Social Environment and Epigenetics

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Abstract Our social environment, from the microscopic to the macro-social, affects us for the entirety of our lives. One integral line of research to examine how interpersonal and societal environments can get "under the skin" is through the lens of epigenetics. Epigenetic mechanisms are adaptations made to our genome in response to our environment which include tags placed on and removed from the DNA itself to how our DNA is packaged, affecting how our genes are read, transcribed, and interact. These tags are affected by social environments and can persist over time; this may aid us in responding to experiences and exposures, both the enriched and the disadvantageous. From memory formation to immune function,

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the experience-dependent plasticity of epigenetic modifications to micro- and macro-social environments may contribute to the process of learning from comfort, pain, and stress to better survive in whatever circumstances life has in store.

Keywords Adversity · Built environment · DNA methylation · Enriched environment · Epigenetics · Histone modifications · Interpersonal · Learning · Pain · Parenting · Social environment · Stress

1 Introduction

To be human is to have a fundamental need for love and belonging. Humans give birth to altricial young who depend on the effectiveness and attentiveness of social bonds from the moment of delivery, not only to thrive, but also to survive. Though this is a unique trait among mammals, it also means humans are exposed to their social environment much earlier in development than most offspring in the animal kingdom. Children's social relationships are arguably the most fundamental component of the early postnatal environment and facilitate both the beneficial and harmful effects of ecological factors. Even meeting necessary nutritional needs through breastfeeding is a social bonding experience with close proximity, ventro-ventral contact, body warmth, and soft touch. As the preeminent developmental psychologist Urie Bronfenbrenner stated: "No society can long sustain itself unless its members have learned the sensitivities, motivations, and skills involved in assisting and caring for other human beings" (Bronfenbrenner 2009).

All children develop within a dynamic social context of both interpersonal relationships and wider social structures, which can shape their cognitive, emotional, and biological processes for the remainder of their lives (Casper 2001). From the first moments with parents to city planning to feeling accepted by the community, the multifaceted nature of the social environment provides ample opportunity for both advantages and hindrances to be embedded "under the skin" (Boyce and Kobor 2015).

Though the debate between solitary contributions of nature and nurture is an academic artifact, there are a variety of overlapping conceptualizations of this embedding process. For example, the concept of vulnerability and resilience, or resistance, is commonly used in psychology and psychiatry (Ingram and Luxton 2005; Luthar 2003), as well as in engineering and ecology (Miller et al. 2010; Proag 2014). These terms have similar meanings even in these disparate fields with vulnerability referring to the underlying potential of an adverse reaction to a negative event, and resilience referring to the innate ability to withstand and recover from a negative event. This is the same principle as an individual genetic predisposition for a particular outcome, either beneficial or detrimental. Similarly, the psychological diathesis-stress model, or dual-risk model, presumes a predisposition that affects the likelihood of developing, or the trajectory of, a disorder (Ingram and Luxton 2005). This diathesis may be genetic, biological, environmental, or psychological and

interacts with some form of biological or environmental stress to alleviate or exacerbate the effect. This also resembles the threshold model of neurobiological reactivity (Moore and Depue 2016). This model proposes that there is a biological constraint on the potency of external stimuli necessary to elicit an emotional response. This model presupposes that there is a predisposition to be stressed by an environment in the first place, in addition to the possibility that the subsequently elicited stress response may exacerbate yet another outcome. This cascade of interactions between innate differences and environmental exposures is addressed in the developmental origins of health and disease (DoHaD) hypothesis (Mandy and Nyirenda 2018; Suzuki 2018). This hypothesis refers to the potential biological programming from environmental exposures that may cause some of the intrinsic predispositions on which later environments may act (Wadhwa et al. 2009).

The most general and often used term for these relationships is gene-by-environment interactions. Ultimately, the distillation of these models equates to a basic understanding that the scaffolding of experience can be secured upon existing biological foundations. With poor foundations or inferior craftsmanship, the overall integrity of the structure may fail. One important aspect of how these pieces come together to build the human experience is through epigenetics (Meaney 2010).

2 Epigenetic Modifications

Epigenetics refers to the varied modifications to the underlying, permanent deoxyribose nucleic acid (DNA) sequence, which subsequently alter gene expression and, ultimately, phenotypes such as health and behaviors. The fundamental purpose of these epigenetic alterations is to achieve a diverse landscape of expression from a single DNA source (Boyce and Kobor 2015). These changes are likely involved in the biological embedding of environmental influence because of both their dynamic nature and sensitivity to experiential feedback. The field of epigenetics is a natural accretion of biological reductionism as it provides evidence that while we may be a product of our biology, our biology is partially a product of our environment.

The most common forms of epigenetic investigations in humans are correlational studies on DNA methylation (mC) and DNA hydroxymethylation (hmC), as discussed elsewhere in this volume. Due to its critical role in cell type differentiation, mC is highly affected by cell type differences and, thus, tissue types, as well as age, ethnicity, genotype, sex, and disease state (Edgar et al. 2017; Hannon et al. 2015; Husquin et al. 2018; Islam et al. 2019; Lienert et al. 2011; Turinsky et al. 2019; Wagner et al. 2015; Yousefi et al. 2015; Ziller et al. 2013). Three of these factors are especially important to highlight: genotype, tissue, and age. When considering genotype, de novo modifications may be affected by the underlying DNA sequence due to potential sites of interaction, a downstream consequence of other modifications, or the result of adaptation to environmental influences that can be passed on through cell mitosis to have long-lasting effects (Bock et al. 2006; Probst et al. 2009; Song et al. 2017). When considering tissue, the two most important aspects are

differences in cell type and cell type proportions among the different tissues and the comparisons that can be made among and between different tissue types. Specifically, it is difficult to make inferences about epigenetic modifications in brain tissue when measuring more peripheral tissues such as blood or saliva; however, there are resources correlating some measures in these tissues that can assist in forming educated inferences (Braun et al. 2019; Edgar et al. 2017).

Finally, when considering age, both its potential as a confounder and variable of interest should be acknowledged. Patterns of epigenetic modifications change with age, including mC (Gopalan et al. 2017; Jones et al. 2015; Koch and Wanger 2011; McEwen et al. 2016, 2017; Sen et al. 2016). Therefore, it is crucial that age be accounted for, selected for, or counterbalanced across groups in the variable of interest. A subsequent benefit of these clear and replicable differences in ages, however, is the ability to predict age using DNA methylation "clocks" that can be both tissue specific and pan-tissue (Horvath et al. 2016; Horvath and Raj 2018; Liu et al. 2019; Marioni et al. 2015; Wagner 2017). By calculating age using DNA methylation, it is also possible to determine the acceleration or deceleration of a person's epigenetic age from their chronological age. Generally, when an adult is predicted to be older than their chronological age (i.e., epigenetic age acceleration), this suggests increased cellular aging and is associated with increases in morbidity and mortality (Fransquet et al. 2019; Horvath et al. 2015; McEwen et al. 2016).

While the field is acutely aware of the importance of accounting for these potential confounders, many early foundational studies in social epigenetics did not account for these differences and are primarily correlational, observational designs. Additionally, due to the difficulty, cost, and technological limitations in conducting epigenome-wide association studies (EWAS), much of the initial work focused on a candidate gene approach. The previous literature on mC in candidate genes should not be disregarded; however, new appreciation of the interconnectedness among mC indicates the benefit of EWAS due to accounting for differences among many correlated sites or regions simultaneously (Moore 2017). While there is crucial work to be done in understanding how social environments affect the underlying biology of developmental sequelae, a healthy dose of skepticism and a critical eye must be maintained both when evaluating past and current literature, as well as developing new experimental designs (Jones et al. 2018). There are also other possible DNA modifications that can affect gene expression that have been significantly less studied than mC. Although not much is known about their relationships with early social environments, additional cytosine modifications formylation and carboxylation, as well as the much rarer methylation at adenine sites on DNA, are ripe for future investigation (Wu et al. 2016b; Yao et al. 2017). Besides modifications directly onto DNA base pairs, there are other ways to affect the complex relationship between DNA structure and protein synthesis.

