INSIGHTS-JOURNAL OF
HEALTH AND REHABILITATION

INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

COMPARATIVE NEUROBIOLOGY OF STEROIDS AND STRESS: IMPLICATIONS FOR MEMORY IN HUMANS AND ANIMALS: A NARRATIVE REVIEW

Narrative Review

Abu Sulman[1], Talha Ahmad[2], Hafiz Aamir Ali Kharl[1]*, Muhammad Dawood[3], Raakia Anam Saeed[4], Rida Fatima[5], Nouman Tariq[6]*, Badar Rasool[7], Shahreen Riaz[8], Mahwish Salman[9], Anam Tariq[9]

[1]Department of Pharmacy, Faculty of Health and Pharmaceutical Sciences, University of Agriculture, Faisalabad, Pakistan.
[2]School of Science and Engineering (Centre of Anatomy and Human Identification), University of Dundee, Scotland, United Kingdom.
[3]Sharif Medical City Hospital, Lahore, Pakistan.
[4]Faculty of Rehabilitation and Allied Health Sciences, RIPHA International University, Islamabad, Pakistan.
[5]Faisalabad Medical University, Faisalabad, Pakistan.
[6]Faculty of Veterinary Science, University of Agriculture, Faisalabad, Pakistan.
[7]Department of Wildlife and Ecology, University of Veterinary and Animal Sciences, Lahore, Pakistan.
[8]Department of Chemistry, University of Agriculture, Faisalabad, Pakistan.
[9]Department of Biochemistry, Government College University Faisalabad, Faisalabad, Pakistan.

Corresponding Author: Hafiz Aamir Ali Kharl, Department of Pharmacy, Faculty of Health and Pharmaceutical Sciences, University of Agriculture, Faisalabad, Pakistan, hafiz.kharl@uaf.edu.pk

Nouman Tariq, Faculty of Veterinary Science, University of Agriculture, Faisalabad, Pakistan, noumantariq0208@gmail.com

Acknowledgement: The authors sincerely acknowledge the contributions of all researchers whose work provided the foundation for this review.

Conflict of Interest: None

Grant Support & Financial Support: None

ABSTRACT

Background: Steroids and stress hormones are central regulators of cognitive processes, influencing memory formation, consolidation, and retrieval across both humans and animals. While acute stress responses may transiently enhance attention and recall, chronic activation of the hypothalamic–pituitary–adrenal (HPA) axis is strongly associated with impaired cognition, reduced memory flexibility, and greater susceptibility to psychiatric and neurological disorders. Understanding these mechanisms has important implications for clinical and veterinary medicine, where corticosteroid use and stress-related conditions remain highly relevant.

Objective: This narrative review aims to provide a comparative perspective on the neurobiology of memory, the physiology of stress, and the role of steroid hormones in shaping cognitive outcomes, highlighting translational insights between human and veterinary contexts.

Main Discussion Points: The review synthesizes evidence from 2018 to 2025, covering the neurobiological basis of memory systems, the mechanistic pathways of stress responses, and the modulatory roles of glucocorticoids. Comparative analysis demonstrates shared mechanisms across species, with differences in stress physiology underscoring the need for careful extrapolation. Animal studies are shown to be critical in understanding human memory disorders such as Cushing's syndrome and post-traumatic stress disorder. Therapeutic strategies, including pharmacological agents, selective glucocorticoid receptor modulators, behavioral interventions, and environmental modifications, are discussed alongside existing limitations and knowledge gaps.

Conclusion: Findings highlight the duality of steroids and stress in enhancing or impairing memory depending on context, while emphasizing the translational value of animal models. Integrative approaches combining neurobiology, pharmacology, and behavioral science are essential to advance therapeutic strategies and protect cognitive health under stress.

Keywords: Neurobiology; Stress; Steroids; Memory; Glucocorticoids; Narrative Review.

INTRODUCTION

Stress is increasingly recognized as a complex physiological response that enables individuals to adapt to environmental and internal challenges. Primarily orchestrated through the hypothalamic–pituitary–adrenal (HPA) axis and the locus coeruleus–norepinephrine (LC–NE) system, stress responses are adaptive in the short term but become detrimental when persistent (1,2). Chronic stress has emerged as a global health concern, with wide-ranging implications for mental and physical well-being, contributing to a significant socioeconomic burden (3). A recent survey by the American Psychological Association highlighted the pervasiveness of stress across all life stages, underscoring its impact on daily functioning (4). Recognizing its significance, the World Health Organization incorporated stress-related disorders into its Comprehensive Mental Health Action Plan 2013–2030 to improve prevention and management strategies worldwide (5). Mounting evidence suggests that sustained stress exposure is strongly linked to neurological conditions, including cognitive impairments, psychiatric disorders, neurodegenerative diseases, stroke, and dementia (6–10). These conditions remain leading contributors to global disability, yet current pharmacological interventions often fail to provide sufficient relief (11,12). This underscores the urgent need to understand the neurobiological mechanisms by which stress shapes disease risk and progression.

At the microscopic and systems levels, stress disrupts hippocampal integrity and neural plasticity. Experimental studies reveal alterations in dendritic architecture, spike activity, neurogenesis, and extracellular signaling, alongside an acceleration of neurodegenerative processes (13). Behaviorally, these changes manifest as impairments in memory-dependent cognition and increased reliance on emotion-driven responses, largely mediated by elevated glucocorticoids acting on corticosteroid receptors in the hippocampus (12,13). Stress also reconfigures communication between memory systems, particularly the hippocampal and striatal circuits, thereby influencing learning, retrieval, and flexibility (14–16). Beyond glucocorticoids and catecholamines, emerging data suggest that neuromodulators such as endocannabinoids interact with these pathways, modulating network activity and often biasing recollection toward emotionally salient memories while reducing short-term cognitive adaptability (17). Despite extensive literature, key questions remain regarding how stress hormones and neuromodulators jointly regulate memory processes across neural circuits and how these mechanisms contribute to long-term neurobehavioral outcomes. Addressing these gaps is essential for developing innovative therapeutic strategies targeting stress-induced cognitive dysfunctions. The objective of this study is therefore to investigate the comparative neurobiology of stress and steroid signaling in relation to memory, aiming to clarify mechanistic pathways that may inform preventive and therapeutic approaches for stress-related neurological disorders.

INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

THEMATIC DISCUSSION

Neurobiology of Memory

Memory in humans and animals is built on the same fundamental systems, though species-specific adaptations influence learning, behavior, and the manifestation of memory dysfunctions. Memory is broadly classified into explicit and implicit forms, and is processed in sequential stages, beginning from sensory registration, to short-term retention, and finally consolidation into long-term storage (4). Key brain structures including the hippocampus, amygdala, and prelimbic prefrontal cortex are deeply involved in these processes (5). The orchestration of memory depends on the coordinated action of multiple neurotransmitter systems—acetylcholine, dopamine, norepinephrine, serotonin, glutamate, and GABA—each exerting distinct yet overlapping influences on encoding, consolidation, and retrieval. These neurochemical interactions form a tightly regulated network, where imbalances may predispose to memory decline and cognitive disorders (6).

Physiology of Stress

Stress is defined as any internal or external challenge that disturbs physiological homeostasis. The body's stress response involves the integration of endocrine, nervous, and immune systems, primarily through the hypothalamic–pituitary–adrenal (HPA) axis, the sympathetic–adreno–medullary (SAM) system, and immune signaling pathways (7). While stress responses are designed to enhance survival by mobilizing energy and sharpening cognition, chronic or maladaptive activation produces detrimental outcomes.

Acute Stress: Acute stress represents a short-term physiological reaction to sudden stimuli. It activates the emergency "fight-or-flight" response, leading to elevated heart rate, secretion of catecholamines such as epinephrine, and heightened alertness. These transient changes can be adaptive and beneficial for immediate survival.

Chronic Stress: Chronic stress arises from prolonged exposure to stressors. Unlike acute stress, its persistent activation of the HPA axis results in allostatic overload, predisposing individuals to cardiovascular disease, depression, anxiety, and immune dysfunction. Its long-term impact on neural circuits contributes to progressive cognitive decline.

Episodic Acute Stress: This pattern occurs when individuals repeatedly experience acute stress episodes, often due to unbalanced lifestyles, deadlines, or interpersonal conflict. The frequent activation of stress pathways elevates risk for metabolic and psychological disorders, disrupting overall well-being.

Traumatic Stress: Severe traumatic events such as natural disasters, violence, or accidents may overwhelm adaptive coping, resulting in post-traumatic stress disorder (PTSD). Traumatic stress is unique in its ability to engrave highly salient emotional memories while impairing cognitive flexibility.

Environmental Stress: Unfavorable living conditions including pollution, noise, and overcrowding constitute environmental stress. These stressors undermine both psychological stability and physiological health, often compounding existing vulnerabilities in exposed populations.

Psychological Stress: Emotional and cognitive factors such as perceived threats, social comparison, and occupational pressures drive psychological stress. Its prevalence is rising globally, reflecting modern lifestyle demands, and is strongly linked to depression and anxiety disorders.

Physiological Stress: Physiological stress originates from internal disturbances including illness, malnutrition, sleep deprivation, or injury. These states activate stress pathways and compromise immune and metabolic functions (8,9).

Mechanism of Stress

Stress mechanisms involve multiple brain centers, including the amygdala, hippocampus, prefrontal cortex, and locus coeruleus. The amygdala plays a pivotal role in processing fear and emotional salience, while the hippocampus provides negative feedback to the HPA axis through regulation of cortisol secretion. The prefrontal cortex contributes to top-down modulation, inhibiting amygdala hyperactivity and promoting adaptive regulation (10). Disruption of these circuits is strongly associated with stress-related psychiatric conditions (11). Activation of the HPA axis results in cortisol release, which in turn influences catecholamine secretion, energy metabolism, and immune suppression. Cortisol and aldosterone regulate energy allocation, cardiovascular stability, and inflammatory processes, while long-term activation leads to immunosuppression, apoptosis of B cells, and heightened vulnerability to infection.

INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

Glucocorticoid and mineralocorticoid receptors widely distributed in the brain mediate these effects, illustrating how stress can reprogram cellular functions, growth, and metabolic balance (12).

Steroids And Their Mechanisms

Steroids represent a diverse class of molecules central to biological processes in plants, fungi, and animals. In humans, steroid hormones derived from cholesterol—including cortisol, aldosterone, testosterone, and estradiol—regulate reproductive, immune, and metabolic functions (13). They exert their effects by crossing cell membranes, binding nuclear receptors, and modulating gene transcription. Their roles extend to critical stages of fetal development, such as cardiovascular and pulmonary maturation, with antenatal glucocorticoids like betamethasone reducing the risk of neonatal respiratory distress syndrome. However, exogenous use may disrupt neurodevelopment and increase long-term risks of hypertension and diabetes (14).

Steroid use in veterinary medicine

In veterinary medicine, steroids are frequently used for their anti-inflammatory, immunomodulatory, and anabolic properties. Corticosteroids mitigate arthritis, allergies, and autoimmune diseases by suppressing pro-inflammatory cytokines and adhesion molecules (14). However, chronic use suppresses the HPA axis and predisposes to adrenal insufficiency. Anabolic steroids, sometimes exploited to enhance muscle growth or feed efficiency, carry risks of hepatic, cardiovascular, and reproductive toxicity (15,16). The dual role of steroids as both therapeutic agents and potential disruptors emphasizes the need for careful clinical regulation.

Limitations of the Glucocorticoid Hypothesis

The glucocorticoid hypothesis proposes that elevated corticosteroids mediate stress-induced hippocampal damage and memory impairment. While intuitive, evidence suggests the relationship is not linear. Corticosterone elevation does not always impair cognition, and in certain contexts, such as physical exercise or enriched environments, increased glucocorticoids may enhance neuroplasticity (17). These inconsistencies highlight that stress outcomes depend on controllability, context, and type of stressor, rather than glucocorticoid levels alone.

Steroids, Stress, And Memory in Humans

Stress influences memory by suppressing neutral information retention while strengthening emotionally salient recollections. This shift is mediated by glucocorticoids and noradrenergic signaling, often through hippocampal–amygdala interactions (15,18). However, glucocorticoid effects remain paradoxical: they may both impair and enhance hippocampal plasticity, as demonstrated by conflicting outcomes on long-term potentiation and BOLD activity (14,15). Acute stress occasionally boosts associative memory and oscillatory synchronization within medial temporal lobe circuits (19). This duality reflects the fine balance between adaptive and maladaptive outcomes, with unresolved questions regarding the precise mechanisms.

Clinical Implications

Understanding stress–memory interactions is clinically significant, as dysregulated stress responses underpin conditions such as PTSD, phobias, and addiction. Therapeutic approaches targeting corticosteroid and noradrenergic signaling have been explored to disrupt maladaptive memory reconsolidation or facilitate extinction learning (9,11). Cognitive therapies likewise seek to reduce intrusive trauma-related memories, though outcomes remain variable (12). The identification of large-scale network disruptions within executive control, default mode, and salience networks provides further insight into the neural underpinnings of maladaptive stress–memory processes (12,18).

THERAPEUTIC APPROACHES FOR MEMORY IMPAIRMENT

Non-pharmacological interventions: Lifestyle interventions including physical exercise, diet, cognitive training, and social engagement have shown promise in maintaining cognitive flexibility, though results across trials remain inconsistent.

Dietary supplements: Nutritional compounds such as omega-3 fatty acids, vitamins, and selenium (Souvenaid) demonstrate modest benefits in memory and functional performance, but results are inconclusive, with vitamin E showing no preventive role.

INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

Pharmacological interventions: Currently approved pharmacological treatments for memory impairment, including cholinesterase inhibitors and memantine, provide symptomatic rather than disease-modifying benefits. Trials of anti-amyloid or NMDA-targeted agents have yet to yield consistent results.

Ginkgo biloba extract: Extracts of Ginkgo biloba show neuroprotective properties with symptomatic improvements in cognition, neuropsychiatric function, and gait stability. Despite favorable safety profiles, large-scale trials reveal mixed outcomes on disease progression (20).

Steroids, Stress, And Memory in Animals

Animal studies provide essential translational insights. In equine models, exercise enhanced learning capacity and reduced cortisol secretion, whereas uncontrollable stress impaired performance and increased cortisol levels, highlighting the interplay between physical activity, stress, and cognition (21). Comparative studies emphasize that species-specific sensory and genetic differences shape stress responses, while prenatal stress permanently alters HPA axis sensitivity, predisposing to later-life cognitive vulnerabilities.

Limitations of Cortisol

Although cortisol is widely used as a biomarker of stress, its interpretation is problematic. Elevated levels may reflect adaptive coping rather than distress, while low levels may indicate HPA exhaustion (22). Thus, cortisol should be interpreted alongside behavioral and physiological data to avoid misleading conclusions (19).

Stress, Welfare, and Cognitive Outcomes in Domestic Animals

Stress in shelter or transport conditions affects both cognition and welfare in domestic animals. Enrichment strategies, such as olfactory stimulation with essential oils, may improve optimism and reduce stress in shelter dogs (18). However, there are no universally accepted biomarkers of stress across species, emphasizing the need for individualized and multimodal assessment. Transport stress, particularly in horses and cattle, induces measurable changes in immune and endocrine markers, reinforcing the physiological burden of stressors encountered in husbandry (23).

Effects of Corticosteroids

Exogenous corticosteroid therapy in animals has been associated with emotional instability, increased reactivity, and urinary changes. Prolonged exposure, such as in Cushing's syndrome, exacerbates cognitive decline and behavioral disturbances, underscoring the importance of behavioral monitoring during treatment (21). Despite clinical observations, systematic studies on corticosteroid-induced cognitive changes in animals remain limited, representing a major research gap.

INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

COMPARATIVE ANALYSIS: HUMANS VS ANIMALS

Neurobiological Similarities

Resting-state fMRI studies confirm that animals and humans share homologous functional networks, supporting the translational validity of animal models in stress–memory research (22). These models allow for controlled exploration of developmental and pathological processes, including the influence of early-life stress on neurodevelopmental trajectories (22,23).

Species-Specific Differences in HPA Axis Regulation

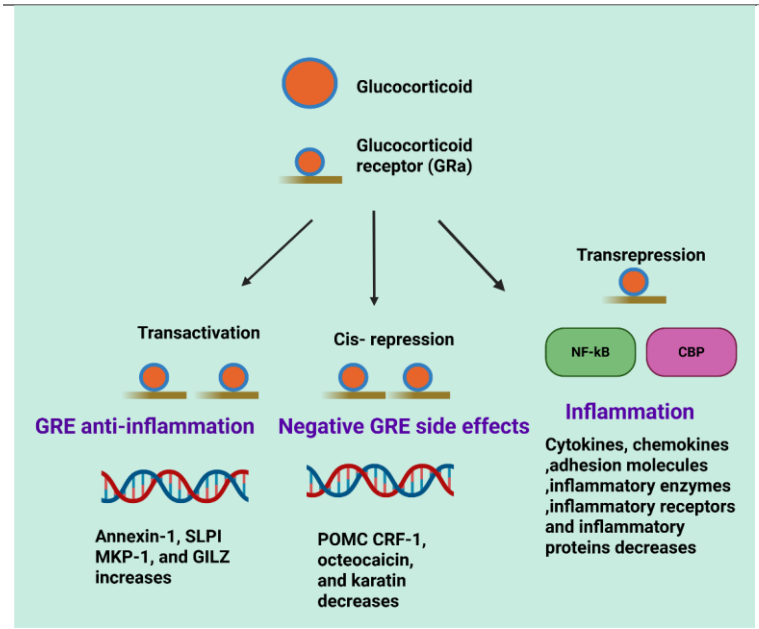
Cortisol regulation differs across species. In horses, salivary cortisol reliably reflects free plasma cortisol, whereas in cows, salivary measures diverge from plasma alterations, highlighting species-specific dynamics (18). Ecological studies further show that social structures and environmental stressors strongly modulate HPA axis function, as observed in feral horses (23).

Relevance of Animal Models to Human Research

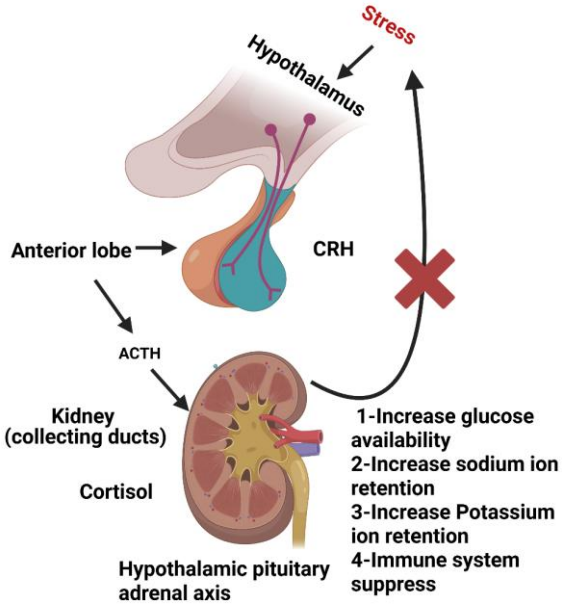
Animal models are indispensable for bridging preclinical and clinical findings. Rodent studies demonstrate parallels in stress-induced network alterations, while also identifying resilience and vulnerability phenotypes. For example, prepubertal stress in rats induces long-lasting changes in prefrontal myelination and oligodendrocyte pathways, echoing alterations seen in human stress-related disorders (22). Such findings validate the relevance of animal models while underscoring the importance of considering interspecies variability in translational applications.

Table 1: Comparative Effects of Stress and Glucocorticoids on Memory in Humans and Animals

Species	Impacts of Acute Stress on Memory	Impacts of Chronic Stress on Memory	Notes / Examples	References
Humans	Acute cortisol increases emotional memory encoding	Chronic stress may remodel hippocampal subfields	Double-blind fMRI hydrocortisone study shows subfield-specific memory shifts	(Sherman et al., 2023)
Humans	Interactions with dogs regulate cortisol and consciousness	—	Presence of a dog decreases heart rate and cortisol response to social and mental stress	(Gandenberger et al., 2024)
Rodents	—	—	No significant recent memory-specific studies	—
Dogs	Longer dog-assisted approaches decrease cortisol in youth	—	Meta-analysis indicates substantial cortisol loss	(Pena-Jorquera et al., 2025)
Horses	Exercise increases learning and decreases cortisol level during work	Elevated cortisol level disturbs learning	Exercised horses learned more rapidly; cortisol inversely associated with trial numbers	(Henshall et al., 2022)



Regulation of Gene expression by glucocorticoids



Hypothalamic-Pituitary-Adrenal (HPA) axis

CRITICAL ANALYSIS AND LIMITATIONS

The existing literature on steroids, stress, and memory offers valuable mechanistic insights but is constrained by several recurring limitations that temper the strength and generalizability of its conclusions. Many human studies rely on small samples drawn from convenience populations (e.g., healthy students or single-center outpatient cohorts), which inflates sampling error and undermines power to detect interaction effects among glucocorticoids, noradrenergic tone, and network-level brain dynamics (1,2). Randomized controlled trials are comparatively scarce in this domain, particularly for interventions that attempt to modulate stress–memory links (e.g., pharmacologic blockade of corticosteroid or noradrenergic signaling paired with exposure therapy). As a result, causal inference often rests on quasi-experimental designs or acute laboratory stress paradigms with short follow-up, limiting conclusions about durability,

INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

relapse, and functional outcomes (3–6). Even where longitudinal work exists, follow-up windows are frequently weeks to a few months, offering little traction on neurodegenerative trajectories or long-term cognitive flexibility after recurrent stress exposure (2,7). Methodological bias and confounding further complicate interpretation. Selection bias is common when studies over-represent mild or high-functioning participants and under-sample individuals with severe psychopathology or medical comorbidity, thereby diluting observable stress effects and reducing external validity (3,6). Performance and detection biases arise when blinding is infeasible—typical in cognitive training, non-invasive brain stimulation, or exercise interventions—allowing expectancy effects to contaminate memory outcomes (5,8). Confounding by sleep, circadian phase, sex hormones, and baseline affective state is not consistently measured or controlled, despite well-documented influences on cortisol reactivity, hippocampal plasticity, and network connectivity (1,9). In animal research, housing conditions, prior handling, and strain or breed differences introduce additional confounds; although often acknowledged, these factors are unevenly standardized across laboratories, contributing to between-study heterogeneity (10–12).

Publication bias is a pervasive concern. The field's emphasis on significant enhancements or impairments of memory under stress risks underreporting of null or equivocal findings, especially for complex multilevel outcomes where directionality may depend on task valence, controllability, or timing of hormone surges (2,9). Evidence of mixed or bidirectional glucocorticoid effects on hippocampal long-term potentiation and BOLD activity is accumulating, yet negative or inconclusive neuroimaging results likely remain underrepresented, skewing meta-analytic signals and theoretical narratives (4,6). Similarly, in veterinary and comparative studies, adverse cognitive or behavioral effects of therapeutic corticosteroids are more often reported in clinical case series than in controlled trials, which may inflate estimates while leaving baseline risks and moderators insufficiently characterized (13–15). Outcome measurement variability further limits cross-study comparability. Human studies deploy diverse memory paradigms (e.g., associative vs item memory; emotionally salient vs neutral stimuli) with different encoding–retrieval intervals; small changes in task design or timing relative to stress induction can invert observed effects (2,4). Biomarker choice and sampling schedules vary widely: some studies rely on single salivary cortisol measures, others on plasma or hair cortisol, and only a minority integrate multimodal indices (catecholamines, heart-rate variability, inflammatory markers) aligned to precise behavioral epochs (3,9). In animals, reliance on cortisol alone as a stress proxy obscures adaptive vs maladaptive responses and ignores circadian/allostatic dynamics that shape endocrine readouts (7,16). These inconsistencies impede direct synthesis and complicate dose–response modeling for endogenous vs exogenous steroids.

Generalizability remains constrained across several fronts. Human samples often lack age, sex, and ethnocultural diversity, limiting applicability to populations at greatest risk of stress-related cognitive decline or to those with multimorbidity (1,3,8). Clinical translation is also hampered by the gap between tightly controlled laboratory stressors and messy, chronic, real-world stress exposures. Non-invasive stimulation and lifestyle interventions show promise, but effect sizes and adherence vary, and benefits do not consistently extend beyond surrogate outcomes to daily functioning (5,8). Animal models provide indispensable mechanistic leverage, yet species-specific HPA features, saliva–plasma cortisol concordance, and ecological context constrain extrapolation to humans; differences in social structure and developmental timing can materially alter stress phenotypes and memory trajectories (10–12). Finally, evidence on long-term cognitive and behavioral consequences of therapeutic glucocorticoids—both in humans and companion animals—remains fragmentary, with few controlled studies examining dose, duration, and recovery of HPA function after tapering (13–15). Altogether, the literature would benefit from adequately powered, preregistered RCTs with longer follow-up; harmonized stress-induction protocols; multimodal, time-locked biomarker panels; and standardized memory batteries sensitive to both emotional salience and cognitive flexibility. Stratified designs that account for sex, developmental stage, controllability of stressors, and baseline network architecture are critical to clarify who benefits or is harmed under which conditions. Greater attention to negative and mixed findings, along with transparent reporting of adherence and blinding procedures, will reduce bias and sharpen therapeutic translation (6,8).

IMPLICATIONS AND FUTURE DIRECTIONS

Therapeutic and Management Implications

The growing body of evidence on stress, steroids, and memory carries important implications for clinical practice in both human and veterinary medicine. In clinical settings, recognition of the cognitive and behavioral side effects of corticosteroids highlights the necessity for careful monitoring during treatment. In dogs, for example, corticosteroid therapy has been associated with increased reactivity and attention deficits, while Cushing's disease is strongly correlated with cognitive impairment (18,19). Although interventions such as trilostane combined with selegiline in canine hypercortisolism or pergolide therapy in equine PPID demonstrate endocrine efficacy, they rarely assess cognitive outcomes, representing a missed opportunity for comprehensive evaluation (20-22).

INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

Conversely, selective glucocorticoid receptor modulators such as relacorilant and mifepristone in humans have shown cognitive and clinical advantages, suggesting that these approaches could be translated into veterinary medicine if systematically tested (23,24). For clinicians, these findings underscore the importance of integrating cognitive assessments into treatment protocols and adopting a balanced approach that weighs endocrine benefits against potential neurobehavioral risks.

Pharmacological interventions

From a therapeutic perspective, pharmacological strategies remain underexplored in veterinary populations compared to human medicine. The limited evidence indicates that while endocrine correction is achievable, cognitive parameters are not routinely measured, which restricts understanding of treatment impact on animal welfare. In contrast, human trials with glucocorticoid receptor modulators suggest tangible improvements in both endocrine balance and cognition, pointing toward the need for similar controlled studies in veterinary practice. Policy development should therefore encourage the inclusion of validated cognitive measures as endpoints in pharmacological trials, ensuring that therapeutic decisions address not only physiological but also behavioral health.

Behavioral and environmental modifications

Environmental and behavioral modifications provide promising adjunctive strategies for managing stress-induced memory disturbances. Evidence from shelter environments demonstrates that olfactory enrichment using essential oils improves cognitive bias and welfare outcomes in dogs, though effects vary depending on formulation (25). These findings illustrate the potential of non-pharmacological interventions, yet stress assessment remains inconsistent due to the absence of standardized biomarkers or reference intervals. Clinical practice and policy alike must emphasize multimodal stress assessment that combines behavioral observation with physiological indicators to enable accurate diagnosis and tailored interventions (26). This approach would also support the development of evidence-based guidelines for veterinary stress management, an area currently lacking formal consensus.

Future therapeutic prospects

Emerging therapeutic avenues such as selective glucocorticoid receptor modulators hold significant promise for both human and veterinary neurology. Experimental studies in rodents indicate that agents like CORT108297 not only improve memory recall but also attenuate hippocampal inflammation and restore metabolic balance through mechanisms such as PDK2 regulation (15,27). These findings highlight novel targets for intervention that extend beyond traditional corticosteroid antagonism. However, their application in veterinary medicine is absent, marking a critical translational gap. Future research should prioritize controlled trials in animal models, explicitly measuring both cognitive and endocrine outcomes to evaluate safety, efficacy, and clinical relevance. Unanswered questions remain around the dose–response dynamics of exogenous glucocorticoids, the reversibility of stress-induced cognitive deficits, and the long-term effects of novel modulators on brain plasticity. Addressing these gaps will require well-designed randomized controlled trials with adequate sample sizes, longer follow-up durations, and harmonized outcome measures across studies. In addition, integration of multimodal biomarkers—ranging from endocrine and inflammatory markers to neuroimaging and behavioral readouts—will be essential for capturing the complexity of stress–memory interactions. Ultimately, advancing this field will depend on bridging human and veterinary research, aligning clinical guidelines with translational evidence, and ensuring that future policies recognize cognitive health as an integral part of therapeutic decision-making.

INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

CONCLUSION

The comparative evidence on steroids, stress, and memory demonstrates the delicate balance between adaptive and maladaptive responses within the brain, where acute stress and transient glucocorticoid activation may enhance memory, yet chronic exposure leads to structural remodeling, impaired flexibility, and cognitive decline. Animal models have provided valuable translational insights into human conditions such as PTSD, Cushing's syndrome, and steroid-induced cognitive dysfunction, though species-specific physiological differences caution against direct extrapolation. The strength of current evidence is tempered by methodological limitations, small sample sizes, and inconsistent outcome measures, underscoring the need for more rigorous and standardized trials. For clinicians, these findings highlight the importance of careful monitoring when prescribing corticosteroids and the potential of emerging strategies such as selective glucocorticoid receptor modulators and integrative behavioral interventions to mitigate cognitive risks. Moving forward, multidisciplinary research combining neurobiology, pharmacology, and clinical sciences is essential to refine therapeutic strategies, close translational gaps between human and veterinary medicine, and develop innovative approaches to safeguard cognitive health under unavoidable stress conditions.

AUTHOR CONTRIBUTION

Author	**Contribution**
Abu Sulman	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Talha Ahmad	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Hafiz Aamir Ali Kharl*	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Muhammad Dawood	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Raakia Anam Saeed	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Rida Fatima	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published
Nouman Tariq*	Contributed to study concept and Data collection Has given Final Approval of the version to be published
Badar Rasool	Writing - Review & Editing, Assistance with Data Curation
Shahreen Raza	Writing - Review & Editing, Assistance with Data Curation

Author	Contribution
Mahwish Salman	Writing - Review & Editing, Assistance with Data Curation
Anam Tariq	Writing - Review & Editing, Assistance with Data Curation

INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

REFERENCES

1. Kim, E. J., & Kim, J. J. (2023). Neurocognitive effects of stress: a metaparadigm perspective. Molecular psychiatry, 28(7), 2750-2763.

2. Vacca, M., Fernandes, M., Spanetta, M., Placidi, F., Izzi, F., Lombardo, C., ... & Liguori, C. (2022). Depressive symptoms in patients with epilepsy and clinically associated features in a single tertiary center. Neurological Sciences, 43(3), 1965-1974.

3. Paduraru, E., Iacob, D., Rarinca, V., Plavan, G., Ureche, D., Jijie, R., & Nicoara, M. (2023). Zebrafish as a Potential Model for Neurodegenerative Diseases: A Focus on Toxic Metals Implications. International journal of molecular sciences, 24(4), 3428.

4. Palamarchuk, I. S., & Vaillancourt, T. (2021). Mental resilience and coping with stress: A comprehensive, multi-level model of cognitive processing, decision making, and behavior. Frontiers in Behavioral Neuroscience, 15, 719674.

5. Palamarchuk, I. S., & Vaillancourt, T. (2022). Integrative brain dynamics in childhood bullying victimization: cognitive and emotional convergence associated with stress psychopathology. Frontiers in integrative neuroscience, 16, 782154.

6. American Psychological Association. Stress in America™ 2020: a national mental health crisis; 2020.

7. World Health Organization. Comprehensive Mental Health Action Plan 2013–2030; 2021.

8. Sanacora, G., Yan, Z., & Popoli, M. (2022). The stressed synapse 2.0: pathophysiological mechanisms in stress-related neuropsychiatric disorders. Nature Reviews Neuroscience, 23(2), 86-103.

9. Franks, K. H., Bransby, L., Saling, M. M., & Pase, M. P. (2021). Association of stress with risk of dementia and mild cognitive impairment: A systematic review and meta-analysis. Journal of Alzheimer's Disease, 82(4), 1573-1590.

10. Botto, R., Callai, N., Cermelli, A., Causarano, L., & Rainero, I. (2022). Anxiety and depression in Alzheimer's disease: a systematic review of pathogenetic mechanisms and relation to cognitive decline. Neurological Sciences, 43(7), 4107-4124.

11. Wingo, T. S., Liu, Y., Gerasimov, E. S., Vattathil, S. M., Wynne, M. E., Liu, J., ... & Wingo, A. P. (2022). Shared mechanisms across the major psychiatric and neurodegenerative diseases. Nature communications, 13(1), 4314.

12. Pena-Jorquera, H., Hernández-Jaña, S., Sanchez-Martinez, J., Espinoza-Puelles, J. P., Martínez-Flores, R., Barreto-Schuch, F., ... & Cristi-Montero, C. (2025). Dog companionship and cortisol levels in youth. A systematic review and meta-analysis. Social Science & Medicine, 369, 117815.

13. Sherman, B. E., Harris, B. B., Turk-Browne, N. B., Sinha, R., & Goldfarb, E. V. (2023). Hippocampal mechanisms support cortisol-induced memory enhancements. Journal of Neuroscience, 43(43), 7198-7212.

14. Carvalheiro, J., Conceicao, V. A., Mesquita, A., & Seara-Cardoso, A. (2021). Acute stress blunts prediction error signals in the dorsal striatum during reinforcement learning. Neurobiology of Stress, 15, 100412.

15. Schwabe, L. (2023). Stress and the control of remembering: balancing hippocampal and striatal forms of memory retrieval. Current Opinion in Behavioral Sciences, 52, 101295.

16. Nwikwe, D. C. (2025). Effects of stress on cognitive performance. Progress in Brain Research, 291, 109-135.

17. Gandenberger, J., Ledreux, A., Taeckens, A., Murphy, K., Forkin, J., Gilmore, A., & Morris, K. N. (2024). The presence of a pet dog is associated with a more balanced response to a social stressor. Stresses, 4(3), 598-613.

18. Holdaway, T. (2024). Memories as Types and Stages. Principals of Psychology-PS200.

19. Eisen, A. M., Bratman, G. N., & Olvera-Alvarez, H. A. (2024). Susceptibility to stress and nature exposure: Unveiling differential susceptibility to physical environments; a randomized controlled trial. PloS one, 19(4), e0301473.

20. Henshall, C., Randle, H., Francis, N., & Freire, R. (2022). The effect of stress and exercise on the learning performance of horses. Scientific reports, 12(1), 1918.

21. Chu, B., Marwaha, K., Sanvictores, T., Awosika, A. O., & Ayers, D. (2024). Physiology, stress reaction. In StatPearls [Internet]. StatPearls Publishing.

22. Devi, S., Kumar, P., & Kaur, G. (2023). Biological Significance of Steroids. In Steroids and their Medicinal Potential (pp. 98-124). Bentham Science Publishers.

23. Ijaz, H., Ali, R., Khan, N. A., Dawood, A., Noman, S., Khan, M. H., ... & Nazeer, M. A (2024). The Role of Pharmaceutical Science in Mitigating the Adverse Effects of Steroids on Animals.

24. Capper, J. L., De Carvalho, T. B., Hancock, A. S., Sá Filho, O. G., Odeyemi, I., & Bartram, D. J. (2021). Modeling the effects of steroid implant use on the environmental and economic sustainability of Brazilian beef production. Translational Animal Science, 5(4), txab144.

25. Wang, C., Cui, C., Xu, P., Zhu, L., Xue, H., Chen, B., & Jiang, P. (2023). Targeting PDK2 rescues stress-induced impaired brain energy metabolism. Molecular Psychiatry, 28(10), 4138-4150.

26. Schwabe, L., Hermans, E. J., Joëls, M., & Roozendaal, B. (2022). Mechanisms of memory under stress. Neuron, 110(9), 1450-1467.

27. Bahtiyar, S., Karaca, K. G., Henckens, M. J., & Roozendaal, B. (2020). Norepinephrine and glucocorticoid effects on the brain mechanisms underlying memory accuracy and generalization. Molecular and Cellular Neuroscience, 108, 103537.

INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION