Review Article

Structural and functional changes in the hippocampus induced by environmental exposures

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ABSTRACT

الحصين، المعروف باسم (قرن آمون)، يلعب دورًا مهما في عمليات التعلم وتكوين الذاكرة والملاحة المكانية . تكشف الأبحاث الحديثة أن هذه المنطقة من الدماغ يمكن أن تخضع لتغييرات في بنيتها و وظائفها بسبب التعرضات البيئية، بما في ذلك الإجهاد والتلوث الضوضائي وانخفاض معدل النوم وانعدام الجاذبية . تلخص هذه المراجعة النتائج من الدراسات التي أجريت على الحيوانات والبشر، مع التركيز على مرونة الحُصين استجابةً لهذه العوامل . كما تدرس المراجعة التغيرات في الحجم والبنية والتكوين العصبي والمرونة المشبكية والتعبير الجيني وتسلط الضوء على فترات حرجة من الضعف للتأثيرات البيئية التي تؤثر على الإدراك والسلوك . كما تبحث هذه المراجعة في الآليات الأساسية مثل إشارات الجلوكوكورتيكويد والتغيرات الجينية والتكيفات في الدوائر العصبية . إن فهم كيفية تفاعل الحُصين مع التعرضات البيئية المختلفة أمر بالغ الاهمية لتطوير الاستراتيجيات لتعزيز المرونة المعرفية والتخفيف من الآثار السلبية على هذه المنطقة الهامة من الدماغ . هناك حاجة إلى مزيد من البحث لتحديد العوامل الوقائية وعوامل الخطر وإنشاء تدخلات فعالة .

The hippocampus, noted as (HC), plays a crucial role in the processes of learning, memory formation, and spatial navigation. Recent research reveals that this brain region can undergo structural and functional changes due to environmental exposures, including stress, noise pollution, sleep deprivation, and microgravity. This review synthesizes findings from animal and human studies, emphasizing the HC's plasticity in response to these factors. It examines changes in volume, architecture, neurogenesis, synaptic plasticity, and gene expression and highlights critical periods of vulnerability to environmental influences impacting cognition and behavior. It also investigates underlying mechanisms such as glucocorticoid signaling, epigenetic alterations, and neural circuit adaptations. Understanding how the HC reacts to various environmental exposures is vital for developing strategies to enhance cognitive resilience and mitigate negative effects on this crucial brain region. Further research is needed to identify protective and risk factors and create effective interventions.

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The hippocampus (HC) is a curving and extended brain region that is found on both sides of the medial temporal lobe. Its name, which has Greek roots, originates from its resemblance to a seahorse (**Figure 1**). The HC can be divided into 3 primary subregions: the dentate gyrus, the cornu ammonis (CA), and the subiculum. The dentate gyrus receives inputs from the entorhinal cortex and projects to the CA region (**Figure 2**). Within the CA region, layered pyramidal neurons are organized into 3 distinct fields: CA3, CA2, and CA1. The CA3 exhibits a notable abundance of recurrent synaptic connections among its pyramidal neurons. The CA1 region projects to the subiculum, which serves as the primary conduit for sending information back to the entorhinal cortex, thereby completing the trisynaptic circuit loop. Functionally, the HC plays a critical role in learning, memory formation, and spatial navigation. It encodes new memories, consolidates them into long-term storage, and facilitates declarative, episodic, and spatial memory types.[1] Its neurons exhibit synaptic plasticity, enabling persistent changes following learning. Furthermore, the HC interacts bidirectionally with other limbic structures, regulating emotional processing, stress response, and hormone levels.[2] The HC has vital cognitive and regulatory functions through its structural organization and extensive connections.

This review consolidates research on the impact of environmental circumstances such as stress, auditory pollution, sleep deprivation, and microgravity on hippocampal changes. It examines findings from animal and human studies, focusing on structural and functional alterations, critical vulnerability periods, and cognitive consequences. The review also addresses underlying mechanisms, including glucocorticoid signaling, epigenetic modifications, and neural circuit adaptations. By

providing an overview of hippocampal plasticity in response to these factors, this review aims to inform strategies for enhancing cognitive resilience and mitigating adverse effects on this vital brain region.

Neuroanatomical basis of the limbic system. The hippocampus is a key structure of the limbic system located in the medial temporal lobe of the brain, as shown in (**Figure 1**), The limbic system is an intricate network of brain structures that are crucial for regulating emotion, memory, and behavior, including the HC, amygdala, cingulate cortex, hypothalamus, fornix, entorhinal cortex, and parahippocampal gyrus.[3] **Figure 3** illustrates the anatomical relationships between key structures of the limbic system, including the hippocampus, amygdala, thalamus, and other related regions. The HC, situated in the medial temporal lobe, plays a vital role in spatial navigation, episodic memory formation, and consolidation, with subregions including the dentate gyrus, cornu ammonis (CA1-CA4), and subiculum. The amygdala, which processes emotions, has strong connections with the HC, affecting the emotional aspects of memory. The cingulate cortex links limbic and higher cognitive functions, while the hypothalamus regulates homeostasis and the stress response via the Hypothalamic-pituitary-adrenal (HPA) axis. The fornix functions as the primary efferent route of the HC, connecting it to other limbic structures. The entorhinal cortex acts as the interface between the HC and neocortex, which is important for spatial memory, and the parahippocampal gyrus facilitates memory encoding and retrieval.[4] The limbic system, with its high plasticity and concentration of stress hormone receptors, is especially vulnerable to environmental impacts. Understanding this neuroanatomical framework is crucial for appreciating how environmental factors affect hippocampal structure and function.

In conclusion, the limbic system's intricate network, centered around the HC, provides a neuroanatomical foundation for emotional processing, memory formation, and behavioral regulation. Its complexity and interconnectedness emphasize vulnerability to environmental influences, highlighting the need to understand its structure and function in relation to neurological and psychological processes.

Importance of the HC in cognition, memory, and learning. The HC is an essential brain structure located in the medial temporal lobe that supports learning, memory formation, and cognitive functions through its complex internal circuitry. It is essential in encoding new information and experiences into memory. The HC processes and consolidates these inputs into a symbolic format through synaptic long-term potentiation (LTP) as we acquire facts, skills, or spatial layouts. This mechanism allows neurons to activate together, reinforcing their connections and facilitating memory formation. Integral to the conscious recollection of experiences, the HC supports episodic and declarative memories by integrating multimodal inputs from the amygdala and entorhinal cortex. This integration forms coherent memory representations, supporting both short-term and long-term consolidations.[5] Additionally, the HC underpins spatial memory and navigation, with place cells firing in specific locations. This neuronal map aids in remembering object arrangements and environmental landmarks. Notably, hippocampal lesions impair spatial learning in animals. The HC also mediates the relational binding of discrete items, events, or concepts to support flexible thinking, reasoning, and decision-making. Its relational coding captures connections between discontinuous experiences. Furthermore, through its widespread cortical and subcortical links, the HC influences attention, executive functions, working memory, language, and social cognition. Damage to the HC results in broad cognitive impairments, underscoring its vital contributions to cognitive function.[6]

In conclusion, the HC is crucial for multiple cognitive processes, especially learning and memory. Its intricate structure and extensive neural connections allow it to integrate diverse information, form coherent memories, and support spatial navigation. The HC influences not only memory formation but also a broad spectrum of cognitive functions, establishing it as an essential element of the brain's cognitive architecture. Understanding its multifaceted roles offers valuable insights into human cognition and the potential implications of hippocampal damage or dysfunction.

Sensitivity of the HC to external environments. Extensive animal and human research shows that the HC undergoes morphological, functional, and molecular alterations in response to diverse environmental exposures across lifespans. Structurally, environmental stimuli like chronic stress, noise, sleep disruption, and microgravity induce changes in hippocampal volume and architecture. Studies reveal gray matter atrophy, reduced dentate gyrus, and CA thickness following these exposures. Functionally, the HC exhibits neurogenic, synaptic, and neuroendocrine plasticity based on environmental conditions. Adult hippocampal neurogenesis, synaptic efficacy via LTP or depression, and Glucocorticoid (GC) signaling are modulated by stress, sensory input, and enriched environments.[7] At the molecular level, environmental stresses cause changes in the expression of genes in the HC that control its form and structure. Genes involved in synaptic remodeling, neurite outgrowth, neurotrophin signaling, and stress pathways demonstrate altered transcription patterns. Epigenetic modifications mediate these effects. The HC exhibits dynamic structural, functional, and molecular plasticity in response to external inputs. However, further research is needed to fully elucidate hippocampal-environment interactions and critical periods of vulnerability across different life stages and exposures.

In conclusion, the HC exhibits significant sensitivity to external environmental factors, showing plasticity at structural, functional, and molecular levels. This adaptability enables the HC to dynamically respond to various stimuli, ranging from stress to enriched environments. While this

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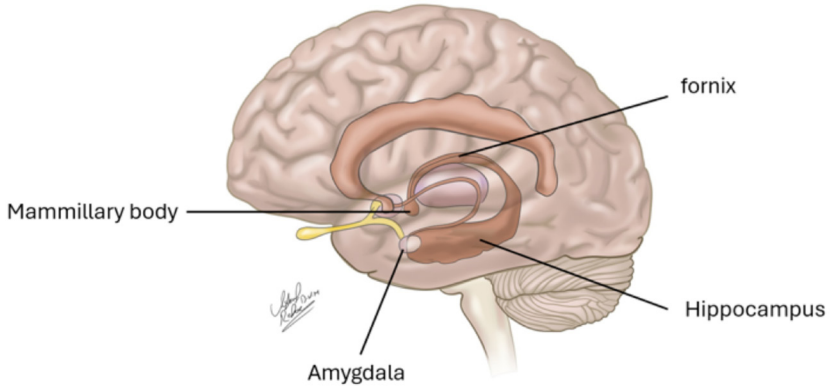

Figure 1 - Illustration of the location and shape of the hippocampus (HC) within the brain. This sagittal view of the brain shows the hippocampus and its spatial relationship to other key structures such as the fornix, mammillary body, and amygdala.