One such way is to affect the packing of DNA through modifications to chromatin, the condensed DNA-protein package that allows a structure as large as DNA to reside within the nucleus of a cell. Within the chromatin package are an octamer of proteins called histones. This package contains two each of four types of histones: H2A, H2B, H3, and H4, the tails of which have at least 14 possible modifications

known to date (Bártová et al. 2008; Huang et al. 2014; Kouzarides 2007). By modifying chromatin structure, the accessibility of the DNA for gene transcription is significantly affected. This is a metric referred to as chromatin accessibility (Buenrostro et al. 2015, 2016; John et al. 2011). One modification that usually increases chromatin accessibility, thus increasing the ability of transcription factors to bind to the DNA, is histone acetylation (Görisch et al. 2005). This is when acetyl groups are deposited on lysines by histone acetyltransferaces (HAT). Alternatively, these groups that typically act to release compacted DNA to facilitate transcription initiation can be removed by histone deacetylases (HDAC), thus reducing chromatin accessibility (Chen and Townes 2000; Shahbazian and Grunstein 2007). There is significant evidence of histone acetylation and deacetylation having social behavioral effects in animal studies (Bukhari et al. 2017; Fitzsimons and Scott 2011; Hunter et al. 2012; Malik et al. 2014; Peixoto and Abel 2012; Saul et al. 2017; Shpigler et al. 2017).

Another possible histone modification is phosphorylation, which is often associated with acetylation, and functions primarily in the histone microenvironment by serving as a platform for communication between other histone modifications and downstream effects (Banerjee and Chakravarti 2011). Phosphate groups are customarily deposited by nuclear kinases and removed by protein phosphstases (Brami-Cherrier et al. 2009; Koshibu et al. 2009). Similar to DNA, histones can also be modified to be methylated, which, like DNA, can lead to both increased and decreased chromatin accessibility depending on the modified site (Kouzarides 2007). Methyl groups are deposited on histones by histone methyltransferases (HMT) and removed by histone demethylases (HDM) (Bártová et al. 2008; Zheng et al. 2015). In addition to their interactions with one another, these modifications are affected by the principle DNA structure, histone chaperones, age, and histone protein variants such as the H2A histone variant H2A.Z (Ausió and Abbott 2002; Bryois et al. 2018; Levine et al. 2012; Mcvicker et al. 2013; Stefanelli et al. 2018; Tessarz and Kouzarides 2014).

Once the DNA has been made available to transcription factors through variations of, and modifications to, DNA, chromatin, and histones, there is yet another epigenetic mechanism which takes place on ribonucleic acid (RNA). Messenger RNA (mRNA) acting as an intermediary between the underlying DNA structure and the protein synthesizing ribosomes, just like histones and DNA, can be modified by the addition or subtraction of hydroxymethyl, acetyl, phosphate, and the most frequently studied, methyl adenine (m^6A) groups (Boccaletto et al. 2017; Meyer and Jaffrey 2014; Saletore et al. 2012). These modifications, sometimes referred to as epitranscriptomics, can affect the structure, binding, transcription, and translational properties of RNA, which in turn has significant implications for downstream protein synthesis (Schwartz 2016). There are also two other families of RNAs that can have significant effects on gene transcription without affecting the underlying DNA sequence: microRNAs (miRNAs) and long non-coding RNAs (lncRNAs). Both miRNAs, which act as complimentary sequences to degrade mRNA and lncRNA, which regulate mRNA, generally reduce transcription and are affected by the underlying DNA sequence (Chu et al. 2011; Kim 2005; Kim and Nam 2006; Lee

2012; Mercer et al. 2009; Younger and Corey 2011). The direct relationship of the social environment on miRNAs and lncRNAs is currently unknown.

This diverse wealth of epigenetic mechanisms does not operate in a vacuum but functions together to have a cascade of comprehensive and varied influences. These modifications can be preserved for a lifetime through biological machinery that accurately maintains the epigenetic pattern (Probst et al. 2009), thus providing the opportunity for dynamic early environmental epigenetic adaption to be maintained throughout a lifetime. Therefore, there are many known epigenetic mechanisms that would allow for the possibility of early life social environments to stably modify phenotypes over the life course without altering the genotype. In this chapter, we discuss the scope of varied epigenetic investigations into the biological consequences of both interpersonal and structural social environments. To begin, we focus on the intersection of social behavioral neurogenomics: learning.

3 Epigenetics and Learning

The social environment is, fundamentally, an inescapable impetus for development and adaption through learning and memory, both positive and negative. Infants are innately attuned to social cues, even before birth. Infants have a strong preference for eyes, faces, and facial configurations (Dupierrix et al. 2014; Goren et al. 1975; Johnson et al. 1991, 2015; Turati et al. 2002). Even third trimester human fetuses preferentially orient toward a face shape when projected through maternal tissue (Reid et al. 2017). This strong preference can be interpreted as an indication of the importance of early exposure to faces and an early orientation toward social stimuli (Morton and Johnson 1991). In addition to the infant's predilection for faces, young infants develop in an especially face-dense environment, even in comparison to older infants (Jayaraman et al. 2017). As young infants have a low range of mobility, this demonstrates an implicit adult drive to place faces in front of developing infants as well. Infants also use touch to communicate with their caregivers and use a variety of movements depending on their needs and the caregiver's responsiveness (Moszkowski and Stack 2007). Additionally, evidence indicates maternal odors enhance neural signaling of facial categorization, but not general activation, in infant brains (Leleu et al. 2019).

Babies' relationship with the social environment is a multi-sensory process. In addition to sight, smell, and touch, infant's hearing is also highly attuned toward social environments and language development. Adults tend to use infant-directed speech (IDS) when with children, which incorporates a larger range of higher frequencies and has more rising contours than adult-directed speech (ADS). Infants are more attentive to, can discriminate sounds better in, and can be emotionally regulated by IDS as opposed to adult-directed speech (Cooper and Aslin 1990, 1994; Fernald 1992; Trehub et al. 1993). Even mothers of deaf children use exaggerated signs to their infants, who are more attentive to the exaggerated infant-directed

signing (Masataka 1998). An infant's world is full of social stimuli to which they can experience, react, and learn.

This rich social environment is used by infants to both survive, via their caregivers, and begin to build their understanding of the world. Therefore, it logically follows that children's cognitive functional development, both normative and deviant, adapts to the social environment (Dishion 2016). Children show a novelty preference almost immediately and are able to respond to traditional behavioral conditioning paradigms (Hulsebus 1974; Thompson et al. 1991). Infants as young as 6 months can reliably show social learning through deferred imitation (Barr et al. 1996; Meltzoff 1988). Additionally, experiential learning generally is essential for normative development both pre- and postnatally (Bale et al. 2010; Mclaughlin et al. 2014; Perry 2002; Roth and Sweatt 2011a, b; Swain et al. 2007; Talge et al. 2007). Learning from and adapting to the early life environment as effectively as possible is crucial for both juvenile and adult survival. It is both demonstrable and logical that children would be learning from their environments, and it is clear that there is an emphasis on the social environment for those associations.

Some connections, such as those learned or imitated in an interpersonal social context, are more readily learned than others. This is called biological preparedness theory, and the belief is that there is an evolutionary advantage to more quickly making these environmentally and survival-relevant associations (Cummins and Cummins 2015; McNally 2016). It is also much more difficult to extinguish these connections once learned (Åhs et al. 2018). Most work has focused on preparedness role in phobias, anxiety disorders (including social anxiety), and taste aversion (de Silva 1988; Ohman and Mineka 2001). Due to the importance of social bonds to human survival, especially for young children, and the extreme innate infant preference for social stimuli, the assumption of an underlying biological preparedness to learn cues from the social environment is reasonable. Albert Bandura, a distinguished behaviorist, acknowledged the unique aspects of social environments. He adapted the behavioral conditioning theory to include the observational process of learning and noted that there are mediating processes between the experience of a stimuli and subsequent response (Bandura 1977). The cognitive ability of children to learn from, and disproportionate attunement toward, their early social environments indicate that these social factors are primed to make lasting neurological, epigenetic, and behavioral impressions.

In order to leave these lasting impressions, first the associations from the social environment need to be learned. The basis for most models of development, learning, and memory in neuroscience is synaptic plasticity, or the ability of synaptic connections to change their strength (Ehrlich and Malinow 2004). Hebbian theory, or cell assembly theory, posits that two mechanisms of synaptic plasticity are long-term potentiation (LTP) and long-term depression (LTD) (Ehrlich and Malinow 2004; Robert C Malenka and Nicoll 1999; Randic et al. 1993). Electrophysiological action potentials are primarily responsible for, or supportive of, cell-to-cell communication through the synapse in the nervous system through rapid cell depolarization that is passed along to adjacent cells.

