Cellular and Molecular Neurobiology (2025) 45:29
https://doi.org/10.1007/s10571-025-01549-x

REVIEW PAPER

Genetic, Epigenetic, and Hormonal Regulation of Stress Phenotypes in Major Depressive Disorder: From Maladaptation to Resilience

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Received: 23 September 2024 / Accepted: 18 March 2025

Abstract

Major Depressive Disorder (MDD) is a complex psychiatric disorder with varied molecular mechanisms underlying its aetiology, diagnosis, and treatment. This review explores the crucial roles of stress, genetics, epigenetics, and hormones in shaping susceptibility and resilience to mood disorders. We discuss how acute stress can be beneficial, while prolonged stress disrupts brain function, leading to MDD. The review also highlights the significance of various animal models in understanding depression pathophysiology, including zebrafish, mice, and rats, which exhibit distinct sex differences in stress responses. Furthermore, we delve into the molecular bases of susceptible and resilient phenotypes, focusing on genetic aspects such as gene polymorphisms, mutations, and telomere length alterations. The review also examines epigenetic aspects including DNA methylation, histone acetylation and deacetylation, histone methylation and HMTs, and miRNA, which contribute to the development of MDD. Additionally, we explore the role of hormones such as estrogen, progesterone, and prolactin in modulating stress responses and influencing MDD susceptibility and resilience. Finally, we discuss the clinical implications of these findings, including recent clinical methods for determining MDD susceptibility and resiliency phenotypes. By consolidating the current knowledge and insights, this review aims to provide a comprehensive understanding of the molecular basis of susceptibility and resilience in mood disorders, contributing to the ongoing efforts in combating this debilitating disorder.

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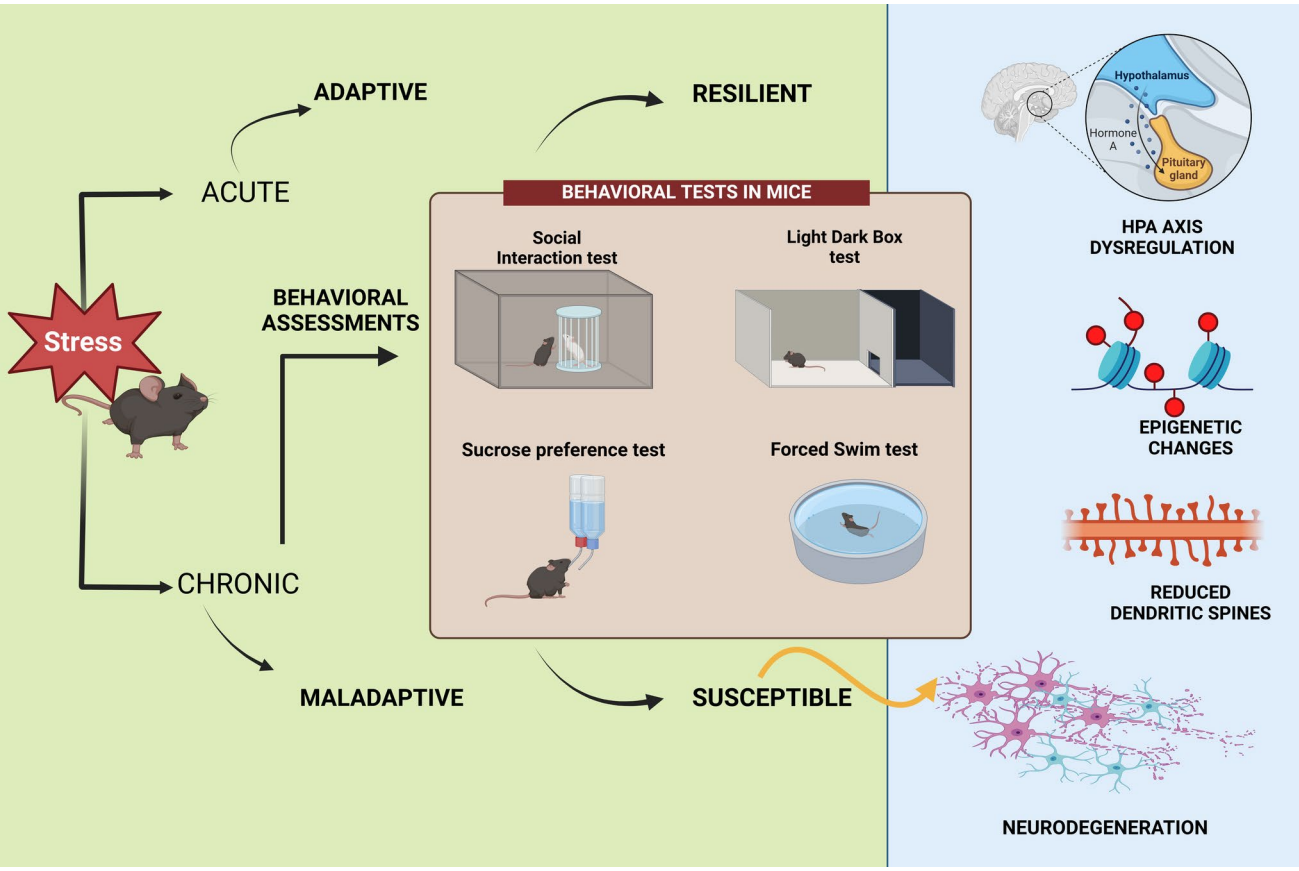
Published online: 26 March 2025

Graphical Abstract

An overview of the types of stress, various molecular bases of susceptibility and resiliency in major depressive disorder, and behavioural assays determining vulnerability or adaptability in animal models. Created with biorender.com.



Keywords Major depressive disorder · Susceptibility · Resilience · Depression · Stress

Abbreviations

MDD	Major Depressive Disorder
CSDS	Chronic social defeat stress
CMS	Chronic mild stress
LH	Learned helplessness
HPA	Hypothalamic–pituitary–adrenal axis
PFC	Prefrontal cortex
PMDD	Premenstrual dysphoric disorder
DMDD	Disruptive mood dysregulation disorder
PPD	Postpartum depression
CRH	Corticotropin-releasing hormone
CSF	Cerebral Spinal Fluid
ACTH	Adrenocorticotropic hormone
CRF	Corticotropin-releasing factor
CRHR1	Corticotropin-releasing hormone R1 receptors
DHEA-S	Dehydroepiandrosterone sulphate
ELS	Early life Stress
PTSD	Post-Traumatic Stress Disorder
RAAS	Renin–Angiotensin–Aldosterone System
RAS	Renin-Angiotensin-System
SNP	Single Nucleotide Polymorphisms
HLA	Human leukocyte antigen
AUD	Alcohol Use Disorder
GR	Glucocorticoid receptor
NPY	Neuropeptide Y
OXTR	Oxytocin receptor gene
MAOA	Monoamine oxidase A
DRD4	Dopamine receptor D4
VNTR	Variable Number Tandem Repeat
COMT	Catechol-O-methyltransferase
GxE	Gene x environment
MGPS	Multilocus genetic profile score
Nrf2	Nuclear factor erythroid 2-related factor 2
TL	Telomere Length
LTL	Leukocyte telomere length

DNAm	DNA methylation
5mC	5-Methyl Cytosine
5hmC	5-Hydroxymethyl Cytosine
MECP2	Methyl-CpG binding protein 2
PPAR-α	Peroxisome proliferator activated receptor
DMPs	Differentially methylated probes
HDACs	Histone deacetylases
BLA	Basolateral amygdala
GABAergic	Gamma-aminobutyric acidergic
MSNs	Medium spiny neurons
RSDS	Repeated Social Defeat Stress
NAc	Nucleus Accumbens
GLP	G9a-like protein
DG	Dentate Gyrus
DRN	Dorsal raphe nucleus
ncRNAs	Long non-coding RNAs
MS	Maternal Separation
SCVS	Sub-chronic variable stress
piRNA	PIWI-interacting RNA
m6A	N6-methyladenosine
GPM6A	Membrane glycoprotein M6a
PRL	Prolactin
CVMS	Chronic variable multiple stress
WKY	Wistar-Kyoto
CORT	Corticosterone
ARS	Acute restrained stress
MR	Mineralocorticoid
HCN	Hyperpolarization activated cyclic nucleotide-gated
UCMS	Unpredictable Chronic mild stress rat model
LHb	Lateral habenula
LTD	Long-term depression
Ang II	Angiotensin II
ACE	Angiotensin-converting enzyme
VS	Ventral Striatum
PVR	Paraventricular region
LPS	Lipopolysaccharide
E2	17β-Estradiol
KL	Klotho
Vglut1	Vesicular glutamate transporter 1
VTA	Ventral tegmental area
P4	Progesterone
TBI	Traumatic brain injury
SI	Suicidal ideation
THC	Delta-9-tetrahydrocannabinol
PRLR	Prolactin receptor
CUS	Chronic Unpredictable Stress
SAA	Social approach-avoidance
VF	Von Frey
IL–12	Interleukin
TNF-α	Tumor Necrosis Factor
IFN-γ	Interferon
iGluRs	Ionotropic Glutamate Receptors
mGluRs	Metabotropic Glutamate Receptors
NMDAR	NMDA receptors
KYN	Kynurenine
PHQ	Patient Health Questionnaire-9
IRI	Interpersonal Reactivity Index
DASS	Depression Anxiety and Stress Scales
STRADL	STratifying Resilience and Depression Longitudinally
fMRI	Functional Magnetic Resonance Imaging
rs-fMRI	Resting-state Functional Magnetic Resonance Imaging
IFG	Inferior frontal gyrus

