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The epigenetic basis of individuality

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This commentary reviews the concept of experience-dependent epigenetic modifications in the CNS as a core mechanism underlying individuality and individuation at the behavioral level. I use the term individuation to refer to the underlying neurobiological processes that result in individuality, with the discussion focusing on individuality of cognitive, emotional, and behavioral repertoire. The review describes recent work supporting the concept of neuroepigenetic mechanisms underlying individuation, possible roles of transgenerational effects, and implications for precision medicine.

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Introduction

Epigenetic mechanisms include molecular processes such as chemical modification of DNA and structural alterations of DNA and its associated proteins. These epigenetic 'marks' operate to regulate gene readout in all cells in the human body. A dominant paradigm and assumption in the epigenetics field traditionally has been that once epigenetic marks are laid down as part of the normal process of development, they are unchangeable thereafter. In other words, the traditional view has been that epigenetic marks are immutable once they are made. This was one of the core dogmas of the epigenetics field, and the thinking arose out of the fully valid model that epigenetic marks subserve lifelong perpetuation of cell fate and cellular phenotype. However, that observation was over-interpreted and taken to imply that all epigenetic mechanisms were static in terminally differentiated, non-dividing cells such as neurons in the adult CNS.

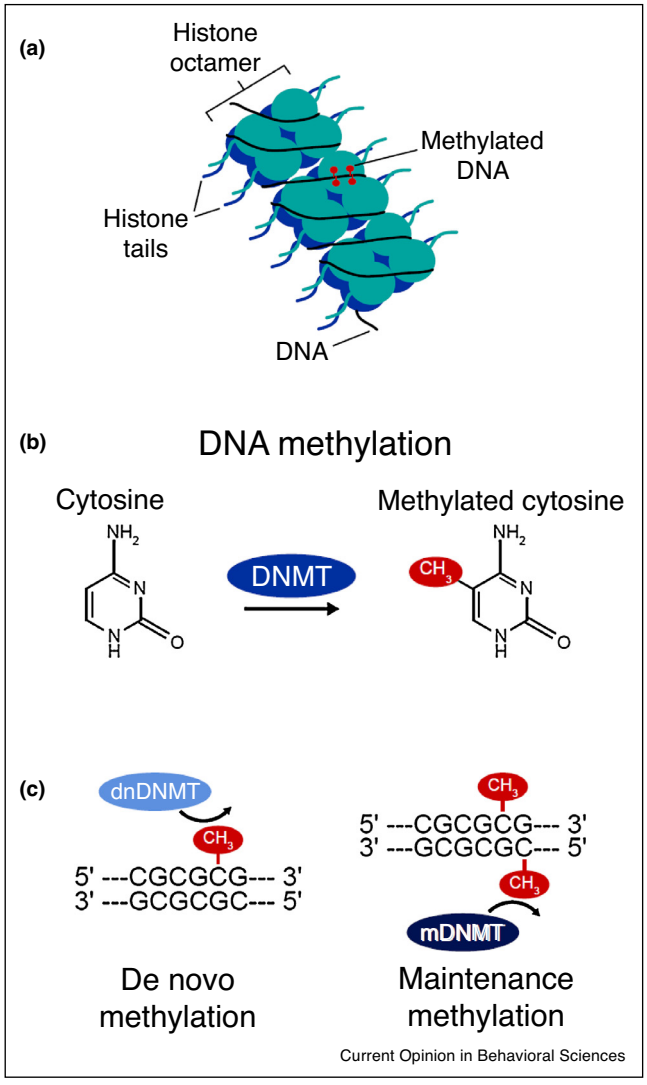
Recent discoveries have directly contradicted this dogma. A new contrarian 'neuroepigenetic' model is emerging wherein the CNS epigenome (or at least components of it) is dynamically regulated [1,2]. Indeed, dynamic experience-dependent epigenetic reorganization, specifically histone post-translational modifications and cytosine methylation of DNA, has recently been discovered to be a critically important regulator of nervous system function, across vast domains of cognition, memory, motor function, decision-making, stress responses, neuropathology, neurodegeneration, perception, executive function, addiction, and acquired behavioral change [3••,4•,5–16]. In brief, such evidence includes direct demonstration of changes in cytosine methylation and histone marking in the adult CNS in response to experience and in correlation with neuropsychiatric disorders, and encompasses findings indicating that epigenetically targeted drugs and gene knockouts can alter an animal's capacity for experience-dependent behavioral change.

