

Review

Climate Change-Induced Stress and Neural Plasticity: Genetic and Epigenetic Mechanisms of Adaptation

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Abstract

Changes in the environment driven by climate change are becoming significant stressors that impact brain function, but the connections between these changes and neural plasticity remain unclear. This review aims to offer a comprehensive synthesis of the impact of climate-related stressors on neural plasticity via genetic and epigenetic mechanisms. A structured literature search (2000-2025) was conducted using PubMed, Scopus, and Web of Science, integrating evidence from in vitro, animal, and human studies. Findings indicate that stressors such as heat, pollution, psychosocial adversity, and hypoxia alter neural plasticity through interconnected pathways, such as oxidative stress responses, mitochondrial adaptation, neurotrophic signaling, and epigenetic regulation. The strength of evidence varies; mechanistic insights are primarily obtained from experimental models, whereas human data are mostly associative. We propose a framework for an adaptive-maladaptive continuum based on the intensity, duration, and timing of stressors in development. Overall, this review highlights key knowledge gaps and provides a structured roadmap to improve causal inference and translational relevance.

Keywords

Neuroinflammation; mitochondrial dysfunction; ROS; HPA axis; DNA methylation; synaptic plasticity markers

1. Introduction

One of the most pressing issues facing the world today is climate change, which has a profound and diverse impact on ecosystems and biological systems. Living things, including humans, are chronically stressed by rising temperatures, harsh weather, and environmental deterioration [1, 2].

Through complex genetic and epigenetic pathways that mediate sensitivity and tolerance across generations, these climate-induced environmental stressors affect behavior, cognition, and neurological health [3, 4]. The brain is especially susceptible to temperature changes, oxidative stress, and environmental pollutants, as it is an extremely energy-dependent and environmentally sensitive organ. Adaptive or maladaptive neural plasticity is how the central nervous system (CNS), which is especially sensitive to homeostatic imbalance, reacts [5-7]. Recent studies have demonstrated how changes in gene expression, DNA methylation, histone modification, and noncoding RNA activity can impact neural plasticity, the capacity of the brain to adjust its structure and function [8, 9]. Therefore, anticipating and reducing the neurobiological effects of climate change requires an understanding of how environmental change affects neuronal plasticity, the brain's capacity to alter structure and function in response to inputs [10]. There is growing evidence that epigenetic alterations, including DNA methylation, histone modifications, and noncoding RNA regulation, are influenced by environmental exposures, such as heat stress, pollution, and changes in resource availability. The effects of climate-related stresses on brain circuits, synaptic plasticity, and behavioral outcomes are mediated by these biological mechanisms [11, 12]. The term "epigenetics" describes heritable variations in gene expression that do not change the underlying DNA sequence but can significantly affect how genes are turned on or off, affecting a person's physiology, development, and susceptibility to disease [13, 14]. Therefore, epigenetic mechanisms act as a dynamic link between the environment and the genome, enabling organisms to modify gene expression without changing the underlying DNA sequence [15]. Additionally, epigenetic research is critical to understanding how these environmental exposures interact with biological systems to affect neurodevelopmental trajectories and cognitive outcomes [16-18]. Understanding how climate-induced stressors such as temperature swings, pollution, and oxidative stress particularly change epigenetic landscapes (such as DNA methylation, histone modification, and noncoding RNA activity) to impact neuronal development and cognitive function is important. Predicting adaptability and vulnerability requires deciphering these biological mechanisms [10, 19]. Furthermore, it is still difficult to link environmental exposures such as air pollution, heat stress, and resource shortages with modifications in brain circuits and behavioral effects. Determining causality and resilience mechanisms is challenging because of the dynamic interaction between genetic predispositions and environmental stressors [16, 20, 21]. Evaluating how climate-stress-induced epigenetic changes are passed through generations and impact long-term brain health and resilience is another significant challenge [22]. Evaluating population-level vulnerability under ongoing climate change pressures requires an understanding of these heritable impacts. From a molecular perspective, exposure to environmental stress is linked to long-term effects on the brain through genetic and epigenetic pathways [23]. Neuroscience, public health, and climate resilience initiatives are all supported by an understanding of how genetic and epigenetic pathways regulate the response to environmental stress. Given that the state of the brain and the environment are inextricably linked, future neuroscience must incorporate ecological and environmental viewpoints [11, 24].

This review crosses a mere descriptive summary, offering a conceptually cohesive and analytically organized synthesis of the impact of climate-related stress on neural plasticity. It rigorously assesses the robustness, limitations, and translational significance of existing evidence, while differentiating experimentally confirmed mechanisms from correlational observations. This work presents an adaptive–maladaptive continuum framework predicated on stressor intensity,

duration, and developmental timing, while systematically stratifying evidence from in vitro, animal, and human studies, thereby providing a more lucid framework for evaluating causal inference. The addition of a final synthesis of research priorities underscores significant deficiencies and offers a framework for subsequent research aimed at enhancing mechanistic comprehension and clinical relevance.

1.1 Conceptual Framework and Evidence Classification

This review adopts an operational framework in which molecular and neurobiological responses are interpreted along an adaptive–maladaptive continuum. Evidence is categorized into four levels: (i) in vitro mechanistic studies, (ii) animal experimental models, (iii) human observational and epidemiological studies, and (iv) longitudinal or interventional human data. Causal inference is considered strongest when findings are consistent across these levels. Causal inference is strengthened when convergent evidence is shown across many levels, particularly when mechanistic results from in vitro and animal studies are validated by longitudinal or interventional human data [25]. Within this framework, adaptive responses are defined as transient or reversible processes that enhance cellular resilience or plasticity, whereas maladaptive responses reflect sustained or dysregulated alterations associated with functional impairment or disease risk.