Introduction

Depression is a debilitating psychiatric disorder characterized by persistent low mood, anhedonia, cognitive impairments, and dysregulation of neurobiological processes. Chronic stress is a key risk factor for the development of depression (Ross et al. 2017), yet not all individuals exposed to stress develop the disorder (Thomas-Odenthal et al. 2024) (aan het Rot et al. 2009). This variability highlights the presence of stress susceptibility and resilience, two distinct phenotypes that influence individual responses to adverse experiences. While stress-susceptible individuals exhibit maladaptive responses leading to depressive-like states, resilient individuals maintain homeostasis and exhibit adaptive coping mechanisms. Animal models have been instrumental in dissecting the molecular and neurobiological underpinnings of stress susceptibility and resilience. Studies utilizing paradigms such as chronic social defeat stress (CSDS), chronic mild stress (CMS), and learned helplessness (LH) have provided insights into differential stress responses at the behavioral, biochemical, and genetic level. The hippocampus, a critical region for stress regulation, has emerged as a key structure mediating individual differences in stress responses. Hippocampal dysfunction including impaired neurogenesis, altered synaptic plasticity, and increased neuroinflammation, has been implicated in stress susceptibility (Larosa & Wong 2022). Conversely, resilience is associated with enhanced neuroplasticity, adaptive hypothalamic–pituitary–adrenal (HPA) axis regulation, and efficient stress coping strategies (Kinlein & Karatsoreos 2020).

Recent findings emphasize the dynamic nature of stress-induced molecular changes, suggesting that resilience is an active process rather than a mere absence of vulnerability. Differential susceptibility theory posits that genetic and environmental factors not only modulate stress vulnerability but also enhance responsiveness to positive experiences, further complicating our understanding of stress-related disorders. Epigenetic modifications, neurotransmitter system

alterations, and immune-inflammatory responses have been identified as crucial mediators of susceptibility and resilience, offering potential therapeutic targets for stress-related psychopathologies. Despite advancements in the field, the translation of animal model findings to clinical applications remains challenging.

In this review, we explore how stress, a ubiquitous aspect of life, can trigger MDD in some individuals while others remain resilient. The review examines the major molecular mechanisms that underlie these contrasting responses, including genetic predispositions, epigenetic modifications, and hormonal influences that consolidate the various pathways and interactions occurring in depression. We also discuss how the latest animal models, serving as simplified representations of human MDD phenotypes, are instrumental in unravelling these mechanisms. Furthermore, the review touches upon the clinical implications of this research, highlighting potential avenues for developing improved diagnostic tools and therapeutic interventions. By synthesizing current knowledge and insights, this review aims to provide a comprehensive yet significant understanding of the molecular basis of susceptibility and resilience in MDD, ultimately contributing to the ongoing efforts to diagnose and treat this debilitating disorder.

Stress: Interpretations and Factors

'Stress' as a term was first elucidated as a contribution of homeostasis and the "fight-or-flight response" exhibited in humans by Walter Cannon; yet the biological definition was given by Hans Selye, describing stress as "a nonspecific response of the body to any demand made upon it" (Cannon 1929) (Selye 1946). The General Adaptation Syndrome was established where non-specific responses to stress, i.e., the alarm phase, resistance phase and the exhaustion phase, formed the foundations of the stress theory in the field of stress biology (Godoy et al. 2018). Stress primarily enables an organism to successfully adapt to an ever-changing environment and therefore, preserve itself. However, exaggerated and prolonged adversity consumes more energy from the organism, which can lead to various diseases and disorders, therefore damaging itself (Kalisch et al. 2024). Hence, the stress response is a necessary mechanism the body employs to bring it back to the state of homeostasis. Stress is primarily classified as acute and chronic based on its long-term implications in the brain. Another classification based on the duration of exposure, source, and response implies a total of seven major types: Acute stress, Chronic stress, Episodic acute stress, Traumatic stress, Environmental stress, Psychological stress and Physiological stress, where the latter five currently are considered as distinct when considering current MDD research directions (Chu et al. 2024). Acute stress occurs over a shorter period of time and is an integral aspect of the development of successful stress adaptations whereas chronic stress occurs over a prolonged period of time. When the wear and tear endured by an individual due to chronic stress is irreversible, an allostatic load is formed and the process of adaptation to stressors to maintain homeostasis is known as allostasis, which can arise from various factors including multiple stressors, prolonged response, an inadequate response, or ineffectual adaptation to stress over time (McEwen & Gianaros 2011).

The amygdala, prefrontal cortex, and hippocampus are the major regions of the brain responsible for the regulation of physiological and behavioural stress (McEwen & Gianaros 2010). The amygdala, located in the temporal lobe, regulates the initial alarm system and alters memory as an effect of stress (Roozendaal et al. 2009), along with the activation of fearful faces, fear inducing images, and fear conditioned cues (Ressler 2010). The amygdala's GABAergic neurotransmission function is known to be negatively affected by the hyperactivity of the HPA axis and corticosterone release, activating glucocorticoid receptors due to the prolonged stressor actions (Zhang et al. 2018). The prefrontal cortex, responsible for cognitive functioning like decision-making and planning, weakens due to chronic exposure to stress by reducing neuronal firing leading to various neurodegenerative diseases in the long term (Woo et al. 2021). The dendrites, spines and gray matter in the PFC are also lost during prolonged stress along with weaker attentional flexibility and impaired memory; numerous studies show how stress takes the PFC "off-line" by inducing high levels of noradrenergic and dopaminergic release, opening K^+ channels, thereby weakening the synaptic connections (Arnsten et al. 2015). Stress also alters the hippocampal volume and neuronal morphology in animals and humans. The hippocampus region of the brain is responsible for learning and memory and the neuroendocrine dysregulation of stress hormones can interfere with hippocampal processes including synaptic plasticity, dendrite morphology maintenance and neurogenesis, partially via the activation of type II corticosteroid (glucocorticoid) receptors and a co-activation role via the amygdala and PFC (Kim & Diamond 2002).

The onset of depression due to stress is multi-pronged and is influenced by factors such as intensity and the duration of the stress, which altogether trigger a depressive episode. Prolonged action of stress factors affect an individual drastically, weakening the stress response required to mitigate it, and leaving the individual in a chronic state of defeat. By weakening this feedback loop, it is therefore deduced that depression can arise from prolonged exposure to stressful situations or stimuli (Van Praag 2004). Major Depressive Disorder, Persistent Depressive Disorder (dysthymia), Premenstrual dysphoric disorder (PMDD), Disruptive mood dysregulation disorder (DMDD), Seasonal affective

disorder, and Postpartum depression (PPD) are some of the numerous chronic conditions that fall under the depression umbrella. Most studies when designing MDD experiments and treatments only focus on a single system like adrenergic, dopaminergic, or serotonergic systems. It is imperative to form a holistic approach to identify markers of susceptibility and resilience, their underlying molecular mechanisms, and their interconnected pathways and interactions.

Stress-Induced Responses

Susceptibility and Resiliency

Susceptibility is the occurrence of consistent, sustained and in some cases, traumatic stress that prevents returning to the state of homeostasis and an unhealthy response ensues, bringing the onset of various psychiatric disorders (Akil & Nestler 2023). Resilience refers to the process by which an individual maintains dynamic equilibrium and recovers its baseline state following exposure to stress. Resilience involves active coping strategies, where the organism actively manages to face adversities and develop traits to mitigate their impacts. In contrast, susceptibility is a passive coping aptitude involving avoidance-like behaviours such as helplessness and vulnerability (Cathomas et al. 2019). A susceptible stress response exhibits a number of characteristics and various biomarkers have been identified that could perhaps assist in diagnosis. Depressed individuals exhibit elevated serum plasma and urine levels of Cortisol, one of the main glucocorticoids released from the adrenal cortex (Thau et al. 2023). High levels of corticotropin-releasing hormone (CRH) in the cerebrospinal fluid (CSF) and adrenocorticotropic hormone (ACTH) in the plasma of depressed individuals can be measured. Another study reported a pivotal role of corticotropin-releasing factor (CRF) in stress susceptibility leading to depression, with CRF systems also exhibiting sexual dimorphism (Waters et al. 2015).

Adaptive Neuroplasticity

Adaptive plasticity refers to the ability of an organism to adjust to environmental changes aided by neurotrophic factors, excitatory amino acids, systemic hormones, and other endogenous factors, that collectively contribute to resilience. Corticosteroid-mediated plasticity is a key facet in this mechanism, along with increased hippocampal neurogenesis where improved plasticity is shown as a factor of resilience; on the other hand, impaired plasticity causes a surge of inflammatory molecules and the phenomenon of the "inflammatory trap of depression" (Paribello et al. 2024). Increasing studies have highlighted the need for a combination of psychological and bio-physiological features in determining resiliency, using measurements of vagal activity and cortisol/DHEA ratio after a stressful event (Lau et al. 2021) and a recent proteomic study revealed specific dysregulated proteins associated with depression-susceptible, anxiety-susceptible, and insusceptible groups of stressed rats (Gong et al. 2021).

