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The Role of Epigenetics in Psychological Resilience

Demelza Smeeth, PhD,

Department of Biological and Experimental Psychology, School of Biological and Chemical Sciences, Queen Mary University of London, London, UK

Stephan Beck, PhD,

UCL Cancer Institute, Paul O’Gorman Building, University College London, London, UK

Elie G Karam, MD,

Department of Psychiatry and Clinical Psychology, Balamand University, St Georges Hospital University Medical Center, Institute for Development, Research, Advocacy and Applied Care (IDRAAC), Lebanon

Michael Pluess, PhD

Department of Biological and Experimental Psychology, School of Biological and Chemical Sciences, Queen Mary University of London, London, UK

Summary

There is significant variation in the response to adversity, with a substantial proportion of individuals displaying psychological resilience. Epigenetic mechanisms are hypothesised to be one molecular pathway of how experiences can become biologically embedded and contribute to individual differences in resilience. However, not much is known regarding the role of epigenetics in the development of psychological resilience. In this review, we propose a new conceptual model for the different functions of epigenetic mechanisms in psychological resilience. The model considers 1) the initial establishment of the epigenome, 2) epigenetic modification due to protective environmental exposures across life, 3) the role of protective factors in counteracting adverse influences, and 4) genetic moderation of environmentally induced epigenetic modifications. After reviewing empirical evidence for the various components of the

Correspondence to: Professor Michael Pluess, Department of Biological and Experimental Psychology, School of Biological and Chemical Sciences, Queen Mary University of London, Mile End Road, London, E1 4NS, UK, m.pluess@qmul.ac.uk, Telephone number: +44 20 7882 8004.

Contributors

DS was responsible for searching the literature for articles included in this Review. DS and MP contributed to the design, writing, preparation, and discussion of the manuscript. SB and EK provided feedback and edited the manuscript. All authors read and approved the final manuscript.

Search strategy and selection criteria

References for this review were identified through searches of PubMed for articles published up to May 31, 2020. We did not apply any additional time restrictions, but we largely focussed on papers published within the past 5 years. We searched article titles and abstracts for the specific keywords (and combinations thereof): “resilien*”, “mental health”, “depress*”, “anxi*”, “trauma*”, “stress”, “advers*”, “environment”, “inherit*”, “epigen*”, “methyl*”, “histone”, “RNA”. We reviewed the articles resulting from these searches and the relevant references cited in those articles. Given the number of studies that certain keyword combinations yielded, we restricted our selection of papers to peer-reviewed papers that covered unique areas of our proposed model. We supplemented these search results with important publications from our personal literature libraries. Only articles published in English were included.

Declaration of interests

The authors declare no competing interests.

model, we identify research areas which should be prioritized and discuss practical implications of the proposed model for epigenetic research on resilience.

Keywords

Epigenetics; DNA methylation; Genetics; Resilience; Mental Health; Developmental Psychopathology

In the face of adversity some individuals develop stress-related disorders such as depression or post-traumatic stress disorder (PTSD). However, a significant proportion exhibit psychological resilience defined broadly as the maintenance of good mental health despite exposure to adversity.¹ A better understanding of the development of resilience is of significant clinical benefit in the prevention and treatment of stress-related disorders.

Introduction to Resilience

Although resilience is generally considered the capacity of an individual to overcome and bounce back from adversity, the exact definition and associated means of measuring it differ considerably. It can be conceptualised in three ways: 1) as a dynamic and malleable process, 2) as a stable trait, and 3) as an outcome in response to adversity. In line with contemporary thinking, we consider resilience to be a dynamic process or complex function of numerous individual (e.g. genetic factors) and social-environmental factors (e.g. social support) which allows an individual to maintain good psychological health despite significant adversity.^{2,3} Importantly, resilience reflects not simply the absence of risk factors but includes also the influence of protective factors which promote positive adaptation. Although resilience has become a common feature of mental health research, the majority of psychiatric studies tend to focus on resilience-reducing or risk-conferring factors, often overlooking the contribution of resilience-promoting factors.