1.2 Literature Search Strategy

A structured literature search was conducted to identify relevant studies examining the effects of environmental and climate-related stressors on molecular and neurobiological mechanisms. Major databases, including *PubMed*, *Scopus*, and *Web of Science*, were searched for articles published between 2000 and 2025. Search terms included combinations of keywords such as ‘climate change’, ‘environmental stress’, ‘brain health’, ‘oxidative stress’, ‘epigenetics’, ‘mitochondrial function’, and ‘neuroinflammation’. Priority was given to peer-reviewed original research articles and high-quality review papers. Both experimental (in vitro and animal studies) and human observational or epidemiological studies were considered to provide a comprehensive perspective. Articles were selected based on relevance to the central theme of adaptive versus maladaptive responses and their contribution to mechanistic understanding. While this narrative review does not follow a formal systematic review protocol, efforts were made to ensure balanced representation of current evidence and to minimize selection bias [26].

2. Environmental Stressors in a Changing Climate

Any external physical, chemical, or psychological problem that disrupts normal physiological or cellular equilibrium in organisms, including the nervous system, that is caused by or made worse by environmental change (such as pollution, habitat loss, or climate change) is considered an environmental stressor [27].

Climate change alters the neural environment through multiple stress modalities:

2.1 Thermal Stress (Extreme Heat)

Climate change-related extreme heat disrupts neuronal homeostasis, resulting in oxidative stress, excitotoxicity, ER stress, mitochondrial malfunction, inflammation, and apoptosis, all of which

eventually damage the structure and function of the brain [28, 29]. Heat stress, for example, suppresses hippocampal neurogenesis, activates caspases (apoptosis), and causes mitochondrial dysfunction by stimulating glial release of proinflammatory cytokines (IL-1 β , IL-6, and TNF- α) [30, 31]. Increased glutamate/aspartate and decreased inhibitory transmitters (GABA/glycine), elevated intracellular Ca²⁺, oxidative stress, DNA damage, and apoptosis are other ways to induce excitotoxicity [32, 33]. Current knowledge predominantly derives from epidemiological correlations and short-term exposure studies, with a scarcity of mechanistic research in humans. The absence of controlled longitudinal data constrains inferences about the enduring neural and cognitive consequences of chronic heat exposure [34, 35].

2.2 Pollution and Toxins

The blood–brain barrier (BBB) can be breached by fine particulate matter (PM_{2.5}) and pollutants (such as heavy metals), which can also cause microglial activation, neuroinflammation, oxidative stress, mitochondrial damage, ER stress, and even neuronal apoptosis [36–39]. In particular, exposure to PM_{2.5} triggers ROS-mediated MAPK and NF- κ B signaling, activation of the NLRP3 inflammasome, and increased production of IL-1 β and IL-18, which results in vascular/neurodegenerative disease and chronic neuroinflammation [40–42]. PM_{2.5} may affect neuronal and vascular health through systemic inflammation and the gut–microbiome–brain axis, in addition to direct inhalation–brain pathways (such as the olfactory nerve) [38, 43]. However, the majority of mechanistic insights connecting pollution to neurobiological changes originate from animal models and in vitro systems, whereas human evidence is predominantly epidemiological. Longitudinal studies establishing causal relationships and precise exposure thresholds remain limited [44, 45].

2.3 Psychosocial Stress (e.g., Displacement, Food Insecurity, and Ecological Instability)

Extreme weather, drought, and resource scarcity are examples of climate change-related disasters that can cause displacement, social unrest, financial hardship, and food and water insecurity, all of which can lead to long-term psychological stress [46]. Chronic psychosocial stress increases stress hormones (cortisol and catecholamines), activates neuroendocrine stress pathways (e.g., the HPA axis), and over time may result in hippocampal atrophy, altered neurotransmitter balance, impaired neural circuitry for emotion and memory, and increased susceptibility to psychiatric disorders [47, 48]. In this field, most evidence comes from observational, population-based studies. Mechanistic insights are often taken from stress models in animals. Differences in how people see and measure stress make it even harder to figure out what causes it and how it applies to other situations [49].

2.4 Hypoxia and Nutrient Deprivation (Environmental Degradation)

The provision of oxygen and micronutrients to tissues, including the brain, can be hampered by environmental degradation (e.g., deteriorated air or water quality, decreased oxygen availability, changes in food production), which compromises mitochondrial function and neurogenesis [50, 51]. Variations in oxygen tension can change ROS production, neural stem cell activation, and neurogenesis, according to experimental research in nonmammalian vertebrates. These findings

suggest that hypoxia (and reoxygenation) can significantly affect brain regeneration and homeostasis [52]. Collectively, these stressors activate systemic and central stress responses, triggering genetic and epigenetic modifications that alter brain structure and function. A significant portion of mechanistic evidence is derived from toxicological and experimental models, whereas human studies are primarily correlational. Difficulties in precisely measuring cumulative exposure and co-exposure effects constrain the robustness of causal inferences [53].

3. Genetic Mechanisms Underlying Neural Adaptation

3.1 Heat Shock and Stress Response Genes

Thermal and oxidative stress cause the upregulation of heat shock proteins (HSPs), such as HSP70 and HSP90. These molecular chaperones prevent neuronal death, preserve synaptic integrity, and stabilize misfolded proteins [54-57]. For example, through ATP-dependent conformational cycles that identify and bind exposed hydrophobic patches on misfolded neuronal proteins, HSP70 and HSP90 inhibit neuronal death. Hsp40 (DnaJ) stimulates Hsp70 ATPase activity, which cycles substrates through high- and low-affinity states to allow refolding [58]. Hsp70 recognizes exposed hydrophobic regions on nascent or misfolded polypeptides and binds them to prevent abnormal aggregation. The Hsp70/Hsp90 network transfers clients to ubiquitin–proteasome or chaperone-mediated autophagy pathways when refolding is unsuccessful. This eliminates species prone to aggregation and stops proteostasis-driven mitochondrial and synaptic damage, which triggers neuronal apoptosis [55, 59].

