REVIEW

Early life stress and the role of environmental and molecular moderators in the ontology of pathological and resilient behavioral phenotypes [version 1; peer review: awaiting peer review]

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Abstract

Early life stress (ELS) in the form of trauma or caregiver abuse and neglect is often associated with psychopathology. However, not everyone exposed to ELS develops a pathology; others display resilience, or the ability to adapt and persevere despite ongoing adversity. Several molecular moderator variables between ELS and behavioral phenotypes have been proposed, including single nucleotide polymorphisms (SNPs) and epigenetic markers. Specifically, several SNPs and aberrant methylation or expression of genes associated with neurotransmitter systems and brain-derived neurotrophic factor have been associated with anxiety, depression or schizophrenia. The present review seeks to explore the relationship between SNPs, epigenomics and disease, and offer data to suggest several SNPs may also predict specific treatment efficacy and psychological resilience. Due to this discrepancy in the literature, it is critical that environmental moderators be equally considered in determining the ontology of resilient or pathological phenotypes; this includes the infant-caregiver relationship, and the degree of control, magnitude, and type of the stressor experienced. Finally, we will offer evidence to suggest that several intervention strategies, including drug treatment, environmental enrichment, or exercise can ameliorate many of the psychological, biological, and molecular consequences of ELS exposure, and help shift one toward a resilient phenotype.
Keywords
Resilience, ELS, epigenetics, polymorphisms (SNPs), intervention, BDNF, development, caregiver

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Introduction

Early life stress (ELS) in the form of caregiver abuse or neglect is often associated with increased incidences of depression (Heim & Binder, 2012; Humphreys et al., 2020; LeMoult et al., 2020; Saleh et al., 2017), anxiety disorders (Guo et al., 2021; Li et al., 2016; Simon et al., 2009), suicidal ideation or attempts (Angelakis et al., 2019; Sekowski et al., 2020), and a perpetuation of abuse and neglect into the next generation (Greene et al., 2020; Roth et al., 2009a; Savage et al., 2019). Indeed, work in humans and animal models has suggested the role of early life programming on both the brain and epigenome through infant-caregiver interactions in the etiology of psychopathology. However, not all of those who experience ELS go on to develop disease. It has been demonstrated that some instances of ELS can improve behavioral flexibility (Gapp et al., 2014), emotional learning (Oomen et al., 2010), facilitate adaptive stress coping strategies (Parker et al., 2019; Santarelli et al., 2017; van der Doelen et al., 2013), and improve self-reported mental health outcomes (Seery et al., 2010). Thus, a critical area of research is examining the moderators that determine the development of pathology, or psychological resilience.

Psychological resilience is often defined as the ability to adapt and persevere despite adversities that would otherwise lead to psychopathology (Afek et al., 2021). Some proposed moderator variables determining psychopathology or resilience include the amount of control one has over the ELS (Feder et al., 2011; Wu et al., 2013), the amount of ELS experienced (Parker et al., 2019), and the infant-caregiver relationship (Beeghly & Tronick, 2011; DiCorcia & Tronick, 2011; Masten & Shaffer, 2006). Stress inoculation is the phenomenon that exposure to and mastery of moderate stressors can facilitate later coping to unpredictable stressors (Brochhurst et al., 2015; Feder et al., 2009; Lyons et al., 2009; Lyons & Parker, 2007; Southwick & Charney, 2012; Wu et al., 2013). The parent-infant relationship is likewise capable of reducing stress physiology and improving self-regulation of offspring, known as maternal buffering (Gunnar & Sullivan, 2017). High-quality caregiving thus has been proposed as a mechanism driving stress resilience (Stevens et al., 2021), with maltreatment or trauma exposure reducing the effectiveness of the buffering effect (Opendak et al., 2019; Robinson-Drummer et al., 2019). Intervention strategies with the goal of improving the caregiving relationship (Bernard et al., 2012; Bernard et al., 2015; Bernard et al., 2017; Dozier & Bernard, 2017; Miller, 2017; Olds et al., 2003), providing environmental enrichment (Dandi et al., 2018; Hegde et al., 2020), and exercise programs (James et al., 2014; Zolfaghari et al., 2021) have been efficacious in ameliorating many of the biological, behavioral, and molecular consequences of exposure to ELS (for review, see Collins et al., 2020). Thus, a critical research focus is examining known psychopathological biomarkers, and what intervention strategies are able to shift activity into a resilient state and improve behavioral and disease outcomes.

The goal of the current review is to outline development pathways to both psychopathology and resilience at the level of single nucleotide polymorphisms (SNPs), gene by environment interactions, and epigenetic markers. Further, we will attempt to reconcile the role of environmental and molecular moderators in the etiology of disease or resiliency as a function of developmental programming, and provide intervention strategies known to improve both epigenetic and psychopathological outcomes. Finally, future directions of resiliency epigenetic research will be discussed.

ELS as a risk factor for psychopathology

ELS includes incidences of adversity that an individual experiences during their prenatal, postnatal and adolescence years. These can include incidences of prenatal stress, (Chang, 2020; Walsh et al., 2019) and postnatal maternal neglect and abuse (Carr et al., 2013), with abuse and neglect frequently co-occurring (Chartier et al., 2010). Much of the literature focuses on stressors that disrupt caregiver-child interactions (physical, sexual, and emotion abuse; domestic violence; extreme marital discord), as opposed to outright neglect. Traumatic experiences throughout development may impair neuroendocrine and neurobiological processes that can persist throughout the lifespan and precipitate disease risk later in life (Carr et al., 2013), including increasing the risk for depression and anxiety disorders (e.g. Humphreys et al., 2020; Li et al., 2016). The use of animals in research has been crucial to our understanding of ELS-associated psychopathology; environments can be controlled, and neural networks can be perturbed. The ethical limitations on using humans in research have reinforced the need for dependable and sustainable animal models to elucidate neurobiological processes (Guzman et al., 2016). Often, ELS models in rodents include maternal separation (Calabrese et al., 2015), limited nesting and bedding (Walker et al., 2017), or maltreatment (Roth et al., 2009a), which have consequences for later behavioral phenotypes.

Through the use of both human and animal models, data have suggested that psychopathological consequences of ELS exposure vary by the type (Carr et al., 2013), severity (King et al., 2017), and timing of exposure (Brenhouse et al., 2019). Generally, ELS affects sensitive periods of neural development (Heim & Binder, 2012), which can impart consequences on the morphology of the brain, including reductions in PFC (Chocyk et al., 2013) and hippocampus (Loi et al., 2014) volumes and morphology (Saleh et al., 2017), and reduce the fractional anisotropy in numerous white matter tracts (Frodl et al., 2012). Indeed, ELS exposure is associated with neuronal atrophy, synaptic loss, and synaptic density reduction in the hippocampus and PFC (for review, see Duman et al., 2016) in those with MDD. Among those with psychopathology, differences in the synthesis, trafficking, storage, and release of several neurotransmitter systems (Sarter et al., 2007) and neurotrophic factors such as brain-derived neurotrophic factor (BDNF) (Yang et al., 2020) have been a
prevailing research area. These differences have brought into focus the role of genetic variations, called SNPs, and how they interact with environmental factors to confer unique disease risk.