Determinants of the Fine Line Between Susceptible and Resilient Phenotypes

In identifying key distinctions in susceptibility and resiliency, the HPA axis is a focal point. When an adversity occurs in an individual, the amygdala activates the hypothalamus to release CRH as part of the initial stress response. CRH initiates the fight or flight response and alters immunity in an organism, activating the pituitary to release ACTH (Kovács 2013). CRH then binds to G-protein coupled receptors (corticotropin-releasing hormone R1 receptors (CRHR1), activating adenylate cyclase and releasing ACTH. In acute stress conditions, the ACTH release only lasts for a short duration which builds resilience but during chronic stress, prolonged exposure to glucocorticoids can lead to damage to various glucocorticoid-sensitive organs, worsening the conditions, leading to susceptibility (Herman et al. 2016).

Early Life Stress

Childhood traumatic experiences disrupt the HPA axis function with sex-specific consequences. In females, a later childhood exposure to a first traumatic event correlates with higher daytime cortisol levels whereas in males, a prolonged early traumatic exposure and experience is linked to elevated morning and evening cortisol but lower levels throughout the day (Kuhlman et al. 2015). Measuring the blood levels of cortisol, adrenocorticotropic hormone, and dehydroepiandrosterone sulphate (DHEA-S) in Post-Traumatic Stress Disorder (PTSD) patients having experienced childhood maltreatment determined the significance of HPA axis biomarker potentials and DHEA-S gene polymorphisms (Kakehi et al. 2023). Early life Stress (ELS) induces various adaptations in stress responses and a study demonstrated that individual characteristics influence children's abilities to adapt during ELS, thus determining their susceptibility or resilience to depression in adulthood (de Maat et al. 2022).

Physiological Aspects

The Renin–Angiotensin–Aldosterone System's (RAAS) Renin-Angiotensin-System (RAS) axis, typically seen in controlling water and sodium homeostasis and regulating blood pressure, is another endocrine system that can discern susceptibility. In the brain, pro-renin promotes the cleavage

of angiotensin and the activation of RAS involved in neurogenic hypertension, which is involved in the pathogenesis of depression (Ali et al. 2024). A novel, single-trauma PTSD model in mice revealed phenotypically accurate long-term maladaptive behaviours and new potential biomarkers, discerning susceptible and resilient individuals (Pascual Cuadrado et al. 2022). The microbiome-gut-brain axis also plays a crucial role in modulating stress resilience and susceptibility, thus highlighting the connection between gut microbiota and mood regulation (Bear et al. 2021).

Emotional regulation and positive stress responses help the brain actively cope with stress and improve resilience (Thayer et al. 2021). It is important to take account of various neurochemical, genetic, epigenetic, and physiological contributors to resilience that help an organism adapt to external stressors. Dopaminergic, serotonergic, and noradrenergic systems mediate stress response and influence resilience (Wu et al. 2013). While the interplay between susceptibility and resilience has been explored in various studies, the underlying mechanisms remain poorly understood in the context of MDD.

Molecular Bases of Susceptible and Resilience Phenotypes

Major Depressive Disorder arises from the dynamicity of genetic, epigenetic, and environmental factors that collectively shape an individual's vulnerability or resilience to stress. Synthesizing evidences from human and animal studies can delineate how genomic variations, epigenetic reprogramming, and stress-induced cellular alterations influence neuroendocrine, synaptic, and immune pathways in MDD pathophysiology. Transgenerational epigenetic inheritance, evidenced by stress-induced miRNA alterations in sperm, indicates the heritable nature of susceptibility. Sex-specific disparities in molecular pathways, such as estrogen's neuroprotective effects or male-biased telomere shortening, further complicate these mechanisms. Together, these multilayered regulatory networks offer a framework for understanding individual differences in MDD risk and resilience, bridging molecular insights to clinical applications in biomarker discovery and precision therapeutics.

Genetic Aspects

A recent study investigated individual genetic variations in stress responses by analyzing biometric data, HPA axis activity, and hippocampal gene expression in mouse variants distinguished by the SNP count. Corticosterone level measurements revealed that genetic differences between mouse strains play a crucial role in mediating chronic stress (Terenina et al. 2019). The human leukocyte antigen (HLA) region is considered one of the most genetically diverse regions in the human genome. Known for its role in inflammation and immunity, research has discovered that MDD phenotypes have lower HLA expression compared to control along with three cellular-senescence genes causing immune dysregulation (Chen et al. 2024). This furthers the claim made by Weitkamp et al. (1981) of HLA-linked genes on chromosome 6 influencing susceptibility.

Gene Polymorphisms and Mutations

The genetic landscape of susceptibility and resilience in mood disorders are shaped by polymorphisms and mutations in stress-responsive genes which modulate neuroendocrine, neurotransmitter, and neuroplasticity pathways. Various allelic polymorphic markers have been found that coincide with resilient phenotypes (Cahill et al. 2022). A major regulatory protein of the HPA axis, FKBP5, known for its involvement in the reduction of Glucocorticoid receptor (GR) translocation during stress response, has found direct genetic association with Alcohol Use Disorder (AUD) patients. AUD patients with the minor T-allele of the Fkbp5 polymorphism rs1360780 had lower resilience than those with the homozygous C allele type, identifying C allele's protective effect (Park et al. 2021). Alcohol dependence therefore is positively correlated with depression and a study in a Han Chinese population reflected interactions between alcohol dependence and different gene polymorphisms as well. The Neuropeptide Y (NPY) gene rs16147: T > C SNP was analysed and the non-carrier population during alcohol withdrawal exhibited a lower degree of depression compared to carriers (Wei et al. 2022). When examining the rs53576 polymorphism in the oxytocin receptor gene (OXTR), a study that assessed the differences in OXTR levels in children with GG, GA and AA genotypes revealed that children with a GG genotype exhibited comparatively more resilience (Cicchetti & Rogosch 2012). Another study established the "A" allele to be associated with lower levels of optimism, mastery, and self-esteem, deeming these individuals more susceptible to depression (Saphire-Bernstein et al. 2011). In a recent study of adolescents, the OXTR gene rs53576 polymorphism was found to be moderating the effect of peer relationships and psychological resilience effects.

Shifting focus to neurotransmitter metabolism, the human monoamine oxidase A (MAOA) gene that codes for MAOA enzyme which breaks down dopamine, serotonin and noradrenaline, contains exon 8 rs6323 (T941G) having a mutation (T → G), that only performs with 3/4th efficiency as compared to the unmutated type. In a study conducted in depressed college students that experienced childhood maltreatment, subjective well-being and MAOA rs6323 had an effect in the onset of depression (Hu et al. 2022). The Dopamine receptor D4 (DRD4)

exon III variable number tandem repeat (VNTR) polymorphism, consisting of a 7-repeat allele, provides neuroprotection and assists in resilient response to stress (Das et al. 2011) but another study showed contrasting results of the same 7-repeat being absent and thus can contribute to resilience (Gervai et al. 2005).

Catechol-O-methyltransferase (COMT) enzyme, responsible for the degradation of dopamine and noradrenaline, has a Val158Met gene variant that is responsible for resilience as its depletion resulted in higher anxiety levels and plasma levels of adrenaline in response to stress (Feder et al. 2009). Individuals who experienced early life adversity and genotyped for the COMT Val158Met polymorphism exhibited smaller cortisol responses (Lovallo et al. 2019). In a case study of adolescent Syrian and Jordanian refugees, various Gene x environment (GxE) interactions were observed to be associated with resilience. Individuals with a high expression of 5-HTTLPR (serotonin transporter linked polymorphic region) in the serotonin transporter gene (SLC6A4) showed lower levels of insecurity and a GxE interaction of 5-HTTLPR was associated with resilience. In individuals not carrying the Met allele (Val homozygotes), a protective effect in COMT was seen causing high resilience to PTSD compared to Met carriers. Furthermore, evidence of these GxE effects emerged over time in these individuals, causing long-term effects (Mulligan et al. 2022). A multilocus genetic profile score (MGPS) approach was used in another study to measure serotonergic multilocus genetic variation of insomnia and interpersonal relationships that bring the onset of depression symptoms of Chinese adolescents, where THP2 gene rs4570625 polymorphism was shown to be significant risk factor (Zeng et al. 2023).

Nuclear factor erythroid 2-related factor 2 (NRF2) is found to regulate myeloid cell-2 (TREM2) transcription, which in turn regulates microglial BDNF expression and NRF2 knockout CSDS mice were seen to have lower levels of BDNF as well, hence proving its significance in MDD pathophysiology (He et al. 2022). The SNP rs6265 in exon 11 of the BDNF gene is known to be associated with resilience. BDNF Val66Met polymorphism is a well-known genetic explanation and it is known to be ethnicity-dependent, where the reoccurrence of this gene was found in Asian-descent more than Caucasians (Verhagen et al. 2010). Preliminary genetic analysis already revealed sex differences in the BDNF Val66Met polymorphism as well. Supporting this, a recent study was found comparing the Val66Met Knock-in mice with non-carrier mice where interestingly, only male Met carrier mice were unable to quickly recover from anxiety-like phenotype (Xavier et al. 2024).

