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, neuropsychiatric disorders, and 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
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, Sweett JD. (2010) DNA methylation and memory formation. Nat Neurosci. 13:1319–23.

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 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.

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
generating the finely detailed neuronal architecture underlying higher-order cognitive function in mammals including humans. The molecular mechanisms underlying these cortical developmental processes remain somewhat mysterious, but epigenetic processes are clearly involved [3*,6,13,14,15,22]. These discoveries illustrate the role of epigenetic processes in individuation during CNS development and maturation, another example of acquired epigenetic marking.

Thus, epigenetic molecular mechanisms certainly are a component of developmental information storage, playing critical roles in cell fate determination and lifelong perpetuation of cellular phenotype in both dividing and non-dividing cells [22,23*,24]. This is the scientific context in which epigenetic mechanisms were originally proposed to exist, and in which they were discovered at the molecular level. A broader question is whether epigenetic mechanisms might be a more universal mechanism for cellular information storage, operating to subserve plastic change in the adult CNS and learned behavior at the organismal level [25*,26–29,30*]. It is in this context that I propose a role for epigenetic mechanisms in individuation and preservation of individual cognitive and behavioral traits.

Transgenerational epigenetic effects
An especially intriguing question regarding mechanisms of individuation concerns whether acquired epigenetic change in parents might be propagated to their offspring. In the context of the current discussion we then might ask; are acquired epigenetic marks transmitted across generations? Some aspects of this question are among the most contentious areas in the epigenetics field at present. Broadly speaking, epigenetic ‘transgenerational’ effects come in two flavors. The first type is not transgenerational in the heritable sense, but rather is experience-dependent. For example, Michael Meaney’s group, his collaborators and scientific descendants have demonstrated that maternal nurturing behavior regarding newborn pups triggers DNA methylation changes in CNS glucocorticoid receptors of offspring that persist into the adult and effect behavioral change [7,13,14]. Discovery of these experience-dependent changes in the epigenome is the prototype for the first category of transgenerational effects, and these sorts of experience-driven epigenomic changes in the CNS have been documented to occur with a number of both positive and negative environmental effects in offspring [3*,6,10]. Thus, several examples of the persisting CNS epigenomic effects on offspring of parental behavior and environmental insult have survived the rigors and skepticism of peer review. At the most basic level these studies demonstrate that early-life experience can trigger lifelong persisting epigenomic changes in brain of an individual, an observation which has clear implications for how epigenetic mechanisms might contribute to CNS health, pathogenesis and individuation over the lifespan.

The second flavor of transgenerational effect is the idea that experience-driven epigenetic changes in an animal might lead to heritable DNA methylation changes that are propagated through the germline, through many or all subsequent generations. This neo-Lamarckian scenario is a truly frightening possibility with interesting implications for topics such as free will, and is being hotly debated even as a possibility at present. A presumed evolutionary role for these types of mechanisms is ‘soft inheritance’, wherein environmental experience/exposure could trigger heritable epigenomic changes that improve survival over a few generations, but that are ultimately reversible because they are based upon epigenomic changes (epimutations) and not upon directly altering the offsprings’ DNA nucleotide sequence. There are several tantalizing and fascinating indications of experience-dependent heritable changes in the CNS.
epigenome in the literature at this point, involving those driven by maternal behavior, paternal behavior, diet, exposure to drugs of abuse, endocrine disruption, and associative conditioning [31,32,33,34]. Definitively determining whether experience-driven acquired epigenetic changes can propagate through the germline and effect behavioral change in subsequent generations is one of the most important areas of contemporary neuroepigenetics research in my opinion. Proof of the existence of such mechanisms has the potential to fundamentally change our outlook on evolutionary biology, psychobiology, and neurophilosophy.

Implications for precision medicine
An understanding that epigenetic marks may drive individual characteristics, including those related to physical and mental health, has important implications for the establishment of precision medicine [30,35,36,37,38,39,40,41,42,43]. It seems clear that if epigenetic mechanisms drive individuality, then including epigenetic analysis as a component of any regimen for implementing precision medicine is appropriate and indeed necessary. Just as understanding genotype, previously experienced disease, and broader demographic characteristics are important for optimizing medical care, knowledge of epigenetic characteristics will be important as well. Therefore, it is not premature to begin visualizing and conceptualizing how an epigenomic basis for individuality might fit into a broader scheme for implementing personalized medical care (see Figure 3).

