Chronic Stress as A Catalyst for Cognitive Decline and Alzheimer's Disease: Integrating Neuroendocrine, Neuroinflammatory, And Gut-Brain Axis Mechanisms

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Abstract. Chronic stress is an increasingly recognized, pivotal modifiable risk factor for accelerating cognitive decline and Alzheimer's disease (AD) pathogenesis. This review systematically synthesizes evidence from the past decade (2015–2025) on the underlying mechanisms and emerging interventions. We delineate how chronic stress triggers a cascade of events, beginning with the sustained activation of the hypothalamic-pituitary-adrenal (HPA) axis, leading to glucocorticoid dysregulation. This, in turn, directly promotes the core pathologies of AD: amyloid-beta (Aβ) deposition and tau hyperphosphorylation. Concurrently, stress induces microglia-mediated neuroinflammation and disrupts the gut-brain axis, exacerbating neuronal damage through systemic and central inflammatory responses. In terms of intervention, promising strategies include pharmacological approaches like the glucocorticoid receptor modulator dazucorilant, natural compounds such as quercetin, and non-pharmacological strategies encompassing specific probiotics, mindfulness-based stress reduction, and multidomain lifestyle interventions. Integrating these multimodal strategies, which target the neuroendocrine, inflammatory, and gut-brain pathways, holds substantial promise for delaying AD onset and mitigating its progression.

Keywords: Chronic stress, Alzheimer's disease, HPA axis, Neuroinflammation, Gut–brain axis, Glucocorticoid, Microbiota.

1. Introduction

Chronic stress, a pervasive condition increasingly recognized as a critical risk factor in aging societies, is significantly associated with the incidence of AD[1] . NPS, notably depression and anxiety, manifest in approximately ninety percent of individuals with AD. These symptoms not only accelerate the trajectory of cognitive decline but also substantially intensify the caregiver burden, presenting a major challenge to healthcare systems[2].

The underlying pathophysiology linking chronic stress to AD involves complex neurobiological interplay. Chronic stress precipitates sustained activation of the HPA axis, leading to aberrant glucocorticoid levels, which in turn promote amyloid-beta (Aβ) Aβ accumulation and tau hyperphosphorylation—hallmark pathologies of AD. Concurrently, stress-induced neuroinflammation and dysregulation of neurotransmitter systems further exacerbate neuronal vulnerability and synaptic dysfunction, creating a permissive environment for AD pathogenesis.

Given the limitations of current mono-therapeutic approaches for AD, which predominantly offer symptomatic management with modest efficacy, there is a pressing need for novel strategies that target these multifaceted pathways, particularly those emanating from chronic stress and associated NPS. Interventions capable of mitigating the impact of chronic stress and its neuropsychiatric sequelae hold promise not only for alleviating patient suffering and caregiver strain but also for potentially modifying the disease course by addressing key upstream drivers of pathology.This review

systematically synthesizes evidence from the past decade (2015–2025) on the underlying mechanisms and emerging interventions.

2. The Epidemiological and Genetic Link Between Stress and Dementia

2.1. Longitudinal Evidence: Stress-Related Disorders as Risk Factors for AD

Beyond genetics, extensive longitudinal epidemiological data corroborate this association. An umbrella review of ten systematic reviews identified several mental disorders, including depression and anxiety, as risk factors for later dementia, with high-strength evidence specifically linking late-life depression to all-cause dementia, AD, and vascular dementia[3]. Supporting this, a major review by Stafford J et al. of 57 studies found that depression was robustly associated with an increased risk of all-cause dementia (relative risk [RR]=1.96), AD(RR=1.9), and vascular dementia (RR=2.71). The associations were particularly pronounced with shorter follow-up periods and more severe or late-onset depression. While data for other disorders like PTSD (RR=2.19) and psychotic disorders were more limited, they consistently pointed towards an elevated risk. This collective evidence suggests that patients with psychiatric disorders constitute a high-risk group meriting continuous monitoring, with the caveat that depression, in some cases, may represent a prodromal manifestation of dementia rather than an independent causal factor[4].

2.2. Shared Genetic Architecture: Insights from Genomic Studies

A growing body of observational evidence has firmly established a link between AD and stress-related psychiatric disorders. However, the extent to which shared genetic susceptibility underpins this connection remained unclear. A recent groundbreaking study by Dang W et al., utilizing UK Biobank data, provided crucial insights by demonstrating significant positive genetic correlations between AD and major depressive disorder. Through cross-phenotype analyses, the study identified specific shared risk variants: 23 in four genes for AD–depression, 13 in six genes for AD–PTSD, and 7 in four genes for AD–anxiety. Functional annotation further revealed 12 genes common to all three comorbidities, enriched in tissues like the spleen and whole blood, highlighting a potential role of neuro-immune interactions. These findings underscore a shared genetic origin that could inform future diagnostic and preventive strategies for stress-related AD[5].

2.3. Allostatic Load: A Measure of Cumulative Physiological Burden

To elucidate the biological pathways linking psychiatric symptoms to dementia, research has turned to the concept of allostatic load (AL), which quantifies the cumulative physiological burden of chronic stress. Zhao Q et al. investigated whether AL profiles mediate the depression-dementia link. Their study identified four distinct AL profiles, with the "multisystem dysregulation" profile (4% of the sample) significantly increasing the risk for all-cause dementia (hazard ratio [HR]=1.72), AD (HR=1.75), and non-AD dementias (HR=1.87). While AL did not mediate the risk, it interacted additively with depression within the multisystem dysregulation profile, suggesting that pervasive physiological dysregulation may heighten the brain's vulnerability to the detrimental effects of depression[6].

Critically, the predictive value of these psychiatric symptoms is not confined to late life. Research indicates that depressive and anxiety symptoms in midlife are already associated with poorer cognitive performance in domains like attention and memory. When these symptoms reach clinical significance, individuals report greater subjective cognitive concerns, an effect that is substantially magnified when depression and anxiety co-occur. This suggests that depressive and anxiety symptoms could serve as valuable clinical markers, helping to identify individuals at the earliest stages of deterioration, long before objective cognitive impairment becomes evident[7]. In summary, the epidemiologic link between stress-related disorders and dementia is robust, supported by shared genetics, longitudinal associations, and underlying physiological mechanisms, positioning psychiatric symptoms as critical indicators in the early prediction of dementia risk.

3. Core Neurobiological Mechanisms of Stress-Induced AD Pathogenesis

3.1. Neuroendocrine Dysregulation: The HPA Axis and Glucocorticoid Toxicity

Dementia, particularly AD which affects over 55 million people worldwide, is a leading cause of morbidity and mortality in older adults. AD is pathologically defined by the accumulation of Aβ plaques and tau neurofibrillary tangles, which gradually erode cognition and often co-occur with distressing neuropsychiatric symptoms. While the precise neural underpinnings of stress-induced cognitive impairment remain uncertain, both clinical observations and animal studies consistently point to pathological changes in a core network including the prefrontal, cingulate, hippocampal, and amygdala regions, driven by synergistic interactions between stress mediators and AD pathologies like Aβ and tau [8]. At the systems level, human neuroimaging studies provide compelling evidence for this link. Research by Zhang NK et al. in older adults revealed that higher levels of worry—a core feature of anxiety—were associated with smaller volumes of the subiculum, a hippocampal subfield among the earliest affected by AD pathology. Conversely, the adaptive emotion regulation strategy of reappraisal was linked to larger subiculum and CA1 volumes, suggesting that psychological factors can directly influence the integrity of these vulnerable brain structures [9]. This stress-related vulnerability is further evidenced in animal models. In a rat AD model induced by Aβ42 infusion, footshock stress acted synergistically with the pathology to worsen memory impairment, heighten anxiety-like behavior, and exacerbate molecular deficits in the prefrontal cortex, including elevated FKBP5 expression and increased neuronal apoptosis [10]. Complementing this, studies in 5xFAD mice demonstrate that AD pathology itself alters neural dynamics in the medial prefrontal cortex, producing signatures of heightened arousal and anxiety that mirror findings in human patients [11]. Zooming into the molecular pathways, the connection between stress systems and AD progression is mediated by several key biological systems. As reviewed by Reyna NC et al., two major stress-regulating pathways—the serotonin system and the corticotropin-releasing factor (CRF) system—are critically involved in AD pathogenesis,presenting opportunities for early intervention and pharmacotherapy[12].

3.1.3 Sex Differences in Neuroendocrine Responses

Importantly, the regulation of these systems exhibits significant sex differences, as detailed by Hodes GE et al., who examine divergent responses in the HPA axis, neurotransmitter systems, neurodegeneration markers, and gonadal hormones. Recognizing these sex-based biological variations is essential for translating preclinical insights into effective therapeutics for stress-related disorders like depression and AD [13].

In summary, a multi-level pathway emerges: chronic stress, through activation of the HPA axis and associated neurochemical systems (e.g., CRF, serotonin, acetylcholine, GABA), exacerbates AD-related pathology and induces neural dysfunction in key brain networks. This convergence of stress biology and AD mechanisms accelerates hippocampal and prefrontal atrophy, disrupts neural dynamics, and ultimately manifests as the cognitive and neuropsychiatric symptoms that define and complicate the clinical course of AD.

3.2. Neuroinflammation and Glial Activation

3.2.1 Microglial Polarization and Pro-inflammatory Cytokine Release

Beyond systemic hormones, individual differences in stress reactivity and anxiety-like behavior significantly modulate disease trajectory in animal models. Research by Dunacka J et al. utilized a model of sporadic AD induced by streptozotocin and classified rats as high or low novelty responders—a proxy for stress reactivity. They found that high responders, characterized by heightened stress sensitivity, developed more severe pathology, including poorer reference memory, elevated anxiety, greater beta-amyloid deposition in the nucleus accumbens, and enhanced microglial activation. This demonstrates that pre-existing behavioral phenotypes can accelerate sporadic AD progression, likely by exacerbating neuroinflammation and amyloid pathology [14].The dorsal raphe

nucleus and its serotonergic neurons emerge as a critical nexus where early tau pathology, stress, and behavioral changes converge. In a mouse model engineered to express pathogenic tau specifically in serotonin neurons, both sexes developed anxiety-like behavior and impaired stress coping, with females exhibiting additional social disinhibition. Electrophysiological recordings confirmed reduced excitability of these neurons, providing a direct mechanistic link between early tau accumulation in a specific mood-regulating circuit and the emergence of pre-cognitive neuropsychiatric symptoms in AD[15].

3.2.2 The Interplay Between Stress, Neuroinflammation, and Neurodegeneration

A rapidly growing body of evidence solidifies the role of chronic stress as a major, non-genetic risk factor for the development and progression of AD. This compelling link has catalyzed extensive research aimed at deciphering the precise biological pathways through which psychological stress accelerates brain pathology. Human studies are now at the forefront, moving beyond correlation to begin delineating the causal impact of specific stress-related hormones on the structure, function, and resilience of the aging brain. In a pivotal investigation by Liebscher and colleagues, the intricate relationship between systemic stress biomarkers and brain vulnerability was meticulously evaluated in a cohort of older adults. Their findings revealed a particularly significant association: elevated circulating levels of the hormone epinephrine (adrenaline) were strongly linked to concerning reductions in both glucose metabolism and blood perfusion (hypoperfusion) within key brain regions known to be highly vulnerable to the earliest stages of AD, namely the posterior cingulate cortex and the precuneus. These areas are critical hubs within the brain's default mode network, and their metabolic impairment is a recognized hallmark of preclinical AD. Furthermore, the study uncovered critical and pronounced sex-specific interactions, suggesting that the neuroendocrine response to stress differs fundamentally between men and women, with distinct consequences for brain health. In women, paradoxically, higher epinephrine levels were associated with a larger volume of the anterior cingulate cortex, a region involved in emotional regulation and cognitive control. This finding may indicate a sexually dimorphic, potentially compensatory neurobiological response to stress hormones in the female brain. Conversely, in men, the classic stress hormone cortisol appeared to exert a more detrimental influence, as increased cortisol levels were directly correlated with poorer performance on tests of episodic memory—one of the primary cognitive domains affected early in AD. Collectively, these nuanced findings underscore a complex reality: stress hormones such as epinephrine and cortisol are not merely peripheral markers of distress but are active mediators that directly influence the brain's vulnerability and resilience against Alzheimer's pathology. The sex-dependent nature of these effects is particularly crucial, as it highlights the imperative for developing future therapeutic and preventative strategies that are personalized, taking into account an individual's biological sex to effectively mitigate the risk posed by chronic stress[16] .

However, the effects of stress on established tauopathy are complex and context-dependent. Lyons CE et al. investigated the impact of different stress paradigms—chronic social stress versus chronic restraint stress—on PS19 tauopathy mice. Intriguingly, chronic restraint stress paradoxically reduced levels of total and phosphorylated tau and attenuated gliosis, yet it failed to rescue cognitive deficits and even heightened anxiety. In contrast, chronic social stress impaired spatial learning without significantly altering tau pathology. This dissociation indicates that psychological and physical stressors exert distinct effects on cognition, affect, and tau biochemistry, suggesting that therapeutic strategies must be tailored to the nature of the stressor[17].

Finally, the developmental timing of stress exposure is critical, with early life events potentially priming the brain for later AD pathogenesis. A study modeling early life stress via maternal separation in 5xFAD mice revealed the emergence of sex-specific AD pathology by just six weeks of age. Female mice showed heightened amyloid-beta immunoreactivity and intraneuronal accumulation, while both sexes exhibited robust neuroinflammation and signs of synaptic dysfunction, including reduced brain-derived neurotrophic factor and synaptophysin. This indicates that early life stress can accelerate AD pathogenesis through persistent neuroinflammation and synaptic damage, laying a maladaptive foundation long before cognitive symptoms appear[18].

3.3. The Gut-Brain Axis: A Critical Mediator

3.3.1 Stress-Induced Gut Dysbiosis and Barrier Disruption

Nafady MH et al. examines how gut dysbiosis might contribute to the origin and progression of AD. They summarized that Gut microbiota dysbiosis is believed to be linked to AD which is defined by cognitive decline and amyloid beta plaques. When the gut community is imbalance, it releases amyloids lipopolysaccharides and neurotoxins that can influence signaling pathways immune activation and proinflammatory cytokines tied to AD development. This dysbiosis is also connected with conditions such as type two diabetes,obesity and neuropsychiatric disorders like depression all of which may act as triggers for AD.

3.3.2 Microbial Metabolites in Neuroinflammation and Synaptic Function

Dysregulation of the gut-microbiota-brain axis(GMBA) plays a pivotal role in the pathogenesis of neurodevelopmental and neurodegenerative disorders, such as Autism Spectrum Disorder(ASD), AD, and Parkinson's disease(PD)[19-20]. The composition of the gut microbiome is shaped by a complex interplay of genetic, dietary, and environmental factors[21-22]. Microbial-derived metabolites, such as short-chain fatty acids (SCFAs) and tryptophan derivatives, influence brain function by modulating neuroinflammation, synaptic plasticity, and the integrity of the blood-brain barrier (BBB) [23-24]. As a result, probiotics, prebiotics, and synbiotics can restore microbial eubiosis and ameliorate behavioral and cognitive deficits associated with these disorders [25-26]. It was found that boron, which has anti-inflammatory properties, can modulate the gut microbiome, and has novel neuroprotective potential against neurodegeneration [27-28]. Supplementing with probiotics or prebiotics has been shown to ease mood symptoms and enhance memory [29].

4. Integrated Pathophysiological Pathways and Moderating Factors

4.1. Structural and Functional Brain Alterations in Vulnerable Networks (e.g., Hippocampus, Prefrontal Cortex)

Key shared pathways include aberrant post-translational modifications of proteins, which can alter their function and stability; a dysregulated microbiota-gut-brain axis, where imbalances in gut microbial communities disrupt bidirectional communication with the central nervous system; and disrupted intracellular signaling cascades that are crucial for neuronal survival, plasticity, and inflammation.

Notably, specific overlapping disturbances are increasingly recognized as central drivers of pathogenesis. These include elevated levels of pro-inflammatory cytokines, creating a state of chronic neuroinflammation that is detrimental to neurons, and alterations in the MAPK/ERK signaling pathway, which is vital for cell growth, differentiation, and survival. Concurrently, gut microbial imbalances, often termed dysbiosis, can exacerbate these processes by contributing to inflammation, impairing the integrity of the gut and blood-brain barriers, and influencing neurotransmitter production. The recognition of these convergent mechanisms opens up innovative avenues for therapeutic intervention. Consequently, promising strategies are emerging that focus on multi-target approaches rather than single-target drugs. These include the use of natural compounds with anti-inflammatory and neuroprotective properties, the repurposing of existing medications to exploit their pleiotropic effects, the design of novel multitarget-directed ligands that can simultaneously modulate several key pathways, and advanced RNA-based interventions aimed at correcting specific genetic or molecular dysregulations. By targeting these shared core mechanisms, such holistic strategies hold the potential to develop more effective treatments for both neurodegenerative and neuropsychiatric disorders, potentially slowing disease progression and improving quality of life for affected individuals. [30]

4.2. Dysregulation of Key Neurotransmitter Systems (Serotonin, GABA, Acetylcholine)

The cholinergic system represents another critical interface between stress and cognition. The cholinergic septohippocampal pathway, essential for memory processes, is profoundly influenced by stress. Kniffin A et al. synthesize evidence on how interactions between the stress axis and this cholinergic system influence hippocampal computations, highlighting dynamic signaling patterns and cellular adaptation mechanisms as potential therapeutic targets for stress-induced cognitive deficits [31]. Furthermore, the balance of neural excitation and inhibition is crucial. Disruption of GABAergic neurotransmission contributes to psychiatric conditions like depression and anxiety. Emerging research focuses on developing selective positive allosteric modulators for specific GABAA receptor subtypes (e.g., α2, α3, α5), with compounds like GL-II-73 and MP-III-022 showing promise in animal models of chronic stress and cognitive decline by restoring inhibitory control with minimal off-target effects [32]

4.3. The Impact of Developmental Timing: Early-Life Stress and AD Trajectory

Neurodegenerative and neuropsychiatric disorders represent a significant and growing health challenge among the older adult population globally. Neurodegenerative conditions, such as Alzheimer's disease and Parkinson's disease, are characterized by a progressive and often irreversible loss of neuronal function, leading to severe memory impairment, cognitive decline, and motor deficits. In contrast, neuropsychiatric disorders like major depressive disorder and schizophrenia primarily manifest as profound alterations in mood, perception, thought processes, and behavior. Despite their distinct clinical presentations, a deeper understanding of their pathophysiology reveals significant overlap in underlying biological mechanisms.

5. Emerging Intervention Strategies Targeting Stress-Related Pathways

5.1. Pharmacological Interventions

5.1.1 Glucocorticoid Receptor Modulators (e.g., Dazucorilant)

The well-established link between chronic stress, glucocorticoid dysregulation, and AD pathogenesis has prompted the investigation of therapeutic strategies that directly target this axis. Given the central role of glucocorticoid receptor (GR) signaling, its selective modulation represents a promising avenue. Dazucorilant, a selective modulator of the glucocorticoid receptor (NR3C1), has demonstrated neuroprotective effects against acute amyloid-beta toxicity. A pivotal study by Canet Gs et al. evaluated its long-term, disease-modifying potential in two distinct mouse models of AD (5xFAD and J20). Chronic treatment with dazucorilant not only improved working and spatial memory but also directly counteracted core pathologies: it normalized plasma glucocorticoid levels, reduced tau hyperphosphorylation, and decreased both the production and aggregation of amyloid-beta. Notably, it also prompted a redistribution of activated glial cells to amyloid plaques, suggesting a restoration of beneficial neuroinflammatory responses. The sustained efficacy across models, coupled with its established human safety profile, provides a compelling rationale for advancing dazucorilant into clinical trials as a potential disease-modifying therapy for AD [33].

5.1.2 Natural Compounds with Multi-Target Actions (e.g., Quercetin)

Complementing the approach of targeted receptor modulation, natural compounds with multi-faceted actions offer alternative strategies to mitigate stress-induced AD risk. Chronic stress contributes to AD pathogenesis partly by stimulating amyloid precursor protein (APP)-related genes and pro-inflammatory cytokines. The flavonoid quercetin, known for its anti-inflammatory and antioxidant properties, was investigated by Safarzadeh E et al. in a rat model combining chronic restraint stress and scopolamine-induced dementia. Their findings demonstrated that quercetin administration improved memory impairment and reduced anxiety. Mechanistically, it lowered levels of pro-inflammatory cytokines (IL-6, TNF-α) in the prefrontal cortex and hippocampus and, crucially,

altered APP messenger RNA expression, notably downregulating hippocampal APP. This suggests that quercetin may activate non-amyloidogenic pathways, enhancing the processing of APP away from the production of beta-amyloid. These anti-amnesic and anti-inflammatory effects position quercetin as a promising nutraceutical for AD prevention, particularly in individuals experiencing chronic stress[34].

In summary, these studies highlight two viable therapeutic strategies emanating from the stress-AD link: the targeted modulation of the glucocorticoid receptor with novel compounds like dazucorilant, and the use of multi-target natural products like quercetin to broadly counteract the neuroinflammatory and amyloidogenic consequences of chronic stress. Both approaches offer promising paths forward for intervention and prevention.

5.2. Non-Pharmacological and Lifestyle Interventions

5.2.1 Microbiome-Targeted Therapies (Probiotics, Prebiotics)

The microbiota-gut-brain axis(MGBA) acts as a complex, bidirectional communication network that intricately links the gut microbiota to central nervous system(CNS) function[35-36].Dysregulation of this axis, a state known as dysbiosis, compromises the integrity of both the intestinal barrier and the BBB. This breakdown promotes neuroinflammation and is implicated in the pathogenesis of neurodegenerative disorders such as AD and PD, as well as neurodevelopmental and psychiatric conditions including ASD and depression[37-39]. Specific probiotic strains, predominantly from the genera Lactobacillusand Bifidobacterium, have been demonstrated to strengthen intestinal and BBB integrity, support the production of neuroprotective brain-derived neurotrophic factor(BDNF), and help regulate immune responses by modulating pro- and anti-inflammatory cytokines[40-41]. Consequently, dietary supplementation with probiotics may serve as an effective adjunctive therapy for managing various neuropsychiatric disorders, although their efficacy is highly dependent on specific strain selection, dosage, treatment duration, and individual host factors.

5.2.2 Psychological and Behavioral Approaches (MBSR, Psychotherapy)

Early detection technologies can now identify people who carry a high risk for AD long before any cognitive symptoms appear. Anxiety depression and other neuropsychiatric complaints often emerge years ahead of measurable memory loss yet rigorous evidence for its efficacy in protecting cognition or emotional well-being in these at-risk groups, while promising, remains less established than for late-life depression..Thirty two studies met inclusion criteria. They used highly varied methods small samples and brief follow up periods. Randomized controlled evidence for improvements in mood or general well being is scarce yet qualitative accounts suggest that cognitive restructuring better disease acceptance and improved quality of life are possible benefits. No clear factors that determine whether a specific therapy will succeed have been identified.The review concludes that early individually tailored psychotherapeutic and psychoeducational interventions are urgently needed to safeguard mental health in people at risk for AD. A central challenge is to adapt these techniques to the different stages of cognitive decline so that each person receives support matched to his or her changing needs. [42] Finally, for those already experiencing neuropsychiatric symptoms, music therapy offers a versatile non-pharmacological tool. A review of ten randomized trials found that music therapy benefits a range of conditions relevant to AD care. It can improve behavior and social communication in autism spectrum disorder, lift mood in depression, enhance sleep quality in insomnia, and ease mood and neuropsychiatric behaviors in dementia, with the magnitude of benefit often correlating with symptom severity. Both active (e.g., playing instruments) and receptive (e.g., listening) methods are employed, making it a flexible intervention to support both physical and psychosocial health, though more research on its long-term effects is warranted.

5.2.3 Multidomain Lifestyle Interventions (Diet, Exercise, Cognitive Training and Sleep)

Dementia related anxiety refers to the fear of receiving a diagnosis of Alzheimer disease or another form of dementia. Maxfield M et al. explores how individuals manage that fear. The results

revealed five main strategies for managing dementia related anxiety. First people monitor their cognitive status both through self observation and objective testing. Second they employ active coping techniques such as using reminders and normalizing the aging process. Third they seek interpersonal support from family friends or support groups. Fourth they engage in practical planning by arranging powers of attorney or saying important goodbyes. Finally they embrace personal responsibility through lifestyle modifications aimed at reducing risk. These findings show that internal and external coping strategies differ in effectiveness and offer guidance for clinical interventions grounded in established psychological theories[43].

Sleep plays a central role in maintaining physical emotional and cognitive wellbeing. When sleep is insufficient the immune system weakens the risk of chronic illnesses such as obesity and diabetes rises and metabolic balance is disturbed. Emotionally restricted sleep provokes irritability depression and other mood disorders while cognitively it produces deficits in alertness and memory that can resemble the effects of alcohol intoxication. Motor coordination suffers leading to a higher likelihood of accidents and in older adults chronic sleep loss accelerates brain aging. Sleep disorders such as epilepsy are made worse by poor sleep and may require interventions like cognitive behavioral therapy or the use of melatonin. Improving sleep hygiene therefore depends on educational outreach supportive policies and consistent lifestyle adjustments. [44]

5.3. Complementary and Alternative Approaches (e.g., Neonatal Tactile Stimulation)

AD is a progressive neurodegenerative disorder characterized by the accumulation of cerebral amyloid-beta plaques and neurofibrillary tangles, accompanied by widespread synapse loss and significant brain atrophy. These pathological changes collectively lead to severe impairments in cognitive abilities, motor functions, and emotional regulation. Compounding these deficits, stress has been identified as a critical exacerbating factor, accelerating disease progression and symptom severity. In their groundbreaking study, Hossain SR and colleagues explored whether gentle tactile stimulation during the neonatal period could counteract Alzheimer's-like pathology in APP NL-G-F mice, a transgenic model genetically engineered to develop Alzheimer's-like symptoms, which had additionally been subjected to prenatal stress. The research demonstrated that adult mice receiving early-life tactile stimulation exhibited remarkable improvements across multiple domains: enhanced cognitive performance in memory and learning tasks, superior motor coordination and balance, and significantly reduced anxiety-like behaviors. Importantly, these behavioral benefits were correlated with a notable reduction in amyloid-beta plaque deposition in key brain regions. Notably, these positive effects were observed consistently in both prenatally stressed and non-stressed mouse groups, suggesting the broad efficacy of this intervention. The findings robustly indicate that neonatal tactile stimulation serves as a simple, non-invasive, and cost-effective therapeutic intervention that may effectively delay the onset and mitigate the severity of dementia-related symptoms in aging animals. This study opens promising avenues for early-life interventions in neurodegenerative disease prevention. [45]

6. Conclusion

6.1. Synthesis of Key Findings: An Integrated Stress-AD Model

Chronic stress has been unequivocally established as a significant and modifiable catalyst for cognitive decline and AD, operating through a complex interplay of neuroendocrine, neuroinflammatory, and gut–brain axis mechanisms. The convergence of genetic, epidemiologic, and molecular evidence underscores a profound shared etiology between stress-related psychiatric disorders and AD. Genetically, studies have identified significant positive correlations and shared risk variants between AD and conditions like major depressive disorder, post-traumatic stress disorder, and anxiety, with functional annotations highlighting the critical role of neuro-immune interactions in stress-related AD pathogenesis[5]. Epidemiologically, robust longitudinal data confirm that mid- and late-life depression and anxiety substantially increase the risk for all-cause dementia, AD, and

vascular dementia, with the concept of allostatic load providing a framework for understanding how cumulative physiological dysregulation amplifies brain vulnerability[3,4,6]

At the neurobiological level, chronic stress induces structural and functional alterations in key brain networks vulnerable to AD, including the prefrontal cortex, hippocampus, and cingulate cortex. Persistent activation of the HPA axis leads to glucocorticoid excess, which directly promotes Aβ accumulation and tau hyperphosphorylation, hallmarks of AD pathology [16,14]. Animal models consistently demonstrate that stress exacerbates memory impairment, Aβ deposition, and neuronal apoptosis, with notable sex-specific differences in stress response and pathology[10,13,15]. Furthermore, stress disrupts crucial neurotransmitter systems, including serotonin and GABA, contributing to the neuropsychiatric symptoms that often precede overt cognitive decline[31-32].

The gut–brain axis emerges as a pivotal mediator, where dysbiosis increases intestinal and blood–brain barrier permeability, allowing microbial metabolites and pro-inflammatory agents to trigger neuroinflammation, thereby accelerating AD progression[29]. Importantly, these overlapping pathways—encompassing HPA axis dysfunction, neuroinflammation, and GMBA disruption—provide a mechanistic basis for the high co-occurrence of neuropsychiatric symptoms and cognitive decline and reveal promising therapeutic targets.

6.2. Clinical Implications for Prevention and Early Intervention

In response to these intricate mechanisms, emerging interventions offer hope for delaying AD onset and mitigating risk. Pharmacologically, selective glucocorticoid receptor modulators like dazucorilant show efficacy in improving memory and reducing Aβ and tau pathology in preclinical models [33]. Natural compounds with anti-inflammatory and antioxidant properties, such as quercetin, demonstrate potential in ameliorating stress- and scopolamine-induced cognitive deficits and anxiety by modulating cytokine levels and amyloidogenic processing [34]. Non-pharmacological strategies are equally vital. Probiotic supplementation with specific *Lactobacillus* and *Bifidobacterium* strains can restore eubiosis, strengthen barrier integrity, and modulate neuroinflammation[30] Psychological interventions, including tailored psychotherapy and the development of adaptive coping strategies, alongside lifestyle modifications targeting sleep hygiene and even complementary approaches like neonatal tactile stimulation, have shown benefits in improving cognitive and emotional outcomes [43-45].

6.3. Gaps in Knowledge and Future Research Directions (e.g., Biomarker-Driven Stratification, Personalized Medicine)

In conclusion, the path from chronic stress to AD is multifaceted yet increasingly delineated. Future research must prioritize biomarker-driven patient stratification, the design of multimodal intervention trials that concurrently target neuroendocrine, inflammatory, and gut–brain pathways, and deeper mechanistic studies to elucidate sex-specific differences and stressor-specific effects. Translating these integrated insights into clinical practice is paramount for developing effective, personalized prevention strategies to alleviate the growing burden of Alzheimer's disease in our aging societies.

In addition to "biomarker stratification" and "personalized medical care",it can also help develop more accurate chronic stress measurement engineers and carry out different types of stress (social vs. Physiological) intervention research. And explore the specific signaling molecular stop in the microbial-intestinal-brain axis.

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References

[1] Tasha Rhoads et al. Differential associations of neighborhood disadvantage, race/ethnicity, and cognitive status with experiences of psychosocial distress in the HABS-HD cohort. Alzheimers Dement. 2024 Dec 23;21(1): e14257.

[2] Chen, Y., Dang, M., and Zhang, Z. (2021). Brain mechanisms underlying neuropsychiatric symptoms in Alzheimer's disease: A systematic review of symptom- general and –specific lesion patterns. Mol. Neurodegener. 16:38

[3] Qin Zhao et al. Systematic evaluation of the associations between mental disorders and dementia: An umbrella review of systematic reviews and meta-analyses. J Affect Disord. 2022.

[4] Jean Stafford et al. Psychiatric disorders and risk of subsequent dementia: Systematic review and meta-analysis of longitudinal studies. Int J Geriatr Psychiatry. 2022 May.

[5] Weijia Dang et al.Investigating shared risk variants and genetic etiology between Alzheimer's disease and three stress-related psychiatric disorders: a large-scale genome-wide cross-strait analysis. Front Aging. 2025 Feb 5; 6:1488528

[6] Jean Stafford et al. Psychiatric disorders and risk of subsequent dementia: Systematic review and meta-analysis of longitudinal studies. Int J Geriatr Psychiatry. 2022 May.

[7] Emmal L Twait et al. Late-life depression, allostatic load, and risk of dementia: The AGES-Reykjavik Study.Psychoneuroendocrinology. 2022 Nov 17; 148:105975.

[8] Nicole K Zhang et al. The neural basis of neuropsychiatric symptoms in Alzheimer's disease.Front Aging Neurosci. 2024.

[9] Joanna Poszwa et al. Integration of Neuroimaging and Molecular Biomarkers in the Diagnosis of Alzheimer's Disease and Frontotemporal Dementia: The Promise of fMRI.Current Alzheimer Research, 2025

[10] Helmet T Karim et al.Hippocampal subfield volume in older adults with and without mild cognitive impairment: effects of worry and cognitive reappraisal.Neurobiol Aging. 2024 May 28; 141:55–65.

[11] Faborode OS et al.Inescapable footshocks induce molecular changes in the prefrontal cortex of rats in an amyloid-beta-42 model of Alzheimer's disease.Behavioural Brain Research 419, 113679, 2022

[12] Filip Kosel.Aberrant cortical activity in 5xFAD mice in response to social and non-social olfactory stimuli.Journal of Alzheimer's Disease 97 (2), 659-677, 2024

[13] Nicole C Reyna et al.Anxiety and Alzheimer's disease pathogenesis: focus on 5-HT and CRF systems in 3xTg-AD and TgF344-AD animal models.Front Aging Neurosci. 2023 Nov 10; 15:1251075.

[14] Joanna Dunacka et al.High Behavioral Reactivity to Novelty as a Susceptibility Factor for Memory and Anxiety Disorders in Streptozotocin-Induced Neuroinflammation as a Rat Model of Alzheimer's Disease.Int J Mol Sci. 2024 Oct 28;25(21):11562.

[15] Nazmus S Khan et al.Behavioral and Neurophysiological Implications of Pathological Human Tau Expression in Serotonin Neurons.ACS Chem Neurosci. 2024.

[16] Dishary Sharmin et al. Synthesis and Receptor Binding Studies of α5 GABAAR Selective Novel Imidazodiazepines Targeted for Psychiatric and Cognitive Disorders.Molecules. 2023.

[17] Carey E Lyons et al. Chronic Social and Psychological Stress Impact Select Neuropathologies in the PS19 Mouse Model of Tauopathy.Psychosom Med. 2024.

[18] M G Garcia et al. Maternal separation differentially modulates early pathology by sex in 5xFAD Alzheimer's disease-transgenic mice.Brain Behav Immun Health. 2023.

[19] Cryan et al.The gut microbiome in neurological disorders.The Lancet Neurology 19 (2), 179-194, 2020

[20] Shabbir et al.Curcumin, quercetin, catechins and metabolic diseases: the role of gut microbiota.Nutrients 13 (1), 206, 2021

[21] Van Ameringen et al.The gut microbiome in psychiatry: A primer for clinicians.Depression and Anxiety 36 (11), 1004- 1025, 2019

[22] Rajoka et al.Interaction between diet composition and gut microbiota and its impact on gastrointestinal tract health.Food Science and Human Wellness 6 (3), 121-130, 2017

[23] Feng, W.; Ao, H.; Peng, C. Gut microbiota, short-chain fatty acids, and herbal medicines. Front. Pharmacol. 2018, 9, 1354.

[24] Agus et al.Gut microbiota-derived metabolites as central regulators in metabolic disorders.Gut 70 (6), 1174-1182, 2021

[25] Fooks, L.; Gibson, G.R. Probiotics as modulators of the gut flora. Br. J. Nutr. 2002, 88, s39–s49.

[26] Kang, D.-W.; Adams, J.B.; Coleman, D.M.; Pollard, E.L.; Maldonado, J.; McDonough-Means, S.; Caporaso, J.G.; Krajmalnik-Brown, R. Long-term benefit of Microbiota Transfer Therapy on autism symptoms and gut microbiota. Sci. Rep. 2019, 9, 5821.

[27] Das, B.C.; Nandwana, N.K.; Das, S.; Nandwana, V.; Shareef, M.A.; Das, Y.; Saito, M.; Weiss, L.M.; Almaguel, F.; Hosmane, N.S. Boron Chemicals in Drug Discovery and Development: Synthesis and Medicinal Perspective. Molecules 2022, 27, 2615.

[28] Lu, C.-J.; Hu, J.; Wang, Z.; Xie, S.; Pan, T.; Huang, L.; Li, X. Discovery of boron-containing compounds as Aβ aggregation inhibitors and antioxidants for the treatment of Alzheimer's disease. MedChemComm 2018, 9, 1862–1870.

[29] Majid T et al.Perturbations in Microbiota Composition as a Novel Mediator in Neuropsychiatric, Neurological and Mental Disorders: Preventive and Therapeutic Complementary Therapies to Balance the Change.Current Alzheimer Research 20 (4), 213-223, 2023

[30] Sixin Li et al.Bibliometric analysis of Alzheimer's disease and depression.Current Neuropharmacology 23 (1), 98-115, 2025

[31] Georgia E Hodes et al. Sex Differences in Stress Response: Classical Mechanisms and Beyond.Curr Neuropharmacol. 2024.

[32] Alyssa Kniffin et al. Septohippocampal cholinergic system at the intersection of stress and cognition: Current trends and translational implications.Eur J Neurosci. 2024 May.

[33] Canet G.Advancing Alzheimer's disease pharmacotherapy: efficacy of glucocorticoid modulation with dazucorilant (CORT113176) in preclinical mouse models.British journal of pharmacology 182 (9), 1930-1956, 2025

[34] Safarzadeh E.Quercetin ameliorates cognitive deficit, expression of amyloid precursor gene, and pro-inflammatory cytokines in an experimental models of Alzheimer's disease in Wistar rats.Experimental Gerontology 193, 112466, 2024

[35] Carabotti, M.; Scirocco, A.; Maselli, M.A.; Severi, C. The gut-brain axis: Interactions between enteric microbiota, central and enteric nervous systems. Ann. Gastroenterol. 2015, 28, 203–209.

[36] Mayer, E.A.; Tillisch, K.; Gupta, A. Gut/brain axis and the microbiota. J. Clin. Investig. 2015, 125, 926–938.

[37] Sharma, R.; Gupta, D.; Mehrotra, R.; Mago, P. Psychobiotics: The next-generation probiotics for the brain. Curr. Microbiol. 2021, 78, 449–463.

[38] Kash, T.L.; Baucum, A.J., 2nd; Conrad, K.L.; Colbran, R.J.; Winder, D.G. Alcohol exposure alters NMDAR function in the bed nucleus of the stria terminalis. Neuropsychopharmacology 2009, 34, 2420–2429.

[39] Bonfili, L.; Cecarini, V.; Cuccioloni, M.; Angeletti, M.; Berardi, S.; Scarpona, S.; Rossi, G.; Eleuteri, A.M. SLAB51 Probiotic formulation activates SIRT1 pathway promoting antioxidant and neuroprotective effects in an AD mouse model. Mol. Neurobiol. 2018, 55, 7987–8000.

[40] Castelli, V.; d'Angelo, M.; Lombardi, F.; Alfonsetti, M.; Antonosante, A.; Catanesi, M.; Benedetti, E.; Palumbo, P.; Cifone, M.G.; Giordano, A.; et al. Effects of the probiotic formulation SLAB51 in in vitro and in vivo Parkinson's disease models. Aging 2020, 912, 4641–4659.

[41] Friedrich Leblhuber etal. Commentary: effect of probiotic supplementation on cognitive function and metabolic status in Alzheimer's disease: a randomized, double-blind and controlled trial. Frontiers in Aging Neuroscience 10, 54, 2018

[42] Rostamzadeh A. Psychotherapeutic interventions in individuals at risk for Alzheimer's dementia: a systematic review. Alzheimer's research & therapy 14 (1), 18, 2022

[43] Maxfield M."Why miss today worrying about tomorrow?" A qualitative investigation of ways middle-aged and older adults manage dementia-related anxiety.Anxiety, Stress, & Coping 38 (2), 219-233, 2025

[44] Shiyi Li.Association between Obesity and Cognitive Function in Chinese Older Adults: The Mediating Effects of Sleep Quality and Blood Pressure.Current Alzheimer Research, 2025

[45] ShaKhawat R et al.Early tactile stimulation influences the development of Alzheimer's disease in gestationally stressed APP NL-G-F adult offspring NL-G-F/NL-G-F mice.Exp Neurol. 2023 Oct.