Given the varied definitions, resilience has been measured in a multitude of ways. A common method is through binary segregation of those that have succumbed to a single mental health disorder at a single point in time compared to those that have not.⁴ Others consider a more nuanced longitudinal approach and utilise complex statistical models to identify discrete, longitudinal trajectories of mental health following adversity.¹ Further methods focus less on the outcome and more on individual attributes which can contribute to resilience in an individual.³ Given the complexity of resilience, its assessment remains a challenge due to the fact that individuals may be resilient in one psychological domain, while vulnerable to another, and resilient at one time, but not another.

How do these social-environmental factors become biologically embedded throughout the lifespan and cause long-term changes to the body's biology that ultimately impact psychiatric outcomes? Epigenetic mechanisms are hypothesised to be one important molecular pathway by which this occurs.^{5,6} There is now a growing body of research that supports the hypothesis that adverse environments impact the epigenome and that epigenetic differences can distinguish vulnerable and resilient individuals.⁵⁻⁷ However, the specific

role of protective environments and associated epigenetic mechanisms that contribute to the development of resilience are often overlooked.

Our aim in this paper is to consider the multiple roles that epigenetic mechanisms might play in psychological resilience, considering the complex relationships with environmental factors and genetics across the lifespan. In particular, we will pay particular attention to resilience-promoting factors. After introducing epigenetics, we present a theoretical model based on theory and empirical literature which outlines three specific ways in which epigenetics could contribute to the development of psychological resilience. We then use this model to assess the current state of research, highlight areas which remain to be thoroughly investigated and provide suggestions for future research.

Introduction to Epigenetics

Whilst the genome remains relatively stable throughout life, the expression of its genes is highly variable. This variability is partially controlled by epigenetic mechanisms, a diverse group of mitotically heritable and long lasting but reversible molecular changes, providing an important layer of control.⁸ Born out of this diversity, there is some disagreement as to exactly which mechanisms comprise epigenetics, but the best understood and most commonly-researched, particularly in relation to mental health, are DNA methylation, histone modification and non-coding RNAs (ncRNAs) (outlined in Panel 1 and fully described in the appendix, page 1). Acquiring, maintaining and eliminating these various modifications allows for a dynamic and multi-level system of control, impacting all stages of gene expression.⁹

The epigenome is modifiable in response to a variety of environmental factors including diet, physical health, and psychological trauma, allowing long-term adaptive changes to gene expression.^{10,11} However, epigenetic changes also occur as a function of normal development (e.g. cellular differentiation). As a result, epigenetic patterns tend to be cell- and tissue-specific. While human post-mortem brain tissue studies have identified epigenetic signatures of resilience,¹² most human studies rely on more easily accessible tissues such as blood, saliva and buccal cells.¹³ The extent to which these mirror the nervous system epigenome is unclear, although there is evidence that peripheral changes in DNA methylation can reflect those occurring centrally, particularly in psychiatric relevant genes,¹⁴ and can also reflect systemic changes relevant to resilience, such as inflammation.¹⁵

A Conceptual Model for the Role of Epigenetics in Resilience

A wide range of epigenetic differences has been observed in individuals with good mental health compared to those with psychiatric disorders.^{5,16,17} These differences can arise in various ways, but some are thought to be influenced by the environment and could mediate the impact of subsequent adversity on mental health.¹⁸ As described above, epigenetic mechanisms have the potential to record the experience of various life events in a lasting manner. The majority of epigenetic research in psychiatry to date has focused on the impact of specific adverse events on the epigenome and how epigenetic differences translate into the development of single psychiatric disorders. These relationships have been covered

in numerous reviews.^{7,17-19} However, much less is known regarding how epigenetics are impacted by *protective and positive* aspects of the environment and how this contributes to the development of psychological resilience. Additionally, research often fails to account for the main effects of genetic variation as well as genetic moderation of environmental influences on epigenetics. This is particularly important as individuals have been shown to exhibit variable sensitivity to both adverse and protective events.²⁰

Hence, we propose a conceptual model for three specific roles of epigenetics in the development of psychological resilience across the lifespan, building upon existing research and theories on the relationships between adversity, epigenetics, and mental health outcomes. Our theoretical model is depicted in Figure 1. At the model's core lies a pathway of resilience resulting in good multidimensional mental health (1), defined by the presence of adversity (2). The resilient outcome can be influenced by epigenetics in at least three ways, which occur throughout the lifespan (3). Firstly, an epigenetic signature of resilience may be partially present from conception, determined by genetic variation (4a) or inherited directly (4b). Secondly, some aspects of the epigenome are more changeable and modified by the environment, particularly during early development (5). Thirdly, specific protective factors during exposure to adversity impact how amenable the epigenome is to this negative event (6). Finally, genetic factors also play an important role, directly influencing resilience (7a) and moderating the effects of the environment on the epigenome (7b). It is necessary to consider all of these factors in order to understand the multiple potential ways that epigenetic factors contribute to resilience. In the remainder of this review, we will summarise the literature that concerns each aspect of this model.

