A review of epigenetics in human consciousness
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Abstract: The field of epigenetics, which is the study of factors regulating gene transcription, is expanding rapidly. Yet one area that has received little attention is the influence of epigenetic factors on human consciousness. We examine this topic by investigating how transcriptional regulation modulates the development and ongoing functioning of the human brain, mediates interactions between the environment and the genome, and may contribute to the evolution of consciousness. Epigenetics is demonstrated to play an instrumental role in human consciousness throughout the lifespan and over the course of multiple generations. Further research is recommended to broaden and deepen our understanding of the relationship between epigenetics and human consciousness.

Subjects: Neuroscience; Neurology; Psychiatry
Keywords: cellular memory; brain; chromatin; DNA; DNA methylation; histone modification; neuroepigenetics; non-coding RNAs; transgenerational epigenetic inheritance

1. Introduction
The study of consciousness has challenged philosophers, psychiatrists and other scientists for years. As Chalmers (2010) stated, “Consciousness poses the most baffling problems in the science of the mind” (p. 3). We have chosen to study epigenetics in order to better understand the interconnectedness of the human brain, the environment, and consciousness.
1.1. Epigenetics
The British biologist Conrad Waddington (1939) proposed the term epigenetics nearly a century ago to describe the molecular events involved in early embryonic development. Subsequently, geneticists and developmental biologists used this term to describe all developmental events that begin with the fertilized zygote and end with the mature organism (Felsenfeld, 2014). Processes that were not easily interpreted in genetic terms but had a heritable component were lumped into the category of epigenetics, without suggesting a mechanism to explain such phenomena (Holliday, 2006).

With Fleming’s discovery of the existence of chromosomes in 1879, evidence began accruing that suggested developmental programs reside within the chromosomes (Felsenfeld, 2014). However, a clear explanation for how somatic cells could follow different developmental pathways remained a mystery. A signal that could influence the expression of genes without changing the genetic code was suggested by the discovery of the inactivation of the X-chromosome in somatic cells (Ohno, Kaplan, & Kinosita, 1959). Subsequently, both Riggs (1975) and Holliday and Pugh (1975) proposed DNA methylation could act as an epigenetic mark, catalyzing an explosion of research into processes that influence transcription of the genome without altering the DNA sequence. With time, it was realized that epigenetic changes provide a mechanism for transmitting information not encoded in the DNA. Such information includes a historical record of interactions between the environment and the genome, which is stored as a form of cellular memory. Studies have shows this epigenetic memory can be passed down to subsequent generations of cells and, in some cases, to an individual’s progeny. This has been demonstrated both in C. elegans (Greer et al., 2014) and humans (Anselmo, Scherberg, Dumitrescu, & Refetoff, 2019), although additional studies are needed to confirm these findings.

Epigenetic memories serve as a historical record of gene-environment interactions for the individual and their progeny, much as the genome serves as a historical record of species-wide adaptations to the environment. Also, epigenetic changes facilitate rapid adaptations to environmental changes across generations, thus facilitating evolution (Bonduriansky & Day, 2018).

The expanded awareness of the multifaceted roles of epigenetic changes created an evolving definition for the term epigenetics. After reviewing many alternatives, we settled on the following definition: “The study of changes in gene expression that do not result from alterations in DNA sequence.”

Research carried out during the last few years demonstrates epigenetic mechanisms are involved in cellular functioning throughout the lifespan, thereby influencing the development, maintenance, and senescent decline of the brain. Within the field of epigenetics, a sub-discipline termed neuroepigenetics has emerged that describes epigenetic changes regulating the nervous system (Day & Sweatt, 2010; Sweatt, 2013).

While research into factors regulating gene transcription has expanded exponentially in recent years, little has been written about the involvement of epigenetics in consciousness. Therefore, we set out to explore this relationship.

1.2. Consciousness
The English word conscious is derived from the Latin conscio (con—“together” and scio—“to know”) meaning “knowing with” or “I know” (Lewis, 1990, p. 181). The definition of the word consciousness has evolved over the centuries and today has multiple meanings. We selected the following definition for our review:

the function of the human mind that receives and processes information, crystallizes it and then stores it or rejects it with the help of the following: the five senses, the reasoning ability of the mind, imagination and emotion, and memory (Vithoulkas & Muresanu, 2014, p. 104).
Based upon this definition, we chose to investigate the relationship between epigenetics and the following four components of consciousness:

(1) perception
(2) cognition
(3) emotions
(4) memory

2. Materials and methods
We conducted a PubMed literature search (1998–2018) looking for English language articles containing the search term “epigenetics” and any of the following terms: “consciousness,” “awareness,” “perception,” “cognition,” “emotions,” and “memory.” Retrieved articles were screened and a subset of relevant abstracts was then selected for a more detailed evaluation. The biographies of these articles were searched for additional references. The final studies selected for inclusion in this review consisted of those resources that directly evaluated the relationship between epigenetics and consciousness.

3. Results

3.1. An overview of epigenetics
The human body consists of approximately 30 trillion cells (Bianconi et al., 2013) of which 80–90 billion are neurons in the brain (Azevedo et al., 2009; von Bartheld, Bahney, & Herculano-Houzel, 2016). Almost all the body’s cells possess a nucleus with 23 pairs of chromosomes containing 3 billion nucleotides of DNA in a double helix structure. Exceptions are egg and sperm cells, which contain only a single copy of each chromosome, and cells without a nucleus, such as mature red blood cells and cornified cells in the skin, hair, and nails. If stretched out to its full length, the DNA in a single cell would extend about 2 meters (Nestler, Pena, Kundakovic, Mitchell, & Akbarian, 2016).

A sequence of DNA base pairs that code for a molecule is called a gene, and every human has about 25,000 genes (Borelli, Nestler, Allis, & Sassone-Corsi, 2008). Information encoded in the entire sequence of base pairs is known as the genetic code (Bonduriansky & Day, 2018) and the entire DNA, with all its genes, is known as the genome (National Library of Medicine, 2018).

The DNA sequence of base pairs that make up a gene is copied or transcribed into a strand of RNA, which is then translated into a protein (see Table 1 for definitions of italicized words). This entire operation is known as gene expression and processes that alter gene expression without modifying the DNA sequence are referred to as epigenetic processes (Nikolova & Hariri, 2015).

Chromosomes consist of a complex of DNA, RNA, histone proteins, and non-histone proteins that together are known as chromatin. Chromatin is formed by segments of DNA measuring ~147 base pairs wrapped around an octamer of histone proteins. This complex of DNA and histones is called a nucleosome. Short strands of amino acid linkers and accompanying DNA of about 50 base pairs, connect the nucleosomes, producing the appearance of beads on a string. Each of the eight histones that make up a nucleosome has a short tail of about 40 amino acids (see Figure 1) (Hudson, 2011).

Two forms of chromatin exist: (1) heterochromatin—a tightly compacted form which is genetically inactive and (2) euchromatin—a more loosely compacted form which is genetically active because it is accessible to DNA transcription factors (Tamaru, 2010).

