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Epigenetic Advances in Behavioral and Brain Sciences have Relevance for Public Policy

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Abstract

Nature and nurture work together to drive development, behavior, and health. Behavioral epigenetics research has uncovered the underlying mechanisms for how this happens. Children's early years in development may offer the greatest opportunity for environmental and experiential factors to influence epigenome (chemical compounds telling our genes what to do), but evidence suggests it is never too late. The policy implications of this research are vast, including relevance for child development, health, and disease intervention and prevention.

Keywords

epigenetics; DNA methylation; prevention; reversible; public policy

Introduction

Behavioral epigenetics research has revolutionized our conversation in regard to what factors drive behavior and help determine who we are. The nature *versus* nurture debate has been replaced by a realization that it is both nature *and* nurture. Simply stated, genes do not operate independent of their environmental contexts (Moore, 2015). Behavioral epigenetics research has uncovered mechanisms through which our environments and experiences interact and link with our biology. This helps us understand the brain's capacity to change because of experience, and reveals some of the mechanisms driving the development of behavior and health.

This article focuses on the science of behavioral epigenetics in relation to neuroscience, psychology, and psychiatry, and the policy implications of this science. Though various flavors of epigenetic mechanisms respond to environments and regulate gene activity, this review focuses on DNA methylation. After a brief primer on DNA methylation, the next sections highlight basic and translational work that demonstrate the exquisite sensitivity of DNA methylation to various environments and experiences, as well as evidence that argues for its causal role in normative and aberrant brain function and behavior. The final section

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Tweet

Epigenetics gives us a new way to think about lifelong development and health: It shows where and how to intervene when things go awry.

outlines policy implications of this science, focusing on empirical support for multigenerational consequences of adversity and the ability to intervene and change the epigenome.

DNA Methylation: The 10,000-foot Overview

DNA in the cell nucleus is condensed and wrapped around proteins called histones, much like thread on a spool. This DNA-protein complex is called chromatin, and if this complex is compact (i.e., DNA is tightly wrapped around the histone proteins), genes tend to be inactive because cellular machinery necessary to drive gene activity cannot gain access to the DNA. On the other hand, if chromatin structure is more relaxed, that machinery can gain access and drive gene activity. Chemical tags that attach to the histones or to the DNA itself influence whether chromatin structure is in a compact or relaxed state.

DNA methylation refers to the addition of methyl groups to cytosines (one of DNA's four main bases) (Lister et al., 2013; Shirane et al., 2013)). Most data demonstrate that DNA methylation is associated with inactive genes and compact chromatin structure (Cedar & Bergman, 2009; Moore, Le & Fan, 2013). In line with this interpretation, many studies have been conducted under the framework that increases in DNA methylation will reflect sustained decreases in baseline levels of gene expression.

Nevertheless, some data argue for a more complicated role of DNA methylation in relation to gene activity. For example, some studies associate DNA methylation with active genes (i.e. (Chahrour et al., 2008; St-Cyr & McGowan, 2015; Uchida et al., 2011)), and even without a change in basal state of gene activity, DNA methylation can affect experience-driven gene activation (Baker-Andresen, Ratnu & Bredy, 2013). Levels of DNA methylation are determined by enzymes (DNA methyltransferases, DNMTs) that introduce the methylation mark (Bestor, 2000; Jeltsch & Jurkowska, 2014; Kinney & Pradhan, 2011), and members of protein families that facilitate active demethylation (Guo, Su, Zhong, Ming & Song, 2011b; Ma, Guo, Ming & Song, 2009; Niehrs & Schäfer, 2012; Williams, Christensen & Helin, 2012).

Factors Changing DNA Methylation

Environmental and experiential factors drive DNA methylation or demethylation; these are ones we know have long-term consequences for physical and mental health outcomes. In the developmental realm, this includes the mother's health while she is pregnant (diet-(Tobi et al., 2014), toxin exposure-(Kundakovic et al., 2015), and mood-(Braithwaite, Kundakovic, Ramchandani, Murphy & Champagne, 2015; Devlin, Brain, Austin & Oberlander, 2010)) and how much stress and adversity an individual is exposed to during childhood (Cicchetti, Hetzel, Rogosch, Handley & Toth, 2016; Klengel et al., 2013; Naumova et al., 2012; Non et al., 2016; Romens, McDonald, Svaren & Pollak, 2015). Relationships between methylation and these early-life factors are detectable in both children and adults (Beach, Brody, Todorov, Gunter & Philibert, 2010; Labonte et al., 2012; Perroud et al., 2011; Tyrka, Price, Marsit, Walters & Carpenter, 2012).