Review of Empirical Evidence

Epigenetic Differences between Psychiatric and Resilient Outcomes

Epigenetic differences have been observed in presumably resilient individuals when comparing unaffected individuals to those with psychiatric disorders, including PTSD, depression, and anxiety disorders. This has been thoroughly examined elsewhere.^{16,17,21,22} The majority of research has focussed on differential DNA methylation in peripheral tissues such as blood and have identified resilience-associated differences in a variety of genes relating to immune function, neuronal plasticity, stress regulation and neurotransmission as well as others with unclear mechanisms of action. However, results are not always consistent and with the advent of hypothesis-free epigenome-wide studies, findings are often not replicated, particularly in the most carefully controlled studies.²³ Although studied far less frequently, some case-control differences in histone modifications and miRNA expression have also been associated with psychopathology.²²

Although these studies have attempted to identify epigenetic signatures of resilience, their approach often focusses on the absence of a single psychiatric outcome and rarely considers the presence of adversity. While not necessarily identifying resilience as we define it here, this approach has identified some similar epigenetic correlates of resilience between different mental health outcomes, although this is commonly due to the overlap in selected and studied candidate genes. For example, elevated DNA methylation of a gene important for neuronal development (*BDNF*)^{4,24} and increased biological age estimated from a

defined selection of DNA methylation loci have been observed in individuals with various psychopathologies.^{12,25} Other findings differ considerably between disorders, which may result from methodological differences, represent mechanisms more closely aligned to the development of specific symptoms or may result from a greater burden of adversity.

In an attempt to reconcile these differences, more recent studies have attempted to identify DNA methylation signatures of multi-dimensional resilience within the same cohort. One such study did not identify shared DNA methylation differences across different psychopathologies in the blood of World Trade Centre survivors²³, while a second found multiple differentially methylated regions in resilient at-risk Brazilian adolescents when considering multi-dimensional psychopathology.²⁶ Hence, evidence for the existence of a *general* resilient epigenome is currently not conclusive.

Importantly, while epigenetic markers may differentiate resilient individuals from those with mental illness, it is not entirely clear when and how these differences arise. They may represent epigenetic differences present from conception, or those that accumulate during development as well as those triggered by acute traumatic events and downstream coping mechanisms. The literature concerning these various possibilities is discussed below.

Inheritance of Epigenetic Resilience

Although epigenetic modifications are amenable to change throughout the lifespan, a certain proportion is set at conception and during the earliest stages of development. This early determination of the epigenome can be due to inherited genetic variation or direct inheritance of epigenetic marks themselves.

Genetic Determination of Epigenetic Variation—Genetic variation is a significant contributor to the epigenome present at conception. While monozygotic twins tend to have similar epigenetic profiles, at least at birth,^{27,28} and allele-specific patterns can be passed from parent to child,²⁹ epigenetic profiles can differ substantially between individuals with different ancestral backgrounds.³⁰ The genome can directly influence the epigenome in numerous ways. For example, genetic variation can directly impact the specific sites at which DNA methylation can occur,³¹ and may also impact the efficacy of sequence-dependent actions of ncRNAs.³²

Significant progress has been made in the discovery of genome-wide significant risk and protective genetic variants for psychopathology, but the majority lie within non-coding regions with unclear functional significance.^{33,34} In many cases, resilience-associated genetic variation is hypothesised to impact gene expression potentially via epigenetic intermediates. For example, psychiatric disease associated SNPs have been found to be enriched for multiple methylation quantitative trait loci (mQTL),^{35,36} while SNPs in the *FKBP5* gene, a key component of the stress response, have been associated with the risk of depression as well as the gene's methylation state.^{37,38} Therefore, genetic variation is likely one important source of epigenetic resilience. Disentangling genetic from epigenetic effects is a complex task but statistical approaches have been developed, and successfully applied to QTLs.^{39,40} Similar approaches are needed to achieve the same for phenotypes like resilience.

Multi-Generational Transmission of Epigenetic Variation—A second way by which epigenetic marks can be inherited is a direct mechanism, independent of genetic variation. Although a controversial subject in mammalian biology, studies indicate that this direct epigenetic inheritance occurs in some animal models.^{41,42} This can occur via inter-generational transmission whereby germline cells or the developing foetus is subject to the same environment as the parent. More interesting is the potential for transmission of epigenetic information to further generations not present at the time of exposure (i.e. trans-generational inheritance). These phenomena may allow molecular adaptation to the environment to be passed from parent to child and, importantly, suggests that the parental environment can impact the health of subsequent generations.

To date, the majority of pre-clinical research in this area has focussed on the epigenetic inheritance of traumatic experiences which elicits increased psychopathology in offspring. In rodents, various stress paradigms can produce depressive and anxiety-like behaviours in multiple subsequent generations and is correlated with specific epigenetic marks hypothesised to elicit their effect through neurodevelopmental or endocrinological mechanisms.^{43,44} The specific molecular mechanisms permitting this inheritance remain to be elucidated and it is unclear whether these specific epigenetic signatures are consistently conserved at the cellular level throughout the generations or are re-established in each subsequent generation.

Currently, the existence of transgenerational epigenetic inheritance in humans has yet to be proven. True transgenerational inheritance is difficult to ascertain due to the number of generations necessary and the confounding due to genetic inheritance and shared pre- and postnatal environments affected by psychopathology. Multiple human studies have indicated that traumas such as combat exposure, forced displacement, genocide exposure, and low maternal bonding may be passed on inter-generationally, and have been associated with both psychopathology in children and DNA methylation in the *FKBP5* gene.^{45,46} Currently, the sole indications that the effects of damaging environments may be passed trans-generationally come from rare and non-replicable cohorts, and have yet to identify corresponding epigenetic changes.⁴²

Importantly, the majority of research in this area has focussed on epigenetic inheritance of adversity, which correlates with reduced resilience in subsequent generations. While this indicates that psychological resilience could be *degraded* due to inherited epigenetic marks, it is unclear whether resilience could also be *promoted* through similar mechanisms. Resilience-promoting influences such as exercise and environmental enrichment have been shown to reduce depressive-, anxiety- and fear-related behaviours in at least one subsequent generation in mice,^{47,48} but further research will be needed to ascertain whether epigenetic modifications allow this inheritance of resilience and whether similar processes occur in humans.

Environmental Influences on Epigenetic Resilience

While some epigenetic marks are inherited or set during organismal development, many exhibit plasticity in response to the environment, allowing molecular adaptation throughout life. While monozygotic twins have relatively similar DNA methylation and histone

acetylation patterns during their early years, large differences are observed in later life suggesting a substantial input from the environment during subsequent years.^{49,50}

Environmental Quality is Associated with Epigenetic Changes—There is a large body of evidence that indicates that the epigenome is susceptible to adversity, including prenatal stress, early life trauma, maltreatment, and social stress, reviewed elsewhere.^{5,25,51,52} The epigenome is particularly sensitive during early developmental stages and resulting epigenetic changes last far beyond the time of adversity.⁵ Although epigenetic outcomes of these events are often studied in isolation, evidence exists for cumulative and longitudinal effects. Time since adversity can moderate the magnitude of epigenetic change,⁵³ while repeated or varied sources of adversity may accumulate to produce larger epigenetic responses.^{54,55} These adversity-inflicted epigenetic changes have been correlated with later sensitivity to adversity and consequently reduced resilience.⁵

Less well understood is the impact that *protective or positive* environmental factors have on the epigenome. While the absence of negative or detrimental factors is expected to shift the trajectory of mental health towards resilience, it is also important to understand which factors directly promote resilience itself. Parental care is one protective factor which has been found to promote resilience alongside epigenetic changes. Research investigating the epigenetic and psychological consequences of naturally-occurring variation in mothering behaviours in rats found that high quality care resulted in offspring with more robust stress hormone responses and reduced depressive- and anxiety-like behaviours alongside reduced DNA methylation at the gene encoding a key receptor in the glucocorticoid stress system (*Nr3c1*) alongside increased histone acetylation in hippocampal tissue.⁵⁶ In humans, preliminary research suggests that aspects of parental care such as breastfeeding and physical contact are also associated with decreased methylation of *N3CRI*, as well as *BDNF*, and increased methylation of the pro-inflammatory gene *TNF*.⁵⁷

Positive aspects of the environment such as cognitive stimulation, healthy diet, and exercise may also promote resilience through epigenetic mechanisms. Environmental enrichment during early development in mice has been found to alter miRNA expression and histone acetylation at the *Bdnf* gene^{58,59} and also rectified epigenetic changes induced by inherited trauma.⁵⁹ Similarly, individual dietary components, such as dietary phytochemicals, have been found to reduce depressive-like behaviours through epigenetic mechanisms targeting systemic inflammation and neuronal plasticity in mice.⁶⁰ Although challenging to translate into humans, healthy lifestyle factors such as moderate physical activity, dietary quality and cognitive stimulation are associated with resilience-building.⁶¹ Little work has been conducted to investigate the impact of these factors upon the epigenome, but minimal alcohol intake, fruit and vegetable consumption, and moderate exercise have been associated with a lower epigenetic age, a resilience-associated epigenetic factor.^{62,63} Further research is needed to understand whether this has a downstream impact upon resilience.

Psychotherapeutic interventions may also impact the epigenome alongside their therapeutic effect. For example, changes in DNA methylation of candidate stress-related genes (*FKBP5*, *SLC6A4*) have been observed in patients undergoing psychological treatments for PTSD, phobia, or anxiety symptoms.⁶⁴⁻⁶⁶ In a more recent hypothesis-free epigenome-

wide approach, treatment-responsive individuals exhibited reduction of PTSD symptoms alongside differential DNA methylation in multiple genes.⁶⁷ However, although epigenetic changes occur alongside symptom reduction, it is not clear whether the psychological therapies rectify the biological “scarring” of prior negative experiences or have their own independent promotive effect.

Importantly, while negative aspects of the environment tend to be thought of as sensitising individuals to further adversity, some negative factors may actually increase resilience through a so-called *steeling effect*.^{68,69} For example, in mice certain mild stress paradigms appear to promote resilience in later life.⁷⁰⁻⁷² Similarly, in a recent cohort study, Brazilian children who experienced prenatal maternal violence exhibited increased resilience to postnatal maternal violence compared to those that only experienced violence postnatally.⁷³ Differentially methylated sites were identified in the *FKBP5* and *NR3C1* genes suggesting a prenatally-derived stress-adaptive mechanism to overcome subsequent adversity. Although this preliminary work suggests that negative life experiences can promote later resilience through epigenetic changes, more work is needed to confirm these findings and to better understand the threshold at which such experiences become detrimental to resilience.

Protective Environmental Influences on Epigenetic Resilience during Adversity Exposure—As outlined above, numerous reports show that environmental influences can alter the epigenome. However, individuals exhibit variability in this response. Some intra-individual variation in the epigenetic response may well be due to specific protective factors, acting concurrently to dampen or counteract the adversity. Individual and social-environmental factors such as good emotional regulation, strong social support, and good familial relationships have been shown to promote resilience.⁷⁴ Little work has been conducted on this, but limited human studies indicate that specific protective factors can moderate the epigenetic outcomes of adversity. For example, the impact of perinatal depression upon the offspring’s DNA methylation of stress-related genes *NR3C1* and *SLC6A4* has been found to be moderated by the quality of maternal care.⁵⁷ Additionally, mothers’ cognitive appraisal of a natural disaster during pregnancy moderated the impact of the disaster upon methylation of the inflammation-related *LTA* gene in children.⁷⁵ However, further work is necessary to confirm and expand upon the specific protective nature of maternal care and cognitive appraisal on the epigenome.

Genetic Moderation of the Environment and Epigenetic Processes

A large body of evidence indicates an important role for genetics in various stress-related disorders, with a substantial overlap between different dimensional outcomes suggesting some shared “resilience loci”.^{33,34,76,77} As outlined above, some of these genetic factors may contribute to resilience through direct effects upon the epigenome. In addition, genetic factors may moderate the impact of the environment upon the epigenome.

Although the environment can have both “scarring” and “steeling” effects upon the epigenome, there is large variation in response to these experiences. This disparity may be explained by sensitivity-conferring genetic variants that increase vulnerability to negative environments but may also promote favourable outcomes in response to positive exposures.