LTP is one cellular mechanism through which the strength of a synapse can be amplified, while LTD is a mechanism for weakening a synapse. LTP primarily

occurs through the action of presynaptic glutamate at two types of postsynaptic ionotropic glutamatergic receptors, N-methyl-D-aspartate (NMDA) receptors and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (Malenka and Nicoll 1999). Though glutamate binds to both NMDA and AMPA, NMDA receptors are gated by a magnesium ion block that prevents calcium ions, to which NMDA receptors are permeable, from entering the postsynaptic neuron. However, AMPA receptors do not have a magnesium block and are activated by presynaptic glutamate release, allowing sodium ions to flow through. When enough AMPA receptors have been activated and sodium ions have entered the postsynaptic neuron, the charge, or potential, of the neuron changes, releasing the magnesium ion block from the NMDA receptors. The NMDA receptors then allow calcium ions into the cell, which target calcium/calmodulin-regulated protein kinase II (CaMKII) (Malenka et al. 1989). CaMKII phosphorylates AMPA receptors, increasing their current, a mechanism of early LTP, and initiates protein synthesis through the MAPK (mitogen-activated protein kinase) pathway and CREB/CRE (cAMP-responsive element binding protein/cAMP response element) mechanisms to begin structural changes in and around the synapse (Giese et al. 1998).

Early LTP results in the addition of more AMPA receptors postsynaptically and a retrograde signal of nitric oxide to the presynaptic neuron, while late LTP adds an entirely new synapse between the two neurons (Sandkühler and Gruber-Schoffnegger 2012). BDNF (Brain-derived neurotrophic factor) is crucial in this process, with reduction leading to insufficient drive for synthesis of synaptic proteins, thus contributing to cognitive dysfunction (Wu et al. 2016a). Both adding more AMPA receptors, thus depolarizing and triggering NMDA receptor activation in the postsynaptic neuron, or adding a new synaptic cleft, increases the strength of the connection between the two neurons. This strengthened connection is sensitized to be activated again and the presynaptic cell is poised to interact with the postsynaptic neuron more quickly and strongly than before.

LTD, on the other hand, takes place when there is consistent low frequency activation. With constant low activation, only some, but not all, AMPA receptors are activated, which is not enough to remove the magnesium ion block from the majority of NMDA receptors. In this case, calcineurin (protein phosphatase 2B) is the target, which results in the removal of AMPA receptors by endocytosis (Malenka and Bear 2004). Though LTD is the weakening of synaptic strength, it plays an integral role in memory formation, most likely through preparing potential pathways for new connections. Additionally, spike-timing dependent potentiation (STDP) adds even more specificity to this relationship by altering the strength of LTP and LTD effects depending on the timing of electrical signals (Fiete et al. 2010). The strengthened relationships among neurons happen within milliseconds and can last from 30 min to years. LTP in multiple synapses can create engrams, or biophysical manifestations of memories, stored as cognitive units of interconnected cells (Poo et al. 2016). The maintenance of these engram connections composes long-term memory. How are these changes generated in the first place? How are they maintained over multiple cell turnovers and conceivably for an entire lifetime? One possibility is through epigenetic mechanisms that alter gene transcription to allow for stable, structural modifications to the synapse.

Contributing to the neuroarchitectural changes associated with learning, brief and distinct changes to neural gene expression are observed, termed genomic action potentials (gAP) (Clayton 2000; Clayton et al. 2019). The pathways activated by calcium interacting with CaMKII and calcineurin lead to increased gene transcription of elements necessary for cytoskeletal changes, termed the immediate early gene (IEG) response (Clayton et al. 2019). This dynamic change results in epigenetic modifications at the transcriptional and chromatin packaging levels (see Clayton et al. 2019 for review). One example is *ARC*, an IEG, which is involved in the endocytosis of AMPA receptors seen following calcineurin activation in LTD (Chowdhury et al. 2006; Rial Verde et al. 2006). Another example of IEG action is *FOS*, which interacts with histone methylation to prime histone acetylation based on neuronal activity. These common IEGs are poised to have quick transcriptional changes in multiple domains such as histone lysine modifications and mRNA interactions (D'Urso and Brickner 2014; D'Urso et al. 2016; Rye et al. 2014). It is also reasonable to hypothesize that, as there are differences in synaptic plasticity depending on the types and locations of neurons, as well as temporal differences such as early vs. late LTP or STDP, this is also true for the IEG associated with these changes (Tyssowski et al. 2018). Additionally, like the pattern of synaptic connections, the gAP differs when encoding different learning experiences (Mukherjee et al. 2018).

Histone and mC modifications, in particular, have been associated with synaptic plasticity and learning outcomes (Blaze and Roth 2013; Chwang et al. 2006; D'Urso and Brickner 2014; Dias et al. 2015; Feng et al. 2010; Kim and Kaang 2017; Levenson and Sweatt 2011; Peixoto and Abel 2012) as well as affording significant contribution to differences in the neural architecture of neonatal socioemotional learning (Ong et al. 2019). Consistently, pharmacological inhibition of mC modifications significantly impairs memory, and many EWAS identify mC modifications in genes involved in neurotransmitter pathways and learning (Day and Sweatt 2011; Mill et al. 2008).

Additionally, increases in histone acetylation and alterations in histone methylation are associated with memory formation, synaptic plasticity enhancement, and increased gene expression (Guan et al. 2002; Pang et al. 2019; Schaefer et al. 2009). For example, oral administration of the HDAC inhibitor suberoylanilide hydroxamic acid (SAHA) restored spatial memory and reduced inflammation in an aging animal model (Benito et al. 2015). There is also evidence that histone lysine methyltransferase complex G9a/GLP facilitates LTD maintenance in the hippocampus and inhibiting HATs significantly impairs learning potential (Oliveira et al. 2007; Sharma and Sajikumar 2018). A specific example of the role of histone methylation is the reduction of H3 histone dimethyl occupancy in the promoter region of a gene associated with long-term memory formation, *HOMER1A*, and an increase in its transcription in the amygdala during auditory fear conditioning (Mahan et al. 2012). Conversely, an increase in HDAC activity results in reduced synaptic plasticity and memory impairment, while pharmacological inhibition of HDAC improves memory formation (Guan et al. 2009; Levenson et al. 2004). Also,

histone acetylation in the hippocampus is a consequence of contextual fear conditioning in rodent models (Levenson et al. 2004).

Another aspect of biological memory beyond encoding and maintenance of explicit and implicit learning is homeostatic conditioning (Clayton et al. 2019). Homeostasis is a summary mechanism maintaining a steady biological equilibrium to best preserve an optimal internal environment (Martin 2008). Depending on the changes to internal and external states, it is sometimes necessary to rebalance these homeostatic systems to reach a new equilibrium. In this case, a synapse changes because of homeostatic mechanisms. A common and illustrative neuronal example of homeostatic compensation is gaining tolerance to opiates (Koob 1996). By activating mu-opiate receptors in the brain at a constant, elevated level, these receptors become internalized and, eventually, broken down, while receptors responsible for opposite reactions, like norepinephrine receptors, are upregulated through increased transcription (Finn and Whistler 2001). This new receptor balance is a reaction to the ingestion of exogenous opiates and is responsible for both increasing tolerance to and withdrawal symptoms from opiates. Similar to Hebbian learning, these fluctuations could not occur without dynamic and maintained changes in gene transcription. Therefore, Clayton et al. (2019) posit an additional function of the gAP which could be regulating homeostatic compensation in a similar fashion. Homeostatic mechanisms working through the gAP at the network level may be more likely in response to large variations that activate homeostatic receptors such as changes in developmental stage, drug ingestion, or significant environmental experiences (Hrvatin et al. 2018; Miyashita et al. 2009; Miyatake et al. 2005; Tyssowski et al. 2018).