Human studies have unavoidable confounds that cloud determining relationships between specific variables and outcomes (i.e., whether a particular prenatal or postnatal event is causally responsible for a particular DNA methylation outcome). Rodent models have been vital in making the case that the environments and experiences mentioned above do affect DNA methylation. For example, rodent models in which the mother's diet has been experimentally altered (Vucetic, Kimmel, Totoki, Hollenbeck & Reyes, 2010; Waterland & Jirtle, 2003), the mother has been stressed while pregnant (Blaze et al., 2017; Mueller & Bale, 2008), or where the caregiving environments vary naturally (Beery, McEwen, MacIsaac, Francis & Kobor, 2016; Peña, Neugut & Champagne, 2013; Weaver et al., 2004) or have been experimentally manipulated (Blaze & Roth, 2017; Doherty, Forster & Roth, 2016; Franklin et al., 2010; Kosten & Nielsen, 2014) have provided direct evidence that these particular factors change methylation states in the brain. Indeed one of the factors consistently shown to influence DNA methylation levels in offspring is parenting, an observation initially made upon examination of genes controlling stress responsivity (Weaver et al., 2004) and plasticity (Roth, Lubin, Funk & Sweatt, 2009) in rodent models and subsequently translated to humans (McGowan et al., 2009; Perroud et al., 2011; Perroud et al., 2013; Tyrka et al., 2012; Weder et al., 2014). Data are consistent with the notion that epigenetic alterations caused by experiences and environmental factors within early development provide a basis for the developmental origins of health and disease (Hales & Barker, 1992; Rosenfeld, 2017).

DNA methylation changes in response to environmental and experiential factors are not exclusive to sensitive periods of development. Again, animal models have been vital for this realization. Work with neuronal cultures (Martinowich et al., 2003), brain slices (Levenson et al., 2006), or rodents subjected to various behavioral tasks (Lubin, Roth & Sweatt, 2008; Miller et al., 2010) provided initial empirical support that active DNA methylation and demethylation still occur in the adult brain and are necessary for brain function and memory. These observations have been replicated and extended (Guo et al., 2011a; Maag et al., 2017; Meadows et al., 2015; Yang et al., 2016), including a remarkable spatial and temporal specificity of methylation changes that occur with various stages of learning and memory (Halder et al., 2016).

Imaging studies provide a link between DNA methylation states and brain function in humans, which could help explain why some individuals are more social (Haas et al., 2016) and why we perceive anger and fear differently (Puglia, Lillard, Morris & Connelly, 2015). One factor that has profound implications for physical and mental health is psychosocial stress, and experimental approaches in both animal models (Hunter, McCarthy, Milne, Pfaff & McEwen, 2009; Makhathini, Abboussi, Stein, Mabandla & Daniels, 2017; Roth, Zoladz, Sweatt & Diamond, 2011; Tsankova et al., 2006; Wright et al., 2017) and humans (Edelman et al., 2012; Mehta et al., 2013; Rusiecki et al., 2013; Uddin et al., 2010; Unternaehrer et al., 2012; Ursini et al., 2011; Yehuda et al., 2013) reliably link stress with epigenetic alterations. For example, subjecting a rodent to psychosocial stress in the form of predatory and/or restraint stress (Makhathini et al., 2017; Roth et al., 2011) or social defeat stress (LaPlant et al., 2010; Wright et al., 2017) evokes robust changes in DNMTs and DNA methylation. Mildly stressful experiences evoke rapid changes in DNA methylation in adult participants of a Trier Social Stress Test, a lab-based stress paradigm useful for studying stress responses

in humans (Edelman et al., 2012; Unternaehrer et al., 2012). Further, US military service members with a PTSD diagnosis show differential patterns of methylation pre- vs. post-deployment (Rusiecki et al., 2013).