**Gene×Environment interactions: Polymorphisms and ELS**

Gene by environment (GxE) interactions occur when exposure to environmental factors, like stress, conditionally affect an individual based on specific variations in a person’s genetic code (for review see Moffitt et al., 2005). GxE interactions are associated with several neuropsychiatric and developmental disorders, including major depressive disorder (MDD) (Lin & Tsai, 2019), conduct disorder and antisocial personality disorder, (Caspi et al., 2002), anxiety (Domshke et al., 2012), and schizophrenia (Le Strat et al., 2009). SNPs refer to genetic variations caused by differences in a single nucleotide in a DNA sequence that often do not affect an individual’s overall health but can predict an individual’s vulnerability to environmental factors, and response to certain drug treatments (Medlineplus, 2022). Specifically, SNPs can be used as genetic markers to determine if a person exposed to ELS is at a greater risk of developing neuropsychological disorders during adulthood due to GxE interactions (Shastry, 2009). Well-studied SNPs known to interact with exposure to stress are found in the genes encoding for BDNF (Shastry, 2009). Well-studied SNPs known to interact with exposure to environmental factors, like stress, conditionally affect an individual based on specific variations in a person’s genetic code (for review see Moffitt et al., 2005). GxE interactions are associated with several neuropsychiatric and developmental disorders, including major depressive disorder (MDD) (Lin & Tsai, 2019), conduct disorder and antisocial personality disorder, (Caspi et al., 2002), anxiety (Domshke et al., 2012), and schizophrenia (Le Strat et al., 2009). SNPs refer to genetic variations caused by differences in a single nucleotide in a DNA sequence that often do not affect an individual’s overall health but can predict an individual’s vulnerability to environmental factors, and response to certain drug treatments (Medlineplus, 2022). Specifically, SNPs can be used as genetic markers to determine if a person exposed to ELS is at a greater risk of developing neuropsychological disorders during adulthood due to GxE interactions (Shastry, 2009). Well-studied SNPs known to interact with exposure to stress are found in the genes encoding for BDNF (Gatt et al., 2009), the serotonin transporter (Caspi et al., 2003), Monoamine Oxidase A, (Caspi et al., 2002), and the D2 dopamine receptor (Klaus et al., 2017).

**BDNF**

Brain-derived neurotrophic factor (BDNF) is a neurotrophin important for learning and memory (Miranda et al., 2019), cellular survival (Ortiz-López et al., 2017), synaptic plasticity (Duman et al., 2016), and has been a proposed biomarker for major depression, specifically with deficiencies observed in the hippocampus (Yang et al., 2020). A well-studied SNP occurring in the genetic sequencing encoding for the BDNF protein causes an amino acid switch from valine to methionine (Egan et al., 2003). This SNP, referred to as Valmet66, is linked with episodic memory impairment (Egan et al., 2003), impaired hippocampal activation (Egan et al., 2003; Franzmeier et al., 2021), decreased activity-dependent BDNF release in the hippocampus (Egan et al., 2003), and decreased hippocampal volume (Jasińska et al., 2017). Further, individuals with the Valmet66 polymorphism may be at an increased risk of developing psychopathology in the context of ELS exposure. Indeed, previous work has shown that the ValMet66 polymorphism interacts with ELS exposure to confer risk for elevated levels of depression (Gatt et al., 2009; Zhao et al., 2018), anxiety (Gatt et al., 2009), and lower hippocampal volume (Carballedo et al., 2013).

Serotonin transporter and monoamine oxidase
dThe serotonin transporter (5-HTT) functions to regulate mood by reuptake and recycling of serotonin from the synaptic cleft (Zhang et al., 2016), and is the main target of selective serotonin reuptake inhibitors (SSRIs) in the treatment of depression (I.E., Frazer, 1997). The serotonin transporter gene solute carrier family 6 member 4 (SLC6A4) contains a SNP at the serotonin-transporter-linked promoter region (5-HTTLPR), which affects transcription of the serotonin transporter (for review see Lesch et al., 1996; Nugent et al., 2011). More specifically, individuals possessing two copies of a short allele have decreased SLC6A4 expression and serotonin (5-HT) reuptake (Lesch et al., 1996). Short allele carriers are reported to show aberrant emotional regulation and cognition, and decreased grey matter density in frontal-cortical regions, the anterior cingulate cortex, and cerebellum (for review see Canli & Lesch, 2007; Canli et al., 2005). Childhood maltreatment interacts with this polymorphism, with short allele carriers exposed to ELS showing an increased risk of developing persistent depression (Houwing et al., 2017; Uher et al., 2011), as well as increased depressive symptomology and suicidality (Caspi et al., 2003; Li & He, 2007).

Monoamine oxidase A (MAOA) is an enzyme involved in the degradation of serotonin (Prah et al., 2020), dopamine (Cho et al., 2021), and epinephrine Fuller & Henrick-Luecke (1981). The MAOA gene contains a SNP located at the promoter region, termed MAOA-L, which is associated with lower MAOA expression and facilitates risks for developing behavioral and psychiatric disorders (Caspi et al., 2002; Enoch et al., 2010). Lower MAOA expression has been linked to trait aggression (Alia-Klein et al., 2008), which is associated with the low-activity allelic variant of this locus (Klasen et al., 2018). Further, ELS has been shown to interact with the MAOA-L SNP, leading to a significant increased risk of developing an antisocial personality disorder compared to individuals with high MAOA activity (Caspi et al., 2002), as well as hyperactivity in children (Enoch et al., 2010) and adolescents (Zohsel et al., 2015). Given that the MAOA enzyme also breaks down serotonin, some evidence suggests that the MAOA and 5-HTTLPR short allele polymorphisms interact in individuals exposed to ELS to further increase depression symptoms (Cicchetti et al., 2007).

**Dopamine**

The DRD2 gene encodes for the dopamine D2 receptor (Hirvonen et al., 2005), and some SNP’s of this gene include C957T and TAQI, which have been implicated in Schizophrenia (González-Castro et al., 2016; Hänninen et al., 2006; Hoemicka et al., 2006; Lawford et al., 2005) and alcohol dependence (Berggren et al., 2010; Swagell et al., 2012). The C957T polymorphism is located on exon 7, and has been associated with decreased dopamine receptor availability in the striatum (Hirvonen et al., 2005) and has been shown to affect fear and categorical learning (Huertas et al., 2010; Xie et al., 2015), and improve both motor (Huertas et al., 2012) and verbal learning (Yue et al., 2016), with deficits seen in executive function exacerbated by ELS (Klaus et al., 2017). To date, little work has explored the interaction between ELS
events, genotype, and phenotypic outcomes at these DRD2 SNP's; thus future research is warranted to elucidate mechanisms surrounding the unique disease risk in these individuals.

Finally, Catechol-o-methyltransferase is an enzyme encoded by the COMT gene that plays a role in dopamine metabolism and schizophrenia risk (Glatt et al., 2003; Harrison & Weinberger, 2005). A SNP in the COMT gene, termed Val158met, has been shown to interact with ELS to increase both positive and negative symptom severity in individuals with schizophrenia (Green et al., 2014). While it was once thought that this SNP could precipitate risk for poor executive functioning given its role in dopamine breakdown, the negative effects of this SNP are controversial with some studies, including a 2008 meta-analysis, reporting no effect of this polymorphism on executive functioning (Barnett et al., 2008), even in those who experienced ELS (Klaus et al., 2017).

Taken together, given the proposed role of aberrant levels of neurotransmitters in the etiology of psychopathology (Sarter et al., 2007), and that SNPs may interfere with reuptake (Serretti et al., 2007), or enzymatic degradation (Bilder et al., 2004; Caspi et al., 2002; Green et al., 2014) of neurotransmitters, SNPs can potentially be used as indicators for multiple neurological and physical disorders in the presence of ELS or trauma. In contrast, absence of the known SNPs involved in the etiology of disease might serve as biomarkers of resilience. However, it is important to remember that individual genes do not act in a vacuum and can be continually influenced by epigenetic and environmental factors throughout the lifespan that may cloud results in these studies. As such, continued research is warranted to elucidate these relationships, especially when considering that some polymorphisms likely interact with each other to confer risk or mediate resiliency for behavioral and psychological dysfunction (For review see Nugent et al., 2011).

Knock-out models: Establishing causality

Animal and human studies confirm that ELS alters the maturation of several neural networks important for cognition and emotion processing, particularly influencing the activation of and crosstalk between the prefrontal cortex, hippocampus, amygdala, and nucleus accumbens (Chen & Baram, 2016). However, developmental stress does not always promote maladaptive neural maturation. Resting-state fMRI studies in humans indicate differences in functional connectivity in mood regulation networks between individuals who are resilient to ELS compared to those who develop mood disorders later in life (Cisler et al., 2013). Current frameworks suggest that genetic differences, such as polymorphisms, leave certain individuals at greater risk after experiencing developmental insults. Genetic engineering in animal models has proven invaluable for elucidating these relationships by helping to establish causality. This feat is accomplished by employing heterozygous and homozygous genetic knockout animal models to determine the importance of various proteins in determining risk versus resiliency, as well as other genetic engineering processes to investigate the effects of stress on

Gene knockout (KO) mice are vital for investigating neural mechanisms behind genetic polymorphisms that leave individuals more susceptible to stress. For example, mice genetically engineered to express low levels of the serotonin transporter (5-HTT KO) show increased anxiety- and depressive-like behaviors that are further exacerbated by early postnatal stress exposure (Carroll et al., 2007). Additional investigation shows that decreased expression of the serotonin transporter genes dysregulates the mitogen-activated protein kinase (MAPK) and neurotrophin signaling pathways in the hippocampus (Van den Hove et al., 2011). This precipitates dysfunction not only in hippocampal function, but the regulatory control the hippocampus has over the hypothalamic-pituitary-adrenal (HPA) axis. In fact, variations in 5-HTT genotype in rats has been shown to differentially alter glucocorticoid receptor (GR) and mineralocorticoid receptor (MR) gene expression in the PFC and hippocampus following ELS exposure (van der Doelen et al., 2014). These data may be informative of genetic susceptibility of depression as dysregulation of MR and GR are implicated in depression etiology (for review see de Kloet et al., 2007). However, the use of knock-in/out models in rodents serve as genetic ablation experiments; while they provide information surrounding the role of gene networks in etiology, they do not directly indicate how aberrant gene expression is programmed by ELS and the perinatal environment.

Epigenetics

Epigenetics, literally translating to “above the genome”, is often defined as the process by which genetic material is activated, or deactivated, in different environmental contexts (Moore, 2017). The most prominent and well-studied epigenetic process is DNA methylation (Weinhold, 2006). In the process of DNA methylation, methyl groups are added to cytosine-guanine (CG) dinucleotides by DNA methyl-transferase proteins (DNMT’s), near the promoter region of a DNA sequence (Bestor, 2000; Smith & Meissner, 2013). However, non-CG methylation has also been recently reported (He & Ecker, 2015). The addition of methyl groups to CG dinucleotides often generates a heterochromatinic state (Rose & Klose, 2014), preventing the binding of transcription factors (TF’s) and repressing gene expression (Moore et al., 2013). Furthermore, methyl groups on DNA sequences can recruit methyl CpG binding protein 2 (MeCP2) (Nan et al., 1993) which can further recruit co-activators such as CREB1 (Chahrour et al., 2008) or co-repression complexes such as nuclear receptor corepressor 1/2 (NcoR1/2) (Tillotson & Bird, 2020), or histone-deacetylases (HDAC’S) (Jones et al., 1998). While the epigenome undergoes maintenance methylation during the cellular replication cycle via DNMT1 (Edwards et al., 2017), de novo methylation occurs via DNMT 3a/3b (Okano et al., 1999) and is a dynamic process that occurs throughout the lifespan (Hackett & Surani, 2013). In both human and animal models, aberrant epigenetic markers have been linked
to the etiology of numerous psychopathologies, including depression (Clark et al., 2019; Ferrer et al., 2019; Fuchikami et al., 2011; Nestler, 2014; Sun et al., 2013), anxiety disorders (Bartlett et al., 2017; Wiegand et al., 2021; Yang et al., 2021), suicidality (Cheung et al., 2020; McGowan et al., 2009; Policicchio et al., 2020), and schizophrenia (Dong et al., 2015; Hannon et al., 2021; Roth et al., 2009b).

BDNF
As aforementioned, BDNF is a neurotrophin critically involved in cellular survival (Ortiz-López et al., 2017), regulating synaptic plasticity (Duman et al., 2016), and in learning and memory (Miranda et al., 2019). Aberrant Bdnf/BDNF expression has been associated with major depressive disorder (Yang et al., 2020), bipolar disorder (Grande et al., 2010; Perroud et al., 2013), anxiety disorder (Suliman et al., 2013), and has been proposed as a target for pharmacological or behavioral interventions (Castrén & Monteggia, 2021). ELS exposure can lower Bdnf expression (Choy et al., 2008; Dandi et al., 2018; Doherty et al., 2016; Lippmann et al., 2007; Roth et al., 2009a) and increase methylation of Bdnf DNA (Collins et al., 2022; Fachin et al., 2021; Roth et al., 2009a) in regions such as the prefrontal cortex (Collins et al., 2022; Roth et al., 2009a) and hippocampus (Doherty et al., 2016). Thus, Bdnf epigenomics has been proposed as a sound biomarker for the etiology (Peng et al., 2018; Rana et al., 2021) and treatment success (Polyakova et al., 2015) of numerous psychopathologies.

Serotonin transporter and monoamine oxidase
Similar to BDNF, aberrant epigenetic activity of the serotonin transporter is associated with the etiology of psychopathology and dysregulated stress reactivity (Abdolmaleky et al., 2014; Booij et al., 2015; Lam et al., 2018), which may be driven by ELS, including childhood maltreatment or trauma (Booij et al., 2015; Kinnally et al., 2010, for review see Soga et al., 2021). While some studies suggest that the SNP at this locus does not mediate the association between epigenetic activity and MDD (Zhao et al., 2013), other studies suggest that lower methylation induced depression specifically among short-allele carriers (Lam et al., 2018), and others report higher methylation among short allele carriers exposed to ELS (Duman & Canli, 2015). Higher methylation of the SLC6A4 promoter is also associated with enhanced connectivity from the anterior cingulate to the left amygdala or left insula in the presence of fearful stimuli, as well as frontal-limbic connectivity during saddening stimuli (Ismaylova et al., 2017). Thus, ELS-induced methylation at this locus can impart numerous consequences at the level of brain and behavior, with consequences potentially specific to the presence of the short allele variant. Moreover, lower methylation of the serotonin transporter has been associated with deficiencies in treatment outcomes of antidepressants (Domschke et al., 2014), which was later replicated in a larger study (Schiele et al., 2021). However, increased methylation of the serotonin transporter is associated with experiencing cognitive behavioral therapy (CBT) (Roberts et al., 2014), suggesting serotonin transporter methylation as a potential biomarker of disease etiology and treatment effectiveness, but the current literature has conflicting findings.

Moreover, aberrant MAOA expression or epigenetic activity is implicated in the etiology of numerous psychiatric disorders (for review see Jones & Raghanti, 2021; Ziegler & Domschke, 2018), including depression and anxiety disorders (Checknita et al., 2018; Melas & Forsell, 2015; Melas et al., 2013; Ziegler et al., 2016). Reducing observed MAOA hypomethylation in panic disorder by CBT therapy improves symptoms (Ziegler et al., 2016), suggesting MAOA methylation is similarly a sound biomarker for both etiology of disease and treatment, as MAOA methylation has been reported to directly predict MAOA levels in the brain (Shumay et al., 2012).

Dopamine
Aberrant methylation or expression of DRD2 has been associated with substance abuse (Hagerty et al., 2020), with data suggesting methylation of DRD2 in the striatum is involved with the severity of alcohol use disorder (Bidwell et al., 2019). While some studies have failed to find a relationship between DRD2 methylation and schizophrenia (Piao et al., 2022; Zhang et al., 2007), others have found a partial relationship between methylation and schizophrenia in a Turkish population (Aytac et al., 2021), and lower methylation in leukocytes in a Japanese population (Yoshino et al., 2016). One potential explanation for these discrepancies is that schizophrenia etiology is characterized by differences in epigenetic regulators, including DNMT1 (Dong et al., 2015; Saxena et al., 2021), and various histone-deacetylases (Bahari-Javan et al., 2017; Kurita et al., 2013; Lang et al., 2011). Similarly, while a recent study found no association between ELS and DRD2 methylation (Piao et al., 2022), others utilizing rodent models have found ELS to lower DRD2 expression in the hippocampus (Wearick-Silva et al., 2019), but work remains limited. Methylation of DRD2 is mediated by Krüppel-like transcription factor 11 (KLF11) (Richards et al., 2017; Seo et al., 2012), which also regulates the transcription of MAOA (Higuchi et al., 2017), making it an important transcription factor to consider in schizophrenia risk. Indeed, recent work has found KLF11 promoter hypomethylation in comorbid depression and panic disorder (Harris et al., 2015; Kollett et al., 2020), and is upregulated in the context of chronic stress (Grunewald et al., 2012; Harris et al., 2015). Together, future research should elucidate both direct and indirect epigenetic mechanisms surrounding DRD2 expression, in the context of ELS.

Molecular resiliency
While evidence presented in this review suggests ELS, genotype, and epigenetic factors interact in the etiology of numerous psychopathologies, not everyone exposed to ELS goes on to develop psychopathology. Indeed, ELS can improve behavioral flexibility (Gapp et al., 2014), emotional learning (Oomen et al., 2010), facilitate adaptive stress coping strategies (Parker et al., 2019; Santarelli et al., 2017; van der Doelen et al., 2013), and improve self-reported mental health.
outcomes (Seery et al., 2010). For example, research has demonstrated that the ability to self-regulate can ameliorate MDD symptoms associated with ELS exposure (Seok et al., 2012), which may be in part due to the stress inoculation phenomenon by which exposure to mild ELS can improve future reactions to stressors (Parker et al., 2019; Santarelli et al., 2017). While several SNPs presented in this review are associated with developing psychopathology, some are equally associated with resilience, and the absence of these SNP’s similarly demonstrate resilient phenotypes.

**GxE interactions in resiliency**

**BDNF**

In one study, having two copies of the val allele was associated with no deficits in working memory accuracy or reaction time, resting or stressed heart rate, and brain morphology with increasing quantity of ELS events commonly seen in the polymorphism (Gatt et al., 2009), suggesting the absence of the MET allele might be indicative of a resilience phenotype. However, other work has suggested that in specific populations, carrying the MET allele is associated with greater antidepressant responsivity (Tsai et al., 2010), and resilience scores among those with MDD (Peters et al., 2021). One reason for these discernible differences might be the presence of other SNPs, and how they relate to BDNF epigenetic activity and behavior. For example, serotonin transporter KO rats exposed to maternal separation stress displayed lower BDNF expression in the ventral hippocampus and ventromedial PFC, and more anxiety and depressive-like behavior. However, heterozygous serotonin transporter-animals display increased BDNF in the dorsal hippocampus and dorsomedial PFC in response to maternal separation (Calabrese et al., 2015). Other work has similarly found that heterozygous serotonin transporter-animals have improved stress coping (van der Doelen et al., 2013), suggesting that the 5-HTTLPR, BDNF epigenetic activity, and resiliency phenotypes are linked. Similarly, increased BDNF expression in the dentate gyrus of the hippocampus in the context of chronic stress exposure has proven efficacious in preventing the etiology of MDD (Taliaz et al., 2011; Zhang et al., 2021), which may be in part due to a BDNF-Interleukin4 (IL4) complex facilitating hippocampal neurogenesis after stress exposure (Zhang et al., 2021). These data highlight the importance of elucidating mechanisms to increase hippocampal BDNF expression concurrent with ELS exposure, but measuring the presence of other SNP’s is critical.

**Serotonin transporter and monoamine oxidase**

As aforementioned, some studies in animals have found that being heterozygous for the serotonin transporter (similar to humans who are homozygous S carriers) can facilitate adaptive stress coping (van der Doelen et al., 2013) and increase BDNF in several brain regions (Calabrese et al., 2015) in the context of maternal separation stress. However, other studies report that heterozygotes with maternal separation have more incidences of depressive-like symptoms (Houwing et al., 2019) and are more vulnerable to psychosocial stress (Bartolomucci et al., 2010). Interestingly, van der Doelen et al. (2013) induced maternal separation for three hours on postnatal days 2–14, and Houwing et al. (2019) induced maternal separation for six hours per day on postnatal days 2–15. Thus, it is possible that the duration of maternal separation can either promote stress inoculation or pathological consequences among homozygous S carriers. However, other work has demonstrated that having two copies of the long allele in humans with increasing incidences of ELS is associated with resilience (González-Giraldo & Forero, 2020). Indeed, L/L genotypes in the presence of ELS do not associate with increased probability of a suicide attempt, and there was no difference between severe and no maltreatment and increased probability of an MDD episode (Caspi et al., 2003). Similarly, long allele carriers have blunted reactivity to fearful stimuli in fMRI (Hariri et al., 2002), and those with two copies of the long allele when faced with trauma have less severe symptoms and presentations of MDD (Goldman et al., 2010). Together, the unique combination of serotonin transporter genotype, ELS exposure, and regional specific epigenetic regulation are all implicated in individual differences in pro-resilience or pro-pathology, with more work in animal models warranted to establish causal relationships (Lesch, 2011). Future work should elucidate how the type, timing, and duration of ELS exposure interacts with serotonin transporter genotype to confer disease risk or resiliency.