One example in humans of genetic deficits in epigenetic modifications resulting in profound cognitive and social dysfunction is Rett Syndrome (Jiang et al. 2004). Rett Syndrome is an intellectual disability disorder that results from a mutation in the *MeCP2* gene, which checks and binds areas of DNA with methylation and ensures DNA is packaged appropriately (Amir et al. 1999). *MeCP2* also affects synaptic formation and hippocampal memory (Jiang et al. 2004; Li et al. 2012; Skene et al. 2010). Extensive histone acetylation increases are a consequence of this *MeCP2* mutation found in mice that are associated with increased stress, social withdrawal, and profound cognitive impairment (Shahbazian et al. 2002). Rett Syndrome is an example of how disrupted mC machinery affects the regulation of histone modifications, and thus gene expression and cognitive and social phenotypes. Another example of the manifest impact of histone modification variations in humans is the intellectual disability disorder Rubinstein-Taybi Syndrome (RTS) (Alarcón et al. 2004). RTS individuals have a mutation in their *CBP* gene, which transcribes for a protein that promotes histone acetylation and, thus, gene expression. Because of this mutation, RTS individuals and animal models of the disease present with profound cognitive impairments and substantial decreases in histone acetylation throughout the genome (Josselyn 2005; Kalkhoven et al. 2003; Korzus et al. 2004). In mouse models of RTS, the epigenetic action of *CBP* is disrupted specifically after separation of the pup from their mother (Wang et al. 2010). Taken together, these two mutations provide evidence for the weighty impact of epigenetic mechanisms in learning and the ensuing social consequences.

There is mounting evidence suggesting the importance of epigenetic modifications specifically affecting *BDNF* gene transcription, necessary for activity-dependent neuronal plasticity. Histone deacetylase 2 (HDAC2), methyl-cytosinephosphate-guanine–binding protein 2 (MeCP2), and DNA methyltransferase 1 (DNMT1) can substantially induce chromatin remodeling in the promoter regions of the *BDNF* gene, which can subsequently modulate hippocampal synaptogenesis and cognitive function (Chen et al. 1967; Kavalali et al. 2011). Transcriptionally, with neuronal activity there is also an increase in mRNA levels and consistent decrease in mC changes at *BDNF* in the CA1 hippocampal region after fear conditioning. Additionally, there is a reduction in the long noncoding antisense RNA that downregulates *BDNF* expression (Lipovich et al. 2012; Lubin et al. 2008). *BDNF* promotes local synaptic protein mRNA translation and plays a necessary role in neuronal development, synaptic plasticity, and learning (Minichiello 2009; Park and Poo 2013; Takei et al. 2004). Epigenetic differences affecting *BDNF* have been associated with early-life adverse experiences, early-life stress, neglectful parenting, depression, posttraumatic stress disorder, and may be a valid biomarker for some psychiatric diseases due to its unique role in their pathology (de Lima et al. 2011; Kang et al. 2013; Roth and Sweatt 2011a, b; Roth et al. 2011; Seo et al. 2016; Zheleznyakova et al. 2016).

Epigenetics acts as the synaptic connection between genes and the environment, even at the synapse itself (Boyce and Kobor 2015). While there is evidence that the prenatal environment affects epigenetic differences, the clear role of epigenetics in the encoding of long-term memories indicates the importance of differences in these mechanisms as a response to postnatal experiences as well. Thus, as expected, there is an abundance of examples in human and animal models of environmental exposures correlating with differences in epigenetic mechanisms, much like environmental exposures correlate with differences in neural architecture and behavior (Araki et al. 2016; Bedrosian et al. 2018; Boyce and Kobor 2015; Essex et al. 2013; Gassen et al. 2017; Klengel et al. 2013; Mcgowan et al. 2009, 2011; Turecki and Meaney 2016; Weaver et al. 2004). Even epigenetic clocks are sensitive to environmental differences throughout the lifespan (Jylhävä et al. 2019). Also, similar to neural development, early life social experiences can sometimes more strongly relate to epigenetic differences than adult experiences, possibly due to the critical period of development and learning occurring at that time (Boyce and Kobor 2015; Bush et al. 2018; Gassen et al. 2017; Klengel et al. 2013; Lam et al. 2012; Wagner et al. 2015). Using the theoretical framework that changes in neural architecture and genomic transcription are reactions to the environment, it naturally follows that these long-term adaptations would happen early in childhood development in order to increase the chance of survival in whatever positive or negative circumstances are present. Learning from the social environment is one mechanism of behavioral neurogenomics where changes to neuroanatomy, epigenetic modifications, and behavior work in concert to adapt to an external stimulus. There are multiple types of stimuli that can act as an impetus for this learning, such as social reward, pain, and stress. We will discuss each of these possible provocations in the relevant social environments.

4 Interpersonal Environments

4.1 Parenting and Enriched Environments

The first social environment a human infant is born into is the uniquely vital and interpersonal relationship with a caregiver. Human altricial young need constant care and affection, which they hopefully receive from their primary caregiver, often a parent. Having a positive, loving relationship in infancy with this person, who responds immediately and effectively to the child's needs, has lifelong effects (Zayas and Hazan 2015). Attachment theory, one of the most well-established social psychological theories, provides a foundation to understand both the impact and quality of early close relationships amid development.

In development, establishing successful relationships with adults and peers provides a foundation of capacities that children will use for a lifetime (Belsky and Cassidy 1994; Pietrornonaco and Barrett 2000; Thompson 2000; Zayas and Hazan 2015). Thus, Bowlby, father of attachment theory, referred to these attachment patterns as being "from cradle to grave" (Bowlby 1979, p. 129), possibly similar to the epigenetic modifications to be established in infancy and lasting through mortality. This attachment theoretical foundation provides a comprehensive account of the ontogeny and developmental sequelae of infant caregiver bonds, as well as a framework for investigating how perturbations of this system may result in individual differences. Additionally, animal models of pair bonding and advances in fMRI technology have contributed to a rich literature delineating the neural systems that underlie attachment behaviors (see Beckes et al. 2015 for review). These manifestations of social bonds in terms of physiology, emotion, and behavior are assumed to reflect the functioning of mental representations.

A defining principle of attachment theory is that past relationships and interactions with the social environment are stored in memory (e.g., Bowlby 1979, 1982; Bretherton and Munholland 2008; Collins et al. 2004; Pietromonaco et al. 2000; Zayas et al. 2011). Mental representations consist of detailed memories of interactions with, and conscious and nonconscious affective evaluations of, attachment figures (Zayas and Shoda 2005, 2015), as well as strategies to regulate negative affect in stressful and threatening situations (Collins et al. 2004; Pietromonaco et al. 2006; Zayas et al. 2009). From a psychological perspective, mental representations are impactful because they implicitly affect perceptions and expectations about likely events and patterns (Baldwin et al. 1993; Günaydin et al. 2012; Zayas et al. 2009). From a neuroscience perspective, these mental representations are akin to the engrams that are formed from a collection of neuronal connections built by LTP and recalled to regulate affect in times of need. Finally, from an epigenetic perspective, these mental representations may reflect the adaptations to early caregiver relationships and social environments that ultimately result in differing phenotypes. In regard to the later, there is a wealth of literature exhibiting reported epigenetic differences correlated with early caregiver relationships.

In animal research, the majority of studies have used rat models from the first 10 days of life, which represents a sensitive period in rat development known to facilitate early learning and infant–caregiver attachment (Roth and Sweatt 2011a, b). To continue the understanding of social epigenetics as adaptation in memories and the capacity for learning, one study found that poor early maternal caregiving in mice led to difficulties in spatial cognitive tasks (Bredy et al. 2004). More recent work in mice also found that expression of glutamate receptors necessary for LTP and LTD such as NMDA and AMPA in the ventromedial prefrontal cortex, the cognitive component of the socioemotional circuit, decreased in socially isolated adolescent, but not adult, mice (Lander et al. 2017). It has also been found that young mice which are not isolated, but receive less sensitivity and care from their mothers have abnormal hippocampal and amygdala *BDNF* gene expression necessary for learning and synaptic plasticity (Macrì et al. 2010). Similarly, amounts of BDNF decreased in the prefrontal cortex and hippocampus of juvenile socially isolated rodents (e.g., Branchi et al. 2004; Branchi 2009; Chatterjee et al. 2007; Choy et al. 2008; Fumagalli et al. 2007; Lippmann et al. 2007; Nair et al. 2007; Zimmerberg et al. 2009). These findings speak simultaneously to both the effect of social relationships on learning and the sensitive developmental period in which the plasticity of this adaptation takes place. In general, these findings are illustrative of the wider, rich literature on the epigenetic effects on plasticity in the prefrontolimbic and hippocampal regions of offspring exposed to reduced, or absent, maternal care (Branchi et al. 2006; Matas et al. 2016).