This represents individual differences in *Environmental Sensitivity* – the degree to which people respond to both negative and positive environments (Figure 2a).⁷⁸⁻⁸² Research has shown that Environmental Sensitivity is a measurable, common, complex, heritable, and polygenic trait⁸³.

A growing number of studies provide evidence that genetics can moderate the impact of negative environmental factors on epigenetic modifications.⁸⁴ For example, epigenome-wide neonate DNA methylation has been shown to result from an interaction between genetic variation in nearby *cis* variants and prenatal factors such as maternal smoking, maternal depression, and gestational age.⁸⁵ Individual genetic variants in the *FKBP5* gene have also been shown to moderate the impact of adversities such as childhood maltreatment or the synthetic glucocorticoid dexamethasone on *FKBP5* DNA methylation.⁸⁶⁻⁸⁸

Of particular relevance to resilience building is the observation that people differ substantially in their response to the positive effects of nurturing experiences as described by *Vantage Sensitivity* (Figure 2b).²⁰ As of yet, little research has been conducted to understand genetic moderation of protective influences on the epigenome, although it is possible that variants which moderate adversity may also moderate positive factors. Polygenic scores for Environmental Sensitivity have been shown to moderate the beneficial outcomes of cognitive behavioural therapy on anxiety symptoms,⁸⁹ and genome-wide and single locus variation in the *SCL6A4* gene the impact of good parenting quality on youth psychopathology.^{89,90} Interestingly, individuals with the highly sensitive *SCL6A4* genotype, did not manifest increased susceptibility to poor parenting suggesting that this variant may specifically provide Vantage Sensitivity rather than general Environmental Sensitivity.⁹¹ However, it remains to be seen whether these psychological outcomes are due to epigenetic changes and genetic moderators of the impact of positive factors on epigenetics have yet to be identified.

Discussion and Directions for Future Research

Here we have presented a theoretical model describing the multiple ways in which epigenetics may contribute to the long term development of psychological resilience. The epigenome is initially defined by direct or indirect inheritance, but is subject to change due to environmental influences during early and later development. This plasticity could be moderated by genetically-derived individual differences in Environmental Sensitivity. The resulting epigenetic profile of resilience therefore reflects an accumulation of these individual and social-environmental factors, and alongside stable genetic influences allows for the successful adaptation to adversity and the maintenance of good mental health. While moderate evidence exists for several aspects of this model, we wish to highlight areas which are currently lacking and make practical suggestions for future research (see Panel 2).

Firstly, the concept of resilience in epigenetic research should be studied in its own right, rather than simply as a disease-free state.² While some studies solely study people that have experienced adversity,²³ or consider the severity of adversity,⁹² others do not. Therefore, identified epigenetic differences may reflect true resilience in some cases, whilst in others they may simply reflect the presence or severity of adversity. Additionally, the consideration

of multiple psychiatric outcomes will allow us to understand the general mechanisms that underlie psychological resilience more broadly, rather than the development of specific sets of mental health symptoms. To this end, adversity must be taken into account and, where appropriate, multi-dimensional psychiatric outcomes should be considered.

Secondly, we must widen our search for environmental factors that promote resilience through epigenetic changes. There is moderate evidence that various forms of adversity can impact the epigenome and consequently resilience, although results are not always consistent and studies rarely consider all three factors. However, there has been little investigation into how positive or protective aspects of the environment could have their own independent or counteracting actions in the epigenetic development of resilience. Furthermore, while it is suggested that reduced resilience may be inherited through inter-generational transmission of epigenetics, this is far from proven in humans and it is unknown whether such mechanisms can promote resilience. Future lines of enquiry should take genetic variation into account to fully appreciate the degree to which the environment can impact the epigenome in different genetic contexts.

Thirdly, the longitudinal nature of the trajectory towards epigenetic change and resilience must be fully considered, taking into account the developmental context and time since exposure. It is also critical to assess the direction of causality between environmental factors, epigenetic changes and psychiatric outcomes as this is rarely done. Hence, it is crucial to adopt a life course perspective utilising longitudinal studies with repeated assessments allowing the investigation of within-person epigenetic changes across different developmental periods and critically before the development of pathological outcomes. Additionally, environmental factors are typically studied in isolation. While informative, such events are unlikely to occur alone in naturalistic settings and have been shown to have cumulative effects on the epigenome and may impact the epigenome and resilience in the form of developmental cascades, impacting the response to further events.^{54,55} This has particular relevance for epigenetics, which is defined by continuous and highly plastic changes, for example through varying ncRNA expression or the methylation of multiple loci in a region.