Telomere Length Alterations

At the cellular level, chronic stress accelerates aging, a phenomenon reflected in the shortening of telomeres, the protective caps at the end of the chromosomes (Vakonaki et al. 2018). In a study on non-human primates, ELS-exposed offspring showed longer telomeres till adulthood than in controls (Ridout et al. 2022). Pollution is also an influential environmental stressor that in recent years has increased and proves to be an important factor in Telomere length (TL) shortening. In children and adolescents affected by natural disasters, a higher telomere shortening was observed in association with post-traumatic symptoms (Miranda et al. 2021).

Research into newborns exhibiting shorter length telomeres from mothers that have undergone stress before or during their pregnancy has increased rampantly. One of the most recent studies highlighted direct prenatal programming effects of maternal psychology on telomere shortening in a sample size of 656 mother–child dyads. Maternal stress was predicted to cause shorter telomeres and maternal resilience predicts a 12% longer TL (Verner et al. 2021). Similarly, a study comprising of Latin mothers revealed that acculturative stress predicted shorter TL, especially in those with high methylation of the FOXP3 promoter region (Incollingo Rodriguez et al. 2022). Interestingly, a connection was recently established between maternal blood pressure and newborn TL, where there was a more significant negative effect of maternal BP on cord blood TL in male infants as compared to females (Sheng et al. 2024). This finding supports a sex difference basis in the effects of stress on TL and another study showed that the effects of exposure to maternal depression on the offspring's TL being dependent on the sex and the temperament characteristic of surgency/extraversion. A greater surgency/extraversion from elevated maternal depression was found to be associated with a shorter TL in males yet again with no significant change in females (Bosquet Enlow et al. 2024). Different degrees of maternal separation were also seen to have varying effects on susceptible ELS rats with PTSD, where telomere shortening was seen in the hippocampus (Teng et al. 2025). The key genetic and epigenetic factors contributing to increased stress susceptibility are illustrated in Fig. 1.

Leukocyte telomere length (LTL) is a convenient parameter that can effectively study cellular aging and is now associated with many MDD diagnostic studies. In a clinical study of African-American depressed individuals, LTL was directly associated with stress caused by racial discrimination, where men with low depressive symptoms using passive coping responses to lifetime racism were reported to have a longer LTL. Similarly, men exhibiting active coping responses with high depression also exhibited longer LTL. Women in this sample size were noted to have longer LTL than men as well (Glover et al. 2021). Using data from the

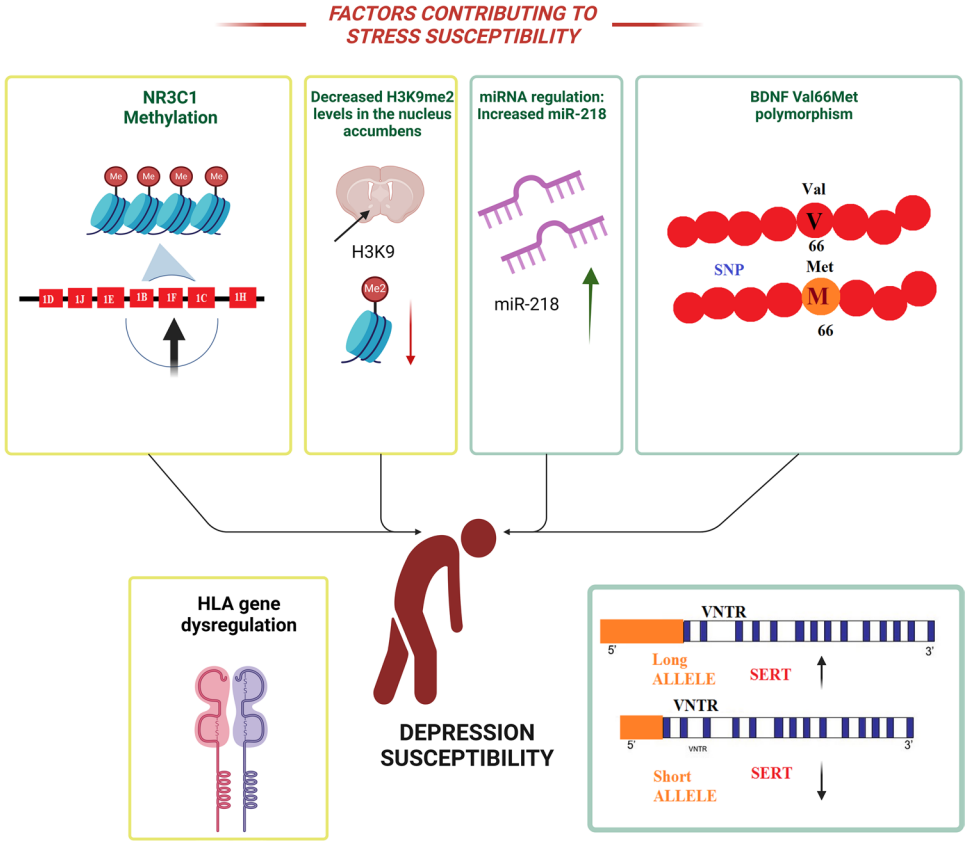


Fig. 1 Figure illustrates key molecular factors contributing to stress susceptibility and depression. Genetic and epigenetic mechanisms, including NR3C1 methylation, decreased H3K9me2 levels in the nucleus accumbens, miR-218 regulation, BDNF Val66Met polymorphism, and HLA gene dysregulation are linked to depression susceptibility. Additionally, serotonin transporter gene (SERT) with long and short VNTR alleles influences stress responses wherein the small allele confers reduced SERT expression. These factors converge to increase vulnerability to depression

UK Biobank, scientists have found a direct relation between trauma-related factors and accelerated facial aging by measuring the LTL (Wang et al. 2024a, b). Shorter LTLs were seen in many Costa Rican adults that have experienced self-perceived stress due to caregiving or health issues as well (Méndez-Chacón 2022). Supporting this, the latest study using the UK Biobank database directly shows that shorter LTL is associated with an increased risk of depression, making it an effective tool for predictive identification of MDD and anxiety-related disorders (Wu et al. 2025).

Epigenetic Aspects

Transgenerational epigenetic contributions are crucial in affecting the stress responses, where research has shown that epigenetic factors causing susceptibility are being transferred to the next generation (Nestler 2016); early stress alters DNA methylation in the stressed male germline and is observed in the subsequent generation (Franklin et al. 2010). Furthermore, various histone methyl transferases are known to be differentially regulated in susceptible conditions.

DNA Methylation

The DNA methylation (DNAm) and demethylation of the GR gene (NR3C1) across several CpG sites (DNA sequence regions of Cytosine followed by Guanine in 5' to 3' direction) in the exon-1F region of NR3C1 was established in depression research (Watkeys et al. 2018). Being one of the first responses towards environmental stress, NR3C1 is expressed in almost all cells of the human body (Liu & Nussloc, 2018). In a study conducted among 101 early adolescents, a higher concentration of NR3C1 DNAm was directly found to be in association with subdued HPA axis reactivity to stress along with lower Autonomic Nervous System stress adaptations (Chubar et al. 2023). Culminations of recent studies revealed the significance of increased ELS causing resiliency having an increased NR3C1 DNAm and a decrease leading to susceptibility (Forum et al. 2025). Research into the intergenerational effects of maternal MDD exposure on the offspring is more prevalent in recent years, where a study has shown that children exposed to traumatic maternal MDD show an increase in NR3C1 DNA methylation and a decrease in FKBP5 DNAm. This was found to be similar to children with MDD (Mendonça et al. 2023).

In an interesting study of post-mortem brains of teenage suicide completers, changes were reported in both 5mC (5-Methyl Cytosine) and 5hmC (5-Hydroxymethyl Cytosine) levels at specific regions in the CpG Island of the Glucocorticoid Receptor and expression of specific GR-1 non-coding variants (Rizavi et al. 2023). In 6 regions of GR analysed for DNA methylation, 5mC content was observed

to be increased in regions R1, R3 and R5 whereas 5hmC was decreased in R3 and R5, causing a shift of alternative exon usage, affecting alternative splicing and expression of GR. Similarly, in ASDS and CSDS models, 5hmC suppression of chromatin remodelling subunits were seen in susceptible mice. Overall, susceptible animals gained 1.5 times more differentially methylated regions compared to the resilient animals (Kuehner et al. 2023).

The GRIN2B gene, encoding the NR2 subunit of NMDA receptors that are known to increase synaptic transmission, was found to have increased DNAm in individuals that experienced childhood adversity and has a high sensitivity to environmental stressors (Engdahl et al. 2021). Further studies must be done to confirm a link between GRIN2B and MDD. On the other hand, the BICD2 gene DNA hypermethylation is shown to be a potential biomarker in peripheral blood to discern MDD individuals among the Chinese Han population (Xiu et al. 2022). Low blood levels of Methyl-CpG binding protein 2 (MECP2) expression suggested an increased risk in a clinical trial of 23 healthy women who reported experiencing childhood adversity but had no history of mental disease (Cosentino et al. 2022).

A Methylome-wide association study conducted in 276 twins to identify epigenetic correlations of resilience to neighbourhood disadvantages, revealed a handful of methylome-wide significant differentially methylated probes (DMPs) associated with academic as well as social resilience and DMPs associated with psychological, academic, social, and across domains phenotypes of resilience, a first of its kind (Vazquez et al. 2024). The peroxisome proliferator activated receptor (PPAR)-α is a recently discovered target associated with emotional behaviour and is known for its neuroprotective effect. In a mouse model of PTSD/suicide-like behaviour, PPAR-α level in the hippocampus decrease was due to increased DNA methylation of CpG sites of the PPAR-α gene along with an increase in histone deacetylases (Matrisciano & Pinna 2021). A new method of identifying resilience-associated DNA methylation signatures using a machine learning method resulted in identifying methylation of resilience-associated genes that play a role in the onset of MDD as well (Lu et al. 2023).

Histone Acetylation and Deacetylation

Histone acetylation involves the loosening of the Chromatin, providing space for transcription whereas histone deacetylation condenses the former, leading to transcription silencing. Many studies have proved that histone deacetylases (HDACs) have significant contributions in various psychiatric disorders (Chakravarty et al. 2014). Elevated levels of HDAC5 are now seen in the CSDS-susceptible group of mice with a reduction in H4K12 acetylation and HDAC5 knockdown also reversed CSDS-induced depression susceptibility (Li et al. 2024). In a 15-day social defeat stress paradigm in mice with a history of experiencing early life stress, H3K4me3-specific genome-wide changes in the expression of genes and alternative splicing was observed in the pre-frontal cortex (Reshetnikov et al. 2021). In male CSDS mice, HDAC3 protein expression was significantly high in the resilient type, inferring its response to chronic stress and reduction of inflammatory damage. In susceptible mice, elevated levels of cytoplasmic HDAC6 were noted but nuclear HDAC6 was significantly less, supporting the shuttling aspect (K V et al. 2021).

SIRT1, another class of HDAC, is known to be expressed in the hippocampus and hypothalamus and has a key role in HPA axis regulation during stress, where it is involved in CRH production (Yamamoto & Takahashi. 2018). In overexpression and knockdown of Basolateral amygdala (BLA) neurons in the CUMS mice model, SIRT1 overexpression in BLA glutamatergic neurons led to depression-like behaviours in non-stressed mice (Guo et al. 2021). Supporting this study, SIRT1 was recently found to coordinate genes associated with the synapse to regulate GABAergic (gamma-aminobutyric acidergic) output of D1- expressing medium spiny neurons (MSNs), causing MDD symptoms in CSDS mice model (Kim et al. 2024). Chronic Vitamin B12 deficiency in female C57BL/6 mice weaning through pregnancy and lactation reveals itself as a stressor causative of anxiety and depression and the mice showed an increased expression of HDAC4 and upregulation of SUV420H1 (Ghosh et al. 2020). A fascinating study in the CSDS model with an acute acetate supplementation improved depression-like behaviour due to more production of Acetyl-CoA, leading to increased H3 and H4 acetylation, thereby causing upregulation in synaptic plasticity, as seen in the increased levels of BDNF (Huang et al. 2021). In a Repeated Social Defeat Stress (RSDS) mouse model, the increased expression of SHATI/NAT8L and BDNF was seen in the susceptible phenotype and a knockdown of SHATI/NAT8L or BDNF blocking strongly increases resilience, indicating its significance. Histone acetylation was enhanced in RSDS-susceptible mice but histone and DNA methylation remained unaffected; this study showed that BDNF and H3K9 acetylation is regulated by SHATI/NAT8L in the dorsal striatum, playing a key role in stress sensitivity. Therefore, it can be considered a potential target for MDD treatment (Miyanishi et al. 2021).

Histone Methylation and HMTs

In a study using cocaine-addicted chronic socially defeated mice, lowered levels of H3K9me2 in the Nucleus Accumbens (NAc) region along with lowered G9a and G9a-like protein (GLP) expression showed an enhancement of susceptibility (Covington et al. 2011). The same was shown in the NAc of post-mortem brains of depressed individuals

along with decreased SUV39H1. Acute restraint stress in rats elevates H3K9me3 levels while diminishing H3K9me1 and H3K27me3 levels in the Dentate Gyrus (DG) and CA1 areas of the hippocampus (Hunter et al. 2009). Recent studies have shown H3K27me1 as the most important histone modification induced in the adult CSDS model and similarly in juvenile and adult mice exposed to ELS. This depicts H3K27me1 as a "chromatin scar" that is seen as a lifelong cause of susceptibility (Torres-Berrío et al. 2024). In the CUMS rat model, three different H3 trimethylation patterns between susceptible and resilient animals were observed. In the hippocampus of resilient rats, hypermethylation of K36, K4 and K9 residues were observed whereas in susceptible rats, a reduction in H3 and hypermethylation of K9 was observed. In the hypothalamus of susceptible rats, K9 hypomethylation and K27 hypermethylation was seen. H3K4me3 and H3k36me3 upregulation was also observed and are associated with promotion of transcription, hence promoting resilience (Santos et al. 2024). In CSDS male and female mice, the dorsal raphe nucleus (DRN), a serotogenic projection neuron-rich region, showed various transcriptional changes. Male mice that exhibited resilience had a lower level of H3K4me3Q5ser, and by directly reducing H3 serotonylation levels in the DRN promoted behavioural resilience (Al-Kachak et al. 2024).

Epigenetic regulators of the JMJD2/KDM4 family of lysine demethylases are critical in mediating chronic stress effects on neurogenesis. JMJD2 regulates various signalling pathways like Hedgehog signalling, hypoxia signalling, and Wnt signalling that are essential in neurogenesis. One of the studies indicated that the susceptible mice group had JMJD2C downregulated and JMJD2D upregulated (Maitra et al. 2020). Another study in the CUMS model was conducted in obese mice which displayed higher susceptibility. A JMJD3 inhibitor GSK-J4 given after a two-week stress exposure improved the abnormal behavioural changes in susceptible control mice compared to obese mice and a noticeable increase in NF-κB and pro-inflammatory cytokine levels in both groups was shown, proving that JMJD3 might be involved in the susceptibility to depressive-like behavior and neuro-inflammation.

MiRNA

Stress exposure also activates certain miRNAs responsible for neurodevelopment, neuronal plasticity, and neurogenesis, benefiting resilience in the organism (Ortega et al. 2021). At the same time, other miRNAs cause vulnerabilities that lead to MDD-like conditions (Gururajan et al. 2016). Several small and long non-coding RNAs (ncRNAs) are known to be epigenetically involved in gene regulation. MiRNAs like miR-212 have been known to regulate an MeCP2 in the dorsal striatum of cocaine-addicted mice and also control BDNF in the process, leading to susceptibility (Im et al. 2010). miR-18 in the paraventricular nuclei of the hypothalamus plays a role in the strain-specific HPA axis response to stress by blocking the translation of the GR mRNA transcript, hence regulating susceptibility to stress in a chronic restraint stress model (Uchida et al. 2010). In a study of CSDS-depressed mice, a 40% reduction in the mRNA expression of Drosha, one of the key proteins in miRNA biogenesis, and an overall decrease in expression of all the members of the miR-30 microRNA family was seen in the DG (Khandelwal et al. 2019). A study in a Maternal Separation ELS rodent model revealed that sex influenced the impact of Maternal Separation (MS) on miRNAs implicated in synapse formation, behaviour, and the negative regulation of nervous system development. It also modulated the effect of MS on miRNA expression for 18 PFC, four amygdala, and 17 hippocampus miRNAs (McKibben & Dwivedi. 2021).

A clinical study using fMRI data of MDD patients having experienced childhood maltreatment showed that miR-9 is associated with early CM experience and later onset of depression (He et al. 2021). Lower levels of certain miRNAs enable an organism to cope with stress better, as stated by a study of three types of Restrained Stressed susceptible mice, where the presence of miR-let-7e was shown to distinguish between susceptible and resilient (Solich et al. 2021). Circulating miR-218 in the mPFC of adolescent CSDS-susceptible mice was found to be upregulated and clear downregulation was seen in resilient animals, making it a target of early intervention (Torres-Berrío et al. 2021). In the PFC of CMS male rats, downregulation of miR-135a-5p was associated with a reduced number of dendritic spines in the stress-susceptible phenotype. This was further validated through synaptic remodelling studies in primary neuronal cultures, emphasizing its role in stress vulnerability (Mingardi et al. 2023). Mir-182-5p emerged recently as a biomarker in MDD treatment where its knockdown in CSDS mice was shown to have reduced the depression-like phenotype by improving impaired neurogenesis (Zheng et al. 2024). Likewise, miR-206 has been implicated in depression, where it is involved in regulating the biosynthesis of BDNF. Resilient mice showed a lower miR-206-3p activity and susceptible mice were found to have a surge. Moreover, miR-206-3p overexpression caused even further notable depressive-like effects by negatively regulating the expression of the BDNF signalling cascade (Guan et al. 2021).

In a study, chronic stress-induced group of mice were bred and the miR content of their sperms were evaluated where it was revealed that the offspring experienced dysregulation in the HPA axis indicating susceptibility and nine significantly increased miRs in the parent sperm observed might have become altered in epigenetic programming during spermatogenesis (Rodgers et al. 2013). In another recent work in 2021, CSDS male mice sperm and their offspring

that have undergone Sub-chronic variable stress (SCVS) paradigm, a general transfer in stress susceptibility was indicated by a tenfold increase in differentially expressed lncRNA, known for sperm functioning, in the susceptible group compared to the resilient group (Cunningham et al. 2021). In an interesting study of sub chronic CSDS mice, seven upregulated and one downregulated miRNA/PIWI-interacting RNA (piRNA) were discovered in their saliva, establishing potential biomarkers (Yoshida et al. 2022). In the hippocampus of LH rats, high N6-methyladenosine (m6A) methylation was seen along with lower expression of plasticity genes. A significant upregulation of miR-124-3p was also seen in the hippocampus (Roy et al. 2022). The GPM6A mRNA regulates the neuronal membrane glycoprotein M6a (GPM6A), essential for neuronal remodeling and plasticity. In chronic restraint-stressed rats, downregulation of GPM6A and BDNF mRNA was observed in the hippocampus, accompanied by a decreased expression of miR-133b and miR-124-3p and an increase in HDAC5 levels, contributing to a stress-susceptible phenotype (Alzuri et al. 2023).

Hormonal Bases of Resiliency and Susceptibility to Depression

Estrogen has been widely associated with cognitive function and emotional processing in the brain. Prolactin (PRL) is a versatile hormone known for modulating stress responses during pregnancy and lactation yet acts as a neuropeptide promoting neurogenesis, neuroprotection and stress adaptations (Torner 2016). In the chronic variable multiple stress (CVMS) mouse model, distinct sex differences have been identified, with CRMP2 protein in the nucleus accumbens (Nac) being downregulated in males and upregulated in females. Additionally, its expression varied in ovariectomized females, confirming that hormonal influences contribute to sex-specific stress responses (Karisetty et al. 2024).

Glucocorticoids, Mineralocorticoids and Cortisol

Cortisol is the primary stress hormone and its levels significantly increase with an increase in stress levels. The cortisol feedback mechanism prompts the body to activate a cascade of stress responses and energy reserves are mobilized by cortisol in preparation for tissue repair (Russell & Lightman. 2019). In a pilot study using SDS exposure to early adolescent rats, an overall resilience was seen by observation of hippocampal BDNF protein expression and plasma corticosterone levels in adulthood. An increase in BDNF was seen with lower corticosterone plasma levels as compared to control (Mancini et al. 2021). The Nociceptin/orphanin FQ receptor system, which modulates the body's sensation of pain and regulates emotional behaviours in the brain, stimulates the HPA axis that increases stress circulating hormones, including CRF and promotes susceptibility (Gavioli et al. 2021).

A fascinating study conducted using hair samples from Irish adults revealed that a higher hair cortisol indicates a risk of developing depression; hair cortisol was measured in individuals 6 years before the COVID-19 pandemic was found to positively predict depressive symptoms, making it an effective risk marker (Feeney & Kenny. 2022). An endogenously depressed rat model, Wistar-Kyoto (WKY) and control Wistar rat model were both found to show chronic social instability stress-induced depression-like phenotype but contrasting corticosterone and endocannabinoid system regulation, where WKY rats showed resilience in Corticosterone (CORT) modulation (Wang et al. 2023). In CMS susceptible rats further exposed to acute restrained stress (ARS), early response genes such as NR4A1 were highly expressed with elevated CORT levels and after ARS, an enhanced expression was seen (Brivio et al. 2023). In a clinical study of 140 depressed outpatients that have ELS experiences, polymorphisms in MDR1 and NR3C2 genes involved in the HPA axis, were observed to be associated with higher plasma levels of cortisol (Pereira et al. 2024).

Mineralocorticoid receptors (MR) and Glucocorticoid receptors (GRs) in the hippocampus primarily mediate the adrenal steroids (Pavlides et al. 1996) and excessive exposure to glucocorticoids mostly causes neurotoxicity of hippocampal neurons leading to neuronal loss (Sapolsky 1999). In GR knockdown rats, clear sex differences were seen, where female GR knockdown rats showed a higher fear response and impaired extinction was seen in the PL-PFC whereas in males, active coping during the forced swim test was observed (Scheimann et al. 2019). Another study demonstrated that glucocorticoids (GC) directly promote fear generalization, as evidenced by the sparse distribution of DG engram cells in male mice (Lesuis et al. 2021). Susceptible rats after the first exposure to the Forced Swimming-Induced Stress paradigm exhibited high CORT in the first 24 h compared to the resilient group but in the next exposure, the resilient group expressed higher levels instead, evidently showing the GR response to be transcriptionally and epigenetically modifiable (Ruiz-sánchez et al. 2021).

RACK1, a scaffolding protein essential for nervous system development and synaptic regulation, is known to promote BDNF expression. It was found to be highly expressed in CMS-resilient mice and is regulated by glucocorticoids (Brivio et al. 2021). GR activation significantly decreased excitatory neurotransmission in the mPFC of FKBP5-deleted mice and reported increased GAD65 expression in FKBP5-deficient hippocampal neurons (Ryu et al. 2021). One study using Tamsulosin uncovered the role of α1-adrenoceptors in increasing vulnerability to depression that is mediated

by endogenous GCs (Holanda et al. 2022). CSDS-susceptible mice exhibited social avoidance and impaired spatial working memory, which was associated with increased perisomatic expression of hyperpolarization-activated cyclic nucleotide-gated (HCN) 1 channels regulated by the glucocorticoid (GC)-glucocorticoid receptor (GR) signalling pathway. This upregulation led to reduced neuronal excitability, suggesting a potential molecular basis for the onset of Major Depressive Disorder (Kim et al. 2022).

In the Unpredictable Chronic Mild Stress (UCMS) rat model, resilience-related effects were observed, characterized by a reduction in GABAergic activity alongside increased activation of glucocorticoid receptors in the dorsal hippocampus (Begega et al. 2023). A recent study in ELS rodents that experienced maternal separation revealed that synaptic long-term depression (LTD) was impaired and extra-synaptic LTD was enhanced in the Lateral habenula (LHb) of the susceptible group that is linked to increased expression of NMDA Receptors (NMDAR) and MR (Kang et al. 2023). Similarly, adolescent male rats that have experienced acute stress showed resilience and delayed anxiety-like effects that was found to be age-dependent and GC-release dependent (Campos-Cardoso et al. 2023).

Angiotensin

The brain RAS shows high significance in the onset of various psychiatric disorders, especially with the direct involvement of angiotensin. Angiotensin, typically regulating the blood pressure and fluid balance in the body, is also known to be dysregulated in the brain. Angiotensin II (Ang II) is known to be involved in the regulation of physiological processes in many brain regions, especially in memory and cognition, and can be converted to Angiotensin III, which is directly involved in BP regulation (Abiodun & Ola. 2020). In a clinical study of Egyptian depressed patients, angiotensin-converting enzyme (ACE) I/D gene polymorphism shows a strong genetic connection, where the D allele was significantly prominent as compared to the control group along with hypercortisolaemia (ElMissiry et al. 2021). Another clinical study revealed that an AT1R blockade decreased negative learning rate and enhanced exploitatory choice behaviours in the ventral striatum (VS), showing Angiotensin's antagonistic effect on MDD (Xu et al. 2022). In an interesting study of SPS rats, a long-lasting increase in AT1R-expressing cells in the paraventricular region of the hypothalamus (PVR) along with increase in PVR microglia and anxiety-like behaviour were observed in males whereas only an increase in PVR microglia with fear extinction was seen in females, suggesting that AT1Rs play a sex-dependent role (Ortiz-Nazario et al. 2023). Ang II was also found to increase NMDA receptor responses in a subpopulation of layer V pyramidal neurons in the prefrontal cortex via a dopaminergic presynaptic connection (Hanuska et al. 2024).

Estrogen, Progesterone and Prolactin

Low estrogen phases of the menstrual cycle in women show a higher negative mood response and lesser hippocampal activity during acute stress and are especially known to show more sensitivity to lower levels of cortisol in repetitive stress (Albert & Newhouse. 2019). A recent study involving the lipopolysaccharide (LPS)-challenged mice model showed that older female mice were more susceptible to depression than male mice and 17β-estradiol (E2) was proved to protect the old female mice from depression by suppressing the inflammatory cytokines via the ERα/SIRT1/NF-κB pathway (Jiang et al. 2021).

Another study suggested that early estradiol exposure resulted in increased repetitive behaviours, reduced exploration, and decreased helplessness in adult animals while sociability and anxiety-related behaviours remained unchanged yet sex differences were seen during juvenile stages, where exploration, repetitive behaviours, and depression-related behaviours were largely reduced in females due to E2-promoting brain masculinization (Seiffe et al. 2021). Similarly, another study showed that E2 had an antidepressant effect in young rats after post-ovariectomy which did not sustain till adulthood (Hernández-Hernández et al. 2022). Another study also showed that pre-pubertal ovariectomy in female mice after the UCMS paradigm protected against the development of anxiety-like behaviour in adulthood, resulting in resiliency (Woodward et al. 2022). Klotho (KL), an aging-suppressor gene, was found to be regulated by estrogen in hippocampal neurons in the female CUMS rat whereas males exhibited a susceptible phenotype. Estrogen was also found to be essential in increasing the number of presynaptic vesicular glutamate transporter 1 (Vglut1)-positive clusters on the dendrites in the hippocampus, playing an important role in synaptic plasticity (Tan et al. 2023). In rodents, the estrous-phase E2 alters neuronal excitability in the ventral tegmental area (VTA), resulting in susceptibility (Shanley et al. 2023) and LHb neurons during the estrous cycle showed decreased resting membrane potentials (RMP) as well (Kim & Chung. 2024). A very recent clinical study showed that a higher E2 level positively enhances memory performance, as seen in fMRI data of the temporal and frontal cortices (Schroeder et al. 2024).

From the Swiss Perimenopause Study, it was revealed that women with higher progesterone (P4) levels were reported to have a higher psychosocial resilience and lower depressive symptoms (Süss et al. 2021). A study on adolescent rats subjected to mild traumatic brain injury (TBI) revealed PRs playing an important role in the onset of depression-like behaviour during the estrous-phase, where the blockage of

PR prevented depression-like phenotype (Giacometti et al. 2022). In pups exposed to short and prolonged maternal separation then as adults exposed to the CUMS paradigm, a depression-like phenotype was seen in the mice that underwent prolonged maternal separation and showed significantly decreased P4 and allopregnanolone levels with an increase in serum levels of CORT, CRH, and ACTH (Bian et al. 2021). In a clinical study involving women with a history of postpartum depression, estradiol and progesterone withdrawal was shown to increase anhedonia and reduce the activation of caudate, putamen, thalamus, insula, and anterior cingulate regions in response to rewards, thereby highlighting the significance of these hormones in MDD pathophysiology (Schiller et al. 2022).

In another clinical study of women exhibiting suicide-related symptoms, increased progesterone (P4)-derived pregnane NAS and P4 were shown to predict higher suicidal ideation (SI) and depressed mood. GABAergic NAS, P4 and inflammatory cytokine IL-6 was also seen to fluctuate throughout the menstrual cycle, making these important markers for diagnostics of SI and MDD (Wenzel et al. 2023). Pregnenolone was found to reverse susceptibility in prenatal THC (delta-9-tetrahydrocannabinol) exposure by normalising mesolimbic dopamine function, thereby rescuing from psychotic-like phenotypes (Frau & Melis. 2023).

Prolactin receptor (PRLR) gene was recently discovered to be associated with the comorbidity of depression seen in Italian families along with Type 2 diabetes (Amin et al. 2024). In CUMS susceptible mice, lower levels of PRL and E2 along with monoamine transmitters were seen in females than in males in the serum, making PRL a potential biomarker (Chen et al. 2022). In ovariectomized female rats, prolactin was shown to reduce passive coping and anhedonia following chronic stress and increased dopamine-producing cells in the VTA, proving its role in conferring resilience during periods of low ovarian hormone secretion (Medina et al. 2024). Chronic Restraint Stressed mothers that experienced brief periods of pup separation showed lower levels of depressive- and anxiety-like behaviors and cognitive decline as compared with longer pup separated mothers and no pup separation, and also exhibited higher PRL levels and adult hippocampal neurogenesis that conferred resiliency (Zhou et al. 2024).

Animal Models for Delineating Resilient and Susceptible Population

Animal models like zebrafish, mice, and rats are popular organisms for behavioural and physiological stress research. Certain animal models established with an intention of creating MDD phenotypes now express different outcomes and a distinct sex difference is observed in a majority of these experiments. Gender matters in the treatment of depression (Ussher 2011) and research shows the contrasts in MDD treatment between Men and Women, revealing that male patients were more likely to receive monotherapy, whereas female patients were more likely to receive four or more psychiatric medications (Seifert et al. 2021). Table 1 summarizes crucial experimental models used in segregating and studying resilient and susceptible populations.

Zebrafish as a model opens up a plethora of opportunities in MDD research studies. A depression-like state in zebrafish is conducive to elevated levels of cortisol, anhedonia, and social isolation seen in humans but there is still a lack of clear markers of depression when compared to

Table 1 Animal models delineating resiliency and susceptibility to stress

Animal model	Species/strain	Stress paradigm	Resilience/susceptibility criteria	Behavioral readouts	References
Chronic Social Defeat Stress (CSDS)	Mice (C57BL/6 J)	Repeated exposure to aggressive CD1 mouse	Resilient: No social avoidance; Susceptible: Social avoidance	Social interaction test, sucrose preference test	(Alves-dos-Santos et al. 2020)
Vicarious Social Defeat Stress (VSDS)	Mice (C57BL/6 J)	Witnessing conspecific defeat	Resilient: No social avoidance; Susceptible: Social avoidance	Social interaction test, EPM	(Qi et al. 2022)
Learned Helplessness (LH)	C57BL/6N	Uncontrollable foot shocks	Resilient: Escape behavior maintained; Susceptible: Failure to escape	Shuttle-box escape test	(Wang et al. 2014)
Stress-enhaned fear learning (SEFL)	C57BL/6	Combines acute stress with fear conditioning	Susceptible mice exhibited persistently elevated freezing during extinction trials; Resilient mice showed reduced freezing	Freezing behavior during extinction	(Daws et al. 2017)

stress phenotypes in other animal models (de Abreu et al. 2022) (de Abreu et al. 2021). In a recent investigation, negative feedback regulation of cortisol was absent in mutant zebrafish leading to a prolonged stress response (Theodoridi et al. 2021). The role of NPY and miR218 as resilience-associated genes in zebrafish larvae was also recently established (Swaminathan et al. 2023). An analysis of the brain proteome profile showed that mitochondrial dysfunction and reduced neurogenesis in chronically stressed zebrafish are associated with anxiety and mood disorders (Chakravarty et al. 2013). The Chronic Unpredictable Stress (CUS) paradigm in zebrafish recently revealed 222 proteins to be significantly altered which control the proliferation or neurogenesis of telencephalon neural progenitor cells, playing a critical role in chronic stress-induced mood disorders (Reddy et al. 2021). Establishing stress-induced phenotypes of depression in zebrafish will aid in the development of a more economical vertebrate model for research.

Studying sex-specific stress responses in rodents (mice/rats) helps in understanding the underlying molecular mechanisms of susceptibility and resilience. Female rodents are shown to be comparatively more resilient to early-life hippocampal stress than males (Loi et al. 2017). Some important resilient features studied in mice are at the level of proteomic changes in mitochondrial processes, downregulated expression of brain BDNF, and binding ability of adrenergic receptors (Strekalova et al. 2022). Molecular pathology of human MDD is imitated well in various chronic stress models of mice. Such models help in examining novel targets, functional pathways, and studying the epigenetic regulatory mechanisms of other complex disease models as well (Scarpa et al. 2020).

Behavioural Tests for Segregation of Resilient and Susceptible Sub-Populations

A variety of behavioural assays performed can distinguish between susceptible and resilient populations. Despite being established years ago, these tests continue to serve as reliable tools for identifying susceptible animal populations for further investigations. Mice are tested mostly using the Sucrose Preference test, Elevated Plus Maze test, Open field test, Forced Swim test and the Social approach-avoidance (SAA) test (Alves-dos-Santos et al. 2020). Other behavioural assays include the Novel object test, Tail Suspension test and the Von Frey (VF) test (Willmore et al. 2022). Certain behavioural assay outcomes are different between the sexes yet again. There is a distinct sex difference in the baseline depression-like behaviour, especially after the introduction of a Splash test that evaluates the apathy endophenotype (Pitzer et al. 2022). The more number and variety of behavioural assays one can employ in experimental studies of MDD, the better understanding of the intricacies of this disease can be observed. Zebrafish also undergo a series of behavioural assays that exhibit their depression-like phenotype after the stress-inducing paradigms are performed. The various assays include the Light–dark box test, the Novel tank diving test (for anxiety-like phenotype), and social interaction tests like mirror test, shoaling test, and social preference test (for learning and memory) (Johnson et al. 2023). Sex differences were seen after behaviour tests revealed that female adult zebrafish exhibited higher levels of anxiety-like behaviour than males (Fontana et al. 2020).

Implications of Resiliency and Susceptibility

The lack of ability to cope with the stressor causes depression, increasing the sensitivity towards further stress types causing susceptibility. Elevated levels of glucocorticoids, triggered by stress, are associated with neurotoxicity contributing to the onset of MDD. Dysregulation of the HPA, neurotransmitter imbalance, and inflammation are neurotoxic processes that contribute to the pathophysiology of depression, though causality remains uncertain (Belleau et al. 2019). Early life stressors like mental or physical abuse influence CRH-containing neural circuits. Glucocorticoid resistance is also observed as a result of activated inflammation driven by stress (Amasi-Hartoonian et al. 2022) and increased production of cytokines like interleukins like IL-6, interferons (IFN-γ), and chemokines are characteristic markers of MDD (Khantakova et al. 2023).