Finally, while work regarding MAOA SNPs and resilience is sparse, in a small sample of Syrian refugees, the lower-activity MAOA allelic variant in males with lower trauma exposure display lower perceived psychosocial stress over time compared to high trauma exposure (Clukay et al., 2019). This finding is interesting, considering that this SNP is typically associated with aggressive behavior (Alia-Klein et al., 2008) and behavioral dysregulation (Enoch et al., 2010; Zohsel et al., 2015). These data further suggest that the degree of trauma exposure interacts uniquely with SNPs to induce either resilience or pathology.

**HDACs**

While direct epigenetic markers and candidate genes of resilience remain elusive, some data in mouse models suggest involvement of the epigenetic regulators histone deacetylases (HDACs). For example, Balb/c mice are more stress-susceptible, anxiety-prone, and immunocompromised compared to C57BL/6 mice, which is associated with deficits in prefrontal cortex-mediated behaviors in this strain (Heinla et al., 2018; Mehta & Schmauss, 2011; NIH gene library, 2022). Balb/c mice also appear to be more sensitive to changes in expression of epigenetic proteins after ELS exposure. A 2011 study showed that HDAC proteins 1, 3, 8, and 10 were upregulated in the hippocampus of Balb/c but not C57BL/6 mice following ELS during infancy (Levine et al., 2012). In this study, downregulation of these HDAC proteins in adulthood was concomitant with increased histone 4 lysine 12 (H4K12) acetylation, which is consistent with the function of HDAC proteins. Interestingly, when this hyperacetylation was corrected by using an HDAC-activating drug treatment, depressive-
anxiety-like behaviors in the Balb/c mice were exacerbated (Levine et al., 2012). Treatment with the antidepressant fluoxetine acted in the Balb/c mice by further potentiating ELS-induced H4K12 acetylation that was accompanied by a more robust behavioral effect than was observed in the normally reared Balb/c mice. Taken together, data from this study suggests that some adaptive epigenetic changes may occur after stress exposure to increase resiliency even after emotional phenotypes have been dysregulated in this stress-susceptible animal model.

ZFP and NPY

There has been some work exploring Zinc Finger Proteins (ZFP’s) and Neuropeptide Y (NPY) in resiliency. ZFP’s are one of the most prevalent protein families, and are involved in a variety of functions, including transcriptional control, ubiquitin-mediated protein degradation, signal transduction, actin targeting, DNA repair, and cell migration (Cassandri et al., 2017). While research on ZFP involvement in ELS and resilience is still ongoing, studies have found that with overexpression of Zfp189 in sections of mice PFC promoted resilience phenotypes after chronic social defeat stress (Lorsch et al., 2019). This is associated with CREB binding to the Zfp189 promoter, activating a resilient-specific transcriptional network, and ultimately promoting behavioral resilience (Lorsch et al., 2019). Finally, NPY is a neuropeptide found densely in the central nervous system with a diverse range of functions, including reducing anxiety (Heilig et al., 1989; Shiozaki et al., 2020; Wu et al., 2011), mediating the stress response (Reichmann & Holzer, 2016; Yang et al., 2018), and acting as an analgesic (Diaz-delCastillo et al., 2018). NPY has been proposed to also mediate stress resilience (Cohen et al., 2011; Enman et al., 2015; Wu et al., 2013), with lower levels being associated with PTSD (Sah & Geracioti, 2013), and higher levels being associated with symptom improvement (Yehuda et al., 2006).

Taken together, the absence of several SNP’s associated with psychopathology, or elevated levels of NPY or ZFP189 may be indicative of a resilience phenotype. However, in certain populations the presence of several SNP’s associated with psychopathology, including the MET allele (Peters et al., 2021; Tsai et al., 2010), the low activity MAOA variant (Clukay et al., 2019), heterozygous s-allele carriers for the serotonin transporter (van der Doelen et al., 2013), and the DRD2 C957T polymorphism (Yue et al., 2016) are associated with resilience after ELS exposure. This discrepancy highlights the need to consider the many environmental moderators that are known to interact with SNPs, including the infant-caregiver relationship, the degree of control over the stressor, the magnitude and type of stressor, and epigenetic markers. The combination of several environmental and genetic moderators are thus critical when determining psychopathological or resilient behavioral outcomes after ELS exposure (Figure 1).

Moderator variables of resilience

Infant-caregiver relationship

Provided that ELS results in resilience in some cases and disease pathology in others, there must be moderator variables influencing these relationships. One proposed environmental moderator is the infant-caregiver relationship. Numerous studies have demonstrated that early life stress in the form of maltreatment or neglect can increase the risk of developing depression, anxiety, obesity, and heart disease later in life (Moffitt & Klaus-Grawe 2012 Think Tank, 2013). On a molecular level,
early-life adversity may alter expression of genes in the brain to shape behavior via epigenetic mechanisms such as DNA methylation, histone modification, and non-coding RNA gene silencing (Levenson & Sweatt, 2005). However, negative epigenetic consequences of early-life maltreatment and neglect are not always present. Emerging research suggests that the relationship between ELS exposure and resilience is nonlinear (Parker et al., 2019). If this relationship is indeed nonlinear, stress may be viewed as a continuum dependent on context where a certain stress threshold may act as a switch for promoting resilience or psychopathological outcomes. Moreover, intervening in early life through various intervention programs has proven efficacious in ameliorating consequences of ELS (Dozier et al., 2006; Fisher et al., 2011) and rescuing aberrant epigenetic activity (Hoye et al., 2019; Non et al., 2016; O’Donnell et al., 2018).

Degree of control over the stressor
The extent to which an individual has control over a stressor may also influence how a stressor modulates psychopathological or resilient phenotypes later in life. When an individual has a lower degree (or perceived) of control over a stressor, there may be more severe neurological consequences. The timing in an individual’s life when a stressor is present is intertwined with the degree of control one has over a stressor. It has been suggested that removal of children from maltreatment early in life can act as an intervention for molecular programming, shifting towards a pro-resilience phenotype (Heim et al., 2019). During infancy, developing humans, non-human primates, and rodents are largely dependent on a caregiver to provide fundamental needs like temperature regulation, nutrition, and stimulation (Blaze et al., 2015). When this caregiving relationship is insufficient or outside stressors occur during this time, it can result in severe consequences. ELS in particular occurs during a window of time of brain development where stress can elicit long-lasting changes in brain development and function (Eachus et al., 2021). Following ELS, epigenetic changes may regulate expression of genes in the brain related to the HPA-axis, neuropeptidies, synaptic plasticity and hormonal activity (Eachus et al., 2021). These biological alterations within the brain via epigenetic mechanisms may then affect behavior long-term, increasing vulnerability to disease or promoting resilience.

