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REVIEW ARTICLE

Stress, stress systems, and Alzheimer's disease

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Abstract

Stress is increasingly recognized as an important, modifiable factor for Alzheimer's disease (AD), yet its roles in initiation, progression, and outcomes remain incompletely elucidated. Epidemiologic studies link chronic stress, early-life adversity, and trauma to increased AD risk, while experimental models have uncovered mechanisms by which stress hormones directly drive core AD pathological processes, including amyloid beta and tau aggregation, neuroinflammation, and neurodegeneration. Complicating the relationship, brain structures that regulate the stress response are themselves selectively vulnerable to early degeneration in AD. As these circuits degenerate, interpreting changes in stress biomarkers becomes more challenging, with physiological measures potentially decoupling from perceived stress. Here, we review evidence connecting stress to AD pathophysiology as both a risk factor and a driver, examine how the degeneration of stress neuroendocrine systems accelerates disease progression, and discuss implications for intervention and clinical trial design.

KEYWORDS
Alzheimer's disease, cortisol, dementia, hypothalamus-pituitary-adrenal axis, neuromodulatory systems, sympathetic-adrenal-medullary axis, stress

Highlights

- Stress acts as a risk factor, driver, consequence, and accelerator of AD.
- Stress hormones directly modulate amyloid, tau, neuroinflammation, and BBB dysfunction.
- Early degeneration of stress circuits confounds interpretation of stress biomarkers in AD.
- Sleep and circadian disruption amplify stress–AD feedback loops via vulnerable circuits.
- Stress biology should be treated as a stage-dependent stratification dimension in AD.

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RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using PubMed and reference mining of primary studies, reviews, ClinicalTrials.gov, and meta-analyses spanning epidemiology, genetics, neuroendocrinology, neuroimaging, neuropathology, and experimental models. We evaluated evidence linking psychosocial stress, stress-related biomarkers, neuromodulatory systems, and sleep-circadian disruption to AD, with particular attention to studies across the disease continuum and to work addressing selective vulnerability of stress-regulatory circuits.
2. **Interpretation**: This review integrates disparate bodies of literature to propose that stress functions simultaneously as a risk factor, mechanistic driver, disease consequence, and accelerator of AD. We show that early degeneration of stress-regulatory circuits fundamentally alters stress signaling, helping reconcile conflicting biomarker findings and challenging assumptions that stress biomarkers directly reflect stress exposure in AD.
3. **Future directions**: Key priorities include longitudinal, stage-aware studies jointly tracking stress measures and AD biomarkers; circuit-specific models of stress signaling in AD; and clinical trials that treat stress biology as a stratification dimension rather than a uniform therapeutic target.

1 | INTRODUCTION

Stress is a psychophysiological state triggered when individuals appraise demand as exceeding their resources. It features coordinated psychological, cognitive, and emotional responses involving neuroendocrine, neuromodulatory, and high-level cognitive processes. Among the risk factors studied for Alzheimer's disease (AD), stress is one of the most consistently identified. Epidemiological evidence links early-life adversity, chronic stress, and acute traumatic events to an increased likelihood of developing AD.[1] Population-level studies further demonstrate that elevated stress-related neuroendocrine signaling predicts future AD.[2–10] Despite these consistent findings, stress's associations with AD mechanisms remain poorly understood.

Convergent studies in cell culture and animal models show that stress hormones and neuromodulators directly promote AD-related pathological lesions, including amyloid beta (Aβ) plaque deposition, neurofibrillary tau tangle formation, synaptic dysfunction, neurodegeneration, and neuroinflammation. Moreover, as AD progresses, the brain regions that regulate stress systems degenerate, leading to dysfunction of stress circuitry and further dysregulation of stress hormones and neuromodulatory systems.[1] Together, these findings suggest the presence of a positive feedback loop in which stress acts as a risk factor, driver, consequence, and accelerator of AD (Figure 1).

This positive feedback loop complicates the clinical interpretation of stress biomarkers. Because the brain networks critical for stress regulation are compromised by neurodegeneration patterns, commonly used biomarkers of stress, such as cortisol, may not precisely reflect the severity or perception of the stress experienced by AD patients. This decoupling of perceived stress from biomarker levels has important implications for both the interpretation of stress measurements in dementia populations and the effectiveness of stress-targeted interventions in altering disease trajectory.

In this review, we will synthesize epidemiological, neuroendocrine, and neuropathological evidence linking stress to AD as both a risk factor and a driver. In doing so, we will highlight how AD degeneration can alter stress biomarker levels and discuss implications for further research, clinical trial design, and interventions.

2 | STRESS AS A RISK FACTOR FOR AD

When homeostasis is challenged by physical extrinsic or psychological intrinsic forces (i.e., stressors), a physiological reaction, termed the stress response, is triggered.[11] The stress response system integrates the central nervous system and peripheral tissues to detect the event, interpret the perceived threat, and respond accordingly.[12,13] The physiological and behavioral changes under stress are adaptive, temporally structured processes that mobilize to meet the threat and then engage restorative mechanisms to reestablish homeostasis.[2] Resources are temporarily diverted from basal homeostatic processes, such as digestion and reproduction, toward systems necessary for immediate action to enhance survival, including the neurologic and motor functions. However, responses can be maladaptive when the intensity, duration, or frequency of stressors is too extreme and the body is unable to exit this state and return to homeostasis.