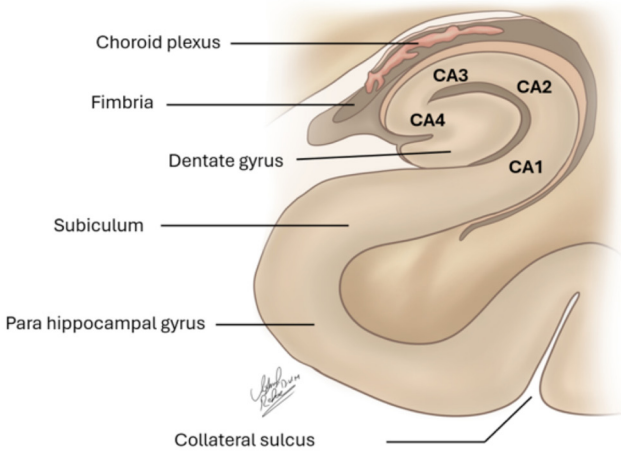

Figure 2 - Illustration of primary subregions of the hippocampus (HC). This diagram shows the key anatomical structures of the hippocampus, including the dentate gyrus, CA1-CA4 regions (Cornu Ammonis), subiculum, fimbria, choroid plexus, parahippocampal gyrus, and collateral sulcus.

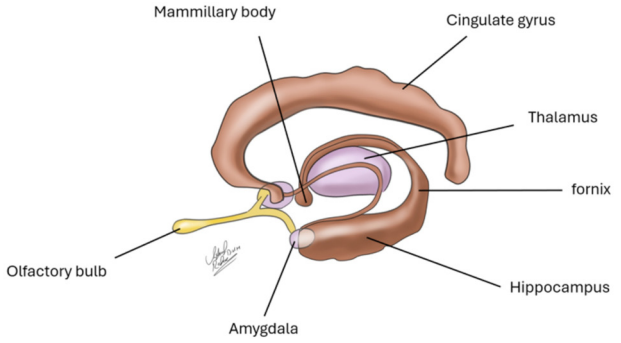

Figure 3 - Illustrates the anatomical relationships between key structures of the limbic system, including the hippocampus, amygdala, thalamus, and other related regions.

plasticity is vital for learning and adaptation, it also makes the HC susceptible to harmful environmental influences. Understanding the complex interactions between the HC and the environment is crucial for grasping how external factors influence cognitive function and for developing strategies to promote optimal hippocampal health throughout life.

Environmental stressors and the HC. Research shows that the HC is highly sensitive and plastic, undergoing structural and functional changes in response to environmental stressors. Neuroanatomically, stressors such as chronic stress, noise, sleep loss, and microgravity lead to reduced hippocampal volume and atrophy of subfields like the dentate gyrus and CA, as seen by magnetic resonance imaging (MRI). Elevated GC levels likely drive these morphological alterations via (HPA) activation.[8] Functionally, stressors modulate hippocampal neurogenesis in the dentate gyrus, impair synaptic plasticity and LTP, and alter GC receptor expression. Molecularly, stress-induced differential gene expression is observed in pathways involved in synaptic remodeling, neuronal outgrowth, neurotrophins, and the stress response itself. Epigenetic modifications mediate these changes in gene regulation. In summary, the HC exhibits substantial neuroplasticity in response to environmental stressors through changes in volume, cellular composition, synaptic connectivity, and molecular mediators.[9] Elucidating the timeline of hippocampal sensitivity across life stages has implications for understanding cognitive resilience and targeting interventions for stress-related disorders.

In conclusion, the HC exhibits notable sensitivity to environmental stressors, displaying various structural, functional, and molecular changes in response to challenges. While this plasticity can be adaptive in the short term, prolonged or severe stress may significantly alter hippocampal structure and function. Understanding these stress-induced changes is essential for grasping the effects of environmental stressors on cognitive function and mental health. This insight may inform the development of interventions aimed at protecting hippocampal integrity and enhancing cognitive resilience in the face of environmental challenges throughout different life stages.

The impact of long-term stress on the formation and functioning of the HC. Extensive research across animals and humans has elucidated the effects of prolonged stress on the structural and functional plasticity of the HC.[10] Chronic stress is associated with a reduction in hippocampal volume, particularly affecting subfields such as the dentate gyrus and CA regions, as revealed by MRI studies. These alterations stem from the dysfunction of the HPA axis and heightened GC activity within the HC. At the cellular level, chronic stress impedes adult neurogenesis in the dentate gyrus, hampering the survival and maturation of new granule neurons. Additionally, dendritic arborization in the CA3 region is suppressed, with retraction of apical dendrites in pyramidal neurons and reduced dendritic spine density observed throughout the HC. Functionally, chronic stress disrupts synaptic plasticity mechanisms, such as LTP and long-term depression, impairing spatial memory formation and contextual learning.[11] Moreover, it exacerbates depressive-like behaviors and cognitive deficits. Molecular investigations reveal dysfunctional regulation of genes participating in neurogenesis, synaptic remodeling, neurotrophin signaling, and GC receptor pathways within the HC under chronic stress conditions. Furthermore, epigenetic modifications mediate stress-induced alterations in hippocampal gene transcription, reflecting the complex interplay between environmental experiences and molecular responses in the brain.[12]

In conclusion, chronic stress profoundly affects hippocampal structure and function, causing changes in volume, neuronal morphology, and molecular signaling pathways. These alterations significantly impact cognitive processes, emotional regulation, and overall brain health. Understanding the interactions between stress and the HC is essential for developing targeted interventions to mitigate the negative impacts of prolonged stress on brain function and psychological health. This underscores the importance of stress management strategies and the potential for innovative therapies to protect and restore hippocampal integrity in the face of chronic stress.

Atrophy and reduced neurogenesis. Chronic stress is known to induce significant structural and functional changes in the HC through complex interactions between the HPA axis and GC receptors. This stressor triggers 2 key effects: hippocampal atrophy and reduced rates of adult neurogenesis. At the neuroanatomical level, prolonged stress leads to hippocampal size loss and degeneration of specific subregions. The MRI studies conducted in both human and animal models show reductions in total hippocampal size as well as thinning of the dentate gyrus and CA fields. The chronic elevation of GC via stress-induced HPA axis dysregulation is believed to mediate these effects by inducing dendritic retraction and neuronal loss over time. At the cellular level, chronic stress diminishes hippocampal neurogenesis within the subgranular zone of the dentate gyrus, reducing the rapid increase of the spread, survival, and maturation of newborn granule cells into functional neurons. Studies employing bromodeoxyuridine labeling have found minimizing numbers of young neurons in the HC of chronically stressed. Chronic stress can also induce dendritic remodeling, such as decreased arborization in the CA3 region. Functionally, reduced hippocampal volume and neurogenesis impair learning and memory processes that depend on the integrity of this structure. Spatial memory formation, contextual fear conditioning, and other hippocampal-mediated tasks are significantly disrupted. Atrophy and decreased neurogenesis may contribute to stress-related cognitive deficits and heightened vulnerability to mood disorders.[13,14]

In conclusion, chronic stress significantly affects hippocampal structure and function, resulting in atrophy and reduced neurogenesis, which contribute to cognitive impairments and heightened vulnerability to psychological issues.

Impairments in memory tasks. There is an abundance of research demonstrating that chronic stress significantly damages memory processes that require the structure and function of the HC. Both animal and human research have documented impairments in many memory areas associated with dysfunction in the HC due to long-term exposure to stress.[15] At the behavioral level, chronic stress disrupts hippocampal-mediated explicit memory involving conscious recall of facts and events. Rodent studies have revealed impaired acquisition of spatial memories necessary to navigate environments like the Morris water maze. Similarly, human studies have shown poorer word recall and retention in verbal episodic memory tests conducted under conditions of chronic life stress.[16] Working memory capacities are also diminished, with chronic stress exhibiting slower reaction times and decreased accuracy on online manipulation challenges such as n-back tasks. Contextual fear conditioning, a process that relies on hippocampal function to associate environments with aversive stimuli, is hindered under chronic stress conditions. These behavioral deficits likely stem from stress-induced hippocampal changes, including suppressed neurogenesis, reduced dendritic complexity and spine density, dampened LTP, and dysregulated plasticity gene programs. Prolonged HPA axis dysfunction and the associated GC burden mediate the remodeling and functional decline of the HC, culminating in deficits across learning, memory, and conditioning paradigms.[17]

In conclusion, chronic stress significantly impairs HC-dependent memory processes, including explicit memory, spatial navigation, working memory, and contextual fear conditioning.

HPA axis involvement. The impact of stress experienced throughout early life on the functioning and structure of the HC. Detailed mechanisms. The HPA axis is crucial in the body's stress response, and early-life stress (ELS) can have significant and long-lasting impacts on this system and the HC.[18] The HPA axis, consisting of the hypothalamus, pituitary gland, and adrenal glands, coordinates the secretion of stress hormones, including corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and glucocorticoids (GCs), in response to stressful events. Research has shown that ELS can lead to long-term

dysfunction of the HPA axis, manifesting as increased baseline cortisol levels, impaired negative feedback regulation, and altered glucocorticoid receptor (GR) regulation in the HC. Research has demonstrated that this chronic elevation of GCs leads to the downregulation of GRs in the HC, which impairs the negative feedback loop and perpetuates HPA axis hyperactivity. For instance, prenatal stress exposure has been associated with altered GR expression in the HC and amygdala in adulthood, leading to increased susceptibility to depression and anxiety.

One of the significant consequences of ELS is the dysfunction of adult hippocampal neurogenesis. This impairment is characterized by decreased production of neural progenitor cells, minimized survival of newborn neurons, and altered differentiation patterns of neural stem cells.[19] Research using bromodeoxyuridine labeling has found reduced numbers of young neurons in the HC of chronically stressed. The mechanism behind this impairment involves elevated glucocorticoids suppressing the regulation of neurotrophic factors like brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF), which are crucial for neurogenesis. Additionally, stress-induced inflammation can further inhibit neurogenic processes. ELS also causes significant changes in hippocampal dendritic morphology, including reduced dendritic length and branching in CA3 pyramidal neurons, as well as decreased spine density in CA1 and dentate gyrus neurons. These changes occur because chronic stress promotes N-methyl-D-aspartate (NMDA) receptors and increases calcium influx, leading to dendritic retraction. Stress also alters the expression of cytoskeletal proteins involved in dendritic maintenance.[20]

Synaptic plasticity in the HC is another area significantly affected by ELS. This includes reduced long-term potentiation (LTP), enhanced long-term depression (LTD), and altered α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor trafficking.[21] Stress hormones interfere with the molecular cascades involved in LTP induction, including mitogen-activated protein kinase (MAPK) and calcium/calmodulin-dependent protein kinase II (CaMKII) pathways. Stress also enhances the internalization of AMPA receptors, promoting LTD.[22] Studies have shown that these alterations in synaptic plasticity can lead to impairments in spatial memory formation, contextual fear conditioning, and other hippocampal-mediated tasks.

