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Chromatin regulation in complex brain disorders

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Chromatin-related phenomena regulate gene expression by altering the compaction and accessibility of DNA to relevant transcription factors, thus allowing every cell in the body to attain distinct identities and to function properly within a given cellular context. These processes occur not only in the developing central nervous system, but continue throughout the lifetime of a neuron to constantly adapt to changes in the environment. Such changes can be positive or negative, thereby altering the chromatin landscape to influence cellular and synaptic plasticity within relevant neural circuits, and ultimately behavior. Given the importance of epigenetic mechanisms in guiding physiological adaptations, perturbations in these processes in brain have been linked to several neuropsychiatric and neurological disorders. In this review, we cover some of the recent advances linking chromatin dynamics to complex brain disorders and discuss new methodologies that may overcome current limitations in the field.

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Introduction

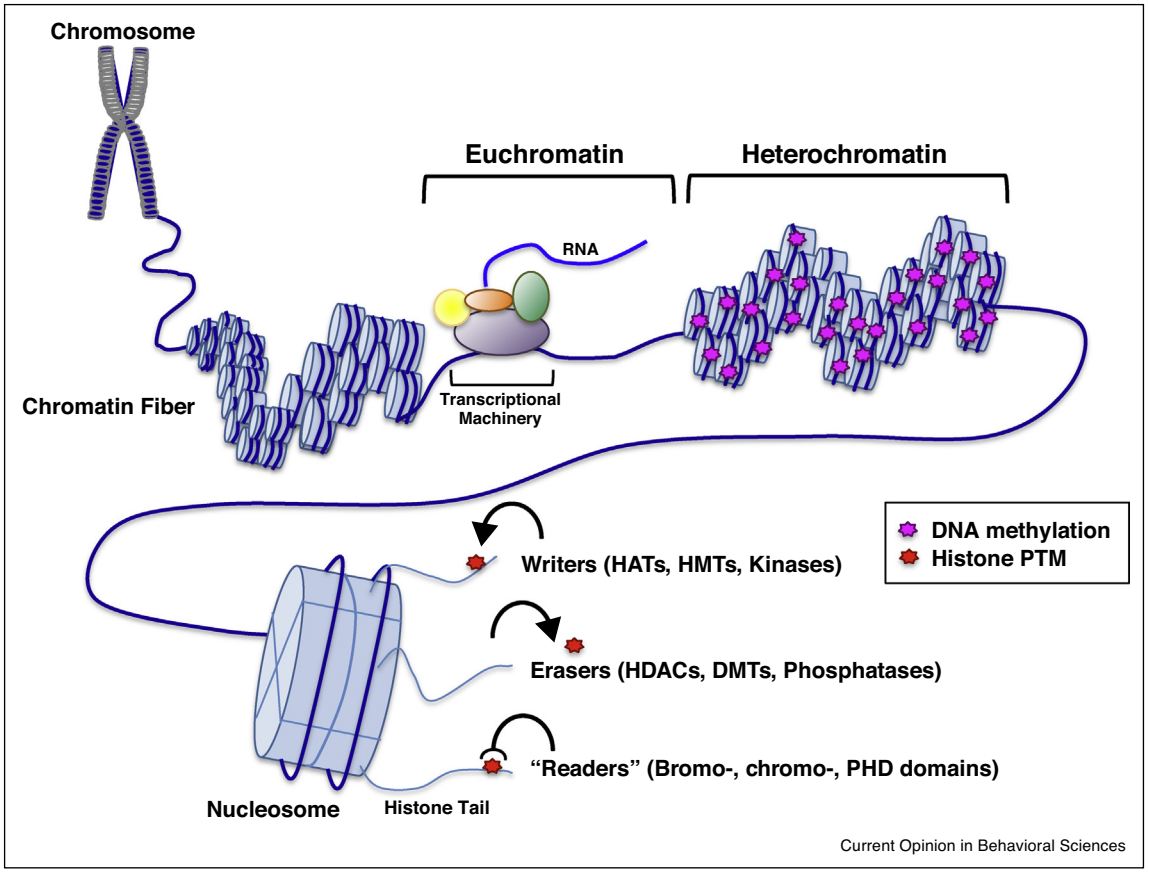
Complex brain disorders impede an individual's ability to function optimally in daily life, and they exert an extreme financial and personal burden on society. Unfortunately, most current therapeutics are only mildly efficacious and produce unwanted side effects. This has led many researchers in the field to try and identify more specific mechanisms of disease origin. While some rare brain disorders are the result of very specific, heritable genetic defects (e.g. mutations), the majority of neurological diseases have low to moderate heritability suggesting that their etiology results from environmental effects on gene expression. At the intersection between environment and gene regulation is epigenetics, which results in gene expression changes without altering the DNA sequence. While identical DNA templates provide the building blocks for every cell in a given individual, only a very small subset of genomic regions within each cell are accessible for regulation, thereby creating unique cellular identities and the promulgation of proper cellular functions. Epigenetics powers these transitions by altering the compaction of chromatin (i.e. DNA wrapped around a core octamer of histone proteins) to either allow access to specific loci of the DNA template for gene transcription (i.e. euchromatic regulation) or reduce access to inhibit gene expression (i.e. heterochromatic regulation). These dynamic conformational changes are driven by enzymes and chromatin-interacting proteins that 'read,' add, or remove chemical modifications on/to DNA and histone proteins (Figure 1).