Chronic stress, repeated acute stress, or intense traumatic events that exceed an individual's threshold to change and adapt can lead to long-term adverse health effects. The downstream consequences depend on various factors, including the individual's perception, past experiences, sex, gender, age, and genetics, as well as the severity, timing, and duration of the stressor.[14] Depending on these factors, there may be short- or long-term consequences. Research shows that stress is critically correlated with the progression and risk of various diseases, from depression and anxiety,[15] to cancer and cardiovascular disease,[16,17] to cognitive decline and neurodegenerative disorders.[1,18–26]

2.1 | Chronic psychosocial stress exposure as a risk factor for AD

Stress is assessed in populations using several methods. Self-rated questionnaires such as the Perceived Stress Scale[27] (PSS), a well-validated instrument frequently deployed in epidemiological studies,

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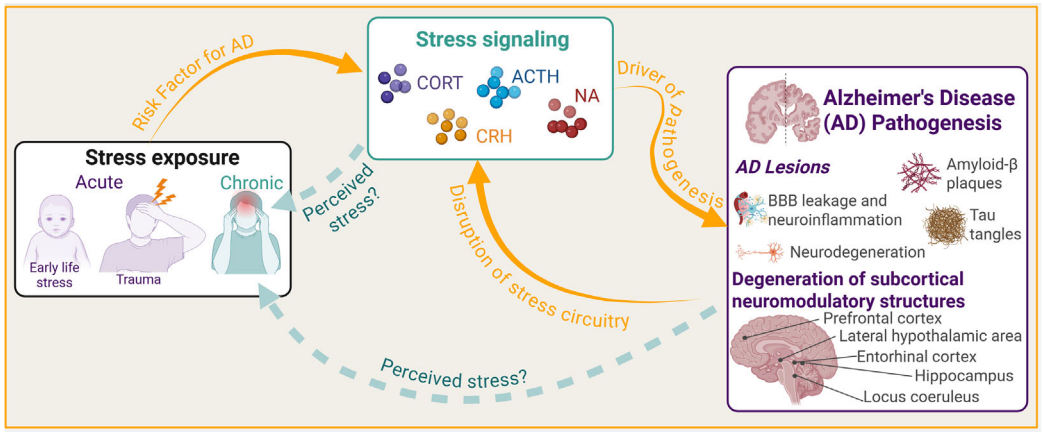


FIGURE 1 Conceptual model linking stress exposure to AD. Exposure to acute and chronic stressors is a risk factor for AD and is associated with increased activation of stress–response systems, leading to elevated levels of stress-related hormones and neuromodulators. These signals, in turn, promote the development and progression of core AD pathological lesions. As the disease advances, neurodegeneration of brain regions involved in stress regulation further disrupts stress signaling, creating a self-reinforcing feedback loop that may accelerate pathophysiology. However, it remains unclear whether disease-driven alterations in stress signaling correspond to increased perceived stress in patients. AD, Alzheimer's disease; CORT, cortisol; CRH, corticotropin-releasing hormone; ACTH, adrenocorticotropic hormone; NA, noradrenaline.

can be used as an objective measure of perceived stress. Studies of the PSS consistently demonstrate relationships between elevated perceived stress scores and increased risk of dementia,[18–21] accelerated dementia progression,[22–24] and AD-related biomarkers.[25,26]

Stress is also frequently inferred from assessments of social isolation and loneliness. These subjective experiences of social disconnection are a robust risk factor for dementia. Large cohort studies show as high as a 1.6-fold increased risk of dementia among socially isolated individuals.[28–33] In fact, many other established etiopathological factors, such as mental health and personal habits, are considered outcomes of social isolation.[28] The 2024 Lancet Commission estimated that 5% of dementia cases could be eliminated by addressing late-life social isolation in the population.[34]

Socioeconomic status is another commonly used proxy for chronic stress. Lower socioeconomic status has clear associations with increased dementia risk.[35] However, this relationship may be mediated by several confounding variables, including educational inequity, a high burden of cardiovascular disease, nutritional deficits, limited access to healthcare, and greater exposure to environmental pollutants.[29,36,37] As such, isolating and tying the psychophysiological effects of low socioeconomic status to dementia risk is challenging in population-based studies.