The ELS can induce lasting epigenetic changes in the HC, including altered DNA methylation patterns of stress-related genes, histone modifications affecting gene expression, and changes in microRNA expression profiles. Stress hormones can directly influence epigenetic enzymes like DNA methyltransferases and histone deacetylases, leading to lasting changes in gene expression patterns.[23] These epigenetic modifications have been linked to long-term alterations in stress responsiveness and susceptibility to mental health disorders later in life.

Chronic neuroinflammation in the HC is another consequence of ELS, characterized by increased microglial activation, elevated pro-inflammatory cytokine levels (e.g., interleukin-1β [IL-1β], tumor necrosis factor-α [TNF-α]), and enhanced oxidative stress.[24] Chronic stress activates the NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome in microglia, leading to sustained release of pro-inflammatory cytokines. This inflammatory state can further impair neurogenesis and synaptic plasticity. Various neurotransmitter systems in the HC are affected by ELS, including reduced serotonergic signaling, altered γ-aminobutyric acid (GABA)-ergic inhibition, and dysregulated glutamatergic transmission. These stress-induced changes in receptor expression and neurotransmitter release contribute to imbalances in excitatory and inhibitory signaling, affecting overall hippocampal function.[25]

The ELS can also impact hippocampal vasculature, leading to reduced cerebral blood flow, decreased angiogenesis, and compromised blood-brain barrier integrity. Chronic stress can lead to endothelial dysfunction and reduced expression of angiogenic factors, potentially compromising neuronal health and function. Magnetic resonance imaging (MRI) investigation in both human and animal models has shown reductions in total hippocampal size as well as thinning of the dentate gyrus and cornu ammonia (CA) fields following chronic stress exposure.

The consequences of HPA axis dysregulation and hippocampal changes due to ELS can extend to multiple domains. Chronic elevation of GCs can lead to alterations in GR expression and dysregulation of GC signaling, contributing to increasing stress-related disorders. Early-life stress can induce volumetric reductions in the HC and amygdala, leading to alterations in neural circuitry and cognitive function. These neuroanatomical changes can cause long-term alterations in neural connectivity, including differential synaptic strengthening and weakening, which can underlie cognitive and emotional impairments.[26] Moreover, early life stress (ELS) may boost the possibility of acquiring mood and anxiety disorders in the future, such as major depressive disorder, generalized anxiety disorder, and post-traumatic stress disorder. Research has demonstrated that persons who experience adversity throughout their early years are two to three times more likely to acquire depression in maturity. Exposure to stress during pregnancy has been linked to changes in the expression of the GR gene in the HC and amygdala during adulthood, resulting in a higher vulnerability to depression and anxiety. Prolonged stress experienced during crucial stages of fetal development might modify the configuration of brain pathways, making the child more susceptible to developing stress-related diseases in the future.

In conclusion, early-life stress profoundly impacts hippocampal function and structure through various interconnected mechanisms, including changes in gene expression, synaptic function, neurogenesis, inflammation, and vascular health. The interplay between HPA axis dysregulation, impaired neurogenesis, synaptic plasticity alterations, epigenetic modifications, neuroinflammation, neurotransmitter imbalances, and vascular changes collectively affects hippocampal health. Understanding how

early-life stress impacts the HC is crucial for developing targeted interventions to mitigate its long-term effects on brain health and cognitive function. This highlights the importance of early intervention and stress management in promoting lifelong brain resilience, potentially through strategies that enhance neurogenesis, prevent atrophy, or modulate HPA axis function.

Long-term changes in size connectivity. Prolonged activation of the HPA axis under prolonged stress leads to sustained high GC levels (cortisol or corticosterone).[27] These GCs bind to mineralocorticoid and GC receptors in the HC, initiating downstream signaling cascades. This changes the regulation of genes involved in neural structure and connectivity, including those regulating neurotrophins, synaptogenesis, and cytoskeletal proteins. Resulting in reductions in hippocampal dendritic branching, spine density, and neurogenesis, leading to the observed decreases in hippocampal volume with chronic stress. Disrupted cellular architecture causes improper neural wiring among the HC and other limbic regions like the amygdala and prefrontal cortex. Miswiring of hippocampal circuitry is evidenced by changes in functional connectivity in MRI studies in humans and rodents following chronic stress. Furthermore, epigenetic modifications like DNA methylation and histone acetylation induced by chronic GC exposure further reprogram hippocampal connectivity patterns.[28] These maladaptive neural circuit changes mediate the long-term effects of early-life stress on hippocampal structure and function. However, chronic HPA axis activation due to stress remodels hippocampal circuits through transcriptional, epigenetic, neurotrophic, and neurogenic mechanisms, resulting in persistent modifications in hippocampal size and connections.

Lasting cognitive deficits. Chronic stress exposure, especially during early developmental periods, can lead to impaired performance on hippocampal-dependent cognitive tasks, including spatial learning and memory, contextual fear conditioning, and pattern separation. Rodent studies have demonstrated that chronic corticosterone treatment or restraint stress leads to deficits in spatial memory acquisition and retention, as indicated by impaired performance in the Morris water maze, radial arm maze, and Barnes maze hippocampal-dependent paradigms. Meanwhile, human studies indicate that childhood trauma or maltreatment is associated with poorer contextual and verbal memory performance later in life. These lasting impairments are mediated by chronic GC-induced changes in hippocampal dendritic architecture, neurogenesis, synaptic plasticity, and neural circuit wiring that disrupt hippocampal processing. Cognitive deficits persist even after the cessation of prolonged stress, reflecting the long-term reprogramming of hippocampal structure and function.[29]

Protective interventions. Animal research suggests that voluntary physical exercise can counteract the adverse impacts of long-term stress on hippocampal size and memory by normalizing GC levels, stimulating neurogenesis, and promoting synaptic plasticity. Environmental enrichment with multisensory stimulation and social interaction preserves hippocampal neuron morphology and hippocampal-dependent memory function against chronic stress in rodent models. Social buffering through peer support mitigates long-term stress impacts on hippocampal structure and spatial cognition in rodent models, likely by regulating GC release. Clinical studies also demonstrate that cognitive-behavioral interventions, mindfulness techniques, social support, and exercise protect against hippocampal atrophy and cognitive decline in chronic stress scenarios.[30] Epidemiological investigations have revealed a link between high traffic noise levels and reduced hippocampal volume in humans. Animal studies corroborate these findings, demonstrating that mice exposed to traffic noise mimic hippocampal atrophy and neuronal morphology changes like reduced dendritic complexity. Possible mechanisms underpinning these effects include noise-induced overactivation of the HPA axis and subsequent increases in GC levels. Noise exposure may also disrupt hippocampal neurogenesis and cause neuroinflammatory changes. Chronic aircraft noise exposure in human cohorts has also been linked to poorer performance on HC -dependent spatial memory and navigation tasks. Mice exposed to simulated airport noise display hippocampal-dependent memory deficits in object location and spatial recognition tasks. Sleep disturbance secondary to noise disruption likely also contributes to hippocampal impairments. Noise has been associated with reduced hippocampal regional homogeneity on MRI, indicating altered neural circuit function. Notably, the effects on the HC are greater with nighttime noise exposure, emphasizing the role of sleep disruption as a mediating factor.[31] Developmental noise exposure causes more pronounced hippocampal reorganization and spatial memory deficits, highlighting windows of vulnerability. In summary, traffic and aircraft noise can induce morphological and functional changes in the HC, disrupting spatial and contextual memory (**Table 1**).

HC and HC-dependent memory. Environmental noise exposure, especially nighttime noise, can cause sleep fragmentation and alter sleep architecture. This results in specific suppression of deep slow, wave sleep, and rapid eye movement (REM) sleep, which play a crucial role in the consolidation of memory. Animal studies show that selective REM sleep deprivation causes dendritic atrophy, spinal loss in hippocampal CA1 neurons, and impaired neurogenesis. These morphological changes likely contribute to hippocampal atrophy and disruptions in LTP observed with sleep deprivation.[56] Human neuroimaging studies demonstrate that sleep deprivation alters hippocampal activation patterns and functional connectivity during memory tasks. Behaviorally, sleep deprivation in rodents and humans reduces performance on HC -dependent functions, such as contextual fear conditioning, spatial navigation, and spatial memory encoding. Cognitive deficits after sleep loss align with the function of slow-wave and REM sleep in consolidating hippocampal spatial and declarative memories. Sleep deprivation also has epigenetic effects on the HC, influencing gene programs linked to synaptic

Table 1 - Enhanced classification of protective interventions for hippocampal function.