By preserving the folding and stability of synaptic proteins, shielding cytoskeletal components, and obstructing toxic extracellular signaling that hinders synaptic transmission, these chaperones also maintain synaptic integrity [54, 56]. To avoid A β -triggered synaptic toxic signaling and activate prosurvival cascades, the cochaperone stress-inducible phosphoprotein 1 (STI1) can be released and disrupt A β binding to the cellular prion protein (PrPC) [59]. Modulating Hsp90 activity can regulate synaptic physiology in neurodegenerative models and lessen amyloid/tau-related synaptic dysfunction, according to in vivo studies [55, 60]. Enhanced tolerance to repeated stress exposure has been linked to chronic activation of HSP genes, indicating a possible adaptation mechanism in susceptible populations [61].

3.2 Oxidative and Mitochondrial Pathways

Antioxidant defense genes are regulated by transcription factors, including NRF2 (nuclear factor erythroid 2–related factor 2), which are activated by climate-related oxidative stress [62, 63]. Similarly, mitochondrial DNA (mtDNA) is plastic in response to environmental stress; mutations and adaptive polymorphisms in mtDNA can alter energy metabolism, impacting neurodegenerative risk and cognitive resilience [64-66].

3.2.1 NRF2-Mediated Antioxidant Defense in Neural Adaptation

Keap1 limits NRF2 transcriptional activity under basal conditions by binding cytosolic NRF2 and directing it toward Cullin3-dependent ubiquitination and proteasomal destruction [62]. Reactive oxygen species alter reactive cysteine residues on Keap1 when neurons experience oxidative or electrophilic stress. This conformational shift hinders Cullin3-mediated ubiquitination of NRF2 and

lengthens its half-life [63]. To bind antioxidant response elements (AREs) and induce genes that produce glutathione, NADPH, heme degradation, and phase II detoxification enzymes, stabilized NRF2 avoids degradation, builds up in the cytoplasm, translocates to the nucleus, and heterodimerizes with tiny Maf proteins [67]. Important antioxidant genes, such as HO-1 (heme oxygenase-1), which breaks down heme and prevents heme-driven oxidative damage; NQO1 (NAD(P)H quinone oxidoreductase 1), which promotes quinone detoxification; and GCLC/GCLM (glutamate-cysteine ligase subunits), the rate-limiting enzymes for glutathione synthesis that increase neuronal GSH levels. In both acute and chronic neurodegenerative models, this coordinated transcriptional response improves survival and maintains mitochondrial function and proteostasis, suggesting a cell-autonomous neuroprotective program powered by ARE targets [62, 68].

3.2.2 Mitochondrial DNA Plasticity and Neural Adaptation

By altering oxidative phosphorylation (OXPHOS) components, mitonuclear coordination, and endoplasmic reticulum–mitochondria coupling, mitochondrial DNA variation directly modifies neuronal bioenergetics. This modifies ATP, reactive oxygen species (ROS), and Ca^{2+} dynamics, which in turn shape cognitive resilience and disease susceptibility [64-66, 69]. Sequence variation is intimately linked to bioenergetic output, as mtDNA encodes 13 key OXPHOS genes, 22 tRNAs, and two rRNAs that control baseline electron transport chain composition and capacity [70, 71]. Changes in the sequence of mtDNA-encoded complex I/IV subunits or tRNAs can modify the respiratory chain's assembly or kinetics, resulting in decreased ATP, elevated ROS, and decreased catalytic efficiency. This mechanism links mtDNA variation to neuronal energy failure [65, 72]. It is anticipated that climate-associated variations, concentrated in complex I subunits ND2 and ND4, will change complex I structure and function, linking environmental selection to OXPHOS tuning [73]. Furthermore, altered mitochondrial dynamics and the integrity of the mitochondria-associated ER membrane (MAM) affect cognitive outcomes in chronic hypoperfusion models, reduce Ca^{2+} transport to mitochondria, and impair the oxidative phosphorylation response during synaptic activity [74]. NAD^+ , acetyl-CoA, and α -ketoglutarate are mitochondrial intermediates that rely on mtDNA-driven flux to regulate nuclear epigenetic marks and gene expression programs that underpin long-term neural adaptation and stress responses [66]. The oxidative stress and mitochondrial adaptation pathways activated by climate-related stressors are illustrated in Figure 1, highlighting NRF2-mediated antioxidant signaling and mitochondrial DNA plasticity as central mechanisms supporting neural resilience.