Experience-dependent accumulation of epigenetic marks over the lifespan

The discoveries outlined above suggest the intriguing possibility of a role for epigenetic mechanisms in experience-dependent change and individuation, for example those experientially driven changes that involve learning, memory formation, environmental effects, and social interactions. At the molecular and neurobiological level epigenetic mechanisms are especially appealing for these roles because epigenetic mechanisms have a very rare attribute biochemically — they can be self-perpetuating ([17,18•] and Figure 1). There are very few bona-fide examples of self-perpetuating molecular changes in biology, the few known and well documented examples include mechanisms such as: epigenetic mechanisms in particular DNA methylation, prion protein self-catalyzed autoconversion to a pathological conformation, and propagation of nucleotide sequence information (gene sequences) through DNA replication with cell division [19]. Thus experience-dependent alterations in the CNS epigenome are particularly viable mechanisms as hypothetical drivers of life-long individuation and the preserving of individual psycho-behavioral characteristics throughout the lifespan.

It is important to note that while self-perpetuating biochemical change is rare (it basically is a form of 'explosive' chain reaction if not strictly controlled), it is a *sine qua non* for a cell being able to overcome turnover of constituent molecules (proteins, RNA, and even DNA) over time. A very long-lived protein has a lifetime of about 6 months at the very most . . . except for DNA and perhaps a few rare

Figure 1



Self-perpetuation of DNA methylation. **(a)** Inside a cell nucleus, DNA is wrapped tightly around an octamer of highly basic histone proteins to form chromatin. Epigenetic modifications can occur at histone tails, or directly at DNA via DNA methylation. **(b)** DNA methylation occurs at cytosine bases when a methyl group is added at the 5′ position on the pyrimidine ring by a DNA methyltransferase (DNMT). **(c)** Two types of DNMTs initiate DNA methylation. *De novo* DNMTs methylate previously non-methylated cytosines, whereas maintenance DNMTs methylate hemi-methylated DNA at the complementary strand. In the event that one strand of DNA is subsequently demethylated, maintenance DNMT an remethylate the hemi-methylated DNA, establishing a self-perpetuating covalent modification. Figure and legend from: Day JJ, Sweatt JD. (2010) DNA methylation and memory formation. *Nat Neurosci.* 13:1319–23.

proteins such as histones, no biological macromolecule that exists in your brain right now was present there a year ago. They have all undergone turnover by breakdown and *de novo* re-synthesis in the intervening time-span. So, how do you store information and perpetuate experientially acquired cognitive and behavioral attributes for years or even a lifetime? The answer is that there must be self-perpetuating biochemical reactions that defeat molecular turnover in the brain that sustain experience-dependent change.

I hypothesize that these acquired epigenetic marks underlie behavioral individuation and life-long perpetuation of individuality at the cognitive and behavioral level. In a general sense they may operate by two principal mechanisms: epigenetic changes in the nucleus that can be self-sustaining and regulate overall neuronal function, and functional changes in memory circuits (based on synaptic plasticity and altered synaptic connectivity) that drive altered behavioral and cognitive output (see Figure 2). Concerning the mechanisms through which epigenetic marks cause these changes in function, the remaining 'black boxes', which are huge ones, are: How do the epigenetic changes contribute to/generate the circuit changes, and How do the circuit changes drive altered behavior and cognition. Addressing these issues is an area of vigorous research at present, but I will not review them here [20].

The interface of genes and experience during development

The preceding section discussed the likely role of epigenetic marking in acquired behavioral change in the adult, but similar (but likely even more robust) epigenetic processes are involved in individuation developmentally. Indeed, the origin of the term 'epigenetic' arose from Waddington's conceptualization of 'epigenesis' during development, wherein he deduced from first principles that some regulatory layer must exist above ('epi' in Greek) the level of the genes, in order to drive the gene readout that makes each different type of cell in the body have its defining characteristics. The role for epigenetic mechanisms in developmental cell differentiation is well established, to the point of dogma. These epigenetic processes are not only involved in neurons and other brain cells achieving their cellular fate developmentally, but also experience during CNS development drives epigenetic changes that underlie refinement of neural circuit structure and synaptic connectivity.

For example, while the human brain is the most complex structure known to exist, and among its most highly evolved sub-structures is the cerebral cortex [21], cortical circuit development and refinement has served as a model system in which to probe the role of epigenetic processes in CNS development. Neurons that are involved in many aspects of human cognition exist in highly and precisely structured layers in the cerebral cortex, and participate in functional circuits underlying information processing, memory storage, and behavioral adaptation. During brain development, both neurogenesis in the cerebral cortex and time-dependent development of a neuronal circuit comprising layers of cortical neurons contribute to