Intervention type	Animal studies	Clinical studies
Physical Exercise	Voluntary wheel running promotes BDNF expression and neurogenesis in the HC[32] Treadmill exercise enhances spatial memory and increases synaptic plasticity-related proteins in the HC[33] Swimming exercise mitigates stress-induced hippocampal damage[34]	- Aerobic exercise boosts hippocampal size in aged adults[35] Resistance training improves hippocampal-dependent memory in older adults[36] High-intensity interval training enhances hippocampal neurogenesis and cognitive function[37]
Environmental Enrichment	An enriched environment promotes dendritic branching and spine density in hippocampal neurons[38] - Environmental enrichment enhances hippocampal neurogenesis and improves spatial memory[39] An enriched environment mitigates age-related decline in hippocampal function[40]	- Cognitive and social stimulation programs improve hippocampal-dependent cognitive functions in older adults[41] - Multimodal lifestyle interventions, including cognitive stimulation, show promise in preserving hippocampal volume[42]
Social Support	- Social housing reduces stress-induced hippocampal atrophy in rodents. - Social play enhances hippocampal plasticity in juvenile rats[42,43]	- Strong social networks are linked with higher hippocampal sizes in older adults - Social engagement is related to reduced risk of hippocampal degeneration in early life[44,45]
Cognitive-Behavioral Interventions	- Cognitive training improves hippocampal-dependent memory in aged animals[46]	- CBT for depression increases hippocampal volume - Memory training enhances hippocampal functional connectivity - Cognitive remediation therapy improves hippocampal activation during memory tasks in schizophrenia patients[47]
Mindfulness Techniques	- Mindfulness meditation increases hippocampal neurogenesis in rats[48]	- Mindfulness-based stress reduction increases gray matter concentration in the HC. - Long-term meditation practice is associated with larger hippocampal volumes - Mindfulness training improves hippocampal-dependent memory in older adults[49]
Dietary Interventions	- Omega-3 fatty acid in food intake enhances hippocampal neurogenesis and cognitive function. - Caloric restriction promotes hippocampal neurogenesis and improves memory. - Ketogenic diet enhances hippocampal neuroplasticity[50,51]	- Mediterranean diet is associated with larger hippocampal volumes in older adults - Flavonoid-rich diet improves hippocampal-dependent memory in older adults - Intermittent fasting enhances hippocampal function and neuroplasticity[52]
Pharmacological Interventions	- Antidepressants enhance hippocampal neurogenesis in animals with depression. - HDAC inhibitors enhance hippocampal-dependent memory formation. - BDNF mimetics promote hippocampal plasticity and cognitive function[53,54]	- Lithium treatment increases hippocampal volume in bipolar disorder patients. - SSRIs can enhance the growth of new neurons in the human HC. - Modafinil enhances hippocampal-dependent memory consolidation[55]

plasticity and memory. Therefore, noise-induced sleep disruption mechanistically remodels hippocampal circuits and physiology to mediate adverse effects on HC-dependent learning and memory.

In conclusion, noise-induced sleep disruption significantly alters hippocampal circuits and physiology, negatively impacting learning and memory. Thus, maintaining good sleep quality is essential for hippocampal function and cognitive health.

Vulnerable periods when the HC is especially sensitive to environmental exposures during development. The HC undergoes an extended postnatal developmental period, making it particularly susceptible to various environmental exposures during early life stages. Animal studies show that exposure to factors like noise, stress, or microgravity during prenatal, perinatal, or childhood periods can cause more pronounced hippocampal changes and cognitive deficits than exposure in adulthood. Early-life exposures can reprogram gene expression patterns, influence neurogenesis, and shape neural circuit formation in the developing HC, leading to lasting structural and functional alterations.[57] Critical periods of vulnerability to environmental insults likely coincide with time windows of rapid hippocampal growth, neuronal migration, and circuit remodeling. Being aware of the repercussions of early-life exposures on hippocampal development is vital for discerning potential long-term consequences on cognitive function and developing preventive strategies and interventions to protect neurodevelopmental processes. The HC's protracted postnatal development highlights the importance of maintaining a healthy intrauterine and early childhood environment to ensure optimal hippocampal maturation and cognitive outcomes, particularly in the context of space exploration and extreme environments.

In conclusion, the HC is highly sensitive to environmental factors during early development, resulting in lasting structural

and functional changes. Identifying these vulnerable periods is crucial for protecting neurodevelopment and preventing long-term cognitive deficits.

During aging. Aging correlates with a decrease in hippocampal size and a decline in HC-dependent memory function. An aging HC exhibits diminished plasticity, reduced neurogenic capacity, and increased inflammation, rendering it more susceptible to the adverse effects of environmental exposures among older populations.[58] Exposure to factors like noise, stress, and microgravity can cause more severe hippocampal impairments and accelerate cognitive aging when experienced by older individuals compared to younger adults. These age-related changes in the HC, combined with the cumulative effects of environmental insults over the lifespan, can exacerbate cognitive deficits and enhance the risk of neurodegenerative dysfunctions.

In conclusion, the aging HC is especially susceptible to environmental factors, which can worsen cognitive decrease and enhance the risk of neurodegenerative disorders. Understanding the relationship between aging and these factors is vital for creating strategies to protect cognitive health in older adults.

During neurodegeneration. Neurodegenerative diseases such as Alzheimer's disease involve accelerated deterioration of the HC. Animal studies demonstrate that environmental exposures can expedite hippocampal damage and exacerbate cognitive symptoms in the context of underlying neurodegenerative pathology.[59] These exposures may interact synergistically with pathological processes, driving greater structural and functional changes in the HC than in healthy individuals. The HC, already compromised by neurodegenerative processes, exhibits heightened vulnerability to the detrimental effects of environmental insults, potentially accelerating the progression of cognitive decline. Understanding the interplay between environmental exposures and neurodegenerative pathologies affecting the HC is very important for developing targeted interventions and mitigating strategies to preserve cognitive function in affected individuals. Identifying and minimizing environmental risk factors could potentially slow the rate of hippocampal degeneration and cognitive deterioration in patients with neurodegenerative diseases, thereby improving their quality of life and functional independence.

In conclusion, the interaction between environmental exposures and neurodegenerative processes worsens hippocampal damage and speeds up cognitive decline. Understanding this interplay is vital for creating targeted interventions to slow hippocampal degeneration, preserve cognitive function, and increase the high standard levels of life for individuals with neurodegenerative diseases.

Space travel and microgravity effects. Studies involving astronauts show that extended missions lead to hippocampal atrophy detectable on MRI, along with reduced spine density. Similarly, rodents flown in space exhibit hippocampal volume reductions and altered neuron morphology.[60] Microgravity disrupts calcium signaling, growth factor expression, and possibly neurogenesis in the HC. These trigger neural reorganization of hippocampal circuits, as evidenced by immediate early gene activation changes. Functional MRI studies reveal impaired hippocampal activation during memory tasks following spaceflight.

In conclusion, prolonged microgravity exposure during space travel causes changes in the HC, potentially impairing memory and cognitive function. Understanding these effects is crucial for developing countermeasures to safeguard astronauts' cognitive health during and after long-duration missions.

Implications on cognition. Extended periods spent in the microgravity environment of space can have significant implications on cognitive functions, particularly those related to spatial orientation, navigation, and memory. Several studies have reported the following observations and implications:

Deficits in spatial orientation and navigation. Astronauts often experience difficulties in spatial orientation and navigation tasks after extended space missions. These deficits may arise from altered sensory inputs and the absence of a consistent gravitational reference frame in microgravity environments.[60]

Memory impairments. In addition to spatial deficits, astronauts have been observed to exhibit memory impairments, especially in tasks that rely on the HC, a specific region crucial for memory formation and spatial cognition.[61]

Observations in rodent studies. Similar spatial memory and mapping deficits have been observed in rodent studies conducted in space or ground-based microgravity analogs. These findings suggest that the microgravity environment can directly impact hippocampal function and associated cognitive processes.[62]

Anatomical and physiological alterations in the HC: The cognitive deficits observed in astronauts and rodents are likely associated with alterations in the HC induced by microgravity. These changes may encompass alterations in neuronal structure, synaptic plasticity, neurogenesis, and neuronal signaling pathways.[63]

Role of the HC in spatial cognition and contextual memory: The HC plays a critical role in spatial cognition, contextual memory formation, and the integration of spatial and contextual information. Disruptions in hippocampal function due to microgravity could lead to impairments across these cognitive domains.[64]

Mood regulation and affective disturbances: Beyond cognitive deficits, alterations in hippocampal function have been linked to mood dysregulation and affective disturbances. This may contribute to the emotional and psychological challenges faced by astronauts during and after long-duration space missions. These findings underscore the importance of understanding the impact of microgravity on the HC and its associated cognitive functions. Addressing these issues is crucial for ensuring the well-being and performance of astronauts during extended space missions, as well as for developing countermeasures and interventions to mitigate the negative effects of microgravity on the brain and cognitive function.

In conclusion, the impact of microgravity on cognitive functions highlights the necessity of understanding how prolonged space travel affects the HC and related cognitive processes. Addressing these cognitive and emotional challenges is vital for maintaining astronaut health and performance during extended missions.

Studying effects on earth. Head-down tilt bed rest investigations, rotating wall vessels, and parabolic flights are ground-based analogs for demonstrating the impacts of microgravity on the HC, a vital brain region for spatial navigation, memory, and cognitive function.

Head-down tilt bed rest investigations simulate microgravity by inducing cephalic fluid shifts and cardiovascular deconditioning, mimicking the effects of spaceflight on the human body.[65]

Rotating wall vessels create a low-shear, low-turbulence environment by suspending cells or tissues in a rotating culture vessel. This mimics certain weightlessness features in 3D culture through hydrodynamic suspension.[66]

Parabolic flights generate short periods of hypergravity followed by freefall, offering insights into the transient effects of microgravity transitions on biological systems.[67]

These ground-based analogs enable researchers to study the morphological and physiological changes in the HC in response to simulated microgravity conditions without actual spaceflight experiments. By investigating the effects of these analogs on hippocampal structure, function, and plasticity, scientists can draw valuable insights into the potential cognitive and behavioral implications of long-duration space missions.

In conclusion, ground-based analogs like head-down tilt bed rest studies, rotating wall vessels, and parabolic flights serve as valuable tools for examining the effects of simulated microgravity on the HC. By exploring how these analogs influence hippocampal morphology, function, and plasticity, researchers can gain insights into the cognitive and behavioral implications of long-duration space missions. This knowledge is crucial for advancing strategies to mitigate the effects of microgravity on astronauts.

