Neuroepigenetic Mechanisms of Psychiatric Disorders:
Implications for the Adlerian Therapist
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Abstract

Neuroepigenetics, a subset of the field of epigenetics, offers a model for understanding the formation of psychiatric disorders. Recent research shows the potential impact of internal and external environments on neuronal expression via multiple mechanisms within the gene transcription process. The human organ is in constant interaction with environmental stimuli from embryonic gestation to death. Coupled with the mental and physical health of both maternal and paternal lineage, the nature-or-nurture argument is now answered with both. Through the lens of neuroepigenetics, mental health practitioners can address depression, schizophrenia and psychosis, bipolar disorder, and trauma, as well as memory, learning, and developmental disorders. Additionally, neuroepigenetics provides evidence needed to endorse Adlerian psychotherapy and is a significant step forward in the evolution of the biopsychosocial model. Neuroepigenetics is distinctly compatible with Alfred Adler’s humanistic-educational model of human beings. That is, the development of the individual is in direct relationship to the environment.

Keywords: epigenetics, neuroepigenetics, depression, schizophrenia, bipolar, fear, memory, trauma, methylation, acetylation, DNA, RNA, protein, histone
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Dedication

To those victimized by their environment, the family and friends who love them, and the professionals who strive to assist them on their endeavor toward healing and growth: You are never alone.
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Neuroepigenetic Mechanisms of Psychiatric Disorders: Implications for the Adlerian Therapist

The genetic blueprint alone does not explain the risk of mental health complications over a lifetime. A mechanism exists in deoxyribonucleic acid (DNA) expression that drives susceptibility toward certain manifestations of mental health: neuroepigenetics. The emerging field of neuroepigenetics allows a new understanding of brain function including psychiatric disorders, mood disorders, memory, and learning. Sweatt and Tamminga (2016) identified four types of neuropsychiatric disorders: neurodevelopmental disorders including autism spectrum disorders, aging-related and neurodegenerative disorders, psychosis and affective disorders, and drug abuse and addiction. As with the broader field of epigenetics, neuroepigenetics explains the relationship between environment and genes as a “clearly delineated and biochemically driven mechanistic interface between nature and nurture” (Sweatt, 2013, p. 624). The epigenetic process is consistent throughout life, beginning within the first month of fetal development and responding to environmental changes over time (Walsh, 2014). From cancer to psychosis, changes in gene expression have been the driving factor behind most physical and mental illnesses (Grayson & Guidotti, 2013; Nordgren & Skildum, 2015). Further insight into neuroepigenetic processes will provide new treatments and interventions for a wide variety of issues that have an impact on the quality of life for those challenged with mental health injury.

Neuroepigenetics is distinctly compatible with Alfred Adler’s humanistic-educational model: the development of the individual is in direct relationship to the environment (Ansbacher & Ansbacher, 1964). The purpose of this paper is to examine various mechanisms of neuroepigenetics, the influence of neuroepigenetics on the central nervous system (CNS) and brain function, fear memory, learning, and trauma. Additionally, neuroepigenetics (i.e., a
modern scientific understanding of brain development) can support and expand Alfred Adler’s theory and become integrated into common therapeutic practice.

**Epigenetics and Neuroepigenetics**

Rastegar (2017) stated the mechanisms of epigenetics affect genetic expression and cellular identity through processes at the molecular level otherwise not present in the genetic information. The prefix *epi* indicates action occurring above or outside the genome, thus the epigenetic process regulates the expression of the gene without altering the gene directly (Gilliam, 2015). More specifically, epigenetics is “potentially heritable, but environmentally modifiable” (Sun, Kennedy, & Nestler, 2013, p. 125) through interaction with mechanisms not inherently related to DNA alone. Epigenetic mechanisms are responsible for modifying genetic expression in response to environmental demands (Ramo-Fernández, Schnieder, Wilker, & Kolassa, 2015) and are active in all life stages from gestation to death (Klenge, Dias, & Ressler, 2016). In ways the field is still discerning, the environment has an acute influence on DNA expression with the potential to persist throughout life through stable and precise modifications in structure (Sun et al., 2013).

Neuroepigenetic mechanisms are activated when significant environmental factors manipulate normative development and differentiation, and in conjunction with genetic predispositions, may manifest in psychiatric disorders (Sun et al., 2013). Zovkic and Sweatt (2013) referred to neuroepigenetics as the “molecular mechanisms in non-dividing neuronal cells … [acting] in response to an organism’s experience” (p. 77) that affect adaptability and behavioral change. A multitude of mechanisms that alter a variety of functions may subsequently result in psychiatric disorders (e.g., psychosis, schizophrenia, or bipolar disorder). Currently, the depth of understanding is limited regarding those disorders.
Sweatt (2013) identified eight biochemical mechanisms at work in neuroepigenetics: Covalent modification of DNA (including *methylation*), histone posttranslational modifications (including *acetylation*), ATP-dependent chromatin remodeling, histone subunit exchange, RE1-siliencing transcription factors (REST)/RESCT corepressor, non-coding RNAs (including microRNAs), line 1 retrotransposition, and prion protein-based mechanisms. (p. 625)

Sweatt (2013) determined at least a dozen significant functions or disorders in which the above mechanisms can be implicated:

- learning and memory,
- maternal nurturing,
- adult neurogenesis,
- stress responses,
- Alzheimer’s disease,
- Rett syndrome,
- fragile X mental retardation,
- schizophrenia,
- Ruebstein-Taybi syndrome,
- Angelman syndrome,
- depression and/or suicide,
- bipolar disorder,
- addiction and reward behavior,
- Posttraumatic stress disorder (PTSD),
- ATR-X syndrome (x-thalassemia mental retardation),
• cognitive aging,
• Coffin-Lowry syndrome,
• Kleefstra syndrome,
• epilepsy, and
• autism.

Similarly, Öztürk, Resendiz, Öztürk, and Zhou (2017) identified how fetal exposure to alcohol disturbs the manufacture of methyl molecules and thus the normative methylation of DNA resulting in fetal alcohol spectrum disorder (FASD) features including thin cortex development. In addition, Sarkar (2015) found epigenetic marks transmitted through maternal and paternal germline; however, the transmission of the marks is presently less understood than acute maternal influence.

Sweatt (2013) stated the influence of the environment on gene expression is manipulated via DNA methylation, histone tail modifications, and micro ribonucleic acids (miRNAs). Sweatt (2013) indicated the complexity of the genome comprised of approximately three billion nucleotides with “hundreds of cellular phenotypes” (p. 630). Additionally, each cellular epigenome contains approximately 100 epigenetic marks. The following is a review of the epigenome and its function within the CNS, the processes of both DNA and histone methylation and acetylation, and the role of miRNAs and long non-coding RNAs (lncRNAs).

**Epigenomic Marks**

Sweatt and Tamminga (2016) found four distinct epigenetic marks that function within the mammalian central nervous system and are the most well-researched and understood of the mechanisms described above. First, genes are conformed to the double helix and its interface with histone proteins (Sweatt & Tamminga, 2016). The structure of the DNA-histone complex
is called the *chromatin*, and the *nucleosome* is the fundamental subunit of the chromatin (Sweatt, 2013). Each nucleosome consists of DNA wrapped twice around eight histones, which contain two duplicates of the nucleosome (Sweatt & Tamminga, 2016).

Second, the DNA strand itself is a target of covalent modification (i.e., the attaching of another molecule), which may occur on either one or both DNA strands and includes the process of methylation (Sweatt & Tamminga, 2016). Methylation of the DNA strand regulates the quality of the information read via RNA at any specific gene site resulting in modified expression of the genetic code (Sweatt & Tamminga, 2016). While DNA methylation is a predominantly transcription-inhibitory process, observation of gene activation occurs.

Third, histone tail modification via acetylation and methylation occurs upon the amino-terminal tails of individual histones within the histone *octamer*, which constitutes the core of the chromatin (Sweatt & Tamminga, 2016). In addition, the octamer in its entirety may be “swapped in and out [via] histone subunit exchange,” and when in combination with methylation, acetylation, or other mechanisms, the result is promotion or prohibition of transcription (Sweatt & Tamminga, 2016, p. 291). The DNA methylation regulates the quality of genetic information read, and histone tail modification regulates the quantity of information. The quantity of information is regulated by either easing access of RNA by loosening the chromatin or restricting access of RNA through constriction of chromatin. Both histone tail and DNA modifications hold potential for developing new therapies and interventions for mental health disorders (Day, Kennedy, & Sweatt, 2015).

Fourth, gene readout regulation may also occur via non-coding RNA interfacing with messenger RNA (mRNA), thus, altering the mRNAs function in the transcription process (Sweatt & Tamminga, 2016). Sweatt and Tamminga (2016) identified five types of RNA
involved in the epigenetic process: long non-coding RNAs (lncRNAs), microRNAs (miRNAs), small non-coding RNAs (snRNAs), silencing RNAs (siRNAs), and RNA interference (RNAi) mechanisms. O’Carroll and Schaefer (2013) stated development of “miRNA-dependent gene expression regulation could present an effective mechanism to ensure tight control of neuronal gene expression” (p. 40). For example, interventions that target miRNA would influence development, function, and maintenance of neuronal cells and activity more effectively and precisely than traditional medication.

**DNA Methylation**

In its evolutionary role, DNA methylation allows the individual to adapt to environmental demands by reducing the expression of genes deemed unnecessary for the survival of the individual and offspring (Kennedy & Sweatt, 2016). Methylation changes DNA expression by the addition of methyl (CH$_3$) molecules in unmethylated sites which regulate transcription (Gilliam, 2015). DNA methylation acts in conjunction with DNA methyltransferases (DNMTs) to “yield 5-methylcytosine (mC)…at cytosine-phosphate-guanine (CpG) dinucleotide sites” (Day, Kennedy, & Sweatt, 2015, p. 3). Genetic expression depends upon the quality of information at the CpG site and the extent of methylation regulating the quantity of information read. Sweatt (2013) considered cytosine 5’-methylation the “prima donna of epigenetics because it is an extremely powerful regulator of gene transcription” (p. 625). In addition to the determination and behavior of neuronal cells, DNA methylation acts as a primary mechanism for the determination and restriction of all nonneuronal genes.

Heinrich et al. (2015) found individuals who experienced childhood abuse exhibited an altered stress response as indicated by inadequate levels of methylation, and subsequently, are more susceptible to stress diseases such as depression. Day et al. (2015) suggested the
perpetuation of methylation marks, and subsequent associated mental health symptoms, via maintenance DMNTs create a dimethylated mark on the necessary CpG site. Kennedy and Sweatt (2016) found when a damaged 5-methylcytosine needs replacement, the “new cytosine can be methylated through maintenance to reconstitute the epigenetic mark” (p. 187). Methylation maintenance is considered a potential factor in the intergenerational transmission of susceptibility, memory, and trauma (Kennedy & Sweatt, 2016).

Sweatt (2013) challenged the historical long-held perspective that methylation patterns are permanent and perpetuated. Recent research revealed the process of active cytosine methylation whereby methylated sites undergo conversion back to an unmethylated state (Sweatt, 2013). Sweatt (2013) identified this process in both the mature nervous system and the fertilized zygote.

Methylation cycle. Walsh (2014) stated there are more than one million methylation reactions per second in the human body, one-third of which are dedicated to the epigenetic mechanisms that interface with our internal and external environments. The cycle begins with the introduction of methionine from the source diet, and via an enzymatic process involving magnesium and adenosine triphosphate (ATP), S-Adenosyl methionine (SAMe) is produced (Walsh, 2014). S-Adenosyl methionine is the source by which all CH$_3$ is provided. Adenosine triphosphate is an energy source so vital to the methylation process that the body will produce a daily quantity of ATP equal to an individual’s body weight (Walsh, 2014). Once CH$_3$ is released to a biochemical group requiring methyl donation, SAMe is converted to S-Adenosyl homocysteine (SAH), which also has epigenetic characteristics (Walsh, 2014). S-Adenosyl homocysteine is converted to homocysteine by the S-Adenosyl-L-homocysteine hydrolase (SAHH) enzyme as well as through the loss of adenosine. Subsequently, homocysteine is
converted back into methionine through both its interaction with trimethylglycine, in which it is converted directly to methionine, and through folate cycle remethylation (Walsh, 2014).

Walsh (2014) found folate remethylation involves the methionine synthase (MS) and methylenetetrahydrofolate reductase (MTHFR) enzymes that convert homocysteine into 5-methyltetrahydrofolate. The methylation cycle can be compromised at any point by single nucleotide polymorphisms (SNPs). Single nucleotide polymorphisms are evolutionary mutations that may weaken enzyme effectiveness. Over 85 million SNPs have been identified, “accounting for 95% of all known sequence variants” (Hoffmann, Sportelli, Ziller, & Spengler, 2017, p. 2). While it is common for an individual to inherit over 1000 SNPs, most will not have any impact on health or development; however, SNPs provide distinct biological markers for physical and psychiatric diseases (Walsh, 2014). Single nucleotide polymorphisms are most common in very large enzymes such as MTHFR, which is comprised of 500 amino acids, and an SNP within this enzyme structure would result in either an out of place or a misplaced amino acid (Walsh, 2014). This type of interference would subsequently decrease the effectiveness of homocysteine reconversion into methionine resulting in hypomethylation.

**Hypomethylation and hypermethylation.** Methylation is an evolutionary process that regulates gene expression per environmental demands. Sweatt (2013) found the potential for 100 epigenetic marks at each of the three billion nucleotides resulting in approximately 300 billion possible epigenetic modifications. Within the billions of possibilities is the differentiation between which cell expresses as a neuronal cell and another as a liver cell. Walsh (2014) found, upon working with more than 30,000 patients over a three-decade period, that 70% of the general population is adaptively and normatively methylated. In addition, 22% of the general population is hypomethylated, and 8% hypermethylated. Walsh (2014) identified 70% of those with mental
disorders exhibit a serious methylation disorder. Sweatt (2013) and Walsh (2014) argued for the methylation status testing in psychiatric diagnosis and recognized the present technological and economical limitations of such testing.

Hypomethylation, or undermethylation, is the state in which there is an inadequate quantity of methyl molecules available for normative and healthy gene expression. Walsh (2014) found a high incidence of hypomethylation within the following psychiatric disorders: autism spectrum disorder (98%), antisocial personality disorder (95%), schizoaffective disorder (90%), oppositional defiant disorder (85%), anorexia (82%), and depression (38%). Sun et al. (2013) found chronic stress reduced methylation in histone site H3K9me3 leading to low levels of serotonin. Depressed individuals with low levels of serotonin responded well to pharmaceutical interventions such as selective serotonin reuptake inhibitors (SSRIs). For other depressive types where decreased serotonin levels are not the primary cause, said interventions may lead to increased symptomology and suicidality. Walsh (2014) found MAT, MS, BHMT, SAHH, and MTHFR enzymes active in hypomethylation.

Walsh (2014) cited three means by which an individual may experience hypomethylation: inheritable enzyme mutation, or SNPs in the methylation cycle, histamine overload, and protein deficiency or malabsorption. Walsh stated hypomethylation manifests in the following symptoms and traits: very strong-willed personality, competitive in nature, obsessive-compulsive tendencies, seasonal allergies, addictive tendencies, high libido, family history of high accomplishment, calm demeanor with high inner tension, high production of bodily fluids, and non-compliance with therapies.

Conversely, Walsh (2014) stated hypermethylation, or overmethylation, results from the disruption of SAMe conversion during creatine synthesis (i.e., the process where 70% of SAMe
are dedicated). The initial stage of creatine synthesis begins with amino acids arginine and glycine, which together with enzyme AGAT, create guanadino acetate. Through the interaction of enzyme GAMT, SAMe and guanadino acetate are synthesized into creatine with SAH as the byproduct similar to the methyl donor process. Hypermethylation may occur within the creatine synthesis process via AGAT, or GAMT-SNP disruption, or perhaps due to amino acid deficiency at the onset of guanadino acetate synthesis process. Disruption in the creatine synthesis process results in an overabundance of unconverted SAMe, which is then available for other methylation processes such as DNA or histone modifications that would not occur within the normative level of SAMe. Walsh (2014) stated the active enzymes in hypermethylation are AGAT, GAMT, CBS, and MT, which are distinct from those involved in hypomethylation, that is, any future enzyme-oriented treatment will be distinct for the level of methylation.

Walsh (2014) found hypermethylation increases levels of norepinephrine and adrenaline. Increased levels of norepinephrine and adrenaline are found in psychiatric disorders such as panic/anxiety (64%), paranoid schizophrenia (52%), ADHD (28%), behavioral disorders (23%), and depression (18%). Unlike depression associated with hypomethylation, SSRIs may be harmful when taken by individuals with hypermethylated epigenomes and may result in elevated symptomology including suicidality (Walsh, 2014). Individuals with hypermethylated epigenomes tend to present with the following symptoms and traits: high anxiety and/or sleep disorders, high energy and verbosity, artistic and/or musical ability, antihistamine intolerance, high empathy for others, non-competitive in nature, food and chemical sensitivities, absence of seasonal allergies, low libido, dry eye and mouth, adverse reactions to SSRIs, low blood histamine, and an elevated SAMe/SAH ratio (Walsh, 2014).
Hypomethylation and hypermethylation pose increased risk for susceptibility to cancer, mental illness, and developmental disorders such as autism during pre-natal DNA expression (Walsh, 2014). Environmental deficiencies in the pre-natal environment may affect genetic expression at any point between embryonic gestation and birth (Walsh, 2014). Gene regulation disruption via histone methylation are second only to DNA methylation in terms of risk susceptibility.

Hypermethylation may be corrected by removal of methyl molecules, primarily via ten-eleven translocation (TET) proteins (Day et al., 2015). Ten-eleven translocation mC dioxygenases convert mC to produce 5-hydroxymethylcytosine (hmC). Day et al. (2015) stated it is unclear what mechanisms convert hmC back to unalkylated cytosine; however, the process is fundamental in the elimination of a methyl mark. Targeting the conversion process will provide means of reducing psychiatric symptoms associated with hypermethylation.

**Histone Modification**

In addition to DNA methylation, histone modification is the most well-researched and understood of all epigenetic mechanisms. Day (2014) found histone modifications are “important regulators of behavioral and synaptic plasticity, trans-generational epigenetic inheritance, and neurological or psychiatric disease states” (p. 349). As stated above, DNA is wrapped twice around each histone to form chromatin, and the nucleosome is the fundamental unit. Histone tails are lysine amino acids that regulate chromatin structure and gene expression via acetylation, the addition of acetyl molecules, although methylation occurs as well (Day, 2014). Machado-Vieira, Ibrahim, and Zarate (2011) stated histones are acetylated or deacetylated at the histone tails through processes “controlled by histone acetyltransferases (HATs), and [histone deacetylases] respectively” (p. 700).
Acetylation changes the structure of chromatin, and therefore, gene expression, through varying degrees of expansion and compaction. Histone acetyltransferases offer access to genetic information by the addition of acetyl groups, which loosen the structure and increase ease of transcription (Machado-Vieira et al., 2011). When DNA is required to access proteins or other transcription factors, the application of acetyl molecules to histone tails lessens the positive charge of the nucleosome and opens the structure (Machado-Vieira et al., 2011). Conversely, the process of deacetylation via histone deacetylases (HDACs) restore the positive charge and constrict the structure of the chromatin, restricting access to necessary proteins and transcription factors and prohibiting gene expression. Differences in acetylation levels may be observed in brain function and behavior. For example, higher levels of histone acetylation have been associated with more efficient memory formation, and lower levels of acetylation have been associated with decreased synaptic plasticity (Peixoto & Abel, 2013).

**Non-Coding Ribonucleic Acids**

Recently research has provided new understanding of the role of non-coding RNA in the transcription process. Barr and Meister (2016) found non-coding RNAs now outnumber coding RNAs and exhibit the ability to both down regulate and upregulate genetic expression. Barr and Meisner (2016) revealed non-coding RNAs assist in “key roles in neurogenesis, neurodevelopment and activity-dependent brain plasticity” (p. 191). Regarding neuroepigenetics, certain miRNAs act as “genetic risk factors in psychiatric disorders” (Barr & Meisner, 2016, p. 191). Sweatt and Tamminga (2014) promoted miRNAs and IncRNAs as an area of interest relative to DNA nucleotide genotyping in psychiatric disorders.

**Micro ribonucleic acids.** Kolshus, Dalton, Ryan, and McLoughin (2014) stated miRNAs regulate gene expression outside of the transcription process and “bridge the current gap in our
knowledge of the biology and treatment of … disabling [psychiatric] disorders” (p. 242). The understanding of the relationship and function of miRNAs has grown considerably since the discovery of the first lin-4 in 1993. Kolshus et al. (2014) stated since their discovery more than 1000 mature miRNA that target messenger miRNA have been identified. The shortest of all RNAs, approximately 21-30 nucleotides in length, the miRNA function was once thought to be strictly gene suppression; however, recent research revealed a reciprocal relationship with certain targets (Kolshus et al., 2014). For instance, expression of miRNA occurs primarily in child development with certain miRNA types devoted to specific organs and areas of the brain. For example, miRNA are pivotal in “synaptic plasticity, neurogenesis, and modulating neuronal functioning,” and show potential for early onset schizophrenia (Kolshus et al., 2014, p. 245).

One of the most fundamental tasks involving miRNA relative to psychiatric disorders is regulating synaptic plasticity. Kolshus et al. (2014) defined synaptic plasticity as the ability of the synapse to adapt per neural circuit activity. Changes include alterations to neurotransmitter release, dendritic density and size, and receptor expression, and all of these changes function as part of significant brain functions such as learning and memory. The dysregulation of any of these brain functions has the potential for the onset of psychiatric disorders (Kolshus et al., 2014). Current therapeutic development targets miRNA in relationship to certain enzymatic processes that regulate cell health and structure and post-natal and adult neurogenesis (Kolshus et al., 2014).

Long non-coding ribonucleic acids. Liu et al. (2015) stated IncRNAs are “transcripts over 200 nucleotides in length … found in …the cytoplasm and nucleus” (p. 1). Due to the highly expressive nature of neuronal IncRNAs, their purpose is “becoming increasingly interesting [regarding] brain functions and disorders” (Liu et al., 2014, p. 1). Long non-coding
RNAs include a wide variety of functions during brain development and function (Liu et al., 2014). Liu et al. stated the importance of lncRNAs relative to neuroepigenetics and mental health cannot be understated. Long non-coding RNAs regulate gene expression through “targeting transcription factors, initiating chromatin remodeling, directing methylation complexes, and [by] blocking transcription” (Liu et al., 2014, p. 7). Additionally, lncRNAs are fundamentally involved with regulating the expression of neighboring genes and influence the development and progression of psychiatric disorders. Liu et al. (2014) clarified the role of lncRNAs with “chromatin modifiers, transcription factors, splicing factors, [and] RNA decay machinery” (p. 1), as well as their part in the development of major depressive disorder.

Due to lncRNA’s association with several neurodegenerative disorders and psychiatric disorders, Liu et al. (2014) implicated the RNA in the development of psychosis, bipolar depression, and autism. Both the upward and downward regulation of lncRNAs, and their relationship with mRNAs are leading to a clearer understanding of the origins of the above mentioned psychiatric disorders. Liu et al. (2014) stated the “current understanding of lncRNA regulation in brain function and disease is in its infancy” (p. 7).

**Neuroepigenetics and Mental Health**

Awareness of the relationship between neuroepigenetics and mental health is burgeoning and has expanded exponentially with as many as 1500-2000 peer-reviewed articles written every year for the past ten years (Sweatt, 2013). Shin, Ming, and Song (2015) stated the direction of research is often dictated by economics, and much of the research has been focused on common psychiatric disorders to develop more appropriate and effective interventions. Additionally, systems-oriented therapies and curricula are being developed for depression, schizophrenia, bipolar disorder, and stress-related disorders including PTSD, as well as memory and learning
processes, particularly those processes related to fear. Sun et al. (2017) proposed evidence that epigenetic “transcriptional dysregulation may underlie the behavioral manifestation of many psychiatric disorders including depression” (p. 125). Sun et al. (2013) found stress during child development has the potential to leave long-lasting epigenetic marks, alter gene expression, and influence neural development and behavior.

**Major Depressive Disorder**

Hoffmann et al. (2017) stated major depressive disorder (MDD) is the primary cause of disability throughout life, including the onset of disease. Hoffmann et al. found MDD affects nearly “300 million people [which] corresponds to 4.4% of the global population and an increase by 18% across the last 10 years” (p. 1). Brody, Yu, Chen, Beach, and Miller (2016) found the offspring of highly depressive mothers experienced elevated hypothalamic-pituitary-adrenal (HPA) and sympathetic nervous system activation in developmental years. Sun et al. (2013) noted MDD affects 16% of the U.S. population and symptoms include “depressed mood, anhedonia, disturbed sleep, appetite, and energy, reduced concentration, excessive guilt, and suicidal thoughts” (p. 124). Suicidal depression claims the lives of nearly “800,000 victims every year [and] represents the second leading cause of death in 15 to 19 year olds” (Hoffmann et al., 2017, p. 1).

As other mental disorders were once considered entirely genetically heritable, Sun et al. (2013) found the heritability of MDD between 31-42%. Additionally, genome-wide studies have not consistently implicated gene sites in the heritability of the disorder. Hoffmann et al. (2017) stated the challenge of identifying a genetic contribution to mental health disorders lies in elucidating high prevalence without high heritability. Additionally, MDD is strongly discordant (50%) in monozygotic twins. Discrepancies relative to other disorders with higher heritability
rates have led to a surge in acceptance toward a more evolved explanation of MDD. Hoffmann et al. (2017) stated the genetic factor in MDD is relatively low and the research into genetic variants will likely not lead to necessary findings to expedite greater understanding of the disorder. As a result, researchers will look toward the contributing environmental factors as they relate to MDD.

According to Sun et al. (2013), the animal model of depression should be examined for its similarities in symptomology to the human experience, namely that of extension of the anhedonic state and adjustments to diet. The study of animal depression is commonly separated into acute and chronic models of stress. In the animal model, Sun et al. (2013) stated acute stress is a forced action upon the rodent that involves time-limited physical stress during which coping is measured by active and passive response times. On the other hand, chronic stress involves exposure to repeated or unpredictable physical stressors or chronic subordination in the social context (Sun et al., 2013).

Animals and humans share similar experiences of acute and chronic stress and the aftereffects of stress are almost indistinguishable on certain levels. For example, Sun et al. (2013) identified that chronic stress and isolation result in significant anhedonic behaviors, “characterized by a decrease in reward-related behaviors such as preferences for sucrose or high fat diets and social interaction” (p. 125). The observed rodent behavior is often found in human chronic stress-related behavior. Chronic stress in animals requires chronic treatment similar to treatment for humans. Additionally, animals and humans respond favorably to pharmacological interventions (Sun et al., 2013).

Hoffmann et al. (2017) reported the most significant factors in the development of MDD are early adverse experiences including “interpersonal loss, parental maladjustment, low
socioeconomic status in childhood, and maltreatment” (p. 4). Furthermore, chronic and recurrent episodes of adversity increase risk of MDD four-fold, and subsequently, the risk of life-long depressive symptoms including completed suicide (Hoffmann et al., 2017). As in the animal model, repeated exposure to stress in humans, coupled with feelings of dislocation from support and safety, “leads to sustained changes in gene regulatory and/or neuronal networks” (Hoffmann et al., 2017, p. 4).

Sun et al. (2013) found exposure to early chronic stress for humans may result in alterations in cognition via the prefrontal cortex and hippocampus, emotion via the amygdala, the reward system in the nucleus acumbens (NAc), and the HPA axis. Hoffmann et al. (2017) cited the importance of the HPA and “the subsequent secretion of glucocorticoids (CG) that normally serve to restore physiological and behavioral homeostasis” (p. 4). Hoffmann et al. (2017) stated CGs may behave contrary to normative operation when the system becomes overwhelmed by chronic stress and isolation.

Animal studies and post-mortem human examinations by Sun et al. (2013) suggested adaptation to stress and depression is regulated by histone acetylation, which is “transiently decreased and then persistently increased in the NAc after chronic social defeat stress” (p. 129). Sun et al. (2013) found the HDAC2 and HDAC5 enzymes in the NAc are involved in moderating the susceptibility to depression and elevated stress response. The HDAC2 enzyme targets in the NAc are hypothesized to endorse resilience and anti-depressant responses, and HDAC5 may increase symptoms of depression and maladaptive stress response (Sun et al., 2013).

Activity in the hippocampus is generally adaptive via increased histone acetylation in multiple areas after acute stress and subsequently supports memory formation (Sun et al., 2013).
Conversely, and opposite to the findings regarding the NAc, Sun et al. (2013) found a “persistent decrease in histone acetylation (H3K14ac) in the hippocampus” (p. 129) after chronic stress. Sun et al. (2013) suggested the likelihood of the persistent decrease being maladaptive is indicated by its reversal after administering imipramine and an HDAC inhibitor (HDACi).

Additionally, Sun et al. (2013) found high-responding (HR) rats, those who had low resilience to chronic stress, had lower levels of acetylation in the hippocampus and exhibited “significant reduction in body mass gain, reduced sucrose preference, and decreased social interaction” (p. 129). On the other hand, low responders (LR) exhibited resilience via increased acetylation after chronic social defeat (Sun et al., 2013). Sun et al. (2013) identified contrary roles for HDAC5 between NAc where it assumes “antidepressant-like actions” compared to the “pro-depressive role in the hippocampus” (p. 131). Treatment with imipramine in socially-defeated mice downregulated HDAC5 in the hippocampus, yet overexpression blocked the “antidepressant effect of imipramine in this paradigm” (Sun et al., 2013, p. 131). Sun et al. suggested the contrary effects by HDAC5 is determined by its relationship to the subset of genes or the gene’s behavioral relationship to the area of the brain. Sun et al. suggested the contrary effects by HDAC5 is determined by its relationship to specific areas of the brain indicating distinct and highly intentional therapies involving HDAC5 will need to be considered.

Although less observed than in the NAc or hippocampus, Sun et al. (2013) revealed the effect of acetylation in the amygdala. Chronic social defeat increases acetylation of H3K14 in the amygdala up to 24 hours after the last defeat, and after that 24-hour period, acetylation returns to baseline. Sun et al. (2013) suggested a diversity of responses to acetylation in the amygdala. For example, acute social defeat decreases H3 acetylation while chronic defeat
asserts no change, and that “chronic variable stress in male rats reduced HDAC5 levels … similar to … [the] NAc after chronic social defeat” (Sun et al. 2013, p. 131).

Sun et al. (2013) found a variety of HDAC and methylation rates in humans. Sun et al. stated HDAC2 and HDAC5 increased during depression. “HDAC6 and HDAC8 were decreased in patients regardless of their state,” and “HDAC4 was increased in the depressive state of bipolar patients” (Sun et al., 2013, p. 132). Sun et al. (2013) suggested histone acetylation in the brain has a high adaptive ability in the mediation of stress and depression.

Sun et al. (2013) found histone methylation as a factor in both depressive and anti-depressive exhibition; however, there is a lack of research to elucidate the findings thus far. Sun et al. (2013) identified the following histone methylation interactions:

- decreased euchromatic gene expression via the enzyme H3K9me2 in susceptible mice,
- overexpressed 9a creating anti-depressant-like behaviors,
- methylation changes due to social defeat and social isolation reversed with chronic anti-depressant treatment, and
- increased global level of H3K9me3 in the hippocampus after acute stress and decreased levels after chronic stress. (Sun et al., 2013) hypothesized H3K9 residue is pro-adaptive in stress regulation).

Roy, Wang, Palkovits, Faludi, and Dwivedi (2017) found a substantial relationship between miRNA and depressive behavior. Roy et al. (2017) postulated the “coordinated and cohesive fashion” of miRNA in gene expression “regulate entire genetic circuitries and thereby play a critical role in managing biological homeostasis” (p. 1). Consequently, disruption in the miRNA expression may result in disrupted homeostasis, or allostasis, by interrupting the normative delineation between healthy and disease states. Roy et al. (2017) found
downregulation of miRNAs in the prefrontal cortex relative to depression. In addition to adaptations in plasticity and transmission, miRNAs were also involved in depression-related phenotypes and suicidality.

Roy et al. (2017) focused on the locus coeruleus (LC) with its direct participation in memory and learning, stress response, and pleasure suppression. Unlike miRNA downregulation in the prefrontal cortex, miRNA in the LC was predominantly upregulated in suicidal individuals. The target genes of altered miRNA develop a “gene regulatory network” that “showed a comprehensive association with neuropsychiatric disorders” (Roy et al., 2017, p. 9) and risk factors for suicidality including depression and anxiety. Additionally, Roy et al. (2017) found altered miRNAs affected signaling pathways and “indicated an overall change in cellular signaling that have been implicated in suicide neurobiology” (p. 9).

**Schizophrenia and Psychotic Disorders**

The prevalence of schizophrenia (SCZ) is approximately 12 million males and nine million females annually worldwide, and the risk of early death is two to two-and-a half times more likely for those living with schizophrenia than the general population (Hoffmann et al., 2017). Symptomatic characteristics of schizophrenia include alterations and distortions in general perception, “thinking, language, emotions, sense of self, and behavior…and give rise ample delusions, that can associate with acoustical (hearing voices), optical, and sensory hallucinations” (Hoffmann et al., 2017, p. 2). Hoffmann et al. (2017) found heart, metabolic, and infectious diseases are the greatest risk factors associated with decreased physical health, quality of life, and death.

In addition to the research on MDD, Hoffmann et al. (2017) studied the overlapping epigenetic mechanisms and life course of schizophrenia and MDD. Although there is a lack of
identifiable diagnostic markers, Hoffmann et al. (2017) found, as with MDD, schizophrenia results from biopsychosocial factors from early neurodevelopment forward. Grayson and Guidotti (2013) found similarities between schizophrenia and bipolar disorder, particularly with psychotic symptoms. Despite the genetics of schizophrenia and bipolar being “perhaps the most studied facet of the disorders … over the last 60 years” (Grayson & Guidotti, 2013, p. 138), no clear etiological factors have been identified. Grayson and Guidotti (2013) suggested altered DNA methylation dynamics “likely underlie the pathogenesis of psychotic symptoms” (p. 138), and as with MDD, histone modification is found to play an active role. Furthermore, Grayson and Guidotti (2013) proposed a direct role of SNPs in the risk and susceptibility of schizophrenia. With clearer understanding of the disruption to GABAergic processes, future treatments targeting the cortex and hippocampus will function to “normalize the functional deficits in GABAergic transmission” (Grayson & Guidotti, 2013, p. 158).

Hoffmann et al. (2017) found “108 loci collectively implicate a total of 305 genes” (p. 4) including those involved in the immune system and synaptic plasticity. Hoffmann et al. highlighted unverified causal variants, pointing to the role of environmental factors. As with MDD and other disorders, childhood adversity is an important risk factor in the development of schizophrenia. Hoffman et al. (2017) identified disturbances in child development via maternal stress and trauma, emotional and psychiatric disorders, infections, and physical illness. Hoffmann et al. found sustained activation of the HPA axis and GC receptors overwhelm the child’s regulatory system that serves to moderate the child. Subsequently, deregulation of the HPA axis is implicated in changes within the structure and epigenome of “individual cells that confer…an increased risk of psychiatric disease” (Hoffmann et al., 2017, p. 5).
Grayson and Guidotti (2013) suggested multiple epigenetic mechanisms are involved in the development of schizophrenia. Homocysteine, the byproduct of SAH conversion, was found to increase the risk of schizophrenia two-fold when elevated during the third trimester of pregnancy (Grayson & Guidotti, 2013). Elevated levels of homocysteine have been reported in the plasma of males with psychosis, and a SNP in MTHFR has been implicated in elevated levels in mothers and their adolescent offspring (Grayson & Guidotti, 2013).

Downregulation of promoter genes RELN and GAD67 in the prefrontal cortex in general, and GABA neurons within the prefrontal cortex specifically, have been found in schizophrenia (Grayson & Guidotti, 2013). Grayson and Guidotti described the importance of the two promoter genes: GAD67 is associated with the formation of GABA, “whereas RELN is … synthesized and secreted in from GABAergic neurons in the adult brain” (p. 147). The altered relationship between GABAergic and glutamatergic neurons in schizophrenia indicated a likely disruption in GABAergic neuron function (Grayson & Guidotti, 2013). The imbalance in inhibitory/excitatory function in “various brain circuitries likely underlies the onset of positive and negative symptoms and the cognitive dysfunction seen in SCZ” (Grayson & Guidotti, 2013, p. 147).

GABAergic functions are closely aligned with DNMT expression, and data indicates a negative correlation between “DNMT1 mRNA levels and the number of GAD67-immunopositive neurons” (Grayson & Guidotti, 2013, p. 148). Grayson and Guidotti (2013) suggested an increase in neuronal DNMT expression may be the primary factor in decreased mRNAs in GABAergic neurons in individuals with schizophrenia. Grayson and Guidotti found potential evidence that due to interrelated nature of neuroepigenetics, alterations in GABAergic neurons may affect all neuronal activity in general.
Grayson and Guidotti (2013) cited multiple methylation factors in the development of schizophrenia, bipolar disorder, and psychosis in general. Hypermethylation was the most common methylation factor, yet it remains an unpredictable factor in psychotic symptom development. Grayson and Guidotti stated that in studies over the past two decades, candidate genes include dopamine D2 receptor (DRD2), RELN, and GAD67. Grayson and Guidotti suggested abnormalities in cortical mRNA expression may result from the “overexpression of DNMTs and the hypermethylation of promoters in GABAergic neurons” (p. 152). Relative to schizophrenia and bipolar disorder, Grayson and Guidotti found hypermethylation was a factor in DRD2, RELN, and in certain genome-wide studies, and that hypermethylation continued to increase with age. Additionally, GAD67 is sensitive to hypermethylation and its downregulated expression has been repeatedly located in brains of those diagnosed with schizophrenia. Grayson and Guidotti (2013) found “methylation at 27,000 CpGs in frontal cortices, cerebellum and pons” indicating a complex relationship between CpG methylation and age, thus a formidable target for therapeutic interventions (p. 151).

Hydroxymethylation via TET-1 proteins where a “5mC mark is modified by hydroxylating the methyl moiety to form 5hmC” (Grayson & Guidotti, 2013, p. 152) is of interest due to its function in the demethylation process. In schizophrenia, there is an increase in TET-1 expression and concurrently reduced mRNA expression, an apparent epigenetic contradiction; however, Grayson and Guidotti (2013) clarified the possibility of a demethylation process hindrance that creates an abundance of unconverted 5hmC, or TET-1 may bind with 5hmC to act as a repressor of certain subsets of genes.

As hypermethylation is a common factor in schizophrenia and other psychotic disorders, demethylation is a target therapy, particularly to reduce DNMTs and increase “expression of
GAD67 in cortical and hippocampal GABAergic neurons” (Grayson & Guidotti, 2013, p. 154).

As GABA downregulation or repression is a key element in the development and maintenance of psychotic symptoms, interventions to decrease interference in GABA synthesis and function will be vital. Therapies that break the blood-brain barrier are more effective in GABAergic treatment as neuronal cells “have a greater potential to change their methylation profile than nonneuronal cells” (Grayson & Guidotti, 2013, p. 151). For example, Grayson and Guidotti (2013) found nicotinic acetylcholine receptors (nAChRs) are downregulated in schizophrenia and as nAChRs regulate the release of GABA, nicotine use may be a way of modulating GABA production. Chronic nicotine use is overwhelmingly harmful to the human body, yet this type of finding leads to new directions in pharmacotherapy.