Stress effects also relate to a poor versus positive early caregiver relationship. An often-cited paper on the topic is by Weaver et al. (2004), on the relationship between maternal licking and grooming with mC differences in the promoter region of the glucocorticoid receptor gene (*NR3C1*). While they found that more licking and grooming from maternal rats lead to hypomethylation in the promoter region of the *NR3C1* and patterns of methylation in a broader surrounding area (Mcgowan et al. 2011), this study has yet to be replicated and is met with some skepticism in the field (Jones et al. 2018). However, more recent work in mice has also found different biological reactions to maternal caregiving in the hippocampus, a region associated with both learning and reactions to stress, and the dorsal raphe nucleus (DRN), the brain center for serotonin production and distribution (Araki et al. 2016; Bedrosian et al. 2018). In the DRN specifically, Araki and colleagues found hypomethylation affecting the GABA(B) receptor, which is a common pharmacological target for depression and anxiety relief (Araki et al. 2016; Felice et al. 2016).

Similar positive relationships between parental nurturance and memory development have also been found in humans (Farah et al. 2008). Generally, increased positive, engaged social environments increase memory formation in both humans and nonhuman primate models (Farah et al. 2008; Kozorovitskiy et al. 2005). Epigenetically, human studies have primarily focused on the mC of a few genes of specific and special prominence in the research, namely *BDNF* (see Zheleznyakova et al. 2016 for review), *NR3C1* (see Turecki and Meaney 2016 for review), *SLC6A4* (see Moore and Kobor 2018 for review), and *OXTR* (see Maud et al. 2018 for review). All of the proteins these genes encode have many functions across learning

and homeostatic change, especially in relation to neurodevelopment and stress. For example, the *BDNF* gene codes for brain-derived neurotrophic factor, the canonical neuronal growth factor in the brain widely involved in the formation of any neuroarchitectural changes. Additionally, *NR3C1* is the most widely researched gene in regards to fMRI and stress-causing environments, such as poor maternal care, in both the animal and human literature (Jones et al. 2018; Turecki and Meaney 2016). One recent study found that increased maternal responsiveness and touch were correlated with hypomethylation in *NR3C1* exon 1F in female children (Ostlund et al. 2016). This sex-dependent response has been replicated in other studies as well, such as Garg et al. (2018) finding the greatest DNA methylation differences among attachment styles in females. Additionally, they found that across the sexes, attachment behavior patterns were correlated to over 10% of global mC differences in children, suggesting large biological responses to the sensitivity and consistency of the parental care environment (Garg et al. 2018).

Another nuanced aspect of the caregiver relationship is soft touch, which is incredibly important in healthy, normative infant development (Barnett 2005). There were significant mC differences between children who received high amounts of soft touch and those who did not as infants. Additionally, infants who were more distressed, yet received lower amounts of touch, were epigenetically younger, possibly indicating a biological developmental delay (Moore et al. 2017). This is most likely due to the social buffering effects of both mental representations and human touch. For example, holding the hand of a stranger can reduce both the subjective experience of pain and its neural signature, but holding the hand of a close relationship partner reduces pain in these areas to an even greater extent (Coan et al. 2006).

Ultimately, the research indicates that having a healthy, supportive early social environment leads to positive epigenetic, neurological, and psychological outcomes. This is most clear when examining the literature on the benefits to enriched environments both in buffering stress and in rescuing memory formation. In humans, for example, having a supportive family environment during development protected against harmful cellular and epigenetic aging due to racial prejudice experiences. However, individuals without a supportive family environment did experience biological weathering (Brody et al. 2016). In animals, enriched environments including both positive caregivers as well as social play and peer interactions associated with global brain differences such as larger total cortical weight, especially the dorsal cortex, and larger ratio of cortex weight to overall brain weight (Rosenzweig and Renner 1986). Although less than some of the more negative aspects of development, there is a respectable amount of literature on the effects of this socially and cognitively enhanced environment in model animals. One such study found that, even with poor early caregiving, having an enriched environment rescued the gene expression of the NR2A and NR2B subunits of the NMDA receptor and AMPA receptor, both suggesting that poor early caregiving is associated in a reduction of learning potential through a reduction of NMDA receptor activity, and that an enriched environment with peer sociality and cognitive stimulation can combat these learning effects (Bredy et al. 2004).

This effect is most likely related to the demonstrated modulation of synaptogenesis by exposure to environmental stimuli (Eckert and Abraham 2010; Fischer et al. 2007; Ramírez-Rodríguez et al. 2014). Being housed in a communal nest as a juvenile, a form of enriched environment, is linked to increased sociocognitive functioning and increased expression of BDNF in rodents (Branchi 2009). In fact, in enriched environments with dynamic social play, overall memory function is improved in rats, and even exposure to chemically induced short-term memory impairment in neonatal rodents can at least be partially rescued through enriched environment alone with no other pharmacological interventions (Shen et al. 2013; Shih et al. 2012). The cognitive disruption of this chemical impairment has been shown to derive through epigenetic protein interactions including such proteins as histone deacetylase 2, methyl-cytosine-phosphate-guanine–binding protein 2, and DNA methyltransferase 1 in the *BDNF* promoter region inhibiting BDNF expression necessary for synaptogenesis during development, which are specifically attenuated by an enriched environmental intervention alone (Wu et al. 2016a). Even in aging mice, which had altered H3 histone acetylation and histone methylation in hippocampal tissue, intervention with an enriched environment improved long-term memory deficits by reversing histone methylation around the *BDNF* gene in rodent hippocampal tissue (Morse et al. 2015). This study also indicated that histone lysine methylation may be a necessary transcriptional mechanism by which environmental enrichment rescues memory formation replicating previous literature in young rodent populations (Kuzumaki et al. 2011). Another pathway through which enriched environment improves memory is by preventing epigenetic changes, especially mC and histone deacetylation, driving oxidative stress (Griñan-Ferré et al. 2016). These environments do not need to be lifelong to have strong effects either. Even a relatively brief exposure to an enriched environment including dynamic social stimulation in juvenile mice enhances LTP through a cAMP/p38 MAP kinase-dependent signaling cascade (Arai et al. 2009).

However, not all early relationships are positive experiences. For example, both maternal and paternal life stress during early life was correlated with adolescent differences in mC in humans (Essex et al. 2013). In rats, newborns exposed to a stress-abusive mother showed increased methylation in the promoter region, and decreased expression, of the *BDNF* gene (Huang and Reichardt 2001). This difference in BDNF concentrations for abused versus non-abused rats appears to persist through adulthood (Roth et al. 2009). In this same study, a different group of newborn rats was also exposed to positive caregiving mothers. Both the maltreatment and beneficial caregiving mothers initially caused an increase in *BDNF* mRNA levels in the hippocampus (Roth et al. 2009). Both experiences, regardless of valance, equitably guided the growth of new neuronal connections in the memory center of the brain. Adaptationally, negative relationships and social environments are just as powerful as positive social learning experiences.

4.2 Pain, Stress, and Trauma

In early care environments, the perception of safety is the most critical component (Porges 2011). Breaching this trust results in negative social experiences that can be both stressful and painful. There are many ways to experience pain, such as acutely, chronically, physically, and emotionally; in abusive early social environments, children are exposed to all four kinds of pain. Pain is such a powerful motivator for learning that is often used in animal models for fear conditioning, which is quick to establish and difficult to extinguish (Hermans et al. 2006). This particular form of learning has been found to require epigenetic modifications to take place and results in epigenetic differences (see Dias et al. 2015 for review). Thus, the epigenetic consequences of such early-life adversity are, undoubtedly, affected by learning and the physiological consequences of experiencing pain.