2.2 | Early-life adversity, trauma, and post-traumatic stress disorder as risk factors for dementia

Early-life stress is strongly associated with increased dementia risk, even independently of covariates like adult socioeconomic status.[38] During sensitive periods of brain development, exposure to adversity such as childhood trauma, neglect, abuse, or chronic family stress can result in permanent dysfunction of stress regulatory systems. Meta-analyses and large cohort studies consistently find increased dementia risk associated with adverse childhood experiences (ACEs).[39–41] Longitudinal studies of specific adversities also show that exposure to traumatic experiences, including parental death, foster care, and war exposure, is associated with increased dementia risk in later life.[38,42–44]

Assessing the long-term outcomes of trauma- and stressor-related disorders can also inform the relative contributions of stress to AD risk. Post-traumatic stress disorder (PTSD), encompassing persistent clinical symptoms following exposure to one or more traumatic events, may contribute to increased risk for AD, although this relationship remains convoluted. Several large meta-analyses and longitudinal studies have shown relationships between PTSD and dementia risk.[45–49] However, biomarker studies of PTSD have suggested that the increased dementia risk likely could also be attributable to non-AD forms of dementia.[50]

Genome-wide cross-trait analyses using large biobank datasets reveal shared genetic risk for stress-related psychiatric disorders and AD, including moderate polygenic overlap between AD and PTSD[36,51] and several shared risk genes with anxiety disorders.[51] However, these findings have not been consistently replicated across cohorts,[47] likely reflecting the substantial heterogeneity of psychiatric diagnoses and their underlying genetic architectures. Improved stratification of stress-related psychiatric disorders into biologically defined subtypes will be critical for identifying patient populations with heightened genetic susceptibility to comorbid AD.

2.3 | Measuring stress signaling

The acute stress response involves the activation of the hypothalamus-pituitary-adrenal (HPA) axis (Figure 2). Following a stressor, the HPA-axis cascade begins with neurons in the hypothalamic paraven-

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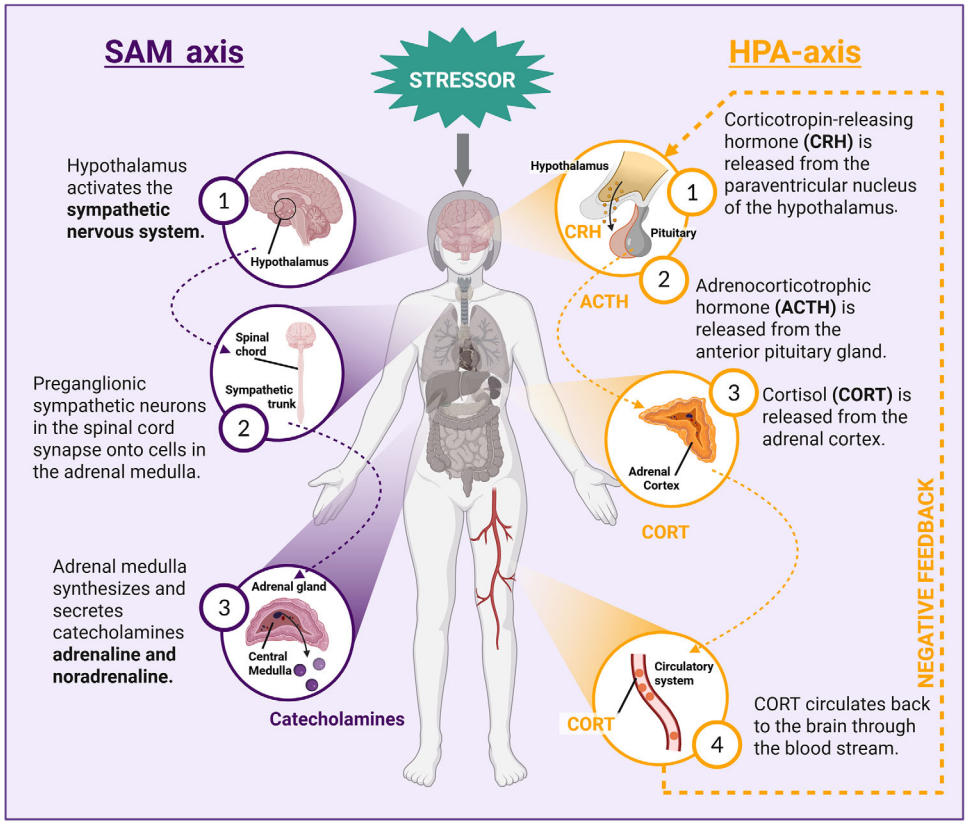


FIGURE 2 Overview of stress–response biology. Stress engages two coordinated systems: the rapid SAM axis (left), which mediates the "fight-or-flight" response and transient increases in alertness and vigilance, and the slower HPA axis (right), which generates a prolonged hormonal response through sequential release of CRH, ACTH, and CORT. Disruption at any level of these pathways alters feedback regulation and leads to stress-system dysregulation.

tricular nucleus releasing corticotropin-releasing hormone (CRH). CRH stimulates the anterior pituitary to secrete adrenocorticotropic hormone (ACTH), which in turn drives glucocorticoid (GC) release from the adrenal cortex. Cortisol is the predominant GC in humans, and corticosterone is the prominent GC in rodents.[52] For clarity and consistency, this review refers to GCs collectively as CORT. CORT mobilizes energy and modulates immune, metabolic, and cognitive processes while exerting negative feedback on the hippocampus, hypothalamus, and pituitary to terminate the stress response. Endocrine markers along this cascade can serve.