**Fear Learning, Memory, and Trauma**

Marshall and Bredy (2016) stated memory formation consists of two components. The primary component is protein-synthesis independent, and the other component is dependent on protein synthesis and gene transcription. Marshall and Bredy (2016) observed how protein synthesis is endorsed through repeated behavioral experiences via memory consolidation and inhibiting protein synthesis in this period inhibits memory formation. Zovkic and Sweatt (2013) stated memory is consolidated via a “complex set of molecular changes in distinct brain regions that support discrete forms of associative learning” (p. 78). Methylation and acetylation, and to a lesser extent hydroxymethylation, are studied to clarify environmental alterations in memory formation and recall. Peixoto and Abel (2013) stated acetylation is the primary epigenetic mechanism in the formation of memory and is involved in “physiological and pathological conditions” (p. 62). Zovkic and Sweatt (2013) suggested DNA methylation is a highly relevant mechanism in the formation and maintenance of memory. Regarding fear memorization, “innate
fear circuits must recruit both behavioral output structures and brain areas devoted to memory formation” (Silva, Gross, & Gräff, 2016, p. 551).

Hack, Dick, and Provençal (2016) described stress as a stimulus that disrupts the homeostasis of cortisol and GCs in the limbic-hypothalamic-pituitary (LHPA) axis. Stress-related changes in LHPA would induce further changes in other functions of the brain via “neurotransmission, synaptic plasticity, and neural architecture of brain regions that play critical functions in LHPA axis” (Hack et al., 2016, p. 4). Hack et al. examined the role of hydroxymethylation in fear-related learning and found a relationship between TET enzymes and brain-derived neurotrophic factor (BDNF). Both TET and BDNF enzymes have a pivotal role in memory and fear learning. Sabbagh et al. (2014) cited the highly influential role of binding protein FKBP51 in the development of stress-related psychiatric disorders, and FKBP51 may well play a role in disruption of the memory and learning process.

Hack et al. (2016) elucidated the processes by which fear learning and memory are studied in animal models via “cued and contextual fear conditioning” (p. 4). Fear conditioning consists of “repeated pairing of a neural conditioned stimulus (CS) (e.g. auditory cue or a particular environmental context) with an aversive unconditioned stimulus (US) (e.g. footshock)” (Hack et al., 2016, p. 4). The CS/US neural integration is moderated by a pathway in the amygdala that does not interact with same-species or social fear-based structure (Silva et al., 2016). After repeated processes, the CS “alone elicits autonomic and behavioral fear-conditioned responses” (Hack et al., 2016, p. 4).

Zovkic and Sweatt (2013) found acetylation of hippocampal histones, particularly H3, regulated contextual fear conditioning, and HDAC inhibitors increased memory formation in adult animals. Additionally, inhibited activity of DNMT showed a reduction in DNA
methylation of the genes promoting plasticity. Zovkic and Sweatt found upregulation of DNMT 1 and 3 occurred in response to contextual fear conditioning and prohibiting hippocampal DNMT activity impairs conditioning of contextual fear. Fear extinction is not the elimination, but the reversal of previously learned associations of contextual and cued fear via continued exposure to the context without unconditioned stimulus (Zovkic & Sweatt, 2013). Acetylation occurs in association with extinction of fear learning via increased levels in the hippocampus and medial prefrontal cortex. Zovkic and Sweatt (2013) suggested histone acetylation is involved in “persistent and brain-region specific effects on extinction of fear learning” (p. 82).

Zovkic and Sweatt (2013) generally associated BDNF with learning and memory, and more specifically, fear memory, and found BDNF subject to memory-associated changes via DNA methylation. Altered DNA methylation may affect BDNF mRNA levels in the hippocampus, which suggests likelihood for a mechanism to influence experiential responses and potential targets for future therapies (Zovkic & Sweatt, 2013). Brain-derived neurotrophic factor is also associated with acetylation processes that follow learning and increases in synaptic plasticity (Peixoto & Abel, 2013). Peixoto and Abel found an increase in acetylation surrounding various BDNFs relative to fear conditioning or fear extinction, suggesting a combination of promoters interact in adapting to environmentally-based fear.

Zovkic and Sweatt (2013) suggested once memories are transferred to the cortex from the hippocampus, a reversal of epigenetic changes transpires in the hippocampus during memory formation. Additionally, storage and maintenance of remote memory is supported by self-sustaining DNA methylation within the cortex (Zovkic & Sweatt, 2013). Methylation’s role in memory storage has been implicated with memory-suppressor genes calcineurin and reelin and temporally-specific DNMT inhibitor effects on remote memory formation. Zovkic and Sweatt
(2013) found non-dividing neuronal cells have adopted traditional epigenetic processes so they can be used for “temporally-specific purposes in memory formation and maintenance” (p. 82).

Silva et al. (2016) summarized that “the processing of acute fear resides in separate circuits at all functional levels depending on the type of threat” (p. 552); these independent circuits interact with the same brain systems to integrate the fearful event into memory. The developing understanding of the epigenetic mechanisms associated with fear and memory formation can be used to develop therapies for a wide variety of fear- and anxiety-based disorders, including PTSD. Symptoms of PTSD are generally known as persistent sympathetic/HPA axis responsivity, chronic anxiety, heightened startle response, and decreased cognitive functioning; symptoms are associated with “DNA methylation in peripheral blood immune cells” throughout the immune system genome (Zovkic & Sweatt, 2013, p. 83). Zovkic and Sweatt (2013) identified a series of future targets for therapy and intervention:

- altered sympathetic, HPA, and parasympathetic responsivity
- interruption of memory reconsolidation to induce memory erasure, which does not affect memory outside of the reconsolidation window;
- DNA methylation and histone modification in the amygdala and hippocampus per the reconsolidation process;
- alteration of the intensity and strength of recalled memory via “cellular processes in the amygdala (for cued memory) and hippocampus (for contextual memory)” (p. 88); and
- DNA methylation in the anterior cingulate cortex is vital for remote fear memory and that disrupting methylation impairs memory recall.

Additionally, Zovkic and Sweatt (2013) suggested enhanced fear extinction as a likely target of research and intervention. Extinction of fear memory does not eliminate initial CS/US
association but forms a new memory. The new extinction memory thus challenges the conditioned memory in a new expression of fear, and when implemented in conjunction with virtual reality therapy “produces improvements in phobia symptoms for at least 3 months after exposure” (Zovkic & Sweatt, 2013, p. 89). Zokvic and Sweatt stated the strength of traumatic memory associated with PTSD increases resistance to extinction, and histone acetylation in the medial prefrontal cortex and hippocampus are significant targets for pharmacotherapies.

**Individual Psychology**

In the literature reviewed for this project, peer-reviewed journal articles did not exist that highlighted the intersection of neuroepigenetic theory with Alfred Adler’s theory of Individual Psychology; however, four of Adler’s classic themes coincide with the contemporary understanding of neuroepigenetics: social interest, life tasks, inferiority feelings, and law of movement (Ansbacher & Ansbacher, 1964). Adler’s Individual Psychology is founded on “one basic driving force behind all humanity”, a striving that “receives its specific direction from an individually unique goal” formed through “biological and environmental factors” (Ansbacher & Ansbacher, 1964, p. 1). Furthermore, Ansbacher and Ansbacher (1964) stated “biological factors and past history . . . do not function as direct causes but provide probabilities only” (p. 2). This comment preceded the language used to define neuroepigenetics by more than half a century.

**Social Interest**

According to Ansbacher and Ansbacher (1964), Gardner stated Adler’s unique perspective on the psychological system was the first to offer a “social-science direction” (p. 126). Adler’s theory of social interest (i.e., *gemeinschaftsgefühl*) promotes the concept that the individual must be understood within the social context, from direct interpersonal relationships
to larger social frameworks. Oberst and Stewart (2003) stated the theory of social interest built
the foundation for humanistic theories including self-actualization and Maslow’s hierarchy of
needs. Social interest, and subsequently psychological health, is measured by satisfaction and
collaboration within social systems, primarily through the life tasks of love, occupation, and
community (Oberst & Stewart, 2003).

Life Tasks

Ansbacher and Ansbacher (1964) stated Adler’s life tasks of love, occupation, and
community developed after the fifth year of life through “preliminary problems” of “relationship
to the other sex” (love), school (occupation), and friendship (community; p. 158). According to
Ansbacher and Ansbacher (1964), Adler suggested the useful side of life tasks is when
individuals develop the goal of personal perfection, and the useless side of life tasks is when
individuals move toward the goal of personal superiority via neurosis, psychosis, criminality,
abnormal behavior, and substance use. Oberst and Stewart (2003) stated the individual develops
a style of life to balance the approach, fulfillment, and completion of the life tasks. The style of
life, or life style, exhibits “how different aspects of the personality function together,” is founded
on the “child’s creative answers” to early experiences and is apparent in all behavior throughout
life (Oberst & Stewart, 2003, p. 19). When the style of life is appropriate to life’s demands,
greater likelihood exists to fulfill the life tasks. As a result, individuals achieve a higher quality
of life and increased psychological well-being.

Inferiority Feelings

Ansbacher and Ansbacher (1964) stated “that to be human means to feel inferior” (p.
115), elucidating the natural condition to identify and to move away from inferiority. Adler’s
theory of inferiority feelings differed from Freud’s in the suggested direction people move from
inferiority. For instance, Adler stated humans move forward toward perfection. On the other hand, Freud stated humans revert to safety (Ansbacher & Anbacher, 1964). Normal inferiority feelings move the child, with genetic inferiorities in the social context of adults, to develop a goal of perfection (Ansbacher & Ansbacher, 1964). In addition, inferiority feelings maintain the adult in consistent states of agitation and unsettledness within a healthy, compensatory pursuit of the goal. Abnormal inferiority feelings arise when the bodily organ, or the environment, are considered inferior and a burden to the child. Subsequently, the child develops a style of life that includes conflict, victimization, and ultimately, overcompensation into feelings of superiority. Abnormal feelings of inferiority are most often hidden from sight, and the individual becomes preoccupied with the strategy of concealment. The original feelings become obscured until the feelings exhibit as a detriment to the individual’s quality of life (Ansbacher & Ansbacher, 1964).

Law of Movement

Ansbacher and Ansbacher (1964) stated “all is movement” on the “way to arrive at the solution of problems and the overcoming of obstacles” (p. 195). Adler’s theory of the individual’s law of movement is the basis of the style of life and often operates without conscious awareness of its existence or intention. Carlson, Watts, and Maniaci (2006) found when individuals strive to move mutually within their group, they do so “on prudent judgement” that creates a “larger, more universal perspective – a sort of wisdom that defies categorization” (p. 87). This law of movement is trained on the goal of perfection. On the other hand, Adler described the “antithetical mode of apperception,” or the dichotomous nature of the law of movement toward superiority, comprised of “either-or, black-white, yes-no,” and other forms of rigid thinking (as cited in Carlson et al., 2006). Just as the theory of neuroepigenetics is the influence of the environment on the body at the molecular level (Rastegar, 2017), Adler’s law of
movement is the influence of unseen factors on the direction and manipulation of the style of life; however, both can be witnessed with the ability to “freeze the movement in order to see it as form” (Ansbacher & Ansbacher, 1964, p. 195).

**Discussion**

Despite the influx of research and scholarly articles supporting neuroepigenetics as a crucial factor in psychiatric disorders, the field of research and practice is particularly young. Relative to the decades of research into the human genome, knowledge of the epigenome is limited; however, genome-wide studies have not produced gene loci that consistently contribute to the onset of psychiatric disorders (Sun et al., 2013) driving researchers toward neuroepigenetics as a means of causation. As the scope of research expands in coming years, so will the understanding of the environmental influence on genetic expression.

Neuroepigenetic mechanisms regulate genetic expression and are a primary factor in brain function, including psychiatric disorders, mood disorders, memory, and learning (Sweat, 2013). Three fundamental mechanisms that influence neural development from gestation throughout life are DNA methylation, histone tail modifications, and microRNAs (Sweatt, 2013). Recent research highlighted the relationship between each neuroepigenetic mechanism and multiple psychiatric disorders such as major depressive disorder, schizophrenia and psychosis, bipolar disorder, and fear memory and learning, including PTSD (Brody et al., 2016; Grayson & Guidotti, 2013; Hack et al., 2016; Hoffmann et al., 2017; Marshall & Bredy, 2016; Peixoto & Abel, 2013; Roy et al., 2017; Sabbagh et al., 2014; Shin et al., 2015; Silva et al., 2016; Sun et al., 2013; Zovkic & Sweatt, 2013).

Depressive symptoms and suicidality have been linked to mechanisms acting in multiple brain areas and affecting various functions. For instance, DNA methylation and histone
modifications may lead to the following issues: cognition distortions via the prefrontal cortex and hippocampus, emotional deregulation via the amygdala, and reward system manipulation in the NAc and HPA (Peixoto & Abel, 2013; Sun et al., 2013; Zovkic & Sweatt, 2013). Disturbance in miRNA in the LC results in possible disruptions in the differentiation of health and disease states (Roy et al., 2017). Changes in neuronal expression result from early and continued exposure to adversity in the mother and the developing child and adolescent. For example, Hoffmann et al. (2017) found chronic and recurrent episodes of adversity, particularly in early childhood development, greatly increases the susceptibility to psychiatric disorders and suicidality.

Schizophrenia, psychosis, and bipolar disorder result from biopsychosocial factors from early neurodevelopment forward (Grayson & Guidotti, 2013). Grayson and Guidotti cited altered DNA methylation as the primary underlying factor in the development of psychosis in general. Histone modification is second to DNA methylation in the onset of psychosis, and SNPs are found to be influential as well (Grayson & Guidotti, 2013). Homocysteine was found to increase the risk of schizophrenia two-fold when elevated during the third trimester of pregnancy (Grayson & Guidotti, 2013). Abnormalities in cortical mRNA expression may result from the hypomethylated DNMT and hypermethylated expression of GABAergic neurons (Grayson & Guidotti, 2013). A perturbation in the expression and overall function of GABAergic neurons may hold a key for future research into treatment of psychosis.

Acetylation is cited by Peixoto and Abel (2013) as the primary epigenetic mechanism in the formation of memory. On the other hand, Zovkic and Sweatt (2013) suggested the broad use of DNA methylation in all stages of memory formation and maintenance. Memory is initiated and maintained via the integration of the amygdala, hippocampus, LPHA, HPA, cortex, NAc,
and prefrontal cortex (Zovkic & Sweatt, 2013). The influence of DNA methylation, histone modification, and miRNAs along any of the pathways between brain regions, can lead to alterations in normative fear memory and learning processes.

The mechanisms that underlie common, severe, and pervasive psychiatric disorders offer a modern lens on the century-old practice of Adlerian therapy. Alfred Adler’s perspective of holistic development and existence runs parallel to the core theory of neuroepigenetics as the bodily organ is responding to internal and external environmental cues for the duration of life (Klengel et al., 2016). In fundamental Adlerian terms, environmental cues may be those of feelings of social connectedness and significance, to isolation and discouragement (Ansbacher & Ansbacher, 1964). Alfred Adler recognized the complexity of influences in terms of psychiatric development, and modern medicine and research is now beginning to show the extent of Adler’s theories.

Adler lamented “the means by which the body is influenced have never been completely explored, and we shall probably never have a full account of them” (as cited in Ansbacher & Ansbacher, 1964, p. 223). Neuroepigenetics appears to be the most succinct biological explanation for the influence of the environment on the individual. Klengel et al. (2016) suggested the earliest environmental influence begins within the gestating embryos in utero as they are particularly vulnerable to the changes of the maternal environment. As a result, maternal depression experienced during pregnancy increases susceptibility to depression in offspring, and maternal exposure to stress and adversity elevates likelihood of psychosis and autism. According to Yehuda, HPA axis alteration occurred in the offspring of 9/11 PTSD victims, which subsequently lowered cortisol and disrupted normative stress response (as cited in Klengel et al., 2016).
Adler postulated psychoneuroses owes its “origin to a style of life which, in the case of failure, shows an inclination to retreat” (as cited in Ansbacher & Ansbacher, 1964, p. 224) into the creative self to preserve the organ from stress and shock symptoms. Van der Kolk (2014) suggested a primary task of trauma recovery is to “reestablish ownership of your body and your mind” and to disengage in previous patterns of being “overwhelmed, enraged, ashamed, or collapsed” (p. 206). Per van der Kolk, restoration of self is in line with Adler’s social interest theory: the degree to which a person can integrate and participate in society reflects their level of mental health and encouragement/discouragement (Ansbacher & Ansbacher, 1964).

The present challenge with neuroepigenetics is the wide array of influences, perturbations, and corrections possible at any point in an individual’s life. The methylation process, with one million cycles occurring every second in the human body, provides innumerable opportunities for stresses to manifest in the body and brain that may not be recognizable until clinical intervention is necessary. Sweatt (2016) stated a considerable number of “human disease genes and molecular processes” (p. 195) influence neuronal behavior and plasticity. Additionally, behavioral approaches to understanding disease genes “provide the real possibility of developing novel therapeutics to alleviate human suffering and death” (Sweatt, 2016, p. 195).

**Implications for Practice**

With neuroepigenetics, the Adlerian therapist has an additional means to assist individuals to “decrease their inferiority feeling and to increase their Social Interest” (Oberst & Stewart, 2013, p. 47). Looking directly at Adler’s perspective on depression, psychosis, and anxiety/fear, there are neuroepigenetic mechanisms that offer a distinct biological explanation for the behavior Adler witnessed and hypothesized upon.
Adler’s view on depression, or melancholia, was that it developed “in individuals whose method of living has from early childhood been dependent upon the achievements and the support of others” (as cited in Ansbacher & Ansbacher, 1964, p. 319). Considering the neuroepigenetic processes of depression, the parallel can be seen between the early exposure to adversity and Adler’s determination of relying on support and achievement. For instance, the child developed in a pre-natal environment of depression may arrive into the world with a temperament toward relying upon others and feel discouraged and unable to develop with awareness and confidence. Should the caregiver continue with depressive symptoms, the child may have no possibility to fulfill the need for support and achievement, thus compounding previously established implicit sensations of uselessness and inferiority. Oberst and Stewart (2003) identified the “aggression that lies behind their dramatically pessimistic views” (p. 44). The Adlerian therapist would connect the neuroepigenetic understanding that depression is an inward expression of anger determined by a distinct hypomethylated gene site, and when hypermethylated, exhibits as oppositional defiant disorder (Walsh, 2014).

The Adlerian perspective of schizophrenia is that the onset is initiated via isolation from the self and others (Oberst & Stewart, 2003). Because of the distortions in the sense of self and others described above, the individual experiencing psychotic symptoms may feel “extremely high feelings of inferiority … [and] strive for extremely high and unattainable goals” (Oberst & Stewart, 2003, p. 46). The lack of self and subsequent retreat into the creative mind may also manifest as paranoia, grandiosity, or any other type of delusion. Neuroepigenetics points to disturbance in GABAergic neurons as a possible factor in the onset of psychosis, and the Adlerian therapist would work with others to develop a means to mitigate GABA disruption.
Adler stated anxiety manifests to place “psychological distance between the individual and his or her life task” (as cited in Oberst & Stewart, 2003, p. 40) to preserve self-esteem in the face of defeat. Oberst and Stewart (2003) stated during a life overcome by anxiety, “everything must be subjugated to [their] anxiety” (p. 40), and all perception is then processed through that lens. Fear learning and memory is increased and concretized by decreasing synaptic flexibility and normative memory recall through repeated stress exposure. The rigidity of the learning and memory process prohibits the ability to switch between the sympathetic and parasympathetic nervous systems, thereby creating a perspective of consistent threat in the external environment. Oberst and Stewart (2003) identified anxiety as the “classical motivator of the hesitating attitude” (p. 40), and the Adlerian therapist understands that a client’s hesitation may be the action of a mind overwhelmed by fear.

The Adlerian approach to manipulating epigenetic mechanisms for health and vitality would include a variety of factors. Adler thought “the mind governs and influences the whole building up of the body” (as cited in Ansbacher & Ansbacher, 1964, p. 225). For instance, Bourassa, Alim, Bultman, and Ratan (2016) stated high-fiber butyrate is a “multi-functional molecule that has significant potential as a therapeutic for the brain, both in its pharmacologic and dietary form” (p. 60). Bourassa et al. (2016) found butyrate acts upon multiple pathways and mechanisms and offers a “relatively low risk method to potentially improve outcomes in patients with brain disorders” (p. 60).

Pre-natal and early developmental changes in environment preclude individual autonomy in manipulating epigenetic mechanisms; however, once personal awareness of distinct mechanisms is achieved, the individual has the power to influence the epigenome via their internal environment, which has as a more immediate affect over any external factor (Sweatt,
Adler’s law of movement did not only apply to words, thoughts, feelings, and actions, as “the body is also subject to the law of movement” (as cited in Ansbacher & Ansbacher, 1964, p. 223). A therapist’s role is to renew the concept of movement to the individual, working to familiarize with natural graces, to recognize the futility of actions once used as survival in the present moment free from harm, and to change the lenses of stress, trauma, and discouragement. Neuroepigenetics provides a profound advancement in the conceptualization and application of Adlerian therapy; it is scientific evidence of the interdependent relationship between the individual and the environment.

**Recommendations for Future Research**

Neuroepigenetics is a young field, so a multitude of opportunities exist for future research. Just as cancer researchers have identified specific gene sites to manipulate in the treatment of tumors, neuroepigenetic researchers have done so with gene sites, histone modification processes, and miRNA manipulation. An appropriate first step would be to correct the testing that determines hypo- or hypermethylated genomes, which is particularly relevant in identifying which form of depression an individual may be experiencing. The methylation cycle provides opportunity to regulate methyl production and utilization when considering the availability of enzymes utilized in the process.

Grayson and Guidotti (2013) cited hydroxymethylation of particular interest for those with a hypermethylated epigenome due to its involvement in the demethylation process. Demethylation is a target therapy to reduce DNMTs and increase “expression of GAD67 in cortical and hippocampal GABAergic neurons” (Grayson & Guidotti, 2013, p. 154) in those with psychotic symptoms. Specific HDACs such as HDAC2 showed consistent anti-depressant-type properties in the NAc, whereas HDAC5 was inconsistent and may rely on other mechanisms to
exhibit anti-depressant properties (Sun et al., 2013). Additionally, manipulated upregulation of miRNA in the prefrontal cortex, and down regulation of miRNA in the LC may assist in decreasing depression and suicidal behavior and ideation.

Zovkic and Sweatt (2013) proposed multiple future targets for treatment of fear memory and learning: enhanced fear extinction, interruption of memory reconsolidation to induce memory erasure, DNA methylation and histone modification in the amygdala and hippocampus per the reconsolidation process, alteration of the intensity and strength of cued memory in the amygdala and contextual memory in the hippocampus, and DNA methylation in the anterior cingulate cortex relative to recall and blocking of fear memory. Specific targets have been proposed to decrease the strength of PTSD memory and its resistance to extinction, particularly via histone acetylation in the medial prefrontal cortex and hippocampus.

The momentum of research and publication of findings indicates that holistic and pharmacotherapies that manipulate neuroepigenetic mechanism are on the cusp of development and implementation. Further research must include acute and practical solutions that individuals can utilize on their own. Empowering people in their own recovery into mental and physical health is a truly epigenetic concept as the internal environment has a direct positive effect on the epigenome (Sweatt, 2013).

**Conclusion**

As a field of research, neuroepigenetics has the potential to influence treatment of psychiatric disorders in humane and compassionate means that consider biopsychosocial aspects of the individual’s style of life. As a supplement to Adlerian therapy, neuroepigenetics provides innovative support to traditional theories and techniques. The Adlerian therapist who integrates neuroepigenetics into practice benefits from advanced biological evidence to enhance their
therapeutic orientation. The client benefits most of all and gains a new level of personal awareness and insight previously unavailable in the traditional therapeutic setting.

All new modalities, therapeutic approaches, and scientific innovations face potential scrutiny and ridicule when first introduced, and neuroepigenetics faces considerable resistance from traditional psychoanalysis and therapy; however, the Adlerian therapist is adept at maneuvering and adapting to suit the needs of the individual and combining aspects from multiple theories to form a personalized therapeutic orientation. Sharpening the focus of the therapeutic lens with the addition of neuroepigenetics also creates a broader perspective of the life of the individual. That is, therapists could see the potential for the onset of disorder to the internal factors and motivators for healing. Neuroepigenetics mirrors the philosophy of Adler in one final way: It emphasizes the importance of relationships, and the system is crucial in the healthy development and vitality of the individual.
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