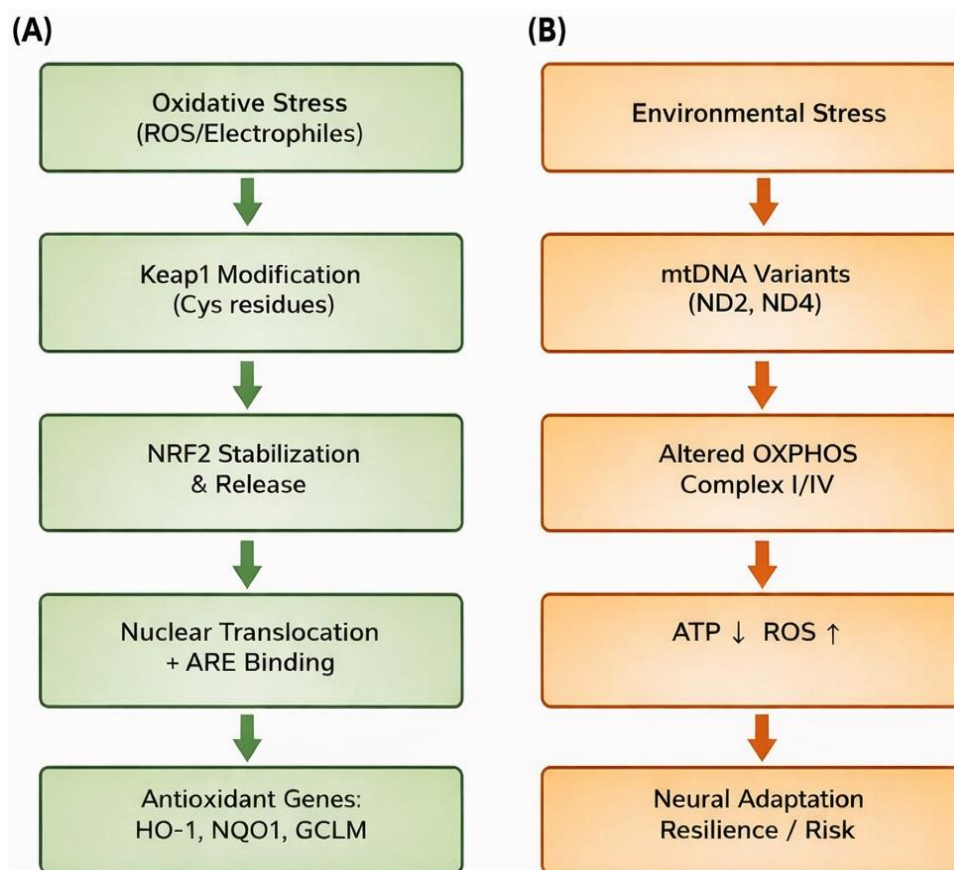


Figure 1 Oxidative stress response and mitochondrial adaptation pathways in neural cells. (A) NRF2 activation pathway: oxidative stress modifies Keap1, releasing NRF2 to translocate to the nucleus and activate antioxidant response element (ARE)-dependent genes [75]; (B) Mitochondrial DNA plasticity: mtDNA variants affect OXPHOS complex assembly, ATP production, and ROS generation, influencing cognitive resilience and neural adaptation [76].

In this context, pathways such as the Keap1–NRF2–ARE signaling and mitochondrial adaptations can be seen as responses that depend on the situation. Moderate activation may make cells more resilient, while prolonged or excessive activation may lead to oxidative damage and cell dysfunction. Nonetheless, the thresholds delineating these transitions are inadequately defined, especially within human systems [77, 78].

3.3 Neurotrophic and Synaptic Genes

Temperature and stress hormones can affect the expression of two key regulators of synaptic plasticity: BDNF (brain-derived neurotrophic factor) and CREB (cAMP response element-binding protein) [79-81]. While brief stress may cause compensatory upregulation that promotes adaptive remodeling, downregulation of these genes under long-term environmental stress is associated with synapse loss and cognitive impairments [82-84]. BDNF and CREB are modulated in a stressor-, time-, and tissue-dependent manner by exposure to ambient heat and hypothalamic–pituitary–adrenal (HPA) axis activation. While protracted or severe heat and chronic stress typically lower BDNF expression and blunt CREB activation, which is correlated with cognitive impairments, acute

heat or mild thermal challenge can sometimes increase BDNF and CREB signaling [79, 80, 85]. Through a variety of intracellular cascades and receptor modifications that differ depending on the timing and intensity of exposure, glucocorticoids and stress signaling interact with BDNF/CREB [81, 86]. Reduced BDNF and neural plasticity following prolonged thermal allostatic loading are linked to changes in telencephalic expression of mineralocorticoid and glucocorticoid receptors (MRs, GR1/GR2) and the inactivating enzyme 11 β -HSD2, suggesting a shift in receptor balance in BDNF regulation during extended stress [79]. Kinase pathways that regulate CREB phosphorylation are impacted by heat and stress: While Akt activation upstream of CREB increases BDNF under protective treatments in heat models, ERK1/2 disruption is associated with decreased CREB phosphorylation and lower BDNF following detrimental heat exposure [83]. To implement synaptic strengthening and structural plasticity, BDNF and CREB work together to control receptor function, gene transcription programs, and local protein synthesis. BDNF activates TrkB-linked cascades (MAPK/ERK, PI3K–Akt, and PLC γ), which influence synaptic effectiveness and NMDA/AMPA receptor activity. In particular, activity-dependent BDNF modulation during heat-related impairment is linked to ERK1/2–CREB coupling [87].

BDNF and other plasticity genes are transcriptionally upregulated when CREB is phosphorylated downstream of PKA, Akt, or ERK. In chronic stress scenarios, decreases in cAMP–PKA–CREB are associated with decreased BDNF mRNA/protein levels and compromised spatial memory [80, 88]. After heat insult, BDNF/CREB signaling maintains synapse-associated protein and dendritic spine density; in the heat-stressed hippocampus, treatments that stimulate Akt–CREB–BDNF restore synaptic protein levels and spine density [81]. In mice, heat-induced disruption of the ERK1/2–CREB–BDNF axis is associated with reduced levels of synaptic markers, decreased spatial memory, and oxidative damage to the hippocampus. Pharmacological or behavioral therapies that restore cAMP–PKA–CREB–BDNF improve cognition. Prolonged unexpected stress reduces the levels of cAMP, PKA, CREB, and BDNF in the hippocampus with concurrent deficits in sucrose preference and spatial learning [86, 89]. BDNF loss and synaptic/cognitive changes are causally linked via BDNF deletion or heterozygosity, which modifies the brain proteome, decreases the number of proteins involved in synaptic function, and modifies behavioral and thermal responses [81]. Neural systems recruit molecular and cellular compensation to preserve function under environmental stress. Activation of the Akt–CREB–BDNF and MeCP2-dependent pathways supports the recovery of adult hippocampal neurogenesis and synaptic protein expression in heat–stress models treated with β -hydroxybutyrate, indicating the recruitment of prosurvival and transcriptional modulators. At high temperatures, the telencephalon of fish exhibits upregulation of corticotropin-releasing factor binding protein (CRFBP) and changes in GR1/GR2 expression, which are interpreted as telencephalic suppression of stress responses that may function as adaptive brakes on HPA-axis signaling [79]. The effects of BDNF on synaptic plasticity can be enhanced or gated by exercise- and activity-related modulators (NMDA, CaMKII, and MAPK), offering pathways for compensation when one pathway is disrupted [87]. The regulation of BDNF and CREB signaling under thermal and stress conditions, including stress-dependent shifts between adaptive and maladaptive plasticity, is summarized in Figure 2.