Epigenetic changes are regulated by sets of enzymes known as writers and erasers that add or remove specific epigenetic marks, and by readers that bind to these modifications and alter the expression of the associated genes (Yao et al., 2016). These changes produce an epigenetic code...
### Table 1. Glossary

| Term                                      | Definition                                                                 |
|-------------------------------------------|---------------------------------------------------------------------------|
| Arealization                              | The partitioning of neocortical functions among regions of the cerebral cortex |
| Brain-derived neurotrophic factor (BDNF) | A protein that encourages the growth, differentiation, survival, and arborisation of neurons, while also regulating synaptic plasticity |
| Chromatin                                 | A complex of DNA, RNA, histones and non-histone proteins that condenses to form chromosomes during cell division |
| Consciousness                             | The function of the human mind that receives information via the senses, then stores this information, processes it with the rational mind, feels emotions, and remembers/learns |
| Epigenetic drift                          | Increased epigenetic variation that occurs with ageing                    |
| Epigenetic memory                         | A collection of changes to a cell’s DNA that do not alter the DNA sequence and are inherited from the cell from which it descends |
| Epigenetics                               | The study of changes in gene expression that do not result from changes in the underlying DNA sequence |
| Epigenome                                 | The sum total of all the epigenetic modifications in an individual’s genome at any given point in time |
| Euchromatin                               | A loosely compacted form of chromatin that is genetically active because it is accessible to DNA transcription factors |
| Experience-dependent plasticity          | The process of creating and organizing neuron connections that occurs as a result of a person’s experiences |
| Genetic code                              | Information encoded in the entire sequence of DNA base pairs in chromosomes |
| Genome                                    | An organism’s complete set of DNA, including all of its genes |
| Heterochromatin                           | A tightly compacted form of chromatin which is genetically inactive        |
| Histone                                   | A water-soluble alkaline protein in the nucleus, and from where the DNA tightly coils around to form the nucleosome |
| Histone code                              | The sum of all histone modifications in an individual’s genome             |
| Histone deacetylases (HDACs)              | A class of enzymes that remove an acetyl group from lysine amino acids on histone proteins, which allows the DNA to be wrapped more tightly |
| Histone tail                              | The N-terminal polypeptide extension of the histone protein, consisting of about 40 amino acids |
| Memory                                    | The capacity to bring elements of an experience from one moment in time to another |
| Methylome                                 | The sum of all DNA methylation changes in an individual’s genome           |
| Neuroepigenetics                           | The study of epigenetic changes regulating the nervous system              |
| Neurogenesis                               | The process through which neural stem cells or neural progenitor cells generate new neurons |
| Neuroplasticity                           | The ability of a neural network to change over time                         |
| Non-coding RNAs (ncRNAs)                  | RNA that does not encode a protein                                         |
| Nucleosome                                | A bead-like chromosomal structure within chromatin consisting of eight histone proteins (octamer) wrapped by a segment of DNA about 147 base pairs in length |

(Continued)
that determines whether a specific gene is transcribed (Day & Sweatt, 2011). The sum total of all epigenetic modifications at any given point in time is referred to as the epigenome (National Human Genome Research Institute, 2016).

Epigenetic processes modulate interactions between individuals and the environment and a wide range of environmental factors can trigger epigenetic modifications. These include toxins (Martin & Fry, 2018; Waring, Harris, & Mitchell, 2016), alcohol (Pandey, Kyzar, & Zhang, 2017), addictive drugs (Godino, Jayanthia, & Cadet, 2015), diet (Sapienza & Issa, 2016), physical exercise (Liu et al., 2017; Sanchis-Gomar et al., 2012), in utero exposure to maternal nutritional factors (Haggarty, 2013; Lee, 2015), and stress/trauma (Yehuda & Bierer, 2008). These factors produce lasting epigenetic changes that influence neuronal development, neuroplasticity, cognition, and behavior (Butler, Webb, & Lubin, 2016; McEwen, Eiland, Hunter, & Miller, 2012). Furthermore, through their influence on the genome, epigenetic changes create a bidirectional crosstalk between the genome and the environment, with the environment influencing genetic transcription and changes in genetic regulation influencing the behavior of the individual toward the environment (Haggarty, 2015).

Epigenetic marks can persist for decades (Haggarty, 2013). For example, individuals who were prenatally exposed to famine during the Dutch Hunger Winter in 1944–1945 exhibited epigenetic changes 6 decades later when compared with their unexposed same-sex siblings (Heijmans et al., 2008).

Epigenetic changes may be transmitted across generations, a process termed transgenerational epigenetic inheritance (Babenko, Kovalchuk, & Metz, 2015). Transgenerational epigenetic inheritance involves the transmission of non-genetic information from parent to offspring via germ cells. Such information has been demonstrated to persist for at least 14 generations (Klosin, Casas, Hidalgo-Carcedo, Vavouri, & Lehner, 2017).

Controversy surrounds the field of transgenerational epigenetic inheritance due to a variety of unresolved issues. These include the use of imprecise definitions, questions about translating findings from animal studies to humans, failure to distinguish between gamete-related epigenetic transmission and epigenetic changes resulting from intrauterine exposure, and questions about how epigenetic programming can escape reprogramming events (e.g. see Nagy & Turecki, 2015; van Otterdijk &Michels, 2016). In mammals, epigenetic reprogramming occurs in germ cells and preimplantation embryos and involves the widespread removal of existing epigenetic information and the establishment of a new epigenetic program that is compatible with totipotency (Hajkova et al., 2002; Prokopuk, Western, & Stringer, 2015). Criticisms of transgenerational epigenetic

| Term | Definition |
|------|------------|
| One-neuron-one-receptor rule | A rule which states that in mammals, each olfactory sensory neuron expresses one, and only one, olfactory receptor. |
| Pluripotency | The ability of a stem cell to give rise to different cell types |
| Synaptic plasticity | Any sustained increase or decrease in synaptic strength |
| Transcription | The creation of a strand of RNA from a segment of DNA |
| Transgenerational epigenetic inheritance | Inheritance of epigenetic information between generations in the absence of continued direct environmental influences |
| Transgenerational memory | The transmission of memories from one generation to subsequent generations |
| Translation | The formation of a protein from mRNA |
inheritance have been met with rebuttals that point out not all epigenetic marks are erased during reprogramming and mechanisms other than DNA methylation and post-translational histone modifications, such as the transmission of acquired traits via ncRNAs, may play a role in the transgenerational transfer of information (Prokopuk, Western, & Stringer, 2015; van Otterdijk & Michels, 2016).

3.2. Epigenetic mechanisms
Epigenetic changes may involve any number of chemical, structural, and positional changes to chromatin that turn genes on or off. Four of the most commonly studied changes are discussed next (see Table 2).
3.2.1. DNA methylation

The covalent bonding of methyl groups to DNA, known as DNA methylation, is a major regulator of gene expression (Bonduriansky & Day, 2018; McGowan & Roth, 2015). DNA methylation involves the transfer of a methyl group from a donor S-adenosylmethionine to the fifth position carbon in the cytosine carbon ring, usually in the context of a CG dinucleotide (i.e. CpG site). This transfer occurs with the aid of enzymes known as DNA methyltransferases (DNMTs). There are three known DNA methyltransferases (DNMT1, DNMT3a, and DNMT3b), all of which are expressed in the brain (Gallegos, Chan, Chen, & West, 2018). Methylation of a gene typically results in that gene being rendered inaccessible for transcription, and therefore the gene is turned off or silenced. The sum of all DNA methylation changes constitutes a DNA methylation code known as the methylome (Feinberg, 2001).

3.2.2. Histone modifications

Another major epigenetic mechanism involves modification of histone proteins. Each histone protein consists of a central globular domain and an N-terminal tail that contains multiple sites for potential modifications. These modifications are catalyzed by specific sets of enzymes. For example, histone acetyltransferases (HATs) transfer an acetyl group to lysine residues in the histone tails whereas histone deacetylases (HDACs) remove the acetyl group (Athanasopoulos, Karagiannis, & Tsolaki, 2016). A variety of modifications of the amino acid residues in the tails of histone proteins can occur including acetylation, methylation, citrullination, ubiquitylation, phosphorylation, sumoylation, biotinylation, as well as others (Boland, Nazor, & Loring, 2014). The covalent binding of acetyl groups to lysine residues removes the positive charge on the histone tails, thereby decreasing the interaction of the N-terminal with the negatively charged phosphate groups of DNA. As a result, acetylated chromatin is less condensed, which facilitates transcription by making the DNA more accessible to transcription factors. In contrast, histone methylation can both activate and repress transcription, depending on the residue being modified and the degree of modification (i.e. mono-, di-, or tri-methylation) (Athanasopoulos et al., 2016; Kleefstra, Schenck, Kramer, & van Bokhoven, 2014).