Sleep deprivation. Research has demonstrated that lack of sleep has negative consequences on the hippocampus (HC), a crucial brain area responsible for memory consolidation, spatial orientation, and the brain's ability to change and adapt (neuroplasticity). Several studies have highlighted the following consequences of sleep deprivation on the HC:

Hippocampal atrophy. Chronic sleep deprivation can reduce the HC volume, a phenomenon known as hippocampal atrophy. This structural change has been linked with impaired cognitive function, particularly in memory and spatial tasks that rely on the HC.[68]

Impaired neurogenesis. The HC is one of the few brain regions where new neurons are continuously generated, a process known as neurogenesis. Sleep deprivation disrupts this process, decreasing the production and survival of new neurons in the HC. Such impairment in neurogenesis can profoundly affect hippocampal function and plasticity.[69]

Synaptic deficits. Sleep deprivation can also impact synaptic plasticity within the HC, which is essential for learning and memory processes. Investigations have demonstrated that sleep deprivation diminishes the strength and stability of synaptic connections and impairments in LTP, a cellular mechanism underlying learning and memory formation.[70]

Disruption of memory consolidation. The HC plays a vital role in memory consolidation, a process involving the stabilization and integration of recently acquired information. Sleep deprivation has been shown to disrupt hippocampal-dependent memory consolidation, particularly during slow-wave sleep and REM sleep, which are critical for memory consolidation and hippocampal plasticity.[71]

Spatial memory deficits. The HC is also involved in spatial navigation and the formation of cognitive maps. Sleep deprivation has been found to impair spatial memory and navigation abilities, possibly due to the disruption of hippocampal function and neuronal activity patterns associated with spatial coding.[72]

In conclusion, sleep deprivation has a significant negative impact on the HC, adversely affecting memory formation, spatial navigation, and neuroplasticity. These findings underscore the importance of consistent, quality sleep for maintaining hippocampal integrity and cognitive functions. Addressing sleep deprivation is essential for preserving cognitive health and enhancing overall well-being, highlighting the critical role of sleep in facilitating effective learning and memory processes.

Light pollution. Sleep deprivation disrupts the circadian regulation of hippocampal physiology, altering the normal rhythmic patterns of various biological processes within the HC. Several studies have highlighted the following effects:

Circadian regulation disruption. The HC exhibits circadian rhythms in its physiological functions, such as neuronal activity, gene expression, and neurogenesis. Sleep deprivation can disrupt these rhythmic patterns, leading to disturbances in the circadian regulation of hippocampal physiology.[73]

Altered clock gene expression: Similar to other brain regions, the HC contains a molecular clock machinery that regulates circadian rhythms through clock gene expression. Sleep deprivation has been shown to alter the expression patterns of these clock genes in the HC, potentially disrupting circadian rhythms and associated physiological processes.[74]

Impaired hippocampal neurogenesis: Sleep deprivation hampers neurogenesis in the HC. This impairment affects cognitive functions and has implications for mood regulation, as hippocampal neurogenesis is believed to play a crucial role in modulating mood and emotional behavior.[75]

Mood dysregulation. The HC is involved in the regulation of mood and emotional processing, with dysfunction linked to mood disorders such as depression and anxiety. Sleep deprivation has been associated with impaired hippocampal function and mood regulation alterations, potentially contributing to the development or exacerbation of mood-related disorders.[76]

The disruption of circadian rhythms and clock gene expression in the HC due to sleep deprivation can have far-reaching consequences for various physiological processes, including hippocampal neurogenesis, cognitive function, and mood regulation. These findings highlight the importance of maintaining adequate sleep and circadian rhythms for optimal hippocampal function and overall brain health. It is worth noting that the effects of sleep deprivation on the HC and circadian regulation may vary based on factors such as the duration and severity of sleep deprivation and individual differences in vulnerability and resilience. Further research is needed to fully understand the complex interplay between sleep, circadian rhythms, and hippocampal function in healthy and pathological states.

In conclusion, light pollution and the resulting sleep deprivation disrupt the circadian regulation of hippocampal physiology, negatively impacting critical processes such as neurogenesis, mood regulation, and cognitive functions. Altered circadian rhythms and clock gene expression within the HC can lead to significant neurological consequences, including impaired mood and an increased risk of mood disorders. These findings highlight the importance of promoting good sleep hygiene and addressing environmental factors like light pollution that contribute to sleep deprivation.

Shared effects. Below are some important similarities between the effects of microgravity and aging on the HC:

1. Reduction in hippocampal volume.
2. Disruption of neurogenesis.
3. Impairments in synaptic plasticity and spatial or contextual memory.
4. Dysregulation of neural circadian rhythms and growth factors that are important for hippocampal function.

Both microgravity exposure during spaceflight and the natural aging process appear to negatively impact the structure and function of the HC through similar mechanisms. These include reduced volume, inhibited neurogenesis, impaired plasticity and memory, and deregulation of molecular processes in the HC. These hippocampal changes may underlie the increased risk of cognitive deficits observed in astronauts after long missions and in older people.

In conclusion, both microgravity and aging have detrimental effects on the HC, revealing significant similarities in their impact on brain structure and function. Key shared effects include reduced hippocampal volume, disrupted neurogenesis, impairments in synaptic plasticity, and dysregulation of neural circadian rhythms and essential growth factors. These changes in the HC may contribute to the increased risk of cognitive deficits experienced by astronauts after prolonged space missions, as well as in the aging population. Understanding these parallels provides valuable insights into the mechanisms underlying cognitive decline in various contexts, emphasizing the need for targeted interventions to mitigate these effects.

Distinct effects. The following are some distinct effects of various environmental factors on the brain:

Stress. Chronic stress activates the HPA axis, which can induce epigenetic changes and dendritic remodeling in the HC, affecting its structure and function.

Noise. Exposure to excessive noise can cause hearing loss and induce changes in the medial prefrontal cortex, a region involved in cognitive control and decision-making.

Microgravity. Spaceflight's microgravity environment can disrupt global calcium regulation, which is crucial for neuronal signaling and synaptic plasticity. It can also affect the vestibular system, impacting spatial orientation and balance.

Radiation. Exposure to ionizing radiation can cause DNA damage, persistent oxidative stress, and neuroinflammation in the brain, potentially leading to cognitive impairments and neurodegenerative processes.

It is crucial to emphasize that these environmental factors can have distinct and overlapping impacts on different brain regions and physiological processes, highlighting the complex interplay between the brain and its environment.

In conclusion, various environmental factors have distinct effects on brain health, each contributing uniquely to alterations in structure and function. Chronic stress activates the HPA axis, leading to epigenetic changes and dendritic remodeling in the HC, while excessive noise primarily affects the medial prefrontal cortex, impacting cognitive control. The microgravity of spaceflight disrupts global calcium regulation essential for neuronal signaling, and radiation exposure can induce DNA damage and neuroinflammation, posing risks for cognitive impairments and neurodegeneration. Understanding these distinctive impacts is crucial for developing strategies to mitigate environmental risks and protect brain health, considering the complex interplay between the brain and its surrounding environment.

The GC signaling. Stress triggers the release of GCs, which alter gene expression programs in hippocampal neurons through GC receptor signaling. This disrupts the expression of genes involved in neurotrophic support, synaptogenesis, and cytoskeletal proteins, contributing to changes in dendritic arborization and spine morphology. Chronic GC exposure can hamper neurogenesis, synaptic plasticity, and neuronal survival in the HC, potentially leading to cognitive deficits and mood disorders. The HC is particularly vulnerable to the harmful effects of GCs due to its high expression of GC receptors and its role in stress response regulation. Understanding the molecular mechanisms underlying GC signaling in the HC is crucial for developing therapeutic interventions to mitigate the negative effects of chronic stress on brain function and mental health.[77–79]

In conclusion, glucocorticoid (GC) signaling plays a crucial role in the brain's response to stress, particularly within the HC. Stress-induced GC release alters gene expression programs, disrupting essential processes such as neurotrophic support, synaptogenesis, and the stability of cytoskeletal proteins. This dysregulation results in detrimental changes in dendritic structure and spine morphology, impairing neurogenesis, synaptic plasticity, and neuronal survival. Given the HC's heightened sensitivity to GCs due to the abundance

of receptors and its critical role in stress regulation, chronic exposure to elevated GCs is linked to cognitive deficits and mood disorders. Therefore, understanding the complexities of GC signaling is vital for developing effective therapeutic strategies to counteract the adverse effects of chronic stress on neurological functioning and mental health.

Consequences of BDNF Alterations. Brain-derived neurotrophic factor (BDNF) is a critical neurotrophin that plays a pivotal role in neuroplasticity, neurogenesis, and neuroprotection within the limbic system, with particularly pronounced effects in the HC. Extensive research has demonstrated that stress significantly alters BDNF expression and signaling, contributing to structural and functional changes in the HC and other limbic regions. These alterations have far-reaching implications for cognitive function, emotional regulation, and overall brain health. Chronic stress has been consistently associated with decreased BDNF levels in the HC and other limbic structures. This reduction in BDNF can lead to a variety of detrimental effects on hippocampal function and structure. Studies have shown that stress-induced BDNF reduction impairs neurogenesis in the dentate gyrus, a key region for adult neurogenesis and memory formation.[80]

The impact of stress-induced BDNF alterations extends beyond structural changes, significantly affecting synaptic plasticity. Long-term potentiation (LTP), a key cellular mechanism underlying learning and memory, is particularly vulnerable to BDNF fluctuations.[81]

Several interconnected mechanisms and pathways mediate the stress-induced alterations in BDNF. The activation of (HPA) axis plays a central role in this process. Chronic stress leads to sustained elevation of glucocorticoid levels, which can directly suppress BDNF gene expression in hippocampal neurons. This suppression occurs through the binding of glucocorticoids to specific response elements in the BDNF promoter region.[82]

Epigenetic modifications represent another crucial mechanism through which stress alters BDNF expression. Chronic stress has been shown to induce epigenetic changes, such as increased DNA methylation and histone modifications, in the BDNF gene promoter regions. These epigenetic alterations can lead to long-lasting suppression of BDNF expression, potentially explaining the persistent effects of stress on hippocampal function.[83]

MicroRNA regulation has emerged as another important pathway in stress-induced BDNF alterations. Stress has been shown to upregulate specific microRNAs, such as miR-124, that target BDNF mRNA, thereby reducing its translation and protein levels.[84]

Neuroinflammation and oxidative stress, both consequences of chronic stress, also contribute to BDNF dysregulation. Stress-induced increases in pro-inflammatory cytokines can interfere with BDNF signaling and suppress its expression. Similarly, oxidative stress can impair BDNF synthesis and signaling through various mechanisms, including damage to cellular components and alteration of signaling pathways.

The intricate relationship between stress, neurotransmitter systems, and BDNF further complicates the picture. Stress affects various neurotransmitter systems, including serotonin and glutamate, which in turn modulate BDNF expression and signaling.

At the molecular level, stress can disrupt the binding of BDNF to its primary receptor, tropomyosin receptor kinase B (TrkB), and alter downstream signaling cascades. This disruption affects various intracellular pathways, including the MAPK/ERK, PI3K/Akt, and PLCγ pathways, which are crucial for neuroplasticity and cell survival.