Regulation of BDNF–CREB Pathways Under Environmental Heat and Stress

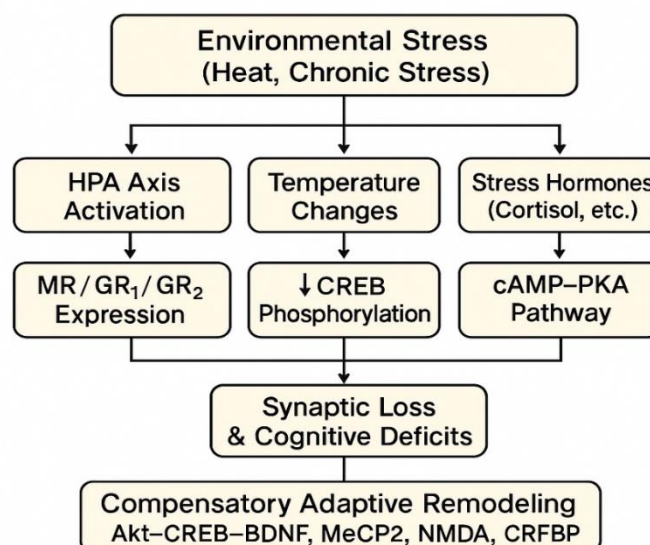


Figure 2 Regulation of BDNF/CREB under heat & stress.

4. Epigenetic Modulation and Neural Plasticity

Epigenetic mechanisms, such as DNA methylation, histone modifications, chromatin remodeling, and noncoding RNAs, which act as essential molecular connections between environmental cues and long-term changes in gene expression, shape neural development, synaptic function, and behavioral outcomes. One significant way the genome responds to its environment is through epigenetic processes. Environmental factors can induce epigenetic marks, leading to long-lasting alterations in gene expression that affect an organism's phenotype [90]. Epigenetic regulation allows neurons in the nervous system to shift from a fixed differentiated state to an adaptive, pliable state in response to learning, stress, and injury. An enzyme called (DNA methyltransferase) DNMT controls DNA methylation, which affects transcriptional programs in neurons that underlie memory formation and synaptic stability. For example, it has been shown that active loops of methylation and demethylation at the promoters of genes linked to plasticity, such as BDNF and CREB, influence long-term potentiation (LTP), a critical substrate of memory consolidation [91].

Histone modifications that control chromatin accessibility and enable rapid transcriptional changes required for brain learning include acetylation (H3K9ac), methylation (H3K4me3 and H3K27me3), and phosphorylation. Histone acetyltransferases (HATs) and deacetylases (HDACs) maintain this dynamic balance, which has been linked to neurodegeneration, cognitive decline, and stress-related behavioral problems [92, 93]. Moreover, noncoding RNAs, particularly microRNAs and long noncoding RNAs, finely modify transcriptional networks that support axonal growth, synaptic scaling, and neuronal differentiation [94]. Table 1 summarizes important epigenetic pathways linking environmental stressors to changes in brain gene expression and cognitive outcomes.

Table 1 Epigenetic mechanisms, environmental stress, and neural vulnerability.

Epigenetic Mechanism	Environmental Trigger	Molecular Mechanism	Effect on Neural Gene Expression	Neural/Cognitive Outcome	References
Acetylation at BDNF Promoters	Activity-dependent stress signals	Acetylation increases promoter accessibility.	Promotes BDNF transcription	Improved neuroplasticity	[95]
BDNF Methylation	Stress, inflammation	Methylation suppresses BDNF promoter activity.	Reduced neuroplasticity and synaptic resilience	Cognitive impairment	[96]
Early-Life Experience–Induced Methylation	Childhood adversity, psychological stress	Stable pre/postnatal methylation changes embed experiences.	Persistent changes in NR3C1 and BDNF expression	Long-term vulnerability to stress, mood disorders	[97]
Global & Gene-Specific DNA Methylation	Pollutants, psychosocial stress, temperature stress	Stress hormones, ROS, and inflammatory signals modulate DNMT/TET activity.	Activates or represses stress-regulatory and plasticity genes	Disrupted stress regulation, altered neural development	[98]
Heat Stress–Induced miRNAs	Thermal stress	Temperature-sensitive miRNA transcription	Controls protein refolding & antioxidant pathways	Neural resilience	[99]
Histone Acetylation (H3K9ac, H4K12ac)	Oxidative stress	Increased HAT activity opens chromatin.	Upregulates synaptic & stress-adaptive genes	Enhanced synaptic resilience	[92]
Loss of Activating Methylation	Inflammatory stress	Reduced H3K4me3 marks	Downregulates memory genes	Impaired learning	[100]
NR3C1 Methylation	Chronic stress, trauma	Altered methylation reduces glucocorticoid receptor transcription.	Impaired HPA-axis feedback	Heightened stress reactivity	[101]
Oxidative Stress–Driven miRNA Changes	ROS, H ₂ O ₂ , radiation	ROS alters miRNA biogenesis enzymes.	Disrupts neurogenesis & inflammation	Neuronal survival deficits	[102]

Repressive Histone Methylation	Chronic stress	Increased G9a/EZH2 activity tightens chromatin.	Silences neurogenesis & mood genes	Cognitive deficits	[103]
Stress-Responsive miRNAs	Psychosocial & oxidative stress	Stress alters pri-miRNA transcription & Drosha/Dicer processing.	Regulates synaptic remodeling	Psychiatric vulnerability	[104]
Thermal Stress–Driven Methylation Shifts	Climate warming, heat waves	Elevated temperature increases global methylation levels.	Alters metabolic and neural regulatory pathways	Modified neural plasticity	[105]

4.1 DNA Methylation and Vulnerability of Neural Systems

Epigenetic changes impact gene expression, which can change an individual's phenotype. A major epigenetic modification that varies throughout a person's life and appears to respond to a range of biological and psychological stressors is DNA methylation [106]. Changes in global and locus-specific DNA methylation, which alter gene transcription without changing the DNA sequence, are mostly responsible for these effects. Stickleback subjected to relatively high temperatures presented an increase in global DNA methylation, in contrast to the interspecific correlations between DNA methylation and ambient temperature [107, 108]. A species's ability to adapt to climate change may be determined by its phenotypic plasticity, which is important in how organisms react to sudden changes in their surroundings [106].