However, the perception one has of their control over the stressor, in addition to the actual degree of control, can impact phenotypic outcomes. Internal locus of control is an individual’s perception of being in control over their outcomes (Pruessner et al., 2005). Interestingly, internal locus of control can be used as a correlate of neuroendocrine cortisol response to stress such that individuals with a high internal locus of control show reduced cortisol levels in response to stress (Bollini et al., 2004). Furthermore, locus of control is related to depression prevalence such that external as opposed to internal locus of control is associated with higher risk of depression (Khumalo & Plattner, 2019). This may be due to the fact that having an external locus of control promotes feelings of learned helplessness, passivity, and hopelessness, all of which can increase vulnerability to depression (Khumalo & Plattner, 2019).

Magnitude and type of stressor
Stress inoculation is an observed phenomenon by which exposure to moderate or mild stressors allows individuals to better cope with future stressors (Wu et al., 2013). Thus, there is an optimal “dose” by which exposure to adversity may facilitate resilient outcomes. Brief, one-hour social separations in squirrel monkeys enhanced cognitive response inhibition, curiosity, exploratory behavior, and emotional regulation (Lyons & Parker 2007; Lyons et al., 2009). The magnitude of ELS exposure and resilience has been proposed to be in a J-shape, such that one or two exposures of ELS facilitate reductions in anxiety, whereas larger doses increase trait anxiety (Parker et al., 2019). In a mouse model of stress-inoculation by which juvenile male mice were exposed to an aggressive breeder, these mice showed lower depressive phenotypes, increased prosocial behavior, and increased fear-extinction (Ayash et al., 2020). Brief separations have also been associated with increased ventromedial prefrontal cortex (VmPFC) volume and increased white matter (Katz et al., 2009). The VmPFC has been proposed to be critical in amygdala regulation, including top-down inhibition (Andrewes & Jenkins, 2019; Motzkin et al., 2015), and is also programmed to inhibit responses to uncontrollable stressors after experiencing ones that the individual has perceived control of (Maier & Watkins, 2010). Taken together, these data suggest that an optimal level of early life stress has the capacity to promote resilience, through changing both brain morphology and behavior later in life.

ELS can include numerous subtypes, including sexual, physical, or emotional abuse, neglect, poverty, and experiencing death or separation from loved ones. While there aren’t many studies comparing all of these different subtypes in disease etiology or psychological resilience, it has been postulated that emotional abuse, sexual abuse, or severe family conflict are associated with major depression (LeMoult et al., 2020; Saleh et al., 2017), with sexual abuse increasing both MDD and suicidality among women (Cankaya et al., 2012), whereas poverty or low socioeconomic status (SES) is associated with anxiety (Lähdepuro et al., 2019), or schizophrenia (Werner et al., 2007). While some studies have reported lower SES associated with MDD (Gilman et al., 2002), a recent meta-analysis did not find this relationship (LeMoult et al., 2020). While the death of a parent is traumatic for children, brief interventions are efficacious in preventing and ameliorating psychopathological outcomes (Bergman et al., 2017). Future studies examining ELS should thus quantify both the magnitude or dose of ELS, as well as type to better elucidate the role of ELS programming on various psychopathological states.

Epigenetic markers
Similar to infant-caregiving experiences being essential in moderating resilience or psychopathological outcomes, the infant-caregiver relationship is able to influence epigenetic
markers (Lester et al., 2018; Roth et al., 2009a; Szyf et al., 2007; Szyf et al., 2005; Weaver et al., 2004), with maltreatment being associated with aberrant DNA methylation (Collins et al., 2022; Parade et al., 2021; Roth et al., 2009a) at various loci. Moreover, improving the caregiving relationship has the capacity to alter aberrant DNA methylation associated with ELS or maltreatment (Brody et al., 2016; Hoye et al., 2019; O’Donnell et al., 2018), and improve infant outcomes (Bernard et al., 2012; Bernard et al., 2015; Bernard et al., 2017; Brody et al., 2016; Miller, 2015). Indeed, the epigenome is attuned to the environment during early development, and can both be a pathway to disease or a target for treatment. Interventions at multiple stages of the lifespan can ameliorate aberrant epigenetic activity and improve mental health outcomes (Collins et al., 2020). The epigenome is a sound target for exploring mechanisms surrounding resilience. If the epigenome is attuned to the environment and moderates the development of disease, and perturbing epigenetic activity can improve outcomes, the epigenome is likely critically important for developing resiliency. The role of epigenetics in resiliency is just beginning to be appreciated (McEwen, 2016; Smeeth et al., 2021), but work remains limited.

**Intervention strategies to promote resilience**

While ELS is associated with a variety of neurological and psychiatric disorders that result in a range of behavioral, psychological, and molecular changes, several intervention strategies exist to ameliorate ELS-associated psychopathological outcomes targeting these domains. Indeed, intervention strategies that have been efficacious include exercise interventions (James et al., 2014), and environmental enrichment (Borba et al., 2021), both of which have also demonstrated the ability to mitigate aberrant epigenetic activity associated with ELS, suggesting a link between ELS, epigenomics, and behavioral phenotypes. Understanding epigenetic changes associated with intervention strategies is crucial in elucidating the difference between those who are pro-psychopathological or pro-resilient in the context of ELS exposure, as these are mechanisms associated with changing behavioral phenotypes and disease outcomes. While the review does not provide exhaustive examples of intervention strategies, we highlight several key examples of how epigenetic activity and the presence of several SNPs are directly related to several treatment modalities, and thus provide examples of epigenetic biomarkers likely important for resiliency and buffering consequences of ELS exposure (Figure 2).

**Drug treatment**

First, it is worth noting that pharmacological compounds currently prescribed may in part exert their effects through epigenetic mechanisms, and directly perturbing epigenetic biomarkers has the capacity to ameliorate both aberrant

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**Figure 2.** Several types of early life stress (ELS), including trauma, abuse, or neglect, interact with several single nucleotide polymorphisms (SNPs) and alters expression or methylation of several genes or epigenetic regulators to promote disease states in the brain. These molecular signatures of ELS and psychopathology provide insight on treatment and intervention modalities that are able to rescue aberrant epigenetic activity to change behavior. Intervention strategies have been capable of increasing and enhancing neurogenesis, *BDNF* expression in the hippocampus and prefrontal cortex, cognition, and synaptic plasticity, which have been demonstrated to buffer the consequences of ELS on pathology. These intervention strategies and the consequential shift in molecular biomarkers provide insight on how resiliency functions in the brain. *BDNF*, brain-derived neurotrophic factor; *SLC6A4*, solute carrier family 6 member 4 (Serotonin transporter); *MAOA*, monoamine oxidase A; *DRD2*, dopamine receptor D2; *DNMT1*, DNA methyltransferase 1; *HDAC*, histone deacetylase; *COMT*, catechol-o-methyltransferase.
epigenetic activity and behavior following ELS. Indeed, while selective SSRIs are one of the most commonly prescribed medications for MDD (Schafer, 1999), OCD (Xu et al., 2021), and generalized anxiety disorder (Strawn et al., 2018), the exact role of serotonin in the etiology and treatment of psychopathology such as MDD has been recently debated (Moncrieff et al., 2022), with some studies reporting SSRIs as efficacious (Arroll et al., 2005), and others reporting larger effect sizes in severe as opposed to minor depression (Fournier et al., 2010), and preventing relapse of a MDD episode (Clevenger et al., 2018). However, recent work has demonstrated that SSRIs also perturb epigenetic mechanisms (for review, see Vialou et al., 2013; Webb et al., 2020). For example, fluoxetine has been shown to increase BDNF expression in the hippocampus (Jin et al., 2017), which can ameliorate MDD etiology and promote resilience after chronic stress exposure (Taliaz et al., 2011; Zhang et al., 2021).

The efficacy of antidepressant type also may depend on the genotype of several candidate genes discussed in this review. For example, in humans and animal models, the presence of the BDNF val66met polymorphism predicted greater efficacy with a selective norepinephrine or tricyclic antidepressant (Colle et al., 2015; Yu et al., 2012), whereas val/val carriers seem to respond better to SSRIs (Colle et al., 2015) or ketamine (Laje et al., 2012). However, other studies report that the presence of the MET allele is sufficient in an Asian population to increase antidepressant response (Tsai et al., 2010), suggesting further moderator variables need investigation. In regard to the 5-HTTLPR, some studies report no difference relative to genotype and antidepressant responsiveness (Taylor et al., 2010), whereas others report lower antidepressant efficacy among S homozygotes (Gressier et al., 2009; Serretti et al., 2007), which may further depend on antidepressant type and gender (Gressier et al., 2009; Huez-Diaz et al., 2009). Efficacy may also depend on epigenetic mechanisms, such that lower methylation of the serotonin transporter has been associated with deficiencies in treatment outcomes of antidepressants (Domschke et al., 2014; Schiele et al., 2021), which is interesting considering some studies suggest lower methylation is associated with MDD etiology (Lam et al., 2018), but that higher methylation is seen in the context of ELS (Duman & Canli, 2015) and a treatment outcome of CBT (Roberts et al., 2014).

Further, MAOA-L carriers don’t have robust responsiveness to tetracyclic antidepressants (Tzeng et al., 2009), and some studies report that SNPs of DRD2 (Chiesa et al., 2014; Saung et al., 2014) or COMT (Chiesa et al., 2014) don’t seem to predict antidepressant responsivity, but other studies report several SNPs of DRD2 can predict response time to SSRIs (Wang et al., 2012), and that the COMT val158 polymorphism does indeed predict antidepressant efficacy (Baune et al., 2008). Taken together, SNPs do seem to be associated with antidepressant efficacy to an extent, which may facilitate more individualized treatment modalities and explain why antidepressants have mixed results in ameliorating symptoms. Indeed, more work is needed to elucidate the complicated relationship of having several different SNPs among gene networks associated with psychopathology and specific antidepressant choice, as findings in this literature have replicability difficulties. As mentioned in this review, moderator variables driving psychopathology or resilience are thus key candidates to decipher how individual experiences associated with individual treatment methodologies and outcomes, with measurable changes in epigenetic activity as sound biomarkers.

Finally, directly perturbing the epigenome via histone deacetylase inhibitors (HDACi) has been efficacious in ameliorating treatment-resistant depression (Meylan et al., 2016). Administering the HDACi sodium butyrate in infancy mitigates the aberrant epigenetic activity of BDNF in males (Doherty et al., 2019), whereas administering valproic acid (VPA) has no effect on BDNF levels, but does lower global methylation (Collins et al., 2022). In rodents, if the DNA methyltransferase inhibitor (DNMTi) zebularine is administered in adulthood, individuals exposed to ELS have normalized BDNF levels and behavioral phenotypes (Keller et al., 2019; Keller et al., 2018), including a lower propensity to perpetuate a maltreating phenotype into the next generation (Keller et al., 2019). While the relationship between epigenetic compounds, ELS, and behavioral phenotypes is just being appreciated, more work is needed to elucidate which compounds are most efficacious in ameliorating ELS-associated psychopathology through the epigenome. Identifying where already existing antidepressants change epigenetic markers in rodents and humans will be critical in determining epigenetic programming of pro-resilient or pro-pathological phenotypes. However, while perturbing epigenetic activity to promote resilience via pharmacological compounds is critical for elucidating important mechanisms, it is important to consider readily and easily implementable interventions, such as environmental enrichment or exercise.

Environmental enrichment
Environmental enrichment (EE) is a form of therapy intervention that increases the novelty and complexity of the rodent’s environment by implementing modifications that enhance the level of physical and social stimulation provided by the captive environment (Würbel et al., 1998), providing the animals with choices and opportunities within its environment to benefit the animal’s behavior and physiology through stress reduction. This form of therapy intervention typically consists of three major components: physical activity (i.e., voluntary running wheels), cognitive stimulation (i.e., toys, tubes, bedding material), and social interaction (i.e., number of animals housed together) (Fabel et al., 2009; Steiner et al., 2008; van Praag et al., 2000). EE has been found to enhance experience-dependent cellular plasticity and cognitive performance compared to standard-housed control in wild-type rodent models (Hannan, 2014). A meta-analysis done on EE therapies in rodent models found that these treatments were beneficial in terms of the behavioral, cellular, and molecular substrates of a large range of neurological and psychiatric disorders, including numerous neurodegenerative disorders (Li et al., 2018a; Li & Stern, 2022; Martorana et al., 2021; Serra et al., 2018; Stuart et al., 2020), depression (Grinberg et al., 2021; Wang et al., 2019), schizophrenia...
(Best et al., 2019), and anxiety (Gong et al., 2018; Hendershot et al., 2016).

As aforementioned, Increased BDNF expression in the dentate gyrus of the hippocampus in the context of chronic stress exposure is effective in preventing MDD phenotypes (Taliaz et al., 2011; Zhang et al., 2021), data which also extend to the PFC (Fukumoto et al., 2020; Li et al., 2018b). Some data suggests EE has the capacity to increase BDNF expression in the hippocampus (Dandi et al., 2005; Iha et al., 2016; Sun et al., 2010) and PFC (Sadegzadeh et al., 2020), as well as promote neurogenesis in the hippocampus (Grońśka-Pęski et al., 2021; Olson et al., 2006). However, other data suggests EE may lower BDNF in the PFC (Rueda et al., 2012), and that the behavioral effects seen are not driven per se by hippocampal neurogenesis (Mashi et al., 2006). Indeed, it has thus been suggested that multiple variables need consideration, including when the EE exposure takes place and for how long (Barros et al., 2019), with females seeing more increases in BDNF in the PFC compared to males (Sadegzadeh et al., 2020). Further, in serotonin transporter KO mice, one study found EE is efficacious in ameliorating anxiety and depressive phenotypes associated with this mouse model (Sbrini et al., 2020), but other studies only found EE efficacious in reducing anxiety (Rogers et al., 2016). However, Sbrini et al. (2020) extended the EE protocol to one month starting on PN140, whereas Rogers et al. (2016) provided EE on PN56 for up to three weeks. Interestingly, this lab group also demonstrated that increasing the duration of EE exposure shifts the results from anxiolytic to antidepressant in nature (Pang et al., 2009; Rogers et al., 2016). In sum, the extended length as well as the timing of EE exposure seems critical in regard to improving pathology and promoting resiliency.