To mitigate potential biases associated with self-reported stress and adverse life events, studies often use HPA-axis hormones as biomarkers for the acute stress response. Researchers have used these HPA-axis biomarkers to monitor stress in AD and other dementia populations, further discussed later in Section 5.1, "Measuring stress system signaling in AD."

The most used stress-related biomarker is CORT. CORT levels in humans are typically measured in blood, saliva, urine, hair, and sweat. Immunoassays (e.g., enzyme-linked immunosorbent assay) and mass spectrometry-based approaches are then utilized. Blood draws have the highest temporal resolution and benefit from analytical standardization but can themselves be stressful and activate stress signaling, biasing results. Saliva, urine, and sweat collection are less likely to spike CORT levels but are susceptible to contamination and have comparatively lower temporal resolution than blood. Moreover, point measurements from blood, saliva, urine, and sweat must control for collection time because CORT levels exhibit circadian rhythms. Hair, on the other hand, integrates CORT levels over weeks to months, making it representative of moving averages. Hair CORT measurements are challenged by a lack of standardization and confounding variables such as hair treatment and hygiene.

CORT has been evaluated in several longitudinal studies focused on assessing AD risk. Overall, studies find that increased CORT levels in older cognitively normal adults are associated with increased risk of developing AD.[2–7] Although less common than CORT, plasma and cerebrospinal fluid ACTH and CRH can also be measured as a marker of patients' sensitivity to stressors.[8–10] There is a paucity of evidence that increased ACTH and CRH in cognitively normal adults is predictive of later incidence of AD.

Alongside the endocrine HPA axis response, acute stress response elicits a rapid activation of the peripheral nervous system sympathetic-adrenal-medullary (SAM) system (Figure 1). Some animal models have suggested that SAM activation, as measured by catecholamine levels, precede cognitive decline in AD, but these findings have not been clearly established in humans.[53,54] Plasma catecholamine levels (mainly adrenaline and noradrenaline) are often used as markers of

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SAM activation. Peripheral norepinephrine levels are lower in AD cases compared to controls,[55] but their predictive value for AD progression is limited. While plasma catecholamine levels are likely poor markers of autonomic dysfunction in AD, physiological markers may be viable.

Physiological markers of stress reactivity include heart-rate variability (HRV), blood pressure, skin conductance level, pupil dilation, respiratory rate, and peripheral temperature. These markers mostly reflect SAM activation but can be affected by many other physiological processes. The emergence of consumer wearables (e.g., so-called smart watches) has increased the adoption of physiological markers of stress in research. Some studies indicate that mid- to late-life changes in SAM markers, such as HRV and blood pressure, are associated with a higher risk of dementia and AD.[56,57]

Neuroradiologic biomarkers of stress reactivity include functional magnetic resonance imaging blood-oxygen-level-dependent (BOLD) measurement of amygdala activation. BOLD hyperactivation in the amygdala is detectable early in AD.[58,59] Task-evoked BOLD abnormalities, including negative BOLD response in the default mode network, are detectable in preclinical AD, and the magnitude tracks with disease progression.[58,60–62]

While there are myriad biomarkers of stress reactivity and methodological approaches to measure them deployed by psychologists and neuroscientists, each has inherent limitations. Careful consideration is necessary as all markers of the stress response exhibit varying temporal resolution, and their levels may be influenced by the matrix in which they are measured.

3 | MECHANISMS UNDERLYING THE RELATIONSHIP OF STRESS TO AD

AD is characterized by specific pathological hallmarks, including extracellular Aβ plaques, intraneuronal neurofibrillary tangles, and, ultimately, synaptic loss and neuronal death. Neuroinflammation, oxidative stress, blood–brain barrier (BBB) dysfunction, glial cell activation, and mitochondrial dysfunction also play an important role in the pathophysiology of AD. The mechanisms by which stress interacts with these key hallmarks and drivers are essential for understanding the interplay between stress and AD. Modeling stress's contributions to AD pathogenesis is challenging but has yielded important insights (Figure 3).

3.1 | Stress hormones and neuromodulators

3.1.1 | Noradrenaline

The central noradrenergic system, a critical regulator of the SAM-axis stress response, is an important point of convergence between stress physiology and early AD pathological processes. The brain's primary source of noradrenaline is the noradrenergic locus coeruleus (LC), which is one of the earliest affected structures in AD.[63–65] The LC is a central node of the brain's stress response, serving to globally mount arousal and adaptive behaviors through activation of the SAM axis and downstream engagement of the HPA axis.[66,67] Activation of the SAM axis results in peripheral adrenaline/noradrenaline release from the adrenal medulla (Figure 2). While there is evidence indicating changes in SAM-axis activity in AD,[57,68–71] it is unclear whether SAM axis structures are directly involved in AD or AD pathogenesis or whether the changes in activation are secondary outcomes of central degenerative changes.