Stress-Induced Inflammation

Stress exerts immunosuppressive effects through glucocorticoid-mediated mechanisms, altering immune function and homeostasis. Elevated cortisol levels suppress immune function by downregulating inflammatory signalling pathways (Alotiby 2024). Glucocorticoids and catecholamines regulate the production of pro-inflammatory and anti-inflammatory cytokines in the body as a stress response. Pro-inflammatory cytokines like Interleukin (IL)–12, Tumor Necrosis Factor (TNF)-α, and Interferon (IFN)-γ are signalling proteins that play a major role in the immune response. Expression of inflammatory genes like IL-1β, IL-6, IL-8, and TNF increase as a result of susceptibility to chronic stress (Nasef et al. 2017). IL-6 is a marker for MDD and microarray studies show that genes associated with MDD are enriched in IL-6-mediated signalling events. Its elevated levels have also been reported in the cerebrospinal fluid of patients with MDD (Zhang et al. 2016).

Stress-Driven Glutamate Signalling and Kynurenine Pathway: A New Perspective

Glutamate is an excitatory neurotransmitter in the Central Nervous System responsible for brain functioning, memory, and learning. Abnormal glutamatergic transmission and loss of glutamatergic synaptic connections are accessories to depression (He et al. 2023). NMDARs have a high affinity to the excitatory neurotransmitter glutamate and as a measure of adaptability of an individual, the stress hormones regulate NMDAR-dependent synaptic plasticity complying to alter behavioural responses based on the environmental stimuli (Rothstein et al. 1994). The social defeat stress (SDS) mouse model exhibits reduced levels of the NMDAR GluN2B subunit and its anchoring protein PSD-95, underscoring their essential role in the induction of long-term depression. (Lee et al. 2021). Corticosterone also alters receptor trafficking, thus modifying the surface dynamics of NMDAR within glutamate synapses (Mikasova et al. 2017). NMDARs are also significant markers of hippocampal plasticity and an interesting study of the CMS model showed the susceptible group having increased levels of Nmda-2r-AR and Nmda-2r-S in the hippocampus (Strekalova et al. 2023). A fascinating study using a new animal model of resilience/vulnerability, i.e., acute footshock (FS) stress in rats showed a spike in basal presynaptic glutamate release in FS susceptible rats and depolarization-evoked glutamate release was seen in both susceptible and resilient groups (Bonifacino et al. 2023). Chronic social defeat stress-susceptible mice displayed an increased expression of metabotropic glutamate receptors, mGlu2/3 in the prelimbic cortex, underscoring the therapeutic potential of this brain region. (Jing et al. 2021).

Chronic stress affects the metabolic pathway responsible for immune function, neurotransmission functions, and the conversion of Tryptophan to Kynurenine, via the kynurenine (KYN) pathway (Battaglia et al. 2023). Tryptophan is the precursor to Serotonin synthesis which is metabolized through the KYN pathway and Kynurenine metabolism is seen to be a linking factor of stress to depression. Neural dysfunction increases as more metabolites are formed via the KYN pathway (Giménez-Gómez et al. 2021). Clinical studies have shown an increase in plasma kynurenic acid in MDD patients (Liu et al. 2018) and oxidative stress and damage to cells are observed in studies associated with KYN-metabolite-linked neurodegeneration (Mor et al. 2021). A clinical study of MDD brains that were MRI scanned revealed imbalanced production of neuroactive metabolites such as kynurenic acid (KynA), 3-hydroxykynurenine (3HK) and quinolinic acid (QA), which influence neuroplasticity, possibly more than other inflammatory molecules and is a major reason why MDD patients show a reduced thickness of the right BA24 and BA32 (Meier et al. 2016). One of the studies determined the significance of the KYN pathway in inducing susceptibility in subchronic CSDS mice; when given dietary hesperidin, KYN levels in the hippocampus and PFC were significantly low and resilience was increased (Sato et al. 2019). In CSD mice, brain KYN was seen to be increased and inhibition of Indoleamine 2, 3-dioxygenase 1 (IDO1) seemed to block the kynurenine pathway activation and excessive fear expression of the mice (Fuertig et al. 2016). A recent study has shown IDO's significance in Parkinson's disease (PD), where the inhibition of IDO-1 reduced neuroinflammation in PD mice (Qiao et al. 2025). IDO-1, a key rate-limiting enzyme in the KYN pathway, plays a crucial role in the degradation of the essential amino acid tryptophan. It is also known to increase QA levels that stimulate NMDARs and cause oxidative stress, in turn causing neuronal damage (Gerónimo-Olvera et al. 2019). Glutamate signalling and the Kynurenine pathway modulate neurotransmission enabling the process of resilience, where the feedback mechanism limits the kynurenine metabolites in the brain thus promoting resilience to stress (Agudelo et al. 2014) (Paribello et al. 2024). Heterogeneity in individual susceptibility and resilience needs to be addressed and studied to understand the total scope of how the KYN pathway and glutamate signalling affect MDD.

Clinical Methods in Determining MDD Susceptibility and Resiliency Phenotypes

The clinical diagnosis of depression types such as MDD primarily relies on standardized self-report questionnaires that assess symptom severity and psychological distress. Commonly utilized tools include the Patient Health Questionnaire (PHQ-9), a 9-item scale scoring from 0 to 27, where a score above 5 indicates depression (Kroenke et al. 2001). Additional assessments include the Perceived Stress Scale (PSS), the Interpersonal Reactivity Index (IRI), the Depression, Anxiety, and Stress Scales (DASS) (Baliyan et al. 2021), and the Simplified Coping Style Questionnaire (SCSQ) (Zhao et al. 2021), each providing insights into stress perception, emotional reactivity, and coping mechanisms. Several questionnaires specifically designed to assess resilience in patients have been developed, as demonstrated in a study by Windle et al. (2011).

The STratifying Resilience and Depression Longitudinally (STRADL) study of Scottish participants aged 35–65 years was conducted specifically to classify MDD using detailed clinical, cognitive, and brain imaging assessments. Clinical assessments included questionnaires, patient family histories, body measurements and lifestyle, a complete blood count, blood and saliva collection for DNA, cognitive tests and interestingly, brain fMRI scanning tests (Habota et al. 2019). Functional Magnetic Resonance Imaging (fMRI) studies have revealed the integration of

functional brain networks, providing a framework for assessing differential susceptibility in individuals with depression (Homberg & Jagiellowicz. 2022). A recent preliminary study using Resting-state fMRI revealed that female depressed patients with a higher psychological resilience demonstrated increased resting state activation in the insula and postcentral gyrus, as well as a more pronounced interaction between the postcentral gyrus and the supramarginal gyrus (Wang et al. 2024a, b). Another study using resting-state functional magnetic resonance imaging (rs-fMRI) demonstrated the functional connectivity between the ventral striatum (VS) and inferior frontal gyrus (IFG) to be closely associated with emotional sensitivity to reward in individuals exhibiting lower depression compared to elevated depressed patients (Li et al. 2022). Clinical diagnosis of MDD subtypes still faces difficulties due to the lack of biochemical evidence in patients, i.e., fluid biomarkers. Many studies have shown that potential biomarkers can be detected in the blood and serums yet find difficulty in validation. Genotyping and sequencing certain genes causing susceptibility or resiliency from blood is a costly affair along with time-taken for animal model establishments and justifications.

Final Considerations

Stress is not fatal to an organism, but stress response or a lack thereof decides the trajectory of the quality of life of an organism. The absence of systematic quantification of stress impedes a thorough understanding of its impact, including the critical threshold at which it disrupts allostasis, leading to depression and other neurological or psychological disorders. Stress and its associated symptoms are often interlinked, creating a self-sustaining loop of dysregulated mechanisms that fosters a chronic state of defeat. This prolonged dysregulation exacerbates risk factors, such as systemic inflammation, ultimately increasing vulnerability to depressive and other neuropsychiatric disorders. There is a wide gap in understanding the link between stress-induced inflammation, resilience, and depression. The role of lymphocytes and the adaptive immune system in stress response is also not investigated thoroughly (Cathomas et al. 2019). The stress and resilience response defined by dynamic bidirectional regulation is intricately interconnected. Resilience indicators identified in rodent models require further investigation in alternative animal models, such as zebrafish, and in vitro systems to enhance understanding at the cellular level. Such an approach will enhance improved understanding by providing clarity on complex mechanisms, which may suggest similar processes in humans. Discovery of new biomarkers will aid in both the diagnosis and prognosis of the depressive disorder umbrella. Glutamatergic signalling and glutamate synapse are important targets for anxiety and depression (He et al. 2023). A comprehensive analysis of the glutamatergic pathway's role in the stress response and resilience is crucial for advancing the development of targeted pharmacological and alternative therapies for depressive disorders. Elucidating the cellular and molecular mechanisms underlying the key stress-related molecules—cortisol, catecholamines, glutamate, and kynurenine—will provide critical insights into their involvement in resilience and the pathophysiology of depression.

Acknowledgements The authors acknowledge the current Director, Dr. Reddy's Institute of Life Sciences (DRILS), Hyderabad, India for his enduring encouragement and support. The authors also express sincere thanks to Shashikant Patel, SRF at CSIR-IICT, Hyderabad, India for his critical editorial assistance in this manuscript.

Author Contributions Study conception was done by ND. Study design was done by ND and AA. The literature search and review were performed by AA, SS and ND. The final draft of the manuscript was written by AA and SS and all the authors, AA, SS and ND commented on previous versions of the manuscript. ND critically revised the work. AA, SS and ND read and approved the final manuscript.

Funding No funding support for this manuscript.

Data Availability No experimental data were generated for the present study.

Declarations

Conflict of interest The authors declare that they have no competing interests.

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