Understanding these mechanisms and pathways provides potential targets for interventions aimed at mitigating the negative effects of stress on BDNF and hippocampal function. Strategies such as antidepressant treatment, regular exercise, and environmental enrichment have shown promise in restoring BDNF levels and promoting hippocampal neuroplasticity in the context of chronic stress.

The stress-induced reduction in BDNF and disruption of its signaling pathways have several consequences in the HC: Reduced Neurogenesis: BDNF is crucial for adult hippocampal neurogenesis. Its reduction leads to decreased proliferation and survival of new neurons in the dentate gyrus.

Synaptic Plasticity Impairment: Lowered BDNF levels result in reduced long-term potentiation (LTP) and impaired synaptic plasticity, affecting learning and memory processes. Dendritic Atrophy: Decreased BDNF signaling contributes to the dendritic atrophy observed in hippocampal neurons under chronic stress conditions.

Increased Vulnerability to Neuronal Damage. The neuroprotective effects of BDNF are diminished, making hippocampal neurons more susceptible to various insults.

Potential therapeutic implications. Understanding the mechanisms of stress-induced BDNF alterations opens avenues for potential therapeutic interventions:

BDNF Mimetics. Development of small molecules that can mimic BDNF's effects and cross the blood-brain barrier.

Epigenetic Modulators. Compounds that can reverse stress-induced epigenetic modifications of the BDNF gene.

Anti-inflammatory Approaches. Strategies to mitigate stress-induced neuroinflammation, indirectly supporting BDNF expression.

TrkB Agonists. Development of drugs that can directly activate or enhance TrkB signaling.

Lifestyle Interventions. Promotion of activities known to increase BDNF levels, such as exercise and enriched environments, as complementary therapies.[85]

In conclusion, stress-induced alterations in BDNF expression and signaling in the HC represent a critical mechanism underlying the detrimental effects of chronic stress on brain function. These changes in BDNF dynamics offer both an explanation for stress-related cognitive impairments and potential targets for therapeutic interventions.

Neuroinflammation. Exposure to factors like radiation can trigger the release of inflammatory cytokines (e.g., IL-1, IL-6, TNFα) in the HC, leading to neuroinflammation. These

inflammatory cytokines can modulate neural progenitor proliferation, survival, and synapse formation, potentially disrupting hippocampal neurogenesis and synaptic plasticity. Neuroinflammation can also impair neurotransmitter systems such as serotonin and acetylcholine, which are crucial for cognitive functions and mood regulation. The HC is particularly vulnerable to the effects of neuroinflammation due to its high density of cytokine receptors and its role in neurogenesis and neurotransmitter regulation. Persistent neuroinflammation in the HC can contribute to cognitive deficits, mood disorders, and potentially neurodegenerative processes, highlighting the significance of developing strategies to mitigate inflammation-induced neural damage.[86]

In conclusion, neuroinflammation triggered by factors such as radiation significantly impacts hippocampal health. The release of inflammatory cytokines, including IL-1, IL-6, and TNFα, disrupts neural progenitor proliferation, survival, and synapse formation, thereby impairing neurogenesis and synaptic plasticity. This inflammation also affects neurotransmitter systems that are critical for cognitive functions and mood regulation. Given the HC's vulnerability due to its high density of cytokine receptors, persistent neuroinflammation can lead to cognitive deficits and mood disorders. Therefore, developing strategies to mitigate inflammation-induced damage is essential for maintaining hippocampal function and overall brain health.

Oxidative stress. Various environmental exposures, such as radiation and toxins, can increase the production of reactive oxygen species (ROS) and cause oxidative damage to hippocampal cells. Oxidative stress may induce neuronal death, lipid peroxidation, and DNA damage in the HC, impairing its normal function. The HC is particularly vulnerable to oxidative stress due to its high metabolic rate and relatively low antioxidant defense mechanisms. Interventions involving antioxidant treatments and compounds with free radical scavenging properties have shown the potential to mitigate the adverse effects of oxidative stress on the HC caused by certain environmental exposures. Maintaining a balance between oxidants and antioxidants in the HC is crucial for preserving neuronal integrity, synaptic plasticity, and cognitive function, particularly in challenging environments. Understanding the mechanisms of oxidative stress and developing targeted antioxidant therapies could be beneficial for protecting the HC and cognitive abilities during spaceflight and other extreme conditions.[87]

In conclusion, oxidative stress resulting from environmental exposures such as radiation and toxins poses significant risks to hippocampal health. Increased production of reactive oxygen species (ROS) can lead to neuronal death, lipid peroxidation, and DNA damage, thereby impairing hippocampal function. The HC is particularly susceptible due to its high metabolic rate and limited antioxidant defenses. Antioxidant treatments and compounds with free radical scavenging properties have shown promise in mitigating these adverse effects. Maintaining a balance between oxidants and antioxidants is essential for preserving neuronal integrity, synaptic plasticity, and cognitive function, especially in challenging environments. Understanding the mechanisms of oxidative stress and developing targeted antioxidant therapies could help protect the HC and cognitive abilities during spaceflight and other extreme conditions.

Epigenetic changes. Environmental exposures can modify epigenetic markers, like DNA methylation and histone acetylation, in genes involved in hippocampal function. These epigenetic changes can alter the expression of genes responsible for neurogenesis, synaptic plasticity, and memory formation in the HC. Epigenetic mechanisms play a crucial role in regulating gene expression patterns in response to environmental cues, thereby influencing hippocampal development, neuronal connectivity, and cognitive processes. The HC is particularly susceptible to epigenetic dysregulation due to its function in learning and memory and its sensitivity to various environmental stimuli. Being aware of the epigenetic landscape of the HC and its modulation by environmental factors can provide insights into cognitive impairments and neurodegenerative disorders associated with exposure to extreme conditions. Targeting epigenetic pathways may offer potential therapeutic avenues for mitigating the detrimental effects of environmental exposures on hippocampal function and cognitive abilities, particularly in the context of space exploration.[88]

In conclusion, environmental exposures can lead to epigenetic changes, such as DNA methylation and histone acetylation, which impact genes critical for hippocampal function. These changes can alter the expression of genes essential for neurogenesis, synaptic plasticity, and memory formation. The HC is particularly vulnerable to epigenetic dysregulation due to its crucial role in learning and memory, as well as its sensitivity to environmental stimuli. Understanding the epigenetic landscape and its modulation can provide valuable insights into cognitive impairments and neurodegenerative disorders related to extreme conditions.

Neurogenesis disruption

Various environmental exposures can suppress the proliferation, differentiation, and survival of neural progenitor cells in the dentate gyrus of the HC. This disruption of adult hippocampal neurogenesis can impair learning, memory, and mood regulation, as newborn neurons in the HC play a crucial role in these processes. Exposures can also affect glutamate and gamma-aminobutyric acid (GABA) receptors, dendritic spine morphology, and the expression of neurotrophic factors like brain-derived neurotrophic factor (BDNF), all of which are important for synaptic plasticity and hippocampal function. The HC is particularly vulnerable to disruptions in neurogenesis and plasticity due to its unique ability to generate new neurons throughout life and its role in learning and memory consolidation. Mitigating the effects of environmental exposures on hippocampal neurogenesis and plasticity is essential for preserving cognitive abilities and preventing neurodegenerative processes, especially in extreme environments like spaceflight.[89–91]

In conclusion, various environmental exposures can significantly disrupt neurogenesis in the dentate gyrus of the HC, inhibiting the proliferation, differentiation, and survival of neural progenitor cells. This disruption adversely affects learning, memory, and mood regulation, as newborn neurons

are integral to these processes. Environmental factors can also impact glutamate and GABA receptors, dendritic spine morphology, and the expression of neurotrophic factors like BDNF, all of which are vital for synaptic plasticity and overall hippocampal function. Given the HC's unique capacity for lifelong neurogenesis and its central role in learning and memory, protecting against these disruptions is crucial, especially in challenging environments such as spaceflight. Understanding the molecular mechanisms behind exposure-induced neurogenesis disruptions will aid in developing targeted interventions to safeguard brain function during space exploration missions.

Conclusion. This review demonstrates the profound impact of environmental exposures on hippocampal structure and function. The HC, crucial for learning, memory, and spatial navigation, exhibits remarkable plasticity in response to various environmental factors, including stress, noise pollution, sleep deprivation, and microgravity. Key findings from animal and human studies reveal that these exposures can significantly alter hippocampal volume, architecture, neurogenesis, synaptic plasticity, and gene expression. The review highlights critical periods of vulnerability across the lifespan, emphasizing the particular sensitivity of the developing and aging HC to environmental influences. The cognitive and behavioral consequences of exposure-induced hippocampal remodeling substantially affect memory formation, spatial navigation, and emotional regulation. Underlying mechanisms, including glucocorticoid signaling, epigenetic modifications, oxidative stress, and neural circuit adaptations, have been elucidated, providing potential targets for intervention. This comprehensive overview underscores the importance of environmental factors in understanding hippocampal function and cognitive health.