Mounting evidence supports the necessity of adequate central noradrenaline levels to prevent and slow AD progression through activation of canonical brain-derived neurotrophic factor-producing pathways.[72–77] As a result, the loss of LC neurons in early AD stages are thought to increase cortical susceptibility to AD proteinopathic lesions.

LC neurons undergo persistent changes through over-activation by stressors.[78–85] Some of these changes may explain why the LC is notably vulnerable to AD. Increased activation of the LC, as is seen during chronic stress exposure, is associated with increased mitochondrial oxidative damage, which can be toxic to neurons.[86–88] A metabolite of noradrenaline, 3,4-dihydroxyphenylglycolaldehyde (DOPEGAL), has been directly implicated in tau aggregation, propagation, and downstream cognitive impairment.[89] Increased noradrenaline production in the LC could, thus, increase pathological tau production and propagation via increased DOPEGAL levels.

3.1.2 | HPA axis

The HPA axis's synthesis and release of hormones (CRH, ACTH, and CORT) are critical components of stress response and regulation. CRH and CORT have been most significantly studied in AD and have been shown to influence AD progression via inflammatory, neuromodulatory, oxidative stress, and vascular systems (Figure 4). There is a relative paucity of evidence connecting ACTH to AD pathophysiology beyond its role in signaling in the HPA axis to increase CORT secretion.

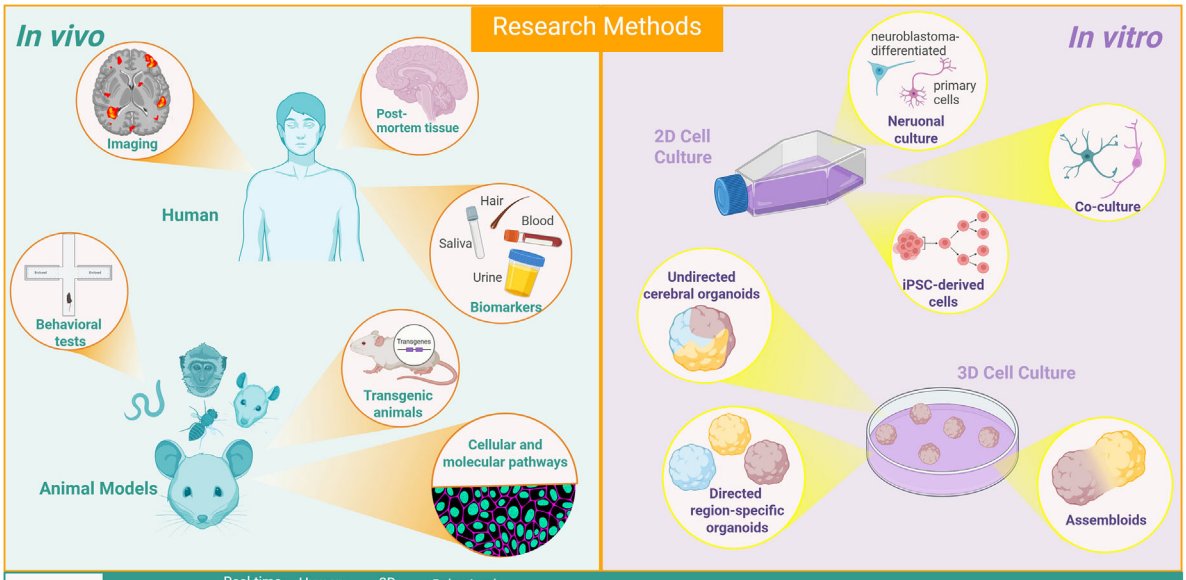
3.1.2.1 Corticotropin-releasing hormone

CRH binds to two distinct G-coupled receptors, CRHR1 and CRHR2.[90] CRH-containing neuronal cell bodies and projections are distributed throughout the brain but are highly expressed in brain areas like the LC, hippocampus, amygdala, and neocortex – notably regions that are prone to degeneration in AD.[91]

CRH can promote the formation of AD-related pathological lesions. The overexpression or infusion of CRH increases Aβ burden in the cortex and hippocampus of transgenic AD mouse models, potentially driven by changes in APP cleavage.[92–94] CRH administration also significantly elevates tau phosphorylation and tau accumulation, effects that can be prevented by blocking CRH receptors.[95,96] An increase in CRH also leads to decreased dendritic branching and dendritic spine density, as well as memory impairment.[93]

Interestingly, the induction of hippocampal tau phosphorylation and Aβ under stress is dependent on CRH. CRH-deficient mice do not exhibit elevated phosphorylated tau levels under acute stress,[96] and pharmacological disruption of CRHR1 inhibits the formation of