Neurons, like most cells, undergo epigenetic regulation during development, which tightly and temporally controls specific gene transcriptional programs leading to differentiation into mature neurons. However, unlike most other cells in the body, post-mitotic neurons remain in this mature state for the entirety of an organism's life. This is not to imply that neurons are static; on the contrary, they are highly dynamic and undergo constant epigenetic gene regulation to aid in adapting and functioning properly in response to an ever-changing environment. Fittingly, dysfunction in these processes is thought to underlie several neurodevelopmental, neurodegenerative and adult neuropsychiatric disorders. In this review, we discuss how epigenetics fits into the etiology of complex brain disorders, how this may lead to novel therapeutics and how future technologies may overcome current limitations in the field.

Learning, memory and related pathologies

In order for mature neurons to respond and adapt to changes in the environment, coordinated firing of neural circuits must result in long-lasting functional changes. One of the most adaptive abilities of the brain is to form new memories, which is critical for driving future behavior and survival. Theories of memory suggest discrete cell populations across many brain regions form neuronal ensembles or 'engrams' that maintain stable, long-lasting connections with each other through alterations iun protein content within the neuron, particularly at the synapse [1•]. Initial learning is established by activity-dependent gene expression, where both heightened extracellular

Figure 1



Epigenetic regulation of gene expression. Chromosomes are comprised of chromatin fibers that contain nucleosomes: DNA (~146 bp) wrapped around the histone octamer (four core histone proteins, with two copies each of H2A, H2B, H3 and H4). Stretches of chromatin can either be open (i.e. euchromatic) or closed (i.e. heterochromatic) to transcriptional regulation. Enzymes and chromatin-interacting proteins that deposit (i.e. 'writers'), remove (i.e. 'erasers') and 'read' chemical modifications on DNA and histone tails alter the compaction of chromatin. DNA methylation is typically associated with heterochromatin, while depending on the type of chemical modification and residue, histone PTMs can either be associated with euchromatin or heterochromatin formation.

stimulation and intracellular signaling reaches the nucleus to initiate *de novo* gene transcription [2]. Importantly, expression of these 'early-response' or immediate early genes (e.g. *Fos*, *Egr1*, *NPas4*, *Arc*, etc.) is under the control of chromatin regulation. Several epigenetic processes have been shown to be critical in memory formation and recall including DNA methylation [3] and hydroxymethylation [4], histone acetylation/methylation [5], histone turnover [6], chromatin looping [7] and DNA damage [8]. While this regulation sets up initial increased responsiveness to stimulation, long-term memories are maintained across extended periods of time that far exceed the turnover rate of any individual protein or histone post-translational modification (e.g. histone acetylation/phosphorylation). Therefore, epigenetic 'priming' of plasticity-related genes within engram memory cells may occur following exposure to a highly salient stimulus or repeated exposure to the same stimulus that produces stable chemical modifications (e.g. DNA methylation/demethylation), substitution of transcriptional co-factors (e.g. CRTC1-KAT5) and incorporation of specific histone variants (e.g. H2A.Z, H3.3, etc.) at given genomic loci to allow for efficient and responsive transcription of memory-stabilizing genes upon reactivation [3,6,9,10]. This theory fits well with recent data indicating that long-term memories can persist even when learning-induced synaptic modifications are erased [11,12•] suggesting that other neuronal compartments (e.g. the nucleus) may be 'tagged' to help maintain specific memories.

While epigenetic priming of synaptic-related and plasticity-related genes supports the maintenance of memories, these same processes are activated following both positive and negative experiences. For example, drug and stress-induced events can create memories that persist across the lifespan of an animal leading to related pathologies. Both drug addiction and post-traumatic stress disorder (PTSD) are brain disorders that involve rewiring of