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References

1. Schröder H, Moser N, Huggenberger S. The Mouse HC BT - Neuroanatomy of the Mouse: An Introduction. In: Schröder H, Moser N, Huggenberger S, editors. Cham (Germany): Springer International Publishing; 2020. p. 267–88.
2. Roesler R, Parent MB, LaLumiere RT, McIntyre CK. Amygdala-hippocampal interactions in synaptic plasticity and memory formation. ***Neurobiol Learn Mem [Internet]*** 2021;184:107490.
3. Banwinkler M, Theis H, Prange S, van Eimeren T. Imaging the Limbic System in Parkinson's Disease—A Review of Limbic Pathology and Clinical Symptoms. ***Brain Sci*** 2022; 12: 1248.
4. Roesler R, McGaugh JL. The Entorhinal Cortex as a Gateway for Amygdala Influences on Memory Consolidation. ***Neuroscience*** 2022: 497: 86-96.
5. Nomoto M, Murayama E, Ohno S, Okubo-Suzuki R, Muramatsu S ichi, Inokuchi K. Hippocampus as a sorter and reverberatory integrator of sensory inputs. ***Nature Communications*** 2022; 13: 7413.
6. Clemente L, Gasparre D, Alfeo F, Battista F, Abbatantuono C, Curci A, et al. Theory of Mind and Executive Functions in Individuals with Mild Cognitive Impairment or Healthy Aging. ***Brain Sci*** 2023;13 :1356.
7. Lee MT, Peng WH, Kan HW, Wu CC, Wang DW, Ho YC. Neurobiology of Depression: Chronic Stress Alters the Glutamatergic System in the Brain—Focusing on AMPA Receptor. ***Biomedicines*** 2022; 10: 1005.
8. Rezaei S, Seyedmirzaei H, Gharepapagh E, Mohagheghfard F, Hasankhani Z, Karbasi M, et al. Effect of spaceflight experience on human brain structure, microstructure, and function: systematic review of neuroimaging studies. ***Brain Imaging Behav*** 2024; 10.1007/s11682-024-00894-7.
9. Sanacora G, Yan Z, Popoli M. The stressed synapse 2.0: pathophysiological mechanisms in stress-related neuropsychiatric disorders. ***Nat Rev Neurosci*** 2022; 23: 86-103.
10. Saeedi M, Rashidy-Pour A. Association between chronic stress and Alzheimer's disease: Therapeutic effects of Saffron. ***Biomed Pharmacother*** 2021; 133: 110995.
11. Hyer MM, Shaw GA, Goswamee P, Dyer SK, Burns CM, Soriano E, et al. Chronic adolescent stress causes sustained impairment of cognitive flexibility and hippocampal synaptic strength in female rats. ***Neurobiol Stress*** 2021; 14: 100303.
12. Surget A, Belzung C. Adult hippocampal neurogenesis shapes adaptation and improves stress response: a mechanistic and integrative perspective. ***Mol Psychiatry*** 2022; 27: 403-421.
13. Culig L, Chu X, Bohr VA. Neurogenesis in aging and age-related neurodegenerative diseases. ***Ageing Res Rev*** 2022; 78: 101636.
14. Bai X, Wang B, Cui Y, Tian S, Zhang Y, You L, et al. Hepcidin deficiency impairs hippocampal neurogenesis and mediates brain atrophy and memory decline in mice. ***J Neuroinflammation*** 2024; 21: 15.
15. Knezevic E, Nenic K, Milanovic V, Knezevic NN. The Role of Cortisol in Chronic Stress, Neurodegenerative Diseases, and Psychological Disorders. ***Cells*** 2023; 12: 2726.
16. Atrooz F, Alkadhi KA, Salim S. Understanding stress: Insights from rodent models. ***Curr Res Neurobiol*** 2021; 2: 100013.
17. Wang W, Zhao F, Ma X, Perry G, Zhu X. Mitochondria dysfunction in the pathogenesis of Alzheimer's disease: recent advances. ***Mol Neurodegener*** 2020; 15: 30.
18. Pechtel P, Pizzagalli DA. Effects of early life stress on cognitive and affective function: an integrated review of human literature. ***Psychopharmacology (Berl)*** 2011; 214: 55-70. 10.1007/s00213-010-2009-2.
19. Leschik J, Lutz B, Gentile A. Stress-related dysfunction of adult hippocampal neurogenesis—an attempt for understanding resilience? ***Int J Mol Sci*** 2021; 22: 7339.
20. Granak S, Hoschl C, Ovsepian SV. Dendritic spine remodeling and plasticity under general anesthesia. ***Brain Struct Funct*** 2021; 226: 2001-2017.
21. Xing B, Barbour AJ, Vithayathil J, Li X, Dutko S, Fawcett-Patel J, et al. Reversible synaptic adaptations in a subpopulation of murine hippocampal neurons following early-life seizures. ***J Clin Invest*** 2024; 134: e175167.
22. Franchini L, Carrano N, Di Luca M, Gardoni F. Synaptic GluN2A-Containing NMDA Receptors: From Physiology to Pathological Synaptic Plasticity. ***Int J Mol Sci*** 2020; 21: 1538.
23. Dion A, Muñoz PT, Franklin TB. Epigenetic mechanisms impacted by chronic stress across the rodent lifespan. ***Neurobiol Stress*** 2022; 17: 100434.

24. Catale C, Gironda S, Lo Iacono L, Carola V. Microglial Function in the Effects of Early-Life Stress on Brain and Behavioral Development. ***J Clin Med*** 2020; 9: 468.
25. Litwiniuk A, Bik W, Kalisz M, Baranowska-Bik A. Inflammasome NLRP3 Potentially Links Obesity-Associated Low-Grade Systemic Inflammation and Insulin Resistance with Alzheimer's Disease. ***Anna Litwiniuk*** 2021; 22(11): 5603.
26. Milligan Armstrong A, Porter T, Quek H, White A, Haynes J, Jackaman C, et al. Chronic stress and Alzheimer's disease: the interplay between the hypothalamic–pituitary–adrenal axis, genetics, and microglia. ***Biol Rev Camb Philos Soc*** 2021; 96: 2209-2228.
27. Zefferino R, Di Gioia S, Conese M. Molecular links between endocrine, nervous and immune system during chronic stress. ***Brain Behav*** 2021; 11: e01960.
28. Lossi L, Castagna C, Merighi A. An Overview of the Epigenetic Modifications in the Brain under Normal and Pathological Conditions. ***Int J Mol Sci*** 2024; 25: 3881.
29. Kim EJ, Kim JJ. Neurocognitive effects of stress: a metaparadigm perspective. ***Mol Psychiatry*** 2023; 28: 2750-2763.
30. Sanaeifar F, Pourranjbar S, Pourranjbar M, Ramezani S, Mehr SR, Wadan AHS, et al. Beneficial effects of physical exercise on cognitive-behavioral impairments and brain-derived neurotrophic factor alteration in the limbic system induced by neurodegeneration. ***Exp Gerontol*** 2024; 195: 112539.
31. Hahad O, Bayo Jimenez MT, Kuntic M, Frenis K, Steven S, Daiber A, et al. Cerebral consequences of environmental noise exposure. ***Environ Int*** 2022; 165: 107306.
32. Lee TH, Devaki M, Formolo DA, Rosa JM, Cheng ASK, Yau SY. Effects of Voluntary Wheel Running Exercise on Chemotherapy-Impaired Cognitive and Motor Performance in Mice. ***Int J Environ Res Public Health*** 2023; 20: 5371.
33. Li B, Mao Q, Zhao N, Xia J, Zhao Y, Xu B. Treadmill exercise overcomes memory deficits related to synaptic plasticity through modulating ionic glutamate receptors. Behav Brain Res 2021; 414: 113502.
34. Sun L, Wang G, Wu Z, Xie Y, Zhou L, Xiao L, et al. Swimming exercise reduces the vulnerability to stress and contributes to the AKT/GSK3β/CRMP2 pathway and microtubule dynamics mediated protective effects on neuroplasticity in male C57BL/6 mice. ***Pharmacol Biochem Behav*** 2021; 211: 173285.
35. Frodl T, Strehl K, Carballedo A, Tozzi L, Doyle M, Amico F, et al. Aerobic exercise increases hippocampal subfield volumes in younger adults and prevents volume decline in the elderly. ***Brain Imaging Behav*** 2020; 14: 1577-1587.
36. Won J, Callow DD, Pena GS, Jordan LS, Arnold-Nedimala NA, Nielson KA, et al. Hippocampal Functional Connectivity and Memory Performance After Exercise Intervention in Older Adults with Mild Cognitive Impairment. ***J Alzheimer's Dis.*** 2021; 82: 1015-1031.
37. Hugues N, Pellegrino C, Rivera C, Berton E, Pin-Barre C, Laurin J. Is High-Intensity Interval Training Suitable to Promote Neuroplasticity and Cognitive Functions after Stroke? ***Int J Mol Sci*** 2021; 22: 3003.
38. Wang H, Xu X, Xu X, Gao J, Zhang T. Enriched Environment and Social Isolation Affect Cognition Ability via Altering Excitatory and Inhibitory Synaptic Density in Mice HC. ***Neurochem Res*** 2020; 45: 2417-2432.
39. Khodadadegan MA, Negah SS, Saheb M, Gholami J, Arabi MH, Hajali V. Combination effect of exercise and environmental enrichment on cognitive functions and hippocampal neurogenesis markers of rat. ***Neuroreport*** 2021; 32: 1234-1240.
40. Dahan L, Rampon C, Florian C. Age-related memory decline, dysfunction of the HC and therapeutic opportunities. ***Prog Neuropsychopharmacol Biol Psychiatry*** 2020; 102: 109943.
41. Key MN, Szabo-Reed AN. Impact of Diet and Exercise Interventions on Cognition and Brain Health in Older Adults: A Narrative Review. ***Nutrients*** 2023; 15: 2495.
42. Arora S, Santiago JA, Bernstein M, Potashkin JA. Diet and lifestyle impact the development and progression of Alzheimer's dementia. ***Front Nutr*** 2023; 10: 1213223.
43. Molina SJ, Lietti ÁE, Carreira Caro CS, Buján GE, Guelman LR. Effects of early noise exposure on hippocampal-dependent behaviors during adolescence in male rats: influence of different housing conditions. ***Anim Cogn*** 2022; 25: 103-120. 10.1007/s10071-021-01540-1.
44. Duffner LA, DeJong NR, Jansen JFA, Backes WH, de Vugt M, Deckers K, et al. Associations between social health factors, cognitive activity and neurostructural markers for brain health – A systematic literature review and meta-analysis. ***Ageing Res Rev*** 2023; 89: 101986.
45. van der Velpen IF, Melis RJF, Perry M, Vernooij-Dassen MJF, Ikram MA, Vernooij MW. Social Health Is Associated With Structural Brain Changes in Older Adults: The Rotterdam Study. ***Biol Psychiatry Cogn Neurosci Neuroimaging*** 2022; 7(7): 659-668.
46. Dong TN, Kramár EA, Beardwood JH, Al-Shammari A, Wood MA, Keiser AA. Temporal endurance of exercise-induced benefits on HC-dependent memory and synaptic plasticity in female mice. ***Neurobiol Learn Mem*** 2022; 194: 107658. .
47. Thérond A, Pezzoli P, Abbas M, Howard A, Bowie CR, Guimond S. The Efficacy of Cognitive Remediation in Depression: A Systematic Literature Review and Meta-Analysis. ***J Affect Disord*** 2021; 284: 238-246.
48. Joss D, Teicher MH, Lazar SW. Beneficial effects of mindfulness-based intervention on hippocampal volumes and episodic memory for childhood adversity survivors. ***J Affect Disord Reports*** 2024; 16: 100769.
49. Guidotti R, Del Gratta C, Perrucci MG, Romani GL, Raffone A. Neuroplasticity within and between Functional Brain Networks in Mental Training Based on Long-Term Meditation. ***Brain Sci*** 2021; 11: 1086.
50. Kaliszewska A, Allison J, Martini M, Arias N. Improving Age-Related Cognitive Decline through Dietary Interventions Targeting Mitochondrial Dysfunction. ***Int J Mol Sci*** 2021; 22: 3574.
51. Fadó R, Molins A, Rojas R, Casals N. Feeding the Brain: Effect of Nutrients on Cognition, Synaptic Function, and AMPA Receptors. ***Nutrients*** 2022; 14: 4137.
52. Ghaddar B, Veeren B, Rondeau P, Bringart M, Lefebvre d'Hellencourt C, Meilhac O, et al. Impaired brain homeostasis and neurogenesis in diet-induced overweight zebrafish: a preventive role from A. borbonica extract. ***Sci Rep*** 2020; 10: 14496. 10.1038/s41598-020-71402-2.
53. Semenov DG, Belyakov A V. BDNF and Senile Cognitive Decline. ***Neurosci Behav Physiol*** 2022; 52: 287-296.
54. Numakawa T, Odaka H. The Role of Neurotrophin Signaling in Age-Related Cognitive Decline and Cognitive Diseases. ***Int J Mol Sci*** 2022; 23: 7726.
55. Gisabella B, Babu J, Valeri J, Rexrode L, Pantazopoulos H. Sleep and memory consolidation dysfunction in psychiatric disorders: evidence for the involvement of extracellular matrix molecules. ***Front Neurosci*** 2021; 15: 646678.

56. Yan YD, Chen YQ, Wang CY, Ye CB, Hu ZZ, Behnisch T, et al. Chronic modafinil therapy ameliorates depressive-like behavior, spatial memory and hippocampal plasticity impairments, and sleep-wake changes in a surgical mouse model of menopause. ***Transl Psychiatry*** 2021; 11: 116.
57. Rabin JS. Behavioral Epigenetics: The Underpinnings of Political Psychology BT - The Psychology of Political Behavior in a Time of Change. In: Sinnott JD, Rabin JS, editors. Cham (Germany): Springer International Publishing; 2021. p. 55–96.
58. Marzola P, Melzer T, Pavesi E, Gil-Mohapel J, Brocardo PS. Exploring the Role of Neuroplasticity in Development, Aging, and Neurodegeneration. ***Brain Sci*** 2023; 13: 1610.
59. Nabi M, Tabassum N. Role of Environmental Toxicants on Neurodegenerative Disorders. ***Front Toxicol*** 2022: 4: 837579.
60. Desai RI, Limoli CL, Stark CEL, Stark SM. Impact of spaceflight stressors on behavior and cognition: A molecular, neurochemical, and neurobiological perspective. ***Neurosci Biobehav Rev*** 2022; 138: 104676.
61. Stahn AC, Kühn S. Brains in space: the importance of understanding the impact of long-duration spaceflight on spatial cognition and its neural circuitry. Cogn Process 2021; 22: 105-114.
62. Rocha M, Wang D, Avila-Quintero V, Bloch MH, Kaffman A. Deficits in hippocampal-dependent memory across different rodent models of early life stress: systematic review and meta-analysis. ***Transl Psychiatry*** 2021; 11: 231.
63. Krukowski K, Grue K, Becker M, Elizarraras E, Frias ES, Halvorsen A, et al. The impact of deep space radiation on cognitive performance: From biological sex to biomarkers to countermeasures. ***Sci Adv*** 2024; 7: eabg6702.
64. Julian JB, Doeller CF. Remapping and realignment in the human hippocampal formation predict context-dependent spatial behavior. ***Nat Neurosci*** 2021; 24: 863-872.
65. Ahmed SS, Goswami N, Sirek A, Green DA, Winnard A, Fiebig L, et al. Systematic review of the effectiveness of standalone passive countermeasures on microgravity-induced physiologic deconditioning. ***npj Microgravity*** 2024; 10: 48.
66. Navarro-Tableros V, Gomez Y, Brizzi MF, Camussi G. Generation of Human Stem Cell-Derived Pancreatic Organoids (POs) for Regenerative Medicine BT - Cell Biology and Translational Medicine, Volume 6: Stem Cells: Their Heterogeneity, Niche and Regenerative Potential. In: Turksen K, editor. Cham (Germany): Springer International Publishing; 2020. p. 179-220.
67. Ferranti F, Del Bianco M, Pacelli C. Advantages and Limitations of Current Microgravity Platforms for Space Biology Research. ***Appl Sci*** 2021; 11: 68.
68. Fernandez LMJ, Lüthi A. Sleep Spindles: Mechanisms and Functions. ***Physiol Rev*** 2020; 100: 805-868.
69. Kim T, Kim S, Kang J, Kwon M, Lee SH. The Common Effects of Sleep Deprivation on Human Long-Term Memory and Cognitive Control Processes. ***Front Neurosci*** 2022; 16: 883848.
70. Chen P, Ban W, Wang W, You Y, Yang Z. The Devastating Effects of Sleep Deprivation on Memory: Lessons from Rodent Models. ***Clocks Sleep*** 2023; 5: 276-294.
71. Schneider F, Horowitz A, Lesch KP, Dandekar T. Delaying memory decline: different options and emerging solutions. ***Transl Psychiatry*** 2020; 10: 13.
72. Sharma P, Tulsawani R. Ganoderma lucidum aqueous extract prevents hypobaric hypoxia induced memory deficit by modulating neurotransmission, neuroplasticity and maintaining redox homeostasis. ***Sci Rep*** 2020; 10: 8944.
73. Li X, Wang J. Abnormal neural activities in adults and youths with major depressive disorder during emotional processing: a meta-analysis. ***Brain Imaging Behav*** 2021; 15: 1134-1154.
74. Kuijer EJ, Steenbergen L. The microbiota-gut-brain axis in HC-dependent learning and memory: current state and future challenges. ***Neurosci Biobehav Rev*** 2023; 152: 105296.
75. Bolsius YG, Zurbriggen MD, Kim JK, Kas MJ, Meerlo P, Aton SJ, et al. The role of clock genes in sleep, stress and memory. ***Biochem Pharmacol*** 2021; 191: 114493.
76. von Gall C. The Effects of Light and the Circadian System on Rhythmic Brain Function. ***Int J Mol Sci*** 2022; 23: 2778.
77. Segi-Nishida E, Suzuki K. Regulation of adult-born and mature neurons in stress response and antidepressant action in the dentate gyrus of the the hippocampus. ***Neurosci Res*** 2022; S0168-0102: 00233-00234.
78. Gupta S, Guleria RS. Involvement of Nuclear Factor-κB in Inflammation and Neuronal Plasticity Associated with Post-Traumatic Stress Disorder. ***Cells*** 2022; 11: 2034.
79. Komoltsev IG, Gulyaeva NV. Brain Trauma, Glucocorticoids and Neuroinflammation: Dangerous Liaisons for the Hippocampus. ***Biomedicines*** 2022; 10: 1139.
80. Murawska-Ciałowicz E, Wiatr M, Ciałowicz M, Gomes de Assis G, Borowicz W, Rocha-Rodrigues S, et al. BDNF Impact on Biological Markers of Depression—Role of Physical Exercise and Training. ***Int J Environ Res Public Health*** 2021;18:7553.
81. Correia AS, Cardoso A, Vale N. BDNF Unveiled: Exploring Its Role in Major Depression Disorder Serotonergic Imbalance and Associated Stress Conditions. ***Pharmaceutics*** 2023; 15: 2081.
82. Rana T, Behl T, Sehgal A, Srivastava P, Bungau S. Unfolding the Role of BDNF as a Biomarker for Treatment of Depression. ***J Mol Neurosci*** 2021; 71: 2008-2021.
83. Yang T, Nie Z, Shu H, Kuang Y, Chen X, Cheng J, et al. The Role of BDNF on Neural Plasticity in Depression. ***Front Cell Neurosci*** 2020; 14: 82.
84. De Assis GG, Murawska-Ciałowicz E. BDNF Modulation by microRNAs: An Update on the Experimental Evidence. ***Cells*** 2024; 13: 880.
85. Colucci-D'Amato L, Speranza L, Volpicelli F. Neurotrophic Factor BDNF, Physiological Functions and Therapeutic Potential in Depression, Neurodegeneration and Brain Cancer. Int J Mol Sci 2020; 21: 7777.
86. Liu Q, Huang Y, Duan M, Yang Q, Ren B, Tang F. Microglia as Therapeutic Target for Radiation-Induced Brain Injury. ***Int J Mol Sci*** 2022; 23: 8286.
87. El-Missiry MA, Shabana S, Ghazala SJ, Othman AI, Amer ME. Melatonin exerts a neuroprotective effect against γ-radiation-induced brain injury in the rat through the modulation of neurotransmitters, inflammatory cytokines, oxidative stress, and apoptosis. ***Environ Sci Pollut Res Int*** 2021; 28: 31108-31121.
88. Saw G, Tang FR. Epigenetic regulation of the HC, with special reference to radiation exposure. ***Int J Mol Sci*** 2020; 21: 9514.
89. Gulyaeva NV. Glucocorticoid Regulation of the GlutamatergicSynapse: Mechanisms of Stress-Dependent Neuroplasticity. ***J Evol Biochem Physiol*** 2021; 57: 564-576.
90. Sakimoto Y, Oo PM, Goshima M, Kanehisa I, Tsukada Y, Mitsushima D. Significance of GABAA Receptor for Cognitive Function and Hippocampal Pathology. ***Int J Mol Sci*** 2021; 22: 12456.
91. Sbrini G, Brivio P, Bosch K, Homberg JR, Calabrese F. Enrichment Environment Positively Influences Depression- and Anxiety-Like Behavior in Serotonin Transporter Knockout Rats through the Modulation of Neuroplasticity, Spine, and GABAergic Markers. ***Genes (Basel)*** 2020; 11: 1248.