With regard to future implementation of epigenetic approaches in developing regimes of personalized and precision medicine, there are a number of likely challenges/limitations that are worth bearing in mind. First, epigenotyping is for the most part too expensive for immediate broad implementation in precision medicine, both in terms of the necessary epigenomic sequencing and characterization methodologies and the labor-intensive nature of epigenomic bioinformatics. However, future advances and lowered costs for epigenetic and bioinformatics analysis are likely to obviate this limitation.

Second, as already discussed in this commentary, epigenetic marks in both the periphery and CNS are now clearly recognized as manifesting considerable lability over time [1,3,10,43]. These changes can be driven by both environmental and experiential factors, and can concisely be illustrated by time-dependent alterations in epigenomic marking that differ between genetically identical twins [26]. Thus, while the genome may stay constant over time the epigenome clearly will not. This consideration might be both a blessing and a curse for epigenomically based precision medicine. On the one hand it would represent a drifting epigenetic baseline within the same individual over time, complicating analysis and possibly predictive power. Looked at differently however, epigenomic plasticity would represent an advantage vis-à-vis the unchanging genetic sequence, potentially providing a more accurate and up-to-date index of the individual’s overall genomic/epigenomic state.

A third consideration is the still-unknown but clearly ambiguous relationship between brain and peripheral tissue epigenetics. For the most part currently and for the foreseeable future methods for sampling the human epigenome will be limited to acquiring tissue from blood, skin, or potentially the cerebro-spinal fluid (CSF) in exceptional cases. This raises the critically important issue of how well (and even if) peripheral cells ‘report’ the epigenetic status of the CNS [25,42]. This is an active area of research at present and there have been a few promising examples of blood cell epigenomic markers of CNS epigenetic state [37,38,39,40,41]. There clearly are limits on the likelihood of an exact match of a peripheral cell’s epigenetic state relative to that of a specific brain region that might underlie a psychological disorder. Nevertheless, it is worth noting that all that might be necessary is a correlation between two different epigenetic marks (one in the CNS and a different but correlated one in the blood) in order for the peripheral mark to be useful as a diagnostic biomarker.

![Figure 3](www.sciencedirect.com)
Finally, one fears the likely limitations statistically to the predictive power of epigenetic marks in relation to nervous system disorders. For example, even the hard-wired genetic code currently has very poor predictive power overall for behavioral traits and disorders [16,44,45], and there is no theoretical reason why epigenomic marks should perform any better, at least that I can think of at this point. I suppose as an unremitting optimist I can propose that perhaps epigenomics coupled with genomics will give greater predictive power when the two are used together than either can achieve separately.

Summary — epigenetic barcoding for individuality
In conclusion, the discovery of a dynamic neuronal epigenome helps address a long-standing, three-millenial-long philosophical debate concerning Nature vs. Nurture, or Genes vs. Environment. Discoveries in neuroepigenetics imply that a third viewpoint is the correct way to look at this issue. Human behavior is not driven by a static contribution of X percent due to genes and Y percent due to experience [1,3,7,27–29]. Rather, there is a constant molecular interaction between genes and experience that drives behavior, and the interface between the two is neuroepigenetics. There is a synergy between genes and environment such that the whole is greater than the sum of the parts, because there is an ongoing dynamic interaction between experience and the genome, mechanistically mediated by molecular epigenetic mechanisms and driven by experience-dependent regulation of the neuronal epigenome.

Recent advances suggest the realization that epigenetic mechanisms may serve as a basis for human individuality, and as a driver for the uniqueness of individual humans. Interestingly, by extension epigenetic mechanisms may serve to confer exceptional human performance in one individual versus another in a variety of domains of human endeavor. More broadly speaking in the future health context, it is now being realized that the epigome must be taken into consideration concerning personalized, precision medicine. Conceptually, one might think of epigenetic marks as comprising a ‘barcode’ of information that in part establishes and perpetuates human individual differences [46*]. This conceptual epigenetic barcode would sit above the level of genes in cells in the nervous system, registering prior environmental, cognitive and sensory experiences as a long-term storage mechanism. The epigenetic barcode would then be read out by the neurons of the circuits in which the barcode resides, influencing health, attitudes, cognitive function, and learned responses.

Conflict of interest statement
Nothing declared.

Recommended reading
Papers of particular interest, published within the period of review, have been highlighted as:
- of special interest
- of outstanding interest

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Genetic imprinting and behaviour


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