Environmental factors can alter the methylation of histone proteins for multiple generations. For example, changes in temperature produce alterations in chromatin structure that can be transmitted through both eggs and sperm for at least fourteen generations (Klosin et al., 2017). The sum of all histone modifications are referred to as the histone code (Day & Sweatt, 2011).

### Table 2. Epigenetic mechanisms

| **DNA methylation** | A process by which methyl groups are added to the DNA molecule. When located in the promoter region of a gene, DNA methylation tends to repress gene transcription. |
|---------------------|----------------------------------------------------------------------------------------------------------------------------------|
| **Histone modifications** | Covalent, post-translational modifications (PTMs) of the amino acid residues in the tails of histone proteins. PTMs of histones can influence gene expression by altering chromatin structure or recruiting histone modifiers. |
| **Noncoding RNAs (ncNRAs)** | A functional RNA molecule that is transcribed from DNA but is not translated into a protein. ncRNAs function to regulate gene expression. Examples of ncRNAs include miRNA, siRNA, piRNA and lncRNA. |
| **Localization near the nuclear envelope** | The location of DNA within the nucleus influences gene expression. For example, localization of chromatin next to the nuclear lamina that lines the inside of the nuclear envelope is generally associated with gene repression, whereas relocation away from the lamina is associated with gene activation. |
3.2.3. Non-coding RNAs
Less than 2% of the human genome codes for proteins (Elgar & Vavouri, 2008). The remaining 98%, which for decades was considered “junk” DNA, is transcribed into non-coding RNAs (ncRNAs), which perform a variety of functions (Gaudi, Guffanti, Fallon, & Macciardi, 2016). ncRNAs are subdivided into long non-coding RNAs (lncRNA) (>200 nucleotides in length) and small non-coding RNA (snRNA) (<200 nucleotides in length). One type of snRNA, known as micro-RNAs (miRNAs) interferes with translation by binding to mRNAs, thus preventing them from being converted into peptides (Bonduriansky & Day, 2018). Although microRNAs generally repress translation, some microRNAs positively regulate gene expression by enhancing mRNA translation and inducing gene expression via binding to the promoter of the target gene (Butler et al., 2016).

3.2.4. Localization near the nuclear envelope
The location of chromatin within the nucleus affects gene transcription (Zuleger, Robson, & Schirmer, 2011). For example, localization of chromatin next to the nuclear lamina that lines the inside of the nuclear envelope is generally associated with gene repression, whereas relocation away from the lamina is associated with gene activation (Gallegos et al., 2018; Medrano-Fernandez & Barco, 2016).

3.3. Epigenetic effects on the nervous system
Epigenetic mechanisms play a critical role in the development, functioning, and senescent decline of the human nervous system. These influences include epigenetic modulation of cellular differentiation, neurogenesis, neuroplasticity, regulation of CNS functions, and neural degeneration. In addition to influencing the healthy functioning of the CNS, epigenetic mechanisms also contribute to disorders of the CNS including neurodevelopmental disorders, mental illnesses, and neurodegenerative disorders.

3.3.1. Cellular differentiation
Epigenetic processes play a critical role in the development of the CNS. For example, the process of cellular differentiation, during which cells transition from less specialized to more specialized cells, is regulated by epigenetic mechanisms (MacDonald & Roskams, 2009), as is the establishment and maintenance of cellular identity (Suelves, Carrio, Nunez-Alvarez, & Peinado, 2016).

Embryonic stem cells (ESCs) give rise to a number of different cell types, a characteristic known as pluripotency. The transition from pluripotent stem cells to committed and more developmentally restricted cell types is accompanied by a variety of epigenetic changes including DNA methylation and histone modifications. These changes trigger the silencing of pluripotency genes and activation of lineage-specific genes (Boland et al., 2014; Kraushaar & Zhao, 2013; MacDonald & Roskams, 2009; Suelves et al., 2016).

Genomic imprinting is also regulated by epigenetic factors. Genomic imprinting is an epigenetic phenomenon that causes genes to be expressed in a parent-of-origin allele-specific manner. Loss of imprinting results in biallelic gene silencing or expression, that has been implicated in a number of neurodevelopmental disorders, such as Angelman and Prader-Willi syndromes (Millan, 2013).

3.3.2. Neurogenesis
In the embryonic brain, pluripotent embryonic stem cells (ESCs) differentiate into neural stem cells (NSCs), which produce neural progenitor cells (NPCs), that proliferate and give rise to three different cell types: neurons, astrocytes, and oligodendrocytes (Broccoli, Colasante, Sessa, & Rubio, 2015). This process of differentiation is regulated by a variety of epigenetic mechanisms (Akers et al., 2018; Juliandi, Abematsu, & Nakashima, 2010).

Neurogenesis, which involves the activation of NSCs, followed by the production of NPCs that differentiate into neurons (Gage, 2000; Ma et al., 2010; Murao, Noguchi, & Nakashima, 2016), is supported by multiple epigenetic changes (Yao et al., 2016). Neurogenesis occurs in the embryonic,
postnatal, and adult brain (Murao et al., 2016). In the adult human brain, neurogenesis occurs in two regions (Eriksson et al., 1998), the subgranular zone (SGZ) of the hippocampal dentate gyrus (DG) and the subventricular zone (SVZ). These areas retain the ability to produce new neurons throughout the lifespan (Hsieh & Eisch, 2010; Sun, Sun, Ming, & Song, 2011). NSCs in these areas undergo self-renewal to maintain a supply of mature neurons (Hsieh & Eisch, 2010).

The production of new neurons in these regions is under the regulation of brain-derived neurotrophic factor (BDNF) (Hudson, 2011; Scharfman et al., 2005), a member of the neurotrophin family of growth factors that encourages the growth, differentiation, survival, and arborisation of neurons, while also regulating synaptic plasticity (Deinhardt & Chao, 2014; Karpova, 2014; Leal, Comprido, & Duarte, 2014).

Psychosocial stress negatively impacts neurogenesis and the structure of neurons in stress-sensitive areas of the brain such as the hippocampus, amygdala, and prefrontal cortex (Hunter & McEwen, 2013; Numakawa, Odaka, & Adachi, 2017). For example, chronic stress causes dendrites to become shorter and less branched (Hunter & McEwen, 2013).

One epigenetic mechanism affecting neurogenesis involves adjustment of the levels of glucocorticoids (GCs) and BDNF. Blood levels of GCs, which are regulated by the hypothalamus-pituitary-adrenal (HPA) axis, are increased during chronic stress. Increased levels of GCs downregulate the production of BDNF via epigenetic mechanisms, resulting in impaired neurogenesis (Numakawa et al., 2017).

3.3.3. Neuroplasticity

Neuroplasticity refers to the ability of the brain to change over time. Different types of neuroplasticity exist (e.g. structural and functional) and multiple brain regions are involved (e.g. hippocampus, prefrontal cortex, amygdala) (McEwen et al., 2012). Synaptic plasticity refers to any sustained increase or decrease in synaptic strength (Cortes-Mendoza, de Leon-Guerrero, Pedraza-Alva, & Perez-Martinez, 2013).

Each neuron in the human cortex is estimated to have an average of 38,000 synapses and these synapses allow neurons to pass chemical or electrical messages to other neurons (Cragg, 1975). Synapses are constantly being removed or recreated, in large part due to the activity of the neurons that bear them. The activity-dependence of synaptic plasticity means that synapses from neurons that frequently fire an impulse are conserved whereas inactive synapses are removed.

Epigenetic mechanisms contribute to the generation and maintenance of synaptic plasticity via regulation of gene expression (Cortes-Mendoza et al., 2013; Gallegos et al., 2018). For example, DNA methylation influences transcription of the gene that codes for reelin (Reln), a protein that modulates synaptic function (Hudson, 2011) and activity-regulated cytoskeletal (ARC), a protein regulating synaptic plasticity (Epstein & Finkbeiner, 2018).

3.4. The influence of epigenetics on CNS functioning

3.4.1. Perception

Perception (from the Latin perceptio) is the organization, identification, and interpretation of sensory information in order to represent and understand the presented information or the environment (Schacter, Gilbert, & Wegner, 2011). Although research on the influence of epigenetic mechanisms on perception is still in the early stages, we will review what is known about the relationship between epigenetics and perception.

The ability or capacity to perceive begins with the creation of sensory pathways in the CNS and epigenetic regulation is critical to the development of these sensory pathways. During critical periods in development, genes interact with epigenetic factors to create a network of neurons that receive and interpret information from the environment (Huffman, 2012; Sng & Meaney, 2009). As
part of this developmental process, the neocortex, which is generally considered the critical organ of thought and consciousness and which constitutes more than 80% of the total brain volume (Kaas, 2011), is organized into functionally unique subdivisions through a process termed arealization (Alfano & Studer, 2013). Arealization is critical because this partitioning of the neocortex forms the basis for sensory perception (O'Leary & Sahara, 2008).

One component of arealization is patterning of the neocortex during early development. This occurs through a process known as experience-dependent plasticity in which groups of neurons are modified by experience such that neurons that are active together increase their connections, whereas neurons that are not active together weaken their connections (Kolb, Harker, & Gibb, 2017). This patterning is regulated by the differential expression of genes during arealization (Huffman, 2012).

The neocortex has four primary areas and three of these are sensory. The sensory areas are: (1) primary visual cortex, (2) somatosensory cortex, and (3) auditory cortex. The fourth primary area is the motor cortex, which controls voluntary movements. Each primary sensory cortical area receives input from a specific principal dorsal thalamic nucleus and each of these nuclei receive modality specific sensory information from peripheral sense organs or receptors (O'Leary & Sahara, 2008).

3.4.1.1. Olfactory system. Epigenetic factors are involved in the promotion of sensory neuron identities (Hsieh, Alqadah, & Chuang, 2017) and the expression of sensory neuron receptors. For example, in the olfactory system, the ability to detect odors results from a single olfactory sensory neuron expressing a single odorant receptor gene, which is known as the one-neuron-one-receptor rule (Mombaerts, 2004). However, it has been demonstrated that a single neuron initially expresses multiple olfactory receptors (ORs). Later in development, all but one are eliminated through epigenetic mechanisms that suppress transiently expressed ORs (Tan, Li, & Xie, 2015).

In summary, epigenetic regulation plays a critical role in the expression of olfactory receptors, the identity of olfactory neurons, and the arealization of the neocortex, thus laying the neurological foundation for the olfactory system.

3.4.1.2. Visual system. Epigenetic mechanisms have also been implicated in the normal structural and functional development of the visual system, as well as diseases of the visual system (Putignano et al., 2007; Yan, Yao, Tao, & Jiang, 2013).

Interactions with the environment influence brain connectivity during developmental windows known as “critical periods” (CPs) (Berardi, Pizzorusso, & Maffei, 2000). Classic studies performed by Wiesel and Hubel (1963) demonstrated in kittens that if one eye is deprived of vision (“monocular deprivation” or MD), a significant reduction in the proportion of cortical neurons driven by the deprived eye occurs, a process referred to as “ocular dominance” (OD). Subsequent studies demonstrated that OD plasticity occurs in other mammals as well (Blakemore, Carey, & Vital-Durand, 1978; Gordon & Stryker, 1996; Fagiolini, Pizzorusso, Berardi, Domenici, & Maffei, 1994).

The mechanism of OD plasticity was later found to be epigenetically mediated when it was demonstrated that visual experience activates histone acetylation in the visual cortex during the CP. Lending additional support to the role of epigenetics in the development of the visual system was the finding that treatment with trichostatin, a compound that promotes histone acetylation, enhanced plasticity in the visual cortex (Putignano et al., 2007; Silingardi, Scali, Melloumini, & Pizzorusso, 2010).

Subsequently, it was reported that environmental enrichment (EE) increases histone acetylation in the visual cortex of rats. When exposed to an EE during the CP, increased histone acetylation is associated with an accelerated decline of visual cortical plasticity and a faster closure of the CP. These histone modifications occur at the promoters of the gene encoding for BDNF, resulting in increased gene activity and increased production of BDNF in the visual cortex (Baroncelli et al., 2016).
Visual cortical plasticity is not limited to the CP, but can also occur in adult animals. For example, 2 weeks of EE in adult rats induced an increase in histone acetylation in the visual cortex, reinstating a juvenile-like plasticity in the visual system. The authors suggested optimizing the external environment increases neural plasticity in the whole brain, which could potentially aid in recovery from different neural dysfunctions (Baroncelli et al., 2016).

Chronic treatment with the selective serotonin reuptake inhibitor (SSRI) fluoxetine was found to restore plasticity in the visual system of adult rats (Maya-Vetencourt et al., 2008). This increase in plasticity was associated with decreased γ-aminobutyric acid-mediated (GABAergic) transmission and increased levels of BDNF in the visual cortex. Epigenetic changes associated with this rise in BDNF levels included increased histone acetylation at BDNF promoter regions and decreased expression of HDACs (Maya-Vetencourt, Tiraboschi, Spolidoro, Casteren, & Maffei, 2011).

Infusion of diazepam, which enhances GABAergic function, inhibited the reinstatement of visual cortical plasticity. The authors suggested reduced GABAergic inhibition resulting from chronic fluoxetine administration triggers an increase in BDNF expression, resulting in increased neural plasticity. Also important was the finding that chronic administration of fluoxetine increased levels of BDNF in the hippocampus (Maya-Vetencourt et al., 2008), an area of the brain where reduced neurogenesis is associated with depression (Tanti & Belzung, 2013).

Epigenetic changes also influence the development of eye diseases. For example, DNA methylation of several key genes is associated with pterygium, a benign growth on the cornea (Riau et al., 2011) and abnormal DNA methylation patterns are found in age-related macular degeneration (AMD) (Hunter et al., 2012). DNA methylation, histone modifications, and the production of miRNAs have each been associated with susceptibility to a number of other ocular diseases as well (Yan et al., 2013).

3.4.1.3. Tactile system. The majority of research investigating the interaction between epigenetics and the tactile system involves explorations of the role played by epigenetic mechanisms in the development or experience of pain.

Altered gene expression has been found in chronic pain states and epigenetic modulators have been demonstrated to ameliorate pain. Histone acetylation and HDAC1 overexpression in the spinal cord have been implicated in nociceptive sensitization in an animal model of neuropathic pain (Cherng et al., 2014). Furthermore, both the systemic and intrathecal administration of HDACs produce analgesic effects in models of inflammatory pain (Bai, Wei, Zou, Ren, & Dubner, 2010; Chiechio et al., 2010). In a murine model, chronic neuropathic pain was found to be associated with decreased global methylation in the PFC and amygdala, but not the thalamus or visual cortex. Furthermore, these changes in methylation and hypersensitivity to pain were reversed by behavioral intervention (i.e. enriched environment) (Tajerian et al., 2013). Time- and tissue-specific changes in miRNA expression have also been discovered in neuropathic pain models (Jiang, Wang, Yu, Lu, & Zhang, 2019; Sakai & Suzuki, 2013; Yang, Xu, Zhu, & Liu, 2017).

Epigenetic mechanisms have been demonstrated to play a role in the development of pain hypersensitivity as well. For example, in a pre-clinical study, Chao et al. (2016) reported opioid-induced hypersensitivity (OIH) triggered by repeated injections of morphine is associated with upregulation of BDNF in dorsal root ganglion neurons. This increase is BDNF was associated with increased demethylation of promoter regions of the BDNF gene. Furthermore, injection of anti-BDNF antibodies inhibited the hypersensitivity resulting from repeated injections of morphine. These findings suggest that repeated injections of morphine trigger demethylation of the promoter region of the BDNF gene, resulting in higher levels of BDNF, which contributes to OIH. An interesting finding is that curcumin, an inhibitor of histone acetyltransferase activity, blocked the chronic-morphine induced increase in BDNF and morphine tolerance, suggesting curcumin might reduce tolerance to morphine (Matsushita and Ueta 2009).
3.4.1.4. Auditory system. The mammalian inner ear is composed of two sensory organs: the cochlea, which is responsible for hearing, and the vestibule, which is responsible for balance. The sensory epithelium of the cochlea, called the organ of Corti, contains four rows of hair cells that convert mechanical stimuli to electrical signals (Friedman & Avraham, 2009).

Epigenetic mechanisms have been implicated in the normal development and maintenance of the auditory system (Friedman & Avraham, 2009; Weston, Pierce, Rocha-Sanchez, Beisel, & Soukup, 2006). In particular, miRNAs play a critical role in the development of the inner ear (Li & Fekete, 2010). Hundreds of miRNAs have been discovered in the inner ear (Weston et al., 2006) and each one can affect hundreds of downstream targets (Bartel, 2009). miRNAs regulate gene expression via binding to complementary sites in their target mRNAs (Ambros, 2004; He & Hannon, 2004).

In vertebrates, the miR-183 family (consisting of miR-183, miR-96, and miR-182) (Weston et al., 2006) and miR-210 (Riccardi et al., 2016) are expressed in inner ear cells. These miRNAs influence the development and maintenance of hair cells in the inner ear (Li, Kloosterman & Fekete, 2010; Weston et al., 2011).

Pathologies of the human ear are also influenced by epigenetic mechanisms. Hearing loss, for example, which is common in the human population (Lewis et al., 2009), is generally caused by the abnormal development or degeneration and death of cochlear hair cells (Friedman & Avraham, 2009). One factor contributing to the death of these cells is depletion of miRNAs (Weston et al., 2011). Another cause of hearing loss is mutations of miR-96 or its gene (Lewis et al., 2009; Mencia et al., 2009; Solda et al., 2012).

Abnormalities of miRNAs have been reported in other ear pathologies as well. For example, elevated levels of miR-21 have been reported in cholesteatomas (Friedland, Eernisse, Erbe, Gupta, & Cioffi, 2009) and miRNAs have been found to regulate the otitis media inflammatory response (Song, Kwon, Cho, Park, & Chae, 2011).

In contrast to their role in pathological conditions of the auditory system, miRNAs have also been suggested to possess therapeutic potential as a treatment of hearing loss (Mahmoodian-Sani & Mehri-Ghahfarrokhi, 2017). Since aging and exposure to loud noises are two of the most common causes of hearing loss (Lewis et al., 2009) and neurosensory hearing loss is caused by impairment or loss of hair cells (Zhang et al., 2013), regeneration of hair cells could potentially restore hearing impaired individuals. Birds, fish, amphibians, and reptiles regenerate lost hair cells, but mammals lack this ability (Burns & Corwin, 2013). Investigations into the specific miRNAs that trigger hair cell regeneration, as well as their target genes, are being explored as potential new treatments that may one day produce recovery from hearing loss (Doetzlhofer & Avraham, 2017; Revuelta et al., 2017).

3.4.1.5. Gustatory system. Reports investigating the role of epigenetics in the gustatory system are quite limited. However, two studies are reviewed.

The first study found a statistically significant association between reduced DNA methylation at 12 CpG sites and body mass index (BMI) in humans (Ramos-Lopez et al., 2018). Most of these sites were implicated in the sweet taste signalling pathway suggesting that reduced methylation of genes related to sweet taste is an epigenetic mechanism associated with obesity.

A second study examined whether gestational exposure to alcohol was associated with an increased postnatal acceptability of alcohol in rats. The investigators found increased taste-mediated acceptability of both ethanol and quinine hydrochloride (bitter taste) but not sucrose (sweet taste) in adolescent rats who had been exposed to alcohol in utero (Youngentob & Glendinning, 2009). Although the authors suggested epigenetic mechanisms might be involved in transferring maternal patterns of drug use to offspring, they provided no evidence for such epigenetic changes in this study.
In summary, epigenetic modulations have been reported to be instrumental in the development of sensory systems as well as the plastic changes that can occur throughout the lifetime of individuals. Furthermore, epigenetic factors have been implicated in disease processes involving the sensory systems.

### 3.4.2. Cognition

Cognitive functioning is under the influence of epigenetic regulation throughout the lifespan. During the postnatal period, cognitive development depends upon reorganization of synaptic plasticity, which is driven by sensory experience (Hong, West, & Greenberg, 2005). During adulthood, epigenetic regulation of gene transcription continues to play a critical role in cognitive processes (McGowan & Roth, 2015).

Environmental enrichment has been demonstrated to enhance synaptic plasticity and cognition, and these enhancements are transmitted to the next generation. This intergenerational inheritance of an acquired cognitive benefit has been suggested to occur via specific miRNAs (Benito et al., 2018).

Cognitive impairment has been linked to epigenetic dysregulation (Butler et al., 2016) and may play a role in the pathophysiology of a number of disorders including Huntington’s disease (Benevento, van de Molengraft, van Westen, van Bokhoven, & Kasri, 2015), Rett syndrome, (Rudenko & Tsai, 2014a), Rubinstein-Taybi syndrome, Fragile X syndrome, Prader-Willi syndrome, and Angelman syndrome (Rudenko & Tsai, 2014b). These disorders are associated with a wide range of impairments including learning deficits and neurodevelopmental delays (Benevento et al., 2015).

### 3.4.3. Emotions

The study of epigenetic influences on emotions is still in its infancy. Much of the early research exploring the epigenetically mediated relationship between environmental factors and emotions has utilized the stress-fear-response model (Gaudi et al., 2016). In rats, stress induces modified expression of the glucocorticoid receptor (GR) gene in the hippocampus (Hunter, Gagnidze, McEwen, & Pfaff, 2015). The GR is a stress-related transcriptional regulator involved in the epigenetic mediation of stress exposure (Gaudi et al., 2016).

Studies investigating epigenetic regulation of positive emotions have appeared only recently in the literature (e.g. see Puglia, Lillard, Morris, & Connelly, 2015). These studies generally focus on the neuropeptide oxytocin, which plays a key role in the regulation of social cognition and behavior (Kumsta, Hummel, Chen, & Heinrichs, 2013). Oxytocin has also been shown to improve the recognition of emotions and increase the expression of positive emotions in healthy individuals, but not in individuals suffering from psychiatric disorders (Leppanen, Ng, Tchanturia, & Treasure, 2017). Investigations have provided evidence for an association between higher levels of oxytocin receptor gene methylation and increased activation of brain areas involved in emotional regulation (Puglia et al., 2015).

Expression of the oxytocin receptor is regulated by epigenetic processes (Jack, Connelly, & Morris, 2012; McGowan & Roth, 2015). For example, DNA methylation of the oxytocin receptor (OXTR) gene suppresses expression of the gene, and high levels of DNA methylation have been associated with autism spectrum disorders (ASD) (Jack et al., 2012; Kumsta et al., 2013).

### 3.4.4. Memory

Memory, which is defined as “the capacity to bring elements of an experience from one moment in time to another” (Perry, 1999, p. 1), is a critical component of consciousness (Hudson, 2011). A newly formed memory must first be acquired (encoded), then converted to a more persistent state (consolidated), and finally stored so it is available for retrieval. Numerous studies have demonstrated a role for epigenetic mechanisms in the encoding, consolidation, and storage of memories (Sultan & Day, 2011).
The prevailing view of memory postulates the cellular mechanisms responsible for the formation and consolidation of memory involve alterations in synaptic strength in response to neural activity (Guan, Xie, & Ding, 2015; Guzowski et al., 2000). Such alterations include structural and functional remodeling of synapses (Lamprecht & LeDoux, 2004; Martin, Grimwood, & Morris, 2000), particularly in the hippocampus where new information is encoded, and in the neocortex where long term memories are consolidated (Hudson, 2011). Recently, epigenetic mechanisms have been demonstrated to play a critical role in memory. However, additional studies are still needed as currently the majority of evidence supporting the role of epigenetic regulation in long-term memory is associative rather than causative (Guan et al., 2015).

Formation of long term memories requires changes in synaptic strength, which involves the de novo synthesis of RNA and proteins (Guzowski et al., 2000). Candidate genes have been identified on the basis of their rapid induction in brain neurons such as the immediate-early genes (IEGs) BDNF, ARC, zif268, and C/EBPbeta (Hall, Thomas, & Everitt, 2000). Induction of IEGs in hippocampal neurons is under epigenetic regulation (Srivas & Thakur, 2017).

Epigenetic mechanisms influencing the formation and maintenance of memories include changes in DNA methylation (Day & Sweatt, 2010, 2011), histone modifications (Reul & Chandramohan, 2007; Sultan & Day, 2011), and the production of ncRNAs (Butler et al., 2016; McGowan & Roth, 2015).

3.4.4.1. Epigenetic memory. Most cells in the human body contain DNA, which is subject to epigenetic modifications. These epigenetic changes form a code that contains information and this information creates a type of cellular memory known as epigenetic memory. Epigenetic memory can be passed down to a cell’s progeny and, in some cases, to an individual’s progeny. The latter process is referred to as transgenerational epigenetic inheritance (Babenko et al., 2015).

Early mammalian studies exploring transgenerational epigenetic inheritance were performed in mice. For example, Dias and Ressler (2014) exposed male mice (F0) to an odor (acetophenone) and simultaneously applied small electrical shocks. Eventually, the mice developed a conditioned response and would shudder in the presence of the odor, even in the absence of a shock. These mice were then bred and their offspring (F1) demonstrated a similar shudder response when exposed to the same odor, but not to other odors. This response was observed in the next generation (F2) of mice as well. Furthermore, the gene coding for the receptor that recognizes this odor (i.e. olfactory receptor 151 (Olfr151)) was found to be hypomethylated in the F0 and F1 generations, resulting in an increased number of acetophenone-responsive olfactory sensory neurons (OSNs) (Dias & Ressler, 2014).

Transgenerational epigenetic inheritance was demonstrated in another study in which adolescent male mice were exposed to chronic unpredictable stress (CUS). The investigators discovered altered gene transcription in the amygdala, and these changes persisted in the male offspring and grand offspring (Manners et al., 2018).

Human studies have provided evidence suggestive of transgenerational epigenetic inheritance also. For example, the eating habits of grandfathers at critical times in their lives have been shown to influence the life expectancy of their grandchildren (Bygren, Kaati, & Edvinsson, 2001). The offspring of Holocaust survivors demonstrate a higher lifetime prevalence of PTSD, mood disorders and anxiety disorders than the offspring of controls (Yehuda, Bell, Bierer, & Schmeidler, 2008). The offspring of parents with PTSD have significantly lower 24-hour mean urinary cortisol excretion and salivary cortisol levels than offspring of parents who are trauma survivors but do not suffer from PTSD. The authors speculated that offspring of mothers suffering from PTSD may be at increased risk of developing PTSD due to epigenetically-mediated changes in the expression of the glucocorticoid receptor genes (Yehuda & Bierer, 2008). Also, pregnant women who were close to the World Trade Center collapse on 9/11 and
subsequently developed PTSD gave birth to babies who had lower levels of salivary cortisol than mothers who did not develop PTSD (Yehuda & Bierer, 2008). Finally, a recent study found preservation of reduced sensitivity to thyroid hormone (TH) in F2 and F3 descendents of males, but not females, who were exposed to high TH levels in utero due to a heterozygous TH receptor beta gene mutation (Anselmo et al., 2019). The results from the F3 generation confirm inheritance of an epigenetic effect, although the mechanism responsible for this effect remains to be elucidated.

Transgenerationally inherited epigenetic changes are not permanent, but are susceptible to being erased during fetal development. This may explain why some epigenetic changes do not persist indefinitely in future generations. However, some epigenetic changes can persist for multiple generations. For example, in a pre-clinical study using C. elegans, Klosin and colleagues (2017) found that temperature-induced changes in methylation of histone proteins produced altered patterns of gene expression and these acquired traits could be transmitted through both sperm and oocytes for at least 14 generations. This study demonstrated that long-lasting epigenetic memory of environmental change is possible. While replication of this study and similar studies in humans still need to be performed, this finding suggests that environmental influences stored as epigenetic memory may be passed down through multiple generations.

In addition to being passed down to offspring, some epigenetic changes may be transferable between unrelated individuals. For example in the marine mollusk Aplysia, long-term memory has been successfully transferred from one animal to another by injecting RNA from the donor to the recipient. This transfer of memory provides support for a nonsynaptic, epigenetic model of cellular memory in Aplysia (Bedecarrats, Chen, Pearce, Cai, & Glanzman, 2018). The authors of this study theorize that ncRNAs are responsible for the storage and transfer of these memories. Studies are still needed to determine if memories can be transferred between different humans via the exchange of RNAs.

3.5. Senescent decline of the CNS

Normal human aging is associated with changes in the structure and functioning of the CNS such as shrinkage of the brain (Chetelat et al., 2013; Driscoll et al., 2003) and a decline in sensory, motor, and cognitive functioning (Mohammed, Park, Nam, & Kim, 2017). Normal human aging is also associated with a variety of epigenetic modifications that result in altered expression of genes implicated in synaptic plasticity, synaptic structure, vesicular transport, and mitochondrial function (Barter & Foster, 2018; Delgado-Morales, Agis-Balboa, Esteller, & Berdasco, 2017; Mohammed et al., 2017).

Changes in epigenetic modifications increase with ageing, a phenomenon known as epigenetic drift (Mather, Kwok, Armstrong, & Sachdev, 2014; McGowan & Roth, 2015). Epigenetic drift is associated with a loss of euchromatin (Benevento et al., 2015) and has been linked with a number of epigenetic changes including alterations in DNA methylation (Bjornsson et al., 2008; D’Aquila, Rose, Bellizzi, & Passarino, 2013), histone modifications (D’Aquila et al., 2013; Graff & Tsai, 2013; Tan et al., 2011), and miRNA expression (D’Aquila et al., 2013; Hooten et al., 2013). Such shifts in the epigenetic profile can negatively affect gene expression in brain cells and contribute to ageing (Pal & Tyler, 2016) as well as declining cognitive performance (Pirooznia & Elefant, 2013). More specifically, ageing is associated with a decrease in the expression of DNA methyltransferase Dnmt3a2 in the hippocampus of mice, whereas restoration of Dnmt3a2 levels results in the recovery of cognitive abilities (Oliveira, Hemstedt, & Bading, 2012). Although cognitive decline is often considered a normal consequence of ageing, loss of neuronal functioning can also contribute to neurodegenerative disorders such as dementia, Alzheimer’s disease (AD) (Athanasopoulos et al., 2016; Hsieh & Eisch, 2010), Parkinson’s disease (PD), Huntington’s Disease, and amyotrophic lateral sclerosis (ALS) (Benevento et al., 2015; Delgado-Morales et al., 2017).

The development of neurodegenerative disorders is associated with dysregulated epigenetic mechanisms (Delgado-Morales et al., 2017). For example, studies examining cortical tissue from Alzheimer’s disease patients have demonstrated DNA methylation changes in genes involved in
beta-amyloid precursor protein processing (Bakulski et al., 2012; Wang, Oelze, & Schumacher, 2008). Additionally, a depletion of DNMT1 protein has been reported in the cell nuclei extracted from brain tissue of individuals with dementia with Lewy bodies (DLB) (Desplats et al., 2011).

3.6. The pathogenesis and treatment of mental illnesses

A growing body of evidence supports a role for epigenetic changes in the pathogenesis of mental illnesses (Nestler et al., 2016; Schuebel, Gitik, Domschke, & Goldman, 2016; Tsankova, Renthal, Kumar, & Nestler, 2007). Schizophrenia (Dempster et al., 2011; Tsankova et al., 2007), bipolar disorder (Dempster et al., 2011; Fries, Carvalho, & Quevedo, 2018), depression (Deussing & Jakovcevski, 2017; Nagy, Vaillancourt, & Turecki, 2018; Tsankova et al., 2007), anxiety (Bartlett, Singh, & Hunter, 2017; Malan-Muller & Hemmings, 2017; Schiele & Domschke, 2018), eating disorders (Campbell, Mill, Uher, & Schmidt, 2011; Thaler & Steiger, 2017; Yilmaz, Hardaway, & Bulik, 2015) and PTSD (Kwapis & Wood, 2014; Schmidt, Holsboer, & Rein, 2011; Zannas, Provencal, & Binder, 2015) have all been linked to epigenetic changes.

Exposure to traumatic or stressful experiences is a major risk factor for the development of psychiatric disorders. This is true in utero and early in life (Babenko et al., 2015) as well as later in life (Klenge, Pape, Binder, & Mehta, 2014). Epigenetic mechanisms may contribute to psychopathology in a number of ways including impairment in CNS development, dysregulation of neuronal functioning (Nestler et al., 2016), and mediation of environmental influences (Abdolmaleky, Smith, & Thiagalingam, 2008). Environmental factors that have been demonstrated to induce epigenetic changes and therefore may contribute to psychopathology include parenting style (Moore, 2017), socioeconomic status (Swartz, Hariri, & Williamson, 2017), diet (Sepienza & Issa, 2016), exposure to toxins such as tobacco and alcohol (Ghantous, Schussel, & Brait, 2018) and stress (Babenko et al., 2015; Klengel et al., 2014).

Dysregulation of the HPA axis is a prominent finding in some psychiatric disorders (e.g. depression, PTSD, and schizophrenia) and epigenetic modulation of key genes in the HPA axis has been suggested to mediate the effects of environmental stressors on psychiatric disorders (Klengel et al., 2014).

At a hormonal level, the hypothalamic neuropeptides corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) stimulate the release of adrenocorticotropic hormone (ACTH) from the pituitary gland, triggering the release of GCs from the adrenal glands. GCs bind to the glucocorticoid receptor (GR), which is a nuclear receptor that functions as a hormone-dependent transcription factor and can either enhance or suppress gene transcription (Spencer & Deak, 2017).

Another pathway linking the environment with psychiatric disorders is via epigenetic regulation of neurotransmitters and their receptors. Epigenetic dysregulation of neurotransmitters has been demonstrated in a number of mental illnesses and implicated neurotransmitters include serotonin (Paquette & Marsit, 2014), dopamine (Abdolmaleky et al., 2008), GABA, and glutamate (Mill et al., 2008).

Socioeconomic status (SES) also contributes to psychopathology, and epigenetic changes have been suggested to mediate this risk. For example, low-SES is associated with higher rates of depression in adults (Lorant et al., 2003), adolescents, and children (Goodman, Slap, & Huang, 2003; Kubik, Lytle, Birnbaum, Murray, & Perry, 2003; Tracy, Zimmerman, Galea, McCauley, & Stoep, 2008). Low-SES during adolescence is associated with increased methylation of the proximal promoter of the serotonin transporter gene, which predicts greater increases in amygdala activity. Increased amygdala reactivity is associated with activation of the HPA axis and increased risk of depression (Swartz et al., 2017).

Diagnosing mental illnesses is complicated by a lack of identifiable biomarkers. Epigenetic marks provide a potential source of biomarkers. For example, Fuchikami et al. (2011) examined methylation profiles of the BDNF gene in patients with major depression using DNA from peripheral blood.
The investigators were able to distinguish between individuals with major depression and healthy controls based upon methylation profiles of CpG units within the BDNF promoter region. These findings indicate DNA methylation profiles of the BDNF gene may serve as a biomarker for major depression.

Psychotropic medications are associated with epigenetic changes that parallel improvement in symptoms and treatment with antidepressants is known to influence neurogenesis (Epp, Beasley, & Galeo, 2013). Chronic treatment with imipramine increases transcription of the BDNF gene in the hippocampus of mice (Tsankova et al., 2006). Mirtazapine treatment is associated with statistically significant improvement in HAM-D scores and statistically significant increased levels of BDNF (Gupta, Gupta, Tripathi, Bhatia, & Gupta, 2016).

Non-pharmacological treatments may also improve mental health via epigenetic mechanisms. For example, electroconvulsive therapy (ECT) induces DNA methylation of the promoter region of the Arc gene (Dyrvig, Gotzsche, Woldbye, & Lichota, 2015) and enhances neurogenesis in the SGZ and DG (Nakamura et al., 2013; Rotheneichner et al., 2014).

Studies examining the link between diet and epigenetics suggest nutritional factors may influence the epigenome (Haggarty, 2012; Mathers, Strathdee, & Relton, 2010). One way diet can influence epigenetic traits is via exposure to synthetic xenobiotics consumed with contaminated foods, which can affect DNA methylation either directly (e.g. by inhibition of DNMTs) or indirectly (e.g. because the metabolization and inactivation of xenobiotics typically passes through a methylation step, fewer methyl groups are available for physiological reactions) (Fuso & Lucarelli, 2019).

A number of foods and vitamins have been demonstrated to influence the epigenome including tomatoes, onions, garlic, broccoli, Brussels sprouts, apples, oranges, turmeric, cilantro, cinnamon, soybeans, coffee, green tea, black tea (Huang et al., 2019) and vitamins A, B4, B6, B9, B12, C, and D (Carlberg, 2019; Hore, 2017; Kok et al., 2015; Sanchez et al., 2017). Foods and vitamins can shape epigenetic changes through a number of processes including: (1) influencing enzymes that catalyze DNA methylation and histone modifications, (2) altering the availability of substrates for these enzymatic reactions (Kalani et al., 2019), (3) affecting levels of miRNAs (Choi & Friso, 2010; Gomez-Pinilla & Tyagi, 2013; Huang et al., 2019), and (4) modifying the composition of the gut microbiome, which transforms dietary compounds into molecules that influence epigenetic changes (Chittim, Irwin, & Balskus, 2018; He, Marco, & Slupsky, 2013; Hullar & Fu, 2014).

The negative effects of diet-related epigenetic changes include abnormal brain development, impaired learning and memory, hippocampal dysfunction, and apoptosis (Jadavi, Deng, Malsheva, Caudill, & Rozen, 2015; Tomizawa et al., 2015) whereas positive effects include neuroprotection resulting from the amelioration of pathogenetic factors linked to Alzheimer’s Disease (Monacelli, Acquarone, Giannotti, Borghi, & Nencioni, 2017) and improved memory (Bekdash, 2016).

Caloric intake and fat content are additional dietary factors that can affect regulation of the genome. Caloric restriction (CR) restores the loss of DNMT activity and increases HDAC binding, thereby counteracting the effects of aging on neurodegeneration (Li, Daniel, & Tollefsbol, 2011). CR also modifies DNA methylation patterns, which protects against age-related changes associated with neurological disorders (Hadad et al., 2018; Hahn et al., 2017). Additionally, a maternal (Vucetic, Kimmer, & Reyes, 2011) or paternal (Masuyama, Mitsui, Eguchi, Tamada, & Hiramatsu, 2016) high-fat diet (HFD) is associated with epigenetic changes. For example, a HFD influences DNA methylation of the genes for dopamine and opioid receptors in the brain (Vucetic, Kimmel, Totoki, Hollenbeck, & Reyes, 2010; Vucetic et al., 2011). Dopamine receptors have been implicated in a number of psychiatric disorders including schizophrenia (Seeman, 2013), addiction (Chen et al., 2017), and major depressive disorder (Belujon & Grace, 2017) whereas opioid receptors have been suggested to play a role in major depressive disorder (Lutz & Kieffer, 2013) and addiction.
Maternal diet has also been linked with poor cognitive performance in offspring, and epigenetic mechanisms have been proposed to mediate this impairment (Moody, Chen, & Pan, 2017).

Physical exercise affects brain functioning via epigenetic mechanisms. Examples of these effects include memory enhancement, reduction in mental decline associated with aging, and improvement in depression (Fernandes, Arida, & Gomez-Pinilla, 2017). Proposed mechanisms include modified gene expression patterns related to synaptic plasticity and signal transduction via altered expression of DNMTs and HDACs (Abel & Rissman, 2013), and upregulation of BDNF (Zajak et al., 2010).

Psychotherapy is another non-pharmaceutical option for inducing epigenetic changes leading to improved mental health (Jimenez et al., 2018; Yehuda et al., 2013). This discovery lead Stahl (2012) to refer to psychotherapy as “the new epigenetic drug.”

3.7. Epigenetics and the evolution of consciousness
Epigenetic processes mediate environmental influences on gene transcription. In 1802, Lamarck suggested the environment can alter phenotype in a heritable manner. Recent discoveries in environmental epigenetics and the existence of epigenetic transgenerational inheritance provide evidence of so-called Lamarckian evolution (Koonin & Wolf, 2009; Skinner, 2015). This knowledge has significant implications for our understanding of evolution. Rather than being limited to a Mendelian-genetic model of inheritance, evolution can be conceptualized as a combination of genetic and nongenetic inheritance in which rapid and individualized responses to environmental influences occur (Bonduriansky & Day, 2009). Does the same concept hold true for the evolution of consciousness?

Over a quarter of a century ago, Eccles (1992) proposed consciousness evolves in parallel with the evolution of the neocortex. Subsequently, authors have continued to examine the evolution of consciousness by focusing on the neural basis of consciousness (e.g. see Butler, 2008; Mashour & Alkire, 2013). Further studies are needed to investigate how epigenetic changes may influence the evolution of consciousness.

4. Discussion
Human consciousness can be viewed as a function of the brain that receives and processes information utilizing perception, cognition, emotions, and memory. Each of these faculties is dependent upon neural structures within the brain and investigations in the field of epigenetics have demonstrated how interactions between the environment and the genome influence the development, function, and pathology of the brain, thereby influencing human consciousness.

The evidence presented in this review highlights the impact of epigenetics on human consciousness through a variety of mechanisms. These include:

1. influence cellular differentiation during development of the human brain
2. influence the ongoing functioning of the brain via effects on neurogenesis and neuroplasticity
3. influence multiple faculties involved in human consciousness including perception, cognition, emotion, and memory
4. support the formation and maintenance of cellular memories
5. provide a mechanism for the transmission of memories between individuals via transgenerational epigenetic inheritance
6. contribute to the development of neurodevelopmental disorders, mental illnesses, and neurodegenerative disorders
7. create a bi-directional crosstalk between the genome and the environment
8. facilitate rapid adaptation to environmental changes, thus influencing evolution
Understanding the epigenetic mechanisms involved in the development of neurological structures employed by various brain systems may lead to enhanced treatment options for pathologies of these systems. For example, within the sensory system, cross-modal plasticity occurs when sensory deprivation in one modality affects the development of other sensory modalities during early stages of development. Cross-modal plasticity is particularly observed in cases of congenital blindness or deafness (Maya-Vetencourt & Origlia, 2012). Examples include studies showing that individuals who are congenitally blind demonstrate better sound localization abilities compared to sighted individuals (Roder et al., 1999) and better tactile two-point discrimination skills (Bavelier & Neville, 2002). There appears to be a critical period for the development of cross-modal plasticity that ends around the age of 14 (Maya-Vetencourt & Origlia, 2012).

The structural mechanism of cross-modal plasticity involves recruitment of cortical neurons from other sensory areas. For example, functional magnetic resonance imaging studies indicate early deaf individuals use the primary auditory cortex alongside the visual system when observing sign language. In these individuals, the auditory cortex assists with visual and language processing. However, individuals with some hearing loss, but not total deafness, do not show activation of the primary auditory cortex during visual language processing (Lambertz, Gizewski, de Greiff, & Forsting, 2005). This may explain why early deaf individuals, but not late-onset deaf subjects, experience an impaired ability to process language using a cochlear implant in adulthood. In the former, the auditory cortex has been usurped by the visual system and thus cannot process the auditory information provided by the cochlear implant (Doucet, Bergeron, Lassonde, Ferron, & Lepore, 2006).

Could medicines that influence epigenetic upregulation of BDNF and thereby increase neuroplasticity be used to help individuals with early sensory loss? For example, might fluoxetine improve the effectiveness of cochlear implants in adults with early-onset deafness or help early onset blind individuals learn echolocation as adults? Further studies are needed to investigate such possibilities.

Understanding the role epigenetic factors play in cognition may improve treatment of neurodevelopmental and neurodegenerative disorders. For example, early environmental enrichment has been shown to improve cognitive functioning and dysregulated epigenetic mechanisms have been demonstrated to influence the development of neurodegenerative disorders. Increasing our understanding of epigenetics may help explain how environmental enrichment enhances cognitive functioning throughout the lifespan, thereby providing a rationale for additional early childhood interventions to support cognitive development, and suggest new treatments for neurodegenerative disorders.

The influence of epigenetics on emotions suggests new possibilities for the treatment of mood disorders, such as depression and bipolar disorder, as well as the emotional dysregulation that can occur in psychiatric conditions such as borderline personality disorder, attention-deficit hyperactivity disorder, and autism spectrum disorders. For example, epigenetic influences on glucocorticoid and oxytocin receptors point to one area of inquiry that could lead to new therapeutic options for the treatment of these and other psychiatric disorders.

Research exploring neurodegenerative disorders, such as Alzheimer’s disease, Parkinson’s disease, and Huntington’s disease suggests therapeutic interventions designed to target dysregulated epigenetic mechanisms involved in the formation, storage, or retrieval of memories may one day play a role in the enhancement of memory functioning as well as the prevention of neurodegenerative disorders.

The human brain provides the structural and functional basis for consciousness. Through their influences on the development, ongoing functioning, and senescent decline of the human brain, epigenetic changes influence human consciousness by affecting both the healthy and pathological functioning of the brain. Improving our understanding of the role played by epigenetics in brain functions creates opportunities to improve prevention strategies and develop novel treatment approaches for neurodevelopmental, psychiatric, and neurodegenerative disorders.
5. Conclusions

Investigations into the role epigenetics plays in human consciousness are still in their infancy. Numerous opportunities exist to explore the various functions/roles of epigenetics in human consciousness. The effects of epigenetic dysregulation on the development of mental illnesses and neurological disorders, as well as potential new treatments for these disorders based upon epigenetic mechanisms are perhaps the most researched areas thus far. However, the possibility of developing new understandings of previously unexplained phenomena suggest equally appealing areas of inquiry. It is hoped that future investigators will consider the far-reaching effects of epigenetic processes when exploring the interrelatedness of epigenetics and human consciousness.

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