DNA methylation is now often used in humans as a biomarker of psychiatric disorders, with, for example, increased methylation of DNA associated with a key neural development and plasticity gene (*BDNF*) in depression (Fuchikami et al., 2011; Keller, Sarchiapone, Zarrilli & et al., 2010), PTSD (Kim et al., 2017; Smith et al., 2011), anxiety (Chagnon, Potvin, Hudon & Prévile, 2015), bipolar disorder (D'Addario et al., 2012), and border line personality disorder (Perroud et al., 2013). Methylation status of this gene is also used in humans as an index of change following pharmacological or behavioral therapy intervention; decreases in DNA methylation and other repressive chemical tags associated with this gene parallel decreases in disorder symptomatology (D'Addario et al., 2012; Duclot & Kabbaj, 2015; Lopez et al., 2013; Perroud et al., 2013). There is even evidence that doing good things for our minds and body, like regular exercise or meditation, promotes changes in DNA methylation (Niles, Mehta, Corrigan, Bhasin & Denninger, 2014; Ren et al., 2012). Together, data are consistent with the notion that even when we are adults, DNA methylation responds to both good and bad experiences, and methylation is associated with our behavior.

Coincidental or Causal in Relation to Behavioral Outcomes?

The science reviewed thus far was chosen to illustrate the responsiveness of the epigenome, both within and outside of sensitive periods of development. But possible confounds remain a question to address: Do changes in methylation have a causal role in gene activity and behavior, or are the changes coincidental (perhaps a mere trace of an event) with no functional relevance? Experimental work with neuronal cultures, brain tissue slices, and animal models have been necessary to answer this question.

A change in methylation at only a few sites of a gene are sufficient to significantly reduce activity of that gene, with a negative impact on neuronal plasticity (Martinowich et al., 2003) and fear behavior (Baker-Andresen et al., 2013; Lubin et al., 2008). Disrupting DNA methylation disturbs the brain physiology necessary for spatial navigation and memory (Roth et al., 2015), and impairs long-term memory (Lubin et al., 2008; Scott, Smith, Barker, Uney & Warburton, 2017). DNMT knockout mice recapitulate the learning and memory deficits produced with pharmacological inhibition of DNA methylation (Feng et al., 2010), and experimentally changing a specific class of DNMTs in the medial prefrontal cortex of stressed mice is sufficient to dramatically change anxiety-like behavior (Elliott et al., 2016).

Also helping to make the argument that DNA methylation processes have a functional role in brain function and behavior are studies where investigators promote positive changes in the epigenome (generally looser chromatin and less DNA methylation). For example, giving rodents time in an enriched environment with stimulation from toys and other rodents and the opportunity to exercise can change the epigenome in a way that enhances learning and memory (Fischer, Sananbenesi, Wang, Dobbin & Tsai, 2007). Pharmacological strategies that decrease DNA methylation enhance certain behaviors and decrease others (Massart et

al., 2015; Stolzenberg, Stevens & Rissman, 2012; Tremolizzo et al., 2005; Weaver et al., 2004).

A new suite of tools have given us the remarkable ability to control the epigenome with extreme precision, which will allow for direct inquiry of gene and epigenetic pathways in behavior and disease (Day, 2014; Powell, Gregory, Akbarian & Brennand, 2017; Walters, Azam, Gillon, Josselyn & Zovkic, 2016). These techniques utilize unique DNA sequences that seek and target particular regions of the genome to either methylate or demethylate DNA locally. Some of these systems can even be modified to target multiple genes at one time, affording simultaneous inhibition or overexpression of distinct genetic targets. This is important because the majority of behaviors and diseases of interest to neuroscientists, psychologists, and psychiatrists are not under the influence of a single gene. Such technology is already advancing our understanding of the role of methylation in diverse biological processes such as gene regulation (Cheishvili et al., 2017). In terms of memory, editing of a key gene involved in DNA methylation within the dentate gyrus impairs contextual memory, while preserving the integrity of other cognitive abilities (Swiech et al., 2015). Further, simultaneous knockdown of key DNMTs likewise impairs contextual memory (Swiech et al., 2015). These tools offer exciting methods that will allow us to better probe the functional role of DNA methylation in the brain and in behavior.