It is first important to establish that the literature indicates neural reactions to physical and socioemotional pain are exceptionally similar, specifically in regards to the affective processing of pain (Eisenberger and Lieberman 2004; Papini et al. 2015). However, though pain is processed in the same regions, socioemotional pain, such as social rejection or isolation, is more potent on a chronic timescale because it is much more easily relived and remembered than physical pain once the original source of pain has subsided (Meyer et al. 2015). Animal studies have also repeatedly found that any unpredicted reward devaluation, such as through a sudden or bewildering social rejection, triggers the brain circuits involved in pain and stress (Papini et al. 2015). Individuals who experience abuse, especially from a caregiver, may experience the physical pain of abuse, but most certainly experience the social pain of rejection and betrayal in that moment and for years later.

Pain is the hedonically aversive conscious experience of the nociception response to damage (Moseley and Butler 2015). When physical damage to peripheral tissues occurs, this initiates an immune cascade of inflammatory mediators (Benzon et al. 2011). For example, bradykinin produces inflammatory pain and hyperalgesia through activation of G-protein-coupled receptors. Additionally, cytokines such as tumor necrosis factor alpha and interleukin 6 are released to moderate the inflammatory process and promote pain signaling by sensitizing nociceptors (Benzon et al. 2011). While these inflammatory mediators directly cause pain as a signal of tissue damage, they also modify sensory neurons, amplifying pain signal during transmission to the spinal cord, additionally motivating the desire to minimize injury and remove the aversive stimulus. Through subsequent changes in reaction to this acute event, such as gene regulation, receptor expression, glial activation, and sensitization, this pain may be maintained to become chronic pain (Denk and McMahon 2012). This immune response alone may result in epigenetic modifications, especially as immune responses lead to different cell type compositions in the blood as well as differentiation in epigenetic markers through the adaptive immune response (Janeway 2001).

This immune response is an important aspect of the sensory discriminant pain pathway. The input from this pathway passes through the nerves, spine, and brain

stem to the thalamus and insular cortex where the homeostatic relevance and intensity of the signal is discerned (Craig 2003). However, there is also a learning aspect of pain through the formation of a threat memory. This is referred to as the affective motivational pain pathway and requires calcitonin gene-related peptide (CGRP) activity in the amygdala (Han et al. 2015). In fact, CGRP activity in the parabrachial nucleus, a junction between the cerebellum and brain stem, is both necessary and sufficient for pain responses and fear conditioning due to its role in transmitting pain information to the central amygdala (Han et al. 2015). The central amygdala, in turn, sends input to the anterior cingulate cortex, which governs the level of unpleasantness derived from the signal and the quality of the motivational response (i.e., the more unpleasant, the greater the aversive motivation) (Craig 2003). This affective motivational pain pathway is necessary for learning to avoid noxious and harmful stimuli in the future, whether those stimuli are physical or social, while the discriminant response is necessary for acute treatment of the damage in the present.

Both the discriminate and affective pain pathways show clear associations with epigenetic modifications, though most investigations have focused on evaluating potential affective pain mitigation (Odell 2018). For example, one investigation of chronic pain detected 1,147 genes with differing RNA expression enriched for pathways involved in neuronal development and cell differentiation (Alvarado et al. 2015). HDAC levels were shown to be increased in the spinal cord and of critical importance to the induction and maintenance of inflammatory hyperalgesia (Bai et al. 2010). Studies have also been performed demonstrating the efficacy of HDAC inhibitors in improving stress-induced visceral hypersensitivity (Cao et al. 2016; Maloney et al. 2015). Interestingly, although administration of HDAC inhibitors reduces mechanical and thermal hypersensitivity by half, this is only true when HDAC administration occurs preemptively (Denk et al. 2013). Histone methylation also changes with pain, such as the increase in expression of proinflammatory cytokine monocyte chemotactic protein 3 in response to pain correlating with a decrease of histone lysine methylation in that protein's gene promoter region (Imai et al. 2013). Additionally, a reduction of miRNA in the dorsal root ganglia significantly decreased pain-related gene transcription and inflammation, though the affective motivational response to pain was unaffected (Zhao et al. 2010).

DNA methylation differences have also been associated with pain exposure. The promoter region for cystathionine-beta-synthetase, an enzyme in the nociceptive signaling pathway, was demethylated and the protein upregulated when experiencing pain (Qi et al. 2013). A rodent model for neuropathic pain showed that chronic painful neuropathy led to global changes in the degree of mC in the brain. About 6 months following peripheral nerve injury, decreases in global mC were found in the prefrontal cortex and amygdala (Tajerian et al. 2013). In another rodent neuropathic pain model, increased methylation of the mu-opioid receptor gene proximal promoter in the dorsal root ganglion, a key region in pain processing, was demonstrated (Zhou et al. 2014). There is also evidence for miRNA regulation of opioid tolerance in this pathway (He et al. 2010). Mu-opioid receptors, especially, are integral to the pain pathways due to their ability to reduce the affective motivational

component of pain (Simons et al. 2014), even in the absence of any visceral tissue damage (Papini 2009).

Ultimately, pain biology is both a unique, intense, and specific immune response and learning experience. These epigenetic changes related to the experience and sensitization of the pain response, both through immune cascades and neural receptor modifications, should be considered as a possible consequence of socially and physically painful social environments. However, the benefit of pain's relationship to these systems is discovering potential protective environments as well. For example, in a rodent model, increased maternal licking and grooming associated with mC in the interleukin-10 gene correlate with an increase in expression in the nucleus accumbens reward center. This, in turn, increased interleukin-10 protein in nucleus accumbens glial cells and reduced mu-opioid receptor glial activation to exogenous opioids, which resulted in less drug abuse (Schwarz et al. 2011). The inextricable link between pain and learning allows other positive environments such as sensitive maternal care or an enriched social play environment to reduce pain and the necessity of the pain-mitigating pathway response.

The possibility of experiencing pain, because it is such a noxious experience, is highly motivating to mitigate or prevent injury whenever and wherever possible. This causes a combination of constant uncertainty and the need for hypervigilance – a recipe for chronic stress. Though intimately intertwined with the pain pathway, the stress pathway is rooted in the effects of uncertainty. Whereas fear and pain generally have specific and proximal stimuli that trigger these reactions, stress requires no such unique or immediately relevant stimulus. The stress response is the collection of immune, neural, and homeostatic mechanisms that shift into a long-term state of hyperawareness with the anticipation of threats that could appear at any time. While this state can be lifesaving when triggered appropriately, being in a constant state of fearful uncertainty is not a healthy ideal and has lasting deleterious biological effects.

The stress system is extraordinarily far-reaching and complex, but importantly to the current discussion, involves an interaction of epigenetic, neural, and behavioral responses through both the immune system and learning and memory. When there is uncertainty about a potentially aversive or harmful outcome, the downstream stress response is activated by the hypothalamus. The hypothalamus secretes corticotropin-releasing hormone (CRH), which stimulates release of adrenocorticotropic hormone (ACTH) from the pituitary, which in turn signals two different stress pathways, one fast and one slow (Gunnar and Quevedo 2007). The two major stress pathways are the sympathetic-adrenomedullary (SAM) response and the hypothalamic-pituitary-adrenocortical (HPA) response (Gunnar and Quevedo 2007). In the fast, immediate SAM response, the ACTH triggers the adrenal medulla to release norepinephrine and epinephrine, neurotransmitters required to cause a rapid and intense nervous system response and hypervigilant attention (Benarroch 2007). In the slower, long-lasting HPA response, ACTH triggers the adrenal cortex to signal the release of the stress hormones glucocorticoids, the most important of which is cortisol, thus

dysregulating metabolism, suppressing the immune system, and disrupting homeostasis through glucocorticoid receptor binding systemically (Gunnar and Quevedo 2007). During the stress response, homeostatic mechanisms attempt to maintain equilibrium over a wide range adaptive circumstances in order to respond to any possible challenge. Stress is, in essence, a "ready" state from which a large, quick biological response is primed at a moment's notice and equipped with constant vigilance. Therefore, this cascade of biological effects both elicits a physiological and behavioral response, and poises the requisite systems for future environmental reactivity. Unfortunately, when chronically stressed, there is a burden placed on these biological systems such as the immune system and metabolism that becomes harmful, referred to as allosteric load (Gunnar and Quevedo 2007; Gunnar 2017). An excellent theoretical understanding of this facet of the stress response system is to return to the gAP (Clayton 2000; Clayton et al. 2019). The brain has a response to an environmental stressor that leads to transcriptional and epigenetic changes. These changes then trigger a "neuroendocrine action potential" as this neural response triggers both immediate and long-lasting changes throughout the limbic system and multiple organs (Clayton et al. 2019).