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	Method	Real-time manipulation	Human cells	3D physiology	Behavioral readouts	Stress exposure	Stress analysis	AD-related readouts
HUMAN	Imaging	✗	✓	✓	✓	Survey perceived stress and trauma, experimental stress induction	Self-reported stress levels, physiological and behavioral stress biomarkers	Cognitive and functional testing, neuroimaging, and *postmortem* analyses of neurodegeneration, and Aβ and tau aggregation
	Post mortem	✗	✓	✓	✓			
	Bio-samples	✗	✓	✓	✓			
RODENT	WT mouse/rat	✓	✗	✓	✓	Experimental stress induction, administration of stress-related hormones and neuromodulators	Behavioral tests, physiological stress biomarkers, cellular, genetic, and protein assays	Behavioral testing and Aβ-, tau-, and pathway-level AD phenotypes in transgenic APP and tauopathy mice
	Transgenic model	✓	~	✓	✓			
2D CELL CULTURE	Immortalized cells	✓	✓	✗	✗	Treatment with known stress-related hormones and neuromodulators	Stress hormones and neuromodulators, cellular, genetic, and protein-level assays	Single-cell analysis of Aβ- and tau-related pathways, cell-type-specific responses to exogenous Aβ, and disease phenotypes in human genetic AD models
	Primary cells	✓	~	✗	✗			
	iPSC-derived	✓	✓	✗	✗			
3D CELL CULTURE	Organoids	✓	✓	✓	✗	Treatment with known stress-related hormones and neuromodulators	Stress hormones and neuromodulators, cellular, genetic, and protein-level assays	3D Aβ and tau pathway analyses, multicellular responses to exogenous Aβ, and disease development in human genetic AD models
	Assembloids	✓	✓	✓	✗			

FIGURE 3 Considerations when choosing a model system and designing experiments for studying stress interactions with AD. Human studies are essential for examining interactions between stress and AD but are limited by the inability to directly measure or manipulate cellular and subcellular processes in living patients. *Post mortem* human tissue provides insight into disease-associated processes but reflects only end-stage disease and precludes real-time manipulation of stress paradigms. Animal models enable investigation of stress and AD across multiple biological scales, from behavior and cognition to cellular and molecular mechanisms; however, species differences substantially limit their translational relevance. Mice do not naturally develop AD and rely on transgenic expression or knock-in of human risk genes, yet even these models fail to fully recapitulate hallmark features such as neurofibrillary tangles, brain atrophy, and age-appropriate disease progression. In vitro models allow precise, cost-effective, and time-efficient manipulation of stress hormones and signaling pathways in defined human cell types. Two-dimensional neuronal cultures enable controlled interrogation of molecular, cellular, and electrophysiological responses to stress but lack behavioral readouts and poorly capture three-dimensional AD lesions (e.g., Aβ plaques). Recent advances in 3D culture systems, including brain organoids, extend this framework by recapitulating cellular diversity, cytoarchitecture, and spontaneous network activity that resembles the human fetal brain; however, organoids are limited as models of late-onset neurodegenerative disease and exhibit substantial batch-to-batch variability. Across systems, stress research is further constrained by limited standardization, including inconsistent definitions of acute versus chronic exposure, wide variability in CORT dosing, and uncertainty regarding physiologically relevant hormone levels due to temporal fluctuations, measurement limitations, and region-specific brain exposure in vivo. Consequently, understanding the interaction between stress and AD requires careful, question-driven experimental design and rigor that emerges from convergence across complementary model systems.

AD tau lesions.[97] These CRH effects are not due exclusively to the downstream increases in CORT, because preventing increases in CORT with stress does not mitigate tau tangle formation, and CORT injections alone are insufficient to alter Aβ levels, whereas CRH alone does.[94,96,98] Decreased activation of CRHR1 is associated with decreased Aβ production and phosphorylated tau accumulation.[1,97,99] This suggests that CRH plays a vital role in stress-induced changes leading to AD endpoints.

While studies support the conclusion that CRH is sufficient to increase key AD lesions, including Aβ deposition, neurodegeneration, tau phosphorylation, and behavioral deficits, there are also findings indicating that increased CRH can be protective.[91,100–102]