Policy Implications of Behavioral Epigenetics

Work in the field of epigenetics has not only provided further evidence that the perinatal environment can shape both somatic and mental health, but has also helped us understand some of the biology through which this occurs. Many studies make the case that developmental factors like nutrition, stress, and parental care can alter the epigenome, with consequences for long-term health. Evidence even indicates that changes to the epigenome can be transmitted to the next generation (Dias & Ressler, 2014; Franklin et al., 2010; Guerrero-Bosagna, Savenkova, Haque, Nilsson & Skinner, 2013; Tobi et al., 2014; Yehuda et al., 2016).

Such data should be useful to policy-makers in making their case for policies to address child development and health. Having a biological explanation of such phenomena is powerful in shifting public opinion to support health initiatives and policies that focus attention on what we and our children eat and behavioral modifications that parents can adapt prior to conception and for enhancing parenting behavior to promote optimal development of children. These modifications should include reducing pre-conception stress and toxin exposure and providing more synchronous and nurturing as well as less frightening parenting behavior (Barker, 2015; Bernard, Hostinar & Dozier, 2015; Caron, Weston-Lee, Haggerty & Dozier, 2016; Rosenfeld, 2017). This should include policies that aim to neutralize adverse environments and promote healthy development, all of which set the stage for academic performance, economic productivity, responsible citizenship, and successful parenting.

There is often the assumption that early or traumatic experiences and resultant epigenetic changes are determinative. The epigenome however displays remarkable malleability

throughout life. People could also have experiences that would improve the lives of their descendants (Arai, Li, Hartley & Feig, 2009). Non-targeted epigenetic manipulations can reverse epigenetic states (Szyf, 2015), with the ability to change, for example, adult brain and behavioral outcomes associated with early adversity (Roth et al., 2009; Weaver et al., 2004). The epigenome appears equally as responsive to non-pharmacological interventions that can change the brain and mental health. For example, cognitive behavioral therapy can change epigenetic states with concomitant improvement in psychiatric disorder symptoms (Perroud et al., 2013; Yehuda et al., 2013).

Cancer was the first disease to apply DNA methylation-targeted therapeutics, but data continue to amass that DNA methylation-targeted therapeutics could be useful for treating a range of conditions that affect our mood, thinking, and how well we age. To realize the promise of all this, including that of epigenetics in personalized health care, we need continued dialogue between disciplines and dialogue between basic research scientists and clinicians. We need further research exploring preventable and reversible epigenetic states. We need more work aimed at identifying methylation-based biomarkers and designing evidence-based interventions. Using non-human animals will be essential in these efforts, and funding animal research represents not just an investment in the advancement of this science but in human health. Sustained increases in federal funding for biomedical and life sciences research are also critical for these efforts. Discoveries made will be powerful tools in formulating policies aimed at promoting health and successful aging.

Finally, scientists need to take a more active role in educating the public and policy-makers about the links between epigenetics, our brain's capacity to change because of experiences, and lifelong health. Communication is how science thrives, but we typically concern ourselves only with presenting our data within the scientific community, i.e. publishing our data in journals and giving talks at scientific conferences and universities. Influencing public perception of science and better policy solutions depends on our ability to communicate data outside academic venues. To facilitate such change, this might include formal lay communication training in graduate curricula (Brownell, Price & Steinman, 2013). Scientists should also embrace new channels of communication (i.e., social media and blogs) and face-to-face science communication activities (including lectures and outreach events). Such efforts all together hold promise to renew support for the nation's science agencies, to realize the potential of behavioral epigenetics research, and improve individuals' lives through policy.

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Key points

- Environmental and experiential factors, including healthy prenatal environments, parenting, and stress leave their marks on our genetic makeup (DNA) in the form of chemical tags that tell our genes what to do.
- Rodent models (lab animals) have been vital in making the case that these chemical tags have practical consequences for gene activity, brain function, and behavior.
- Epigenetic data should not only inform policy-makers' health initiatives and policies concerning child development, but influence public opinion of these as well.
- DNA methylation-targeted therapeutics could help treat conditions that affect our mood, thinking, and behavior, which should inform intervention research and health initiatives.