Finally, the search for epigenetic factors involved in resilience must be expanded to include a wider variety of mechanisms. As highlighted in this review, the vast majority of studies in relation to epigenetics and resilience aim to identify differential DNA methylation. While this approach has generated a wealth of knowledge, we know relatively little about the involvement of other epigenetic mechanisms including ncRNA expression, ncRNA modification and histone modifications, as well as more recently discovered effects of DNA methylation.^{93,94} As these modifications accumulate and interact with one-another to produce tightly regulated changes in gene expression, it is not sufficient to only study differences in single DNA methylation loci.⁹

Although our model aims to encapsulate and summarise the key components involved in the development of resilience, we acknowledge that further factors may be involved. For example, genetic variation may moderate the impact of epigenetic changes on resilience.⁸⁶ We have also not considered in-depth the specific biological mechanisms by which changes

to the epigenome result in psychological resilience. This is particularly challenging given that the majority of research solely studies epigenetics in peripheral tissues. Although clear etiological processes can be assigned to certain epigenetic changes such as those impacting the systemic stress response system (*FKBP5*, *NR3C1*), hypothesis-free epigenome-wide studies increasingly highlight epigenetic changes without clear downstream effects.

In conclusion, we have outlined the complex mechanisms by which aspects of the environment can become biologically embedded through epigenetic changes and contribute to the development of psychological resilience. We have outlined the research areas which are currently lacking strong evidence and highlighted strategies that will improve future work. In particular, we hope that this review has emphasized certain themes. Firstly, the importance of clearly defining resilience in well-designed epigenetic studies. Secondly, broadening our study of the role of the environment on epigenetics and resilience to include protective and positive factors, the inheritance of epigenetic resilience and the role of genetic moderation informed by theories of Environmental Sensitivity. Thirdly, appreciating the longitudinal and cumulative effects of the environment on the epigenome and resilience. Finally, improving and expanding upon the commonly studied epigenetic mechanisms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Panel 1:**The three major classes of epigenetic modification.****DNA methylation**

The addition or removal of methyl groups directly to the DNA code which impact the tightness of DNA packaging. A common feature in gene promoters, this effectively suppresses expression of the associated gene.

Histone modification

The addition or removal of small chemical groups (e.g. methyl groups) to the histone proteins which form the scaffold for DNA. Depending on the specific modification this modulates the tightness of DNA packaging and consequently the expression of nearby genes.

Non-coding RNAs

Diverse species of RNA which can impact the many stages of gene expression from transcription to post-translational modification. The most commonly studied species in psychiatric research is micro RNAs which act by binding to messenger RNAs to prevent them from being translated into proteins.

Panel 2:**Practical Suggestions for Future Research**

Research Aim	Practical Suggestion
Measure resilience in a consistent and appropriate way	<ul style="list-style-type: none"> • Consider multiple dimensions of mental health, for example through the concurrent use of multiple scales or the p factor⁹⁵ • Conduct repeated measures over time following a defined and measurable adverse event
Characterise epigenetic changes throughout the lifespan	<ul style="list-style-type: none"> • Utilise prospective studies which examine the impact of predictable adverse influences on epigenetics (e.g. military deployment) • Examine intra-individual variation in DNA methylation across development (e.g. EpiDelta) • Utilise cumulative risk and protective scores which capture the combined exposure to the environment
Understand the interplay between genetics and epigenetics	<ul style="list-style-type: none"> • Conduct parallel genome-wide epigenetic and genetic approaches to tease apart genetic and epigenetic effects • Utilise polygenic and (poly)epigenetic risk scores
Consider a wider variety of epigenetic mechanisms in an unbiased and genome-wide manner	<ul style="list-style-type: none"> • Utilise advanced methods that have recently become more economically viable (e.g. whole-genome bisulphite sequencing)
Identify the biological mechanisms underpinning epigenetically-derived resilience	<ul style="list-style-type: none"> • Investigate the cross-tissue correspondence of peripheral epigenetic signatures to interpret findings using existing tools (e.g. BECon)⁹⁶ • Identify multi-site signatures which correspond to systemic changes (e.g. epigenetic ageing clocks)⁹⁷