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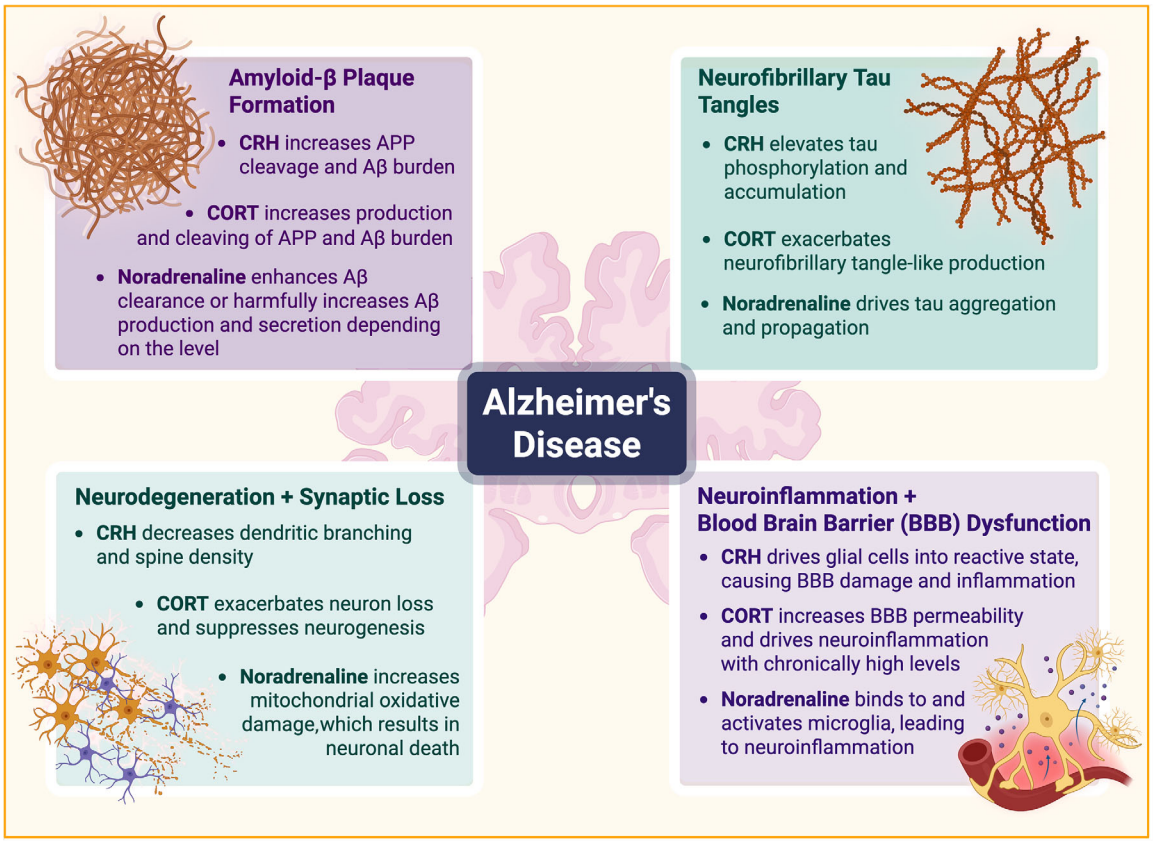


FIGURE 4 Summary of stress as a driver of key AD phenotypes. Stress hormones and neuromodulators directly modulate cellular signaling and protein processing, thereby promoting Aβ and tau aggregation, neurodegeneration, BBB leakage, and neuroinflammation.

The protective effects of CRH-treated neurons against Aβ toxicity are attributed to the stabilization of cellular calcium homeostasis.[91] Moreover, while acute stress increases neurofibrillary tangle burden in CRH-knockout mice, repeated chronic stressors result in lower tau tangle burden in CRH-knockout mice compared to WT controls.[98] A potential explanations is that CRH release activates the stress–response pathway after detecting toxic protein accumulation, thereby driving immune activation and initially helping to curb disease progression. Therefore, the duration of the stressor, the amount of CRH and the brain region must all be considered in assessing how elevated CRH levels influence vulnerability to AD-related pathological lesions.

3.1.2.2 CORT

CORT exhibits an inverted U-shaped relationship with physiological function: Optimal levels support adaptive stress responses, whereas both excessive and insufficient CORT signaling is detrimental. This dual role as both an activator and a terminator of stress responses complicates its use as a biomarker. In AD, both higher and lower CORT levels have been linked to pathological lesions.[1,103,104] Individuals carrying high-risk AD genotypes exhibit altered stress biology prior to the onset of clinical symptoms. Apolipoprotein E (APOE) ε4 carriers have a chronic elevation in CORT[105] and are more susceptible to cognitive impairment after stressor exposure.[106–108]

CORT has been shown to exacerbate neurofibrillary tangle-like production and neuronal vulnerability to damage.[90,109] Exogenous CORT administration in animal models induce abnormal hyperphosphorylation of tau in the hippocampus and prefrontal cortex, leading to behavioral changes.[110] CORT-binding sites, known as glucocorticoid response elements (GREs), are present in the promoters of two Aβ-related genes, *APP* and the β-secretase enzyme *BACE1*, indicating that GCs can bind and influence Aβ production. In fact, both APP and BACE1 are increased with GC administration, which is hypothesized to lead to the increase in Aβ formation.[109] Taken together, these findings support the view that CORT elevations are not only a consequence of AD-related neural and HPA-axis dysfunction but also contribute to the development and progression of pathological lesions.

Finally, CORT-related genetic susceptibility is also seen to drive AD. Polymorphisms in stress-related genes can substantially influence HPA-axis reactivity and CORT sensitivity, thereby modulating vulnerability to AD. Variants in *NR3C1*, the gene encoding the glucocorticoid receptors (GRs), which reduce receptor sensitivity or function have been associated with altered stress responses and, in some cases, reduced AD risk. For example, the ER22/23EK polymorphism, which reduces GR sensitivity to CORT, has been associated with a lower risk of AD.[111] In contrast, genetic variants that increase GC activation appear to confer greater susceptibility to AD.[112] A rare haplotype

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in the 5′ regulatory region of the gene encoding the CORT-degrading enzyme 11β-hydroxysteroid dehydrogenase type 1 (*11β-HSD1*) leads to elevated CORT levels and is associated with increased AD risk.[113]

3.2 | Neuroinflammation and the BBB

The BBB is a highly selective, semipermeable interface of the neurovascular unit, composed of endothelial cells together with astrocytes, pericytes, microglia, and the surrounding basement membrane. Disruption of BBB integrity is increasingly implicated in AD[114] and is strongly influenced by stress-related signaling, positioning the BBB as a key convergence point where chronic stress may interact with and accelerate neurodegenerative pathology. Under acute stress, the BBB undergoes reversible increases in permeability,[112,115–117] whereas chronic stress leads to long-term, irreversible structural damage.[118]

Stress disrupts BBB integrity through multiple convergent pathways, including inflammation, oxidative stress, and activation of the HPA axis. CORT increases the expression of endothelial tight junction proteins.[119] In addition, disruption of the HPA-axis negative feedback loop has been shown to hyperactivate the peripheral immune system, resulting in BBB hyperpermeability.[120]

Under conditions of sustained stress, astrocytes and microglia shift into reactive states.[121,122] Stress systems and AD converge on these reactive glial populations, promoting a pro-inflammatory state that is initially protective but becomes detrimental when reactivity persists.[123,124] Reactive astrocytes and microglia secrete vascular endothelial growth factors, matrix metalloproteinases, nitric oxide synthase, and pro-inflammatory cytokines, which downregulate tight junction proteins including claudin-5, occludin, and zonula occludens-1.[125–128] During sustained inflammation, reactive microglia migrate to the cerebral vasculature, phagocytose astrocytic endfeet, and increase BBB permeability.[129] In cellular models, cytokine exposure induces upregulation of BACE1, directly implicating reactive inflammatory states in fibrillogenic Aβ peptide formation.[130] Notably, astrocytes located near Aβ plaques exhibit more sustained reactive states when exposed to elevated CRH.[130]

4 | SLEEP AND CIRCADIAN RHYTHMS AS MEDIATORS AND AMPLIFIERS OF STRESS'S RELATIONSHIP TO AD

There is a notable interplay among the circadian, sleep, and stress systems, complicating efforts to isolate the contributions of stress to AD pathogenesis independent of the mediating effects of sleep. Stress has been shown to affect the circadian phase, and stress-related disorders are strongly associated with disturbances in sleep and circadian rhythms.[131] A single stress induction can shift the phase of locomotor activity and reprogram suprachiasmatic nucleus (SCN) activity in rodent models.[132–134] Conversely, circadian disruption and sleep disturbance are also core features of stress-related disorders and are commonly observed in PTSD, highlighting a reciprocal relationship in which stress-induced circadian disruption and sleep dysfunction reinforce one another.[135]

Circadian disruption is increasingly implicated in the pathogenesis of neurodegenerative disease, including AD. Patients with AD exhibit marked alterations in circadian rhythms, including phase shifts and reduced amplitudes of core body temperature and activity rhythms compared with age-matched controls.[136,137] Similar disturbances are recapitulated in multiple transgenic mouse models of AD, where alterations in circadian locomotor activity often precede the appearance of classical pathological hallmarks such as Aβ plaques and neurofibrillary tangles.[136,138] These findings suggest that circadian dysfunction may represent an early and contributory feature of disease progression rather than a secondary consequence.

Stress may exacerbate these vulnerabilities by engaging wake-promoting neuromodulatory circuits that are themselves selectively affected early in AD.[139] Activation of the HPA axis and CRH signaling recruits arousal-promoting systems, including the LC and orexin/hypocretin neurons, to sustain wakefulness and vigilance.[140,141] Orexin signaling can directly stimulate HPA-axis output, while CORT and stress-related neuromodulators further enhance wake drive, establishing bidirectional coupling between stress neuroendocrine activation and arousal circuitry.[142,143] In AD, early tau inclusions and degeneration within the LC and other wake-promoting nuclei provide a substrate through which stress-induced hyperarousal may intersect with selective circuit vulnerability.[63,139,144–147]

Sleep disruption is increasingly recognized not only as an outcome of AD but also as a driver of pathological processes. Experimental sleep deprivation and sustained wakefulness increase interstitial Aβ levels and accelerate plaque deposition in animal models, with orexin signaling acting as a critical mediator of this effect.[148,149] In humans, reduced slow-wave sleep and increased sleep fragmentation are associated with greater Aβ and tau aggregate burden, as measured by cerebrospinal fluid and positron emission tomography biomarkers.[150–152] A possible mechanism linking sleep to AD pathogenesis is the glymphatic system, a brain-wide perivascular network that clears metabolic waste, including Aβ and tau.[153] Glymphatic activity markedly increases during slow-wave sleep compared to wakefulness, driven by delta oscillations that rhythmically expand interstitial spaces and promote cerebrospinal fluid influx.[154] The system depends on aquaporin-4 (AQP4) water channels on astrocytic endfeet, and AQP4 polarization is disrupted by both poor sleep