The clear, widespread effect of stress throughout all physiological systems makes it an understandable and unique candidate for understanding the epigenetics of social environment. Many adverse environments, both in the interpersonal, such as traumatic and abusive relationships with caregivers and peers, and the societal, such as minority stress and socioeconomic status stress, can trigger these same underlying processes, as all are sources of aversive, potentially harmful uncertainty. It is then understandable why the most commonly researched gene in social epigenetics is *NR3C1*, the glucocorticoid receptor gene (Turecki and Meaney 2016). In Turecki and Meaney's study (2016), they found consistent mC at the *NR3C1* in exon 1F/17 regarding parental stress, but inconsistent in other types and later life stressors. Additionally, recent work found that stress affected mRNA methylation in a region-specific manner, ultimately altering fear learning and synaptic plasticity (Engel et al. 2018).

The literature does appear to indicate that chronic stress in early life has a greater impact on mC patterns than those that occur in later life, but more research in this area is needed to make a definitive statement (Austin et al. 2018; Esposito et al. 2016). Work on cumulative stress, as opposed to early life or later life considered separately, also indicates an association with accelerated epigenetic aging (Zannas et al. 2015a). If this stronger association with stress and mC at younger ages is robust, it may be due to differences in the immune system's environmental sensitivity during early development (Miller et al. 2011). Additionally, a key component of the attachment relationship is to learn and support affect regulation (Hazan and Shaver 1987); having a responsive, consistent caregiver helps children express and deal with their negative emotions without triggering the endocrine stress response as if an uncertain threat had been detected; however, in abusive relationships, the parent is the source of uncertainty and danger (Repetti et al. 2014). While it is true that a recent, large study in humans did not replicate findings from smaller studies that

reported correlations between mC patterns and chronic social stress (Marzi et al. 2018), this may be due to differences in sample size, population, and consistency among ecologically valid measures of the type, context, and experience of stress. More replications with standardized measures and large sample sizes are needed to make any definitive statements about detectable mC differences among those who have experienced chronic stress.

In addition to *NR3C1*, there is a robust literature associating early-life adversity such as social, physical, or parental stressors, with epigenetic changes in *BDNF* gene expression (Roth and Sweatt 2011a, b). These differences may correlate with a reduction in socioemotional learning and plasticity, and have shown an increased capacity for fear learning (Dias et al. 2015). Impacted learning has also been implicated in more specific associations than general stress, such as the several reported associations between trauma, abuse, and differences in epigenetic modifications (e.g., Dickson et al. 2018; Klengel et al. 2014; Lutz and Turecki 2014; Mehta et al. 2013; Roberts et al. 2018; Suderman et al. 2014; Weder et al. 2014) as well as associations specifically with posttraumatic stress disorder (see Zannas et al. 2015b for review). Though there is a range in the findings of epigenetics in regards to early life adversity from both candidate gene approaches and EWAS approaches, overlapping genes associated with stress, pain, learning, and the immune system were common. For example, one study found immune cell differences and accelerated epigenetic age associated with lifetime PTSD severity (Rutering et al. 2016).

It is possible that trauma and pain in early life leads to learning and adaptation to a harsher world that requires more vigilance instead of a conservative homeostasis, a molecular push toward fear conditioning instead of socioemotional development, and a greater sensitivity to pain in order to more quickly identify threats. Those who develop in positive, enriched environments, on the other hand, thrive with reduced allosteric load and have resilience that seems especially prominent in stress coping and synaptic plasticity. Instead of being able to learn more and put their energy toward other endeavors, these adaptations in a world of agonizing uncertainty could be primed or activated by epigenetic modifications for the sole purpose of survival. A plausible model of chronic life stressors proposes a similar line of reasoning and theorizes with significant evidence that epigenetic modifications set into motion by the cascade of stress hormones both affect and prime a traumatized individual for accelerated aging and biological weathering (Gassen et al. 2017). Supporting this hypothesis, a high number of sites used in mC epigenetic clocks are located within glucocorticoid response elements (Zannas et al. 2015a).

However, though it may not undo the harmful developmental environment, social support, especially touch, has been associated with stress buffering in many studies (Coan et al. 2006; Cohen and Wills 1985; Matthews and Gallo 2011; Ozbay et al. 2007, 2008). This is most likely through the dual mechanisms of affect regulation through a social buffer so as to not trigger the stress hormone cascade, and through the mu-opiates that are released in social reward reducing affective motivational pain in the nociceptive pathways and the intensity of perceived threats (LaGraize et al. 2006; Troisi et al. 2011). This may be why we see rescue effects of social, enriched environments for memory deficits as discussed above. This may also contribute to

the difficulty in reproducing many social epigenetic findings, as adverse effects are often accounted for, but buffering and resiliency effects are not.

5 Societal Environments

5.1 Minority Status and Socioeconomic Status

Chronic stress has clear physiological, psychological, neurological, and epigenetic effects. However, not all chronic stress stems from abuse or trauma. In fact, not all chronic stress stems from interpersonal relationships at all. As a social species, we have developed a society with biases, prejudices, and hierarchies. Our modern social environments remain embedded by historical power relationships. Though there is much work being done to correct these injustices, racial, ethnic, gender, sexuality, or religious minorities, as well as those with a low socioeconomic status (SES) and social position, face considerably more stress from societal pressures and inequities than their counterparts. This stress may then exacerbate these inequalities through cellular means, as well as societal.

A minority group that is illustrative of how social structures can affect epigenetics and, ultimately, associate with extreme behavioral phenotypes are people living with schizophrenia. Schizophrenia is a mental illness often characterized by flat affect, hallucinations, and psychosis for which the polygenetic burden is significantly associated with epigenetic variation, suggesting that regulatory variation of the disorder stems from both the genome and environment (Cromby et al. 2019). Schizophrenia is the most thoroughly studied psychiatric disorder from an epigenetic perspective, mostly likely due to the clear environmental effects in its presence, onset, and trajectory. Specifically, there is evidence associating schizophrenia presence and onset with low SES, ethnic differences and racial discrimination, immigration, urban living, childhood adversity and trauma, and parental absence (Cromby et al. 2019). Though there is an underlying genetic component to the disorder clear from family clustering, this risk is compounded by exposure to these social environmental factors, such as minority status (Hutchinson et al. 1997). There is significant evidence that minority status, or seeming apart from society in any way, increases the likelihood of developing schizophrenia most likely due to the chronic societally based stress of social position (Bourque et al. 2011; Cromby et al. 2019; Selten 2005; Van Os et al. 2010). For example, Black Caribbean immigrants to the UK who grew up in the Caribbean do not express any increased risk of psychosis; however, their children, born and raised as Black Caribbean immigrants in the UK, had a seven times higher risk of psychosis (Hutchinson et al. 1997). This was familial risk within an ethnically homogenous sample, pointing toward a significant association with the chronic stressors of immigrant and racial minority status being significant drivers of schizophrenia risk. Even more physical variables, such as urban neighborhood residence,

that have been found to increase psychosis risk, appear to be more driven by social fragmentation than physical environment (Zammit et al. 2010).

Often compounding the chronic stress associated with minority status is the stress associated with class and SES. Most likely due to many social, physical, and biological factors encompassed in SES, there is a plethora of associations between SES and epigenetic changes. As SES is societally constructed, it is difficult to create an ecologically valid animal model with which to investigate epigenetic modifications; therefore, the majority of epigenetic research is focused on mC associations in humans. Low SES, especially during youth, has a significant and robust association with age acceleration and sites connected to immune function, development, and age-related diseases (Austin et al. 2018; Bush et al. 2018; Chen et al. 2011; Fiorito et al. 2017; Lam et al. 2012; McCrory et al. 2019; Mcdade et al. 2019; Simons et al. 2016; Tehranifar et al. 2013). Even with low-SES youth, greater self-control associates with improved socioemotional functioning and general success, but also epigenetic age acceleration, supporting the idea that increased allosteric load may contribute to worse health outcomes among the disadvantaged (Miller et al. 2015).