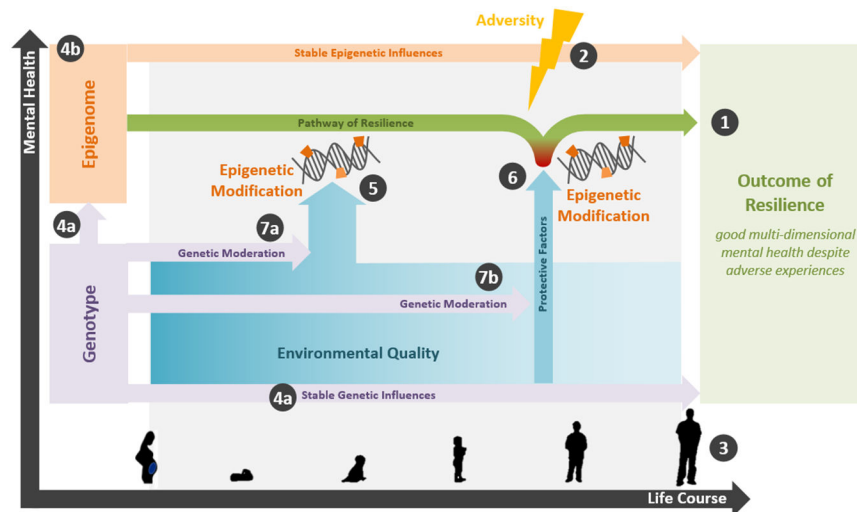


Figure 1. Theoretical model outlining the contribution of epigenetics in the development of psychological resilience.

This model focusses on the development of multidimensional resilience (1), defined by the presence of an adverse event (2). This resilient outcome can be influenced by epigenetics in three key ways, which occur at different stages throughout the lifespan (3). Firstly, resilience-associated epigenetic differences may be determined by genetic variation (4a) or inherited from previous generations (4b). Secondly, the epigenome can be modified by the environment, particularly during early life (5). Thirdly, specific protective factors during adversity exposure will affect how modified the epigenome is (6). Genetic factors can directly influence resilience itself (7a) and can moderate the effects that the environment and protective factors have on the epigenome (7b).

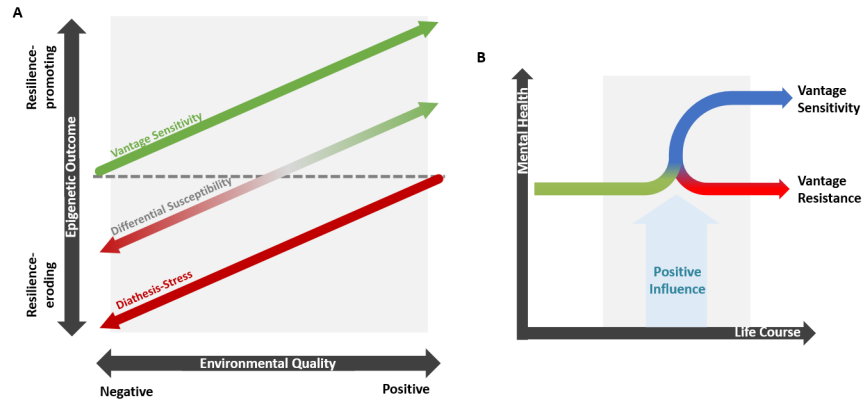


Figure 2. Models of Environmental Sensitivity and Vantage Sensitivity

(A) Illustration of the three models of Environmental Sensitivity: Vantage Sensitivity, Differential Susceptibility and Diathesis-Stress. These models describe the inter-individual differences in response to both positive and negative environmental factors, and have been applied to epigenetic changes in the context of resilience. Diathesis-Stress describes individual differences in response to negative factors whereas Vantage Sensitivity describes variability regarding positive factors. Differential Susceptibility represents a combination of diathesis-stress and vantage sensitivity with heightened sensitivity to both negative and positive experiences. Figure adapted from Pluess, 2015.⁷⁸ (B) The Vantage Sensitivity model which outlines the differential variation in benefit specifically from positive influences. Figure adapted from de Villiers et al. 2018.⁹⁸