Finally, while work regarding EE and the epigenetic regulators of resiliency is sparse, a recent paper found that EE over 40 days has the potential to reverse consequences of maternal deprivation and rescue aberrant HDAC and DNMT activity in females (Borba et al., 2021). Together, while EE has been efficacious in ameliorating the etiology of psychopathology, the type, timing, and duration of EE must be considered when investigating epigenetic programming. Nonetheless, the capacity of epigenetic activity to associate with behavioral change posits EE might help shift epigenetic activity into a pro-resilient state.

Exercise

Exercise has many neuroprotective effects, including synaptogenesis, (Rhodes et al., 2003; Swain et al., 2012; Van Praag et al., 2005), and neurogenesis (Grońśka-Pęski et al., 2021; Kobilo et al., 2011; Swain et al., 2012; Vivar et al., 2013; Voss et al., 2013) in the hippocampus throughout development and can mitigate the reduction of neurogenesis associated with ELS exposure (Daniels et al., 2012; Fabricius et al., 2008). Exercise therapy has been used to treat both the motor and cognitive symptoms of Parkinson’s Disease (Crowley et al., 2019), depression (Babjak et al., 2000; Carek et al., 2011; Craft & Perna, 2004; Gujral et al., 2017; Hu et al., 2020) and anxiety disorders (Aylett et al., 2018; Anderson & Shivakumar, 2013; Carek et al., 2011; Henrikkson et al., 2022; Kallen et al., 2008; Kandola & Stubbs, 2020); while some data suggests higher intensity is more efficacious (Aylett et al., 2018), other findings suggest similar effect sizes for low and higher intensities (Henrikkson et al., 2022). Moderate exercise is also recommended to supplement additional treatments for depression, such as psychotherapies and medications (Johnson et al., 2020). Exercise also reduces anxiety symptoms in people without anxiety disorders (Kandola & Stubbs, 2020).

Comparing structural abnormalities of the brain associated with depression and effects of exercise on the brain suggests epigenetic mechanisms may regulate the effect of exercise on depressive symptoms, hence supporting exercise as effective treatment (Gujral et al., 2017). Indeed, exercise therapy has been efficacious in increasing BDNF expression in the hippocampus (Liu & Nusslock, 2018; Sleiman et al., 2016), with higher intensities further increasing BDNF in the PFC (Cefisi et al., 2019; Slusher et al., 2018). Similar increases in BDNF in the hippocampus promoted resilience against MDD after chronic stress exposure (Taliaz et al., 2011), suggesting that exercise may act on similar mechanisms to promote resiliency.

However, in addition to intensity, research also focuses on the role of voluntary versus involuntary exercise. Involuntary exercise models allow for the rodent to exercise for the duration and intensity set by the researcher. Involuntary exercise has been associated with decreased immobility times during a forced swim test after maternal separation, producing an antidepressant-like effect (Sadeghi et al., 2016). These results were not replicated during forced treadmill exercise (Sadeghi et al., 2016), but there are conflicting findings. Tuon et al. demonstrated that forced exercise in the form of treadmill running and swimming can alleviate the depressive behavior in mice as exercise promotes hippocampal neurogenesis (2014). Furthermore, voluntary aerobic exercise has been shown to promote neurobiological factors associated with resilience (Patki et al., 2014) and have antidepressant-like effects in rodent models (Shin et al., 2017; Sigwalt et al., 2011). Together, these studies highlight the instrumental role that exercise intervention could have on preventing the disease and other such neurological diseases altogether, as well as alleviating the symptoms of those already affected.

Taken together, although much remains to be determined of the mechanisms modulating the neuroprotective effects of exercise, further research is necessary to determine effects of intensity and duration of exercise on mental health in the long-term (Zhao et al., 2020), and how epigenetic programming may generate a resilient state after ELS exposure. Although human and animal models both support exercise in promoting resilience and treating ELS, further research is necessary to determine the importance of these factors and inform future intervention practices.

Discussion

To date, few studies have directly explored molecular substrates of resiliency. However, understanding how stress is more
readily managed at the molecular level is a critical research focus. Provided that not everyone exposed to ELS develops psychopathology, and some can even demonstrate improvements in cognitive function, mental health outcomes, and stress-coping techniques (Gapp et al., 2014; Parker et al., 2019; Santarelli et al., 2017; Seery et al., 2010; van der Doelen et al., 2013), understanding what factors moderate pro-psychopathological or pro-resilient outcomes, and how those are programmed molecularly, can provide critical information about proper intervention strategies and how to measure their effectiveness. Current work in this area has demonstrated the infant-caregiver relationship (e.g., Levenson & Sweatt, 2005; Moffitt & Klaus-Grawe 2012 Think Tank, 2013; Roth et al., 2009a; Weaver et al., 2004), and the magnitude, type and timing (e.g., Heim et al., 2019; LeMoult et al., 2020; Saleh et al., 2017) of stress all influence biological and epigenomic markers in the brain. Similarly, intervening early in life with environmental enrichment (e.g., Li et al., 2018a; Li & Stern, 2022), exercise (e.g., Daniels et al., 2012; Fabricius et al., 2008), or infant-parenting programs such as the attachment and biobehavioral catchup (Hoye et al., 2019) can mitigate consequences of ELS exposure at the level of the epigenome. Furthermore, directly perturbing epigenetic mechanisms via pharmacological compounds (e.g. Doherty et al., 2019; Keller et al., 2019) rescues both aberrant DNA methylation and changes behavior, providing evidence that ELS programming, epigenetic activity, and future behavior is linked. Given that ELS exposure and the development of resilience has been proposed non-linear (Parker et al., 2019), future research should explore how the known environmental and molecular moderator variables of pathology or resilience operate in a “dose-dependent” fashion to promote behavioral resilience, given these known stable epigenetic markers of pathology can persist throughout the lifespan (e.g., Roth et al., 2009a) and be inherited across generations (e.g. Franklin et al., 2010).

Further, if we conceptualize ELS as having a dose-dependent relationship for behavioral phenotypes, epigenomics is a promising mechanism worth exploring, as methylation and gene expression are similarly on a continuum and offer an opportunity for intervention at numerous points during the lifespan (Collins et al., 2020). Finally, there also may be direct programming of pro-resilience gene networks, driven by zinc-finger-proteins such as ZFP189 (Lorsch et al., 2019) or neuropeptide Y (Cohen et al., 2011). Future research should elucidate other gene networks associated with resiliency given other ELS subtypes. Considering the complicated nature of the interaction among numerous SNPs, epigenetics, and environmental moderators, genome-wide approaches (Ryan & Ryznar, 2022) with multiple variables seems critical to elucidate both mechanisms of resilience and intervention potential. Indeed, understanding the molecular programming associated with resiliency can provide further insight on the etiology of disease states, and how to improve mental health outcomes for those exposed to ELS. Unique relationships among genotype, epigenetic programming, and pro-pathology/pro-resilient environmental moderators suggest these variables all need to be considered when making choices regarding proper intervention strategies throughout the lifespan.

Data availability
No underlying data are associated with this article.

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