Molecularly, DNMTs add methyl groups to cytosine (5-mC) at CpG dinucleotides via the use of S-adenosylmethionine as a methyl donor. In contrast, active demethylation is accomplished via TET-mediated oxidation of 5-mC and base-excision repair. The environmental cues that "embed" early-life experiences into gene regulation include glucocorticoids, oxidative stress, and inflammatory mediators. Research on both humans and animals has demonstrated that epigenetic modification of the glucocorticoid receptor NR3C1 results in maladaptive stress reactivity profiles by altering receptor transcript levels and HPA-axis feedback [109]. The new study expands on previous findings by showing links between NR3C1 hypermethylation, ego under control, and emotional lability or negativity, all of which are connected to underlying processes of psychopathology [101].

4.2 Histone Modifications and Vulnerability of Neural Systems

Acetylation and methylation, the two most prevalent histone modifications, interact with related proteins and genes to alter the structure and function of neurons, affecting multiple crucial pathways. Examining the structural connections of proteins linked to these changes and their targets (DNA and histones) is crucial for comprehending processes and ultimately aids in the development of therapeutic medications for several disorders [110]. Climate-related oxidative stress alters chromatin structure and influences the transcription of genes associated with cognitive development by altering the histone acetylation and methylation levels. Posttranslational histone modifications, which affect gene expression, are altered by free radicals and oxidative stress [111]. Examples of epigenetic changes that respond to temperature and aid in climate change adaptation include changes in chromatin and histones [112, 113]. Stress-adaptive gene transcription is increased, and chromatin accessibility is improved by increased histone acetylation, especially H3K9ac and H4K12ac. Activity-dependent histone acetylation at BDNF promoters, especially promoters I and IV, is an adaptive neuroprotective mechanism that promotes synaptic resilience and functional recovery following acute stress exposure [92, 114].

Additional evidence suggests that histone methylation has a major impact on brain vulnerability as well. The accumulation of restrictive methylation marks, such as H3K9me2 and H3K27me3, caused by prolonged stress inhibits the transcription of genes linked to neurogenesis and emotional regulation [103]. Conversely, loss of activation marks at synaptic plasticity genes, such as H3K4me3, reduces neuronal firing efficiency and results in cognitive deficits [100, 115]. Together, these histone modifications act as dynamic interfaces that enable environmental stressors to modify neuronal chromatin, thus impacting memory, mood regulation, and the stress response.

4.3 Noncoding RNAs Vulnerability of Neural Systems

MicroRNAs (miRNAs) are significant posttranscriptional regulators of neuronal gene expression that control neurogenesis, stress response, and synaptic plasticity [116]. Because they modulate pathways linked to dendritic remodeling, neurotransmission, and neuroinflammatory signaling, stress-responsive miRNAs, such as miR-34a, miR-132, and miR-124, are significant mediators of brain vulnerability [104, 117]. Climate change miRNA expression patterns are linked to oxidative and temperature stress, altering regulatory networks that maintain brain homeostasis. For example, oxidative stress caused by radiation or hydrogen peroxide changes the expression of more than 20 miRNA species, directly disrupting redox-sensitive transcriptional processes [102, 118]. Environmental stressors impact: (1) the transcription of primary miRNAs (pri-miRNAs) via stress-activated transcription factors (e.g., p53 for miR-34a); (2) the efficiency of Drosha and Dicer processing, which controls the availability of mature miRNAs; and (3) RNA-binding proteins, such as HuR or TDP-43, which stabilize or degrade specific miRNAs [119, 120].

Additionally, heat stress triggers intricate miRNA networks that govern protein refolding, mitochondrial metabolism, and antioxidant defense, whereas temperature changes trigger small RNA responses that regulate neural adaptation and thermal tolerance [99, 121, 122]. The three main processes that determine neuronal resilience or vulnerability, synaptic plasticity, neurogenesis, and neuroinflammation, are ultimately impacted by these environmentally sensitive changes in miRNA [123, 124].

5. Adaptive and Maladaptive Outcomes

The transition between adaptive and maladaptive responses is probably controlled by several factors that interact, such as the intensity and length of the stressor, the timing of development, and the person's susceptibility. Adaptable responses are defined by reversibility, homeostatic restoration, and functional advantage, while maladaptive responses are marked by persistence, dysregulation, and correlation with pathological results [125]. To enhance operational clarity, the primary elements defining the adaptive–maladaptive continuum are (i) stressor intensity (the extent of exposure), (ii) duration (acute versus chronic exposure), and (iii) developmental timing (such as early-life versus adult exposure). These characteristics interact to determine whether molecular and cellular responses remain adaptable or transition to maladaptive results [126].