Another aspect of the relationship between SES and epigenetic modifications is that lower SES correlates with both smoking and drinking behavior (Sweeting and Hunt 2015; Van Oers et al. 1999). Not surprisingly, social stress also triggers the urge to smoke and drink (Fouquereau et al. 2003; Niaura et al. 2002). There is evidence that drinking increases emotional experiences and smoking temporarily reduces arousal as evidenced by reduced neurological event-related potentials, supporting a self-medication hypothesis of legal drug use (Choi et al. 2015; Sayette 2017). This relationship of SES with smoking and drinking, possibly as a way to deal with stress, may exacerbate epigenetic disparities due to the strong, reproducible effects of smoking and drinking on mC, especially on sites related to age, immune, and cardiovascular function (Brückmann et al. 2017; Goldowitz et al. 2014; Hillemacher et al. 2008; Mahnke et al. 2017; McCartney et al. 2018; Ponomarev et al. 2017; Tulisiak et al. 2017).

In addition to smoking and drinking, it is important in every mC investigation to account for cell type proportions, as these are the primary drivers of variation, but this is especially true in explorations of SES due to the significant immune system effects of the chronic stress system. For example, one study found that leukocyte composition of peripheral blood covaried with patterns of mC at many sites and mC was strongly associated with the monocyte inflammatory response (Lam et al. 2012). Monocytes also epigenetically aged faster in those exposed to low SES in early life (Austin et al. 2018). These immune responses, most likely from stress, may contribute, at least in part, to the association of SES, especially early life SES, with epigenetic age acceleration and aging-related disease risk, even controlling for related factors such as smoking and drinking (Austin et al. 2018; Simons et al. 2016). When Simons et al. (2016) investigated the main environmental driver of epigenetic age acceleration in a low SES sample, they found that it was the stress of financial insecurity that drove the SES and accelerated aging association, providing further evidence for the link between early life stress, immune response, epigenetic change, and health outcomes (reviewed in Miller et al. 2011). However, similar to other early exposures to

stress, the effects of low SES on immune response can be buffered through social support in the form of warm, positive caregiving (Chen et al. 2011).

5.2 *Social Effects on Physical Environment*

Though it may not be interpersonal or even seem entirely social, there is a social environment in the construction of our societies in the types of nutrients we can access, the configuration of neighborhoods in which we live, the services to which we have access, and the physical environments to which we are exposed. Both physical and social environments can affect our epigenetic modifications (Mcdade et al. 2017). The social administration of our physical environments is yet another form of social environmental influence to which we are able to learn and adapt psychologically and biologically, whether it is conscious or unconscious.

One major aspect in the construction of socially administered environments is the spatial sorting of people based on their SES, race, or ethnicity. As discussed above, there is evidence chronic stress that accompanies being in a reduced societal position, whether through racism or classism, as well as the stress of deprivation, associates with epigenetic change. However, in addition to this divide, health differences among neighborhoods persist even after adjusting for SES and demographic factors, most likely due to the impact of broad environmental factors such as access to nutrition or exposure to pollution (Mair et al. 2008; Paczkowski and Galea 2010; Pickett and Pearl 2001; Roux and Mair 2010). Factors linked to differences in physical environment most likely contribute to and reinforce the detrimental effects of chronic societal stress on low SES and minority communities (Bleich et al. 2012; LaVeist et al. 2011). Unsurprisingly then, physical environment and location are also tied to risk of schizophrenia (March et al. 2008).

One example of how physical environments may perpetuate the biological differences among classes and races are food deserts. These are areas, either particularly urban or rural, where fresh produce and other healthy foods are either not available or too expensive to be purchased as an everyday source of caloric intake. Low SES neighborhoods are especially likely to be located in a food desert (Ghosh-Dastidar et al. 2014). Food availability and food advertising, which is different for lower SES neighborhoods, influence energy intake and the nutritional value of foods consumed (Grier and Kumanyika 2008; Harris et al. 2009). The wealth of literature on the epigenetics of nutrition, especially prenatal nutrition, pales only in comparison to epigenetic work in cancer (Anderson et al. 2012). The importance of a balanced, healthy diet from conception and throughout life on epigenetic modifications is an incredibly robust finding, as are similar results for morbidity and mortality (e.g., Anderson et al. 2012; Gabbianelli and Damiani 2018; Lillycrop and Burdge 2012; Mathers 2006; Milagro et al. 2013; Navarro et al. 2017; Zhang 2015). Along similar lines, the structure of a socially administrated physical environment can also be linked to differences in children's physical activity (Bringolf-Isler et al. 2010; Davison and Lawson 2006; Galvez et al. 2010; Sallis and Glanz 2006). Physical activity is often

linked to morbidity and mortality, as well as epigenetic modifications, learning, and aging (e.g., Kaliman et al. 2011; Kashimoto et al. 2016; Kirchner et al. 2013; Ling and Rönn 2014; Mikkelsen et al. 2017; Moylan et al. 2013; Rodrigues et al. 2015; Zimmer et al. 2016). Another example is physical proximity to hazardous sites and pollution, which tend to be more prevalent in low-income or minority neighborhoods (Brulle and Pellow 2006; Mohai et al. 2009; Morello-Frosch et al. 2011). The effects of exposure to air pollution are well evidenced in both morbidity and epigenetics research (e.g., Barouki et al. 2018; Brook et al. 2010; Chen et al. 2016; Clifford et al. 2017; Gref et al. 2017; Laumbach and Kipen 2012; Luyten et al. 2018; Mustafíc et al. 2012; Rider et al. 2016; Somineni et al. 2016; Tzivian 2011). This is most likely due to the immune responses to breathing in toxic exogenous factors (Tzivian 2011).

Additionally, neighborhood conditions can create stress, such as feeling unsafe, as well as acting as social buffers against adverse effects of stress such as social cohesion or integration into the neighborhood or environments such as work or school (Cutrona et al. 2006; De Silva et al. 2005; Do et al. 2011; Mair et al. 2008; Merkin et al. 2009). One possibility of why some immigrant groups have better morbidity and mortality than other groups in the same city is the social support and cohesion within the community (Matthews et al. 2010). As discussed above, the stress response affects many systems and may lead to widespread epigenetic modifications, especially during early development. Once again, even the midst of possible adaptation to a harmful environment, a positive, enriched social environment shows ecological rescue effects for health. Our epigenetic mechanisms modify, our neurological mechanisms encode, and our psychological mechanisms learn from our social environments.

6 Conclusion

From the moment we are born, our social relationships are a key component of how the world affects us. They are one of the first postnatal inputs afforded to the rapidly developing neonatal biology and are essential for survival. While data on epigenetics and the social environment have been spread out across disciplines, one can imagine potential examples for stringing these findings together cohesively. One example of this cell-to-society effect could be a child born in a family with insensitive caregivers who consistently do not respond to the child's needs or give contact comfort. This, in turn, could lead to the hypermethylation of the promoter region for the *BDNF* gene, less *BDNF* transcription, and less BDNF present in the hippocampus and socioemotional circuit of the brain. This would then decrease the ability of the child to learn from their social environment and affect their ability to have successful interpersonal relationships. This lack of social efficacy could then make it more likely the individual would experience social pain and more difficult to receive social support to buffer stressful experiences throughout their lives. Without social buffering, the stress response could be triggered more often, resulting in reduced immune responses and homeostatic compensation through epigenetic modifications.

Over time, these cumulative biological and behavioral responses could increase allosteric load and possibly lead to accelerated aging and health decline, which may also affect access to services, financial earning ability, and physical environment to further exacerbate biological and sociological disparities seen at a population level.

These social environments are an opportunity for adaptation through experience seen pandiscipline through concepts such as mental representations, LTP and memory engrams, and epigenetic change such as histone lysine trimethylation affecting the promoters of synaptic plasticity-related genes. Fundamentally, all psychological, neurobiological, and epigenetic reactions to these social environments are opportunities to learn from and adapt to them in order to best thrive in the world as it is, whether that environmental situation be ideal, violent, or deprived. The experience-dependent plasticity gained from the interaction between neuroscience and epigenetics is integral to this adaptation (Clayton et al. 2019). These systems may be working as a new state of vigilance. Although the context of the social environment is paramount in the specific reaction and modification, the ultimate goal and underlying mechanistic interplay remain largely the same – to learn from our social world to better survive in the environment we find ourselves in.

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