information, but with largely unexplored functional implications and therapeutic potential. Here I provide specific examples how cell-type specific epigenome mapping in human brain, in conjunction with studies in genetically engineered mice, could illuminate the role of chromatin structure and function for cognition and behavior. These include surprisingly locus-specific disintegration of megabase scale chromosomal conformations and large topologically associated domains (superTADs) after genetic ablation of chromatin regulatory proteins in differentiated brain cells. These findings offer the exciting perspective that *in vivo* editing of enhancer and other regulatory non-coding DNA by RNA-guided nucleases including CRISPR-Cas, or designer transcription factors, could provide a pipeline for novel therapeutic approaches aimed at improving cognitive dysfunction in neurological and psychiatric disease.

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