The duration and severity of environmental stress affect how adaptation and disease are balanced. The capacity of an organism to modify its characteristics (shape, function, and behavior) in response to changes in its surroundings, thereby improving survival and reproductive success (fitness) without changing its underlying genes, is known as adaptive plasticity. In brief, adaptive plasticity allows for fast recovery from mild stress, resilience to environmental perturbations, and flexible circuit remodeling functions that are probably advantageous for evolution in changing contexts. Brief genetic upregulation (e.g., BDNF and HSP70), short-term stress exposure can improve synapse efficiency, cognitive flexibility, and resilience [127, 128]. Transient neuroprotective mechanisms that improve synaptic efficiency and cognitive function can be activated by brief or moderate stress exposure [129]. It causes the hippocampus to produce the transcription factor heat shock factor 1 (HSF1), which attaches to the promoters of the brain-derived neurotrophic factor (BDNF) gene, namely, promoters I and IV, increasing the expression of BDNF mRNA and protein [127]. Long-term potentiation (LTP), synapse strengthening, and effective memory consolidation

are all supported by BDNF overexpression. In a similar vein, the stimulation of molecular chaperones such as HSP70 and HSP90 improves proteostasis and aids in defense against oxidative or proteotoxic stress, and maintains the integrity and functionality of neurons [130]. Crucially, these adaptive responses are fueled by neurotrophic signaling cascades, short-lived transcriptional programs, and quick chromatin changes (such as chromatin opening around BDNF promoters). Together, these mechanisms enable flexible circuit remodeling and increased resilience without imposing long-term metabolic burden [131].

However, the same plasticity pathways may become dysregulated in situations of chronic, recurrent, or severe stress (or during critical developmental windows), leading to maladaptive plasticity and disease. Extreme or prolonged stress causes neuroinflammation, neuronal shrinkage, and long-term epigenetic regulation of plasticity genes, all of which contribute to conditions such as depression, anxiety, and cognitive loss [132-134]. Long-term deficiencies in neurotrophic support can result from prolonged stress and persistent activation of the hypothalamic–pituitary–adrenal (HPA) axis, which increases glucocorticoid levels. Over time, this process can downregulate BDNF transcription (e.g., by reducing the CREB phosphorylation at BDNF promoters) [135, 136]. Concurrently, long-term stress frequently triggers glial cells, particularly microglia, which release proinflammatory cytokines such as TNF- α and interleukin-1 β (IL-1 β). By interfering with BDNF-TrkB signaling, altering actin cytoskeleton dynamics (lowering F-actin production in dendritic spines), and weakening LTP maintenance, these inflammatory mediators decrease synaptic function [137-140].

For example, we propose that temporary activation of antioxidant pathways enhances neural resilience, while persistent activation amid continuous environmental stress may lead to redox imbalance and neurodegeneration. Moderate mitochondrial adaptations may facilitate metabolic flexibility, whereas prolonged stress-induced mtDNA modifications may lead to cellular dysfunction [141, 142]. Chronic stress causes structural changes, such as dendritic retraction, spine loss, and reduced synaptic connections, particularly in the hippocampus and prefrontal cortex (PFC), which are important areas for memory, emotion regulation, and cognition. Working memory, decision-making, mood control, and a greater risk of mental diseases are associated with these alterations [143-145]. Maladaptive plasticity, a condition characterized by decreased neuronal flexibility, compromised connections, and increased susceptibility to long-term cognitive and emotional dysfunction, results from these combined molecular, epigenetic, inflammatory, and structural alterations [146, 147].

In the context of swift environmental change, these two results highlight the evolutionary conflict between adaptability and fragility. An evolutionary trade-off is reflected in both adaptation under short-lived stress and disease under chronic stress: the same stress–response pathways that offer quick, adaptive advantages under brief natural stressors become detrimental when they are consistently active [148]. Organisms may use these plasticity systems more frequently as environmental stressors (such as long-term adversity, pollution, metabolic stress, and chronic socioenvironmental stress) increase, thereby surpassing their capacity for adaptation and increasing vulnerability. Thus, comprehending this equilibrium is essential for understanding how stress impacts the brain in various contexts and throughout life. Short-term exposure to elevated temperatures may transiently elevate the levels of heat shock proteins and BDNF, facilitating synaptic adaptation and resilience. Conversely, prolonged or recurrent exposure to elevated temperatures can induce oxidative stress, mitochondrial dysfunction, and reduced neurotrophic signaling, indicative of maladaptive plasticity [149, 150].

6. Future Directions and Research Gaps

Early-life brains undergo rapid synaptogenesis, axon guidance, and myelination because environmental stresses have varying effects on neural gene networks across developmental stages [151]. Pollutants trigger inflammatory cascades that interfere with neurodevelopmental pathways, hypoxia stimulates HIF1 α -regulated metabolic genes, and high heat can trigger excessive heat-shock protein (HSP) responses in early life. Instead of affecting structural maturation in adults, the same stressors impact proteostasis, neuroimmune signaling, and oxidative-stress control [152, 153]. Research on rats and zebrafish has demonstrated that while adult exposure results in more fleeting, homeostatic reactions, early exposure causes long-lasting transcriptional reprogramming. These results corroborate age-dependent brain sensitivity, but few comparative developmental models exist, leaving a crucial knowledge gap about how climate stressors alter gene networks across life [154, 155]. Furthermore, epigenetic modifications can be introduced by environmental stress, but their reversibility varies depending on cell type, developmental stage, and chromosomal location. Certain marks, such as smoking-associated CpG methylation at AHRRs, which decreases after cessation, are reversible. Other signals, such as metabolic stress signals in PGC-1 α -related pathways, are only partially reversible [156, 157]. On the other hand, more persistent methylation alterations, such as those in NR3C1, are frequently produced by early-life trauma and persist into adulthood [158]. Reversibility is mechanistically dependent on chromatin remodeling factors, histone-modifying complexes, and active DNA demethylation through TET enzymes [159]. However, short-term studies provide the majority of the evidence. There is still a significant research gap, such as the lack of longitudinal studies that measure behavioral, physiological, and molecular results in the same subjects before and after an intervention. These findings limit our knowledge of which epigenetic marks caused by stress are indeed reversible [160, 161]. A more thorough understanding of how environmental stresses affect brain function can be obtained by combining behavioral neuroscience with genomics, epigenomics, and transcriptomics. Single-omic techniques are inadequate because epigenetic markers by themselves cannot predict gene expression or behavioral output, and DNA variations cannot capture dynamic transcriptional responses. Multiomics enhances the prediction of stress susceptibility or resilience and helps identify causal pathways [162]. For example, transcriptome signatures have been demonstrated to predict behavioral resilience under chronic stress, and research combining genome-wide association studies (GWASs) with methylation profiles has connected inflammation-related genes to depression risk. However, many gaps still exist, most notably, the absence of datasets that simultaneously capture genome-wide chemical profiles and real-time behavioral tracking under stress situations connected to climate change. Mechanistic models are not complete without such integrated data [163-165].

A major gap in the field is the absence of standardized criteria for classifying adaptive versus maladaptive responses, as well as limited integration across experimental systems to establish causality [166]. Previous reviews have looked at the neurological effects of climate change. Still, this one goes further by putting molecular, mitochondrial, and gene-regulatory mechanisms within a structured adaptive-maladaptive framework and taking into account the hierarchy of evidence and causal interpretation [167]. To enhance interpretability, the synthesized evidence is categorized by study type, encompassing in vitro systems, animal models, human observational studies, and longitudinal or interventional human data. The strength of evidence is deemed greatest when

results align across various levels. This structured synthesis also separates stress responses included by experiments from those caused by real-life, long-term exposures, making the reported mechanisms clearer in terms of how they can be applied in real life [168]. As summarized in Table 2, the strength of evidence varies considerably across stressor categories, with pollution-related exposures supported by relatively robust epidemiological data. In contrast, hypoxia and combined stressor models remain underexplored. Notably, most mechanistic insights derive from animal and in vitro systems, underscoring the need for longitudinal human studies to establish causality [169, 170].

Table 2 Structured synthesis of climate-related stressors, evidence strength, and research priorities.

Stressor	Developmental Window	Neurobiological Endpoint	Key Molecular/Epigenetic Markers	Evidence Type	Strength of Evidence	Research Priority	References
Thermal stress (heat)	Early-life, aging	Hippocampal neurogenesis, synaptic plasticity	BDNF, CREB, HSP70, DNA methylation changes	Animal, limited human epidemiology	Moderate	Chronic exposure models; longitudinal human studies	[171]
Pollution and Toxins	Childhood, prenatal	BBB disruption, cognitive decline, neuroinflammation	NF-κB, ROS, miRNAs	Animal models, human epidemiology	Strong (associative)	Mechanistic human studies	[172]
Psychosocial stress	Adolescence, early life	HPA-axis dysregulation, hippocampal atrophy	NR3C1 methylation, cortisol-related pathways	Human observational	Moderate	Standardized stress metrics	[173]
Hypoxia	Developmental stages	Neurogenesis, mitochondrial dysfunction	HIF-1α, ROS, mtDNA variation	Animal, non-model species	Limited	Translational models; human validation	[174]
Combined/ Multi-exposure	Lifespan	Network-level dysfunction, behavioral outcomes	Multi-pathway (BDNF, NRF2, and inflammatory markers)	Very limited	Weak	Multi-exposure longitudinal and systems biology approaches	[175]

7. Conclusion

Neural structure and function are altered both directly and indirectly by the ubiquitous and complex stressor of climate change. The data presented here show that common genetic and epigenetic pathways that control brain plasticity, resilience, and susceptibility are affected by environmental stressors, including intense heat, pollution, psychological hardship, hypoxia, and nutritional instability. An adaptive interface between the environment and the genome is formed by a combination of stress-responsive genes, antioxidant and mitochondrial systems, neurotrophic signaling, and dynamic epigenetic mechanisms. Crucially, under climate stress, brain plasticity is not intrinsically advantageous or detrimental; rather, its effects depend on the degree, duration, and timing of development and the biological environment of the person. Through reversible transcriptional and chromatin-based pathways, transient or moderate stress can enhance synapse function and cognitive flexibility by promoting adaptive plasticity. On the other hand, maladaptive plasticity, which is typified by persistent epigenetic suppression, neuroinflammation, synapse loss, and heightened vulnerability to cognitive and emotional problems, is driven by prolonged or extreme stress. These results highlight an evolutionary trade-off: when environmental stress surpasses adaptive capacity, molecular systems that evolved to facilitate rapid adaptation in changing settings become pathogenic. The likelihood of exceeding this threshold increases with the severity of climate change and the duration of stress exposure, especially during critical developmental windows. Longitudinal, multiomics, and cross-species methods that combine genetic, epigenetic, transcriptomic, and behavioral data will be necessary for future advancements. These frameworks are crucial for forecasting resilience vs. vulnerability, determining the reversibility of stress-induced epigenetic marks, and identifying causative pathways. In the end, understanding how climate change alters the brain at the molecular and systems levels is crucial for neuroscience, public health, and global resilience, supporting the idea that brain health and planetary health are inextricably linked.

Author Contributions

Taslim Uddin: Conceptualization, supervision. Fatema Tuz Zohora: Investigation, Writing-original draft. Tajmin Khanam: Supervision, Investigation. Moumita Akter: Methodology, Formal analysis. Lubaba Ibnul Himika: Resources, Writing- Review & Editing. Anika Tabassum Aziz: Writing-original Draft. Fariha Tabassum: Writing- Review & Editing. Syeda Marjia Kajol Tushy: Data Curation, Revision. Salaha Aktar: Writing- Review & Editing. Maisha Maliha Misha: Investigation, revision. Shaikh Nuzhat Nawshin Nimu: Project Administration, Validation. Sadia Tasnim: Writing- Review & Editing. Shammi Akter Joya: Project Administration, Validation. Israt Tasnim Mahisa: Formal analysis, Resources, Supervision. Shahrin Akter Pinky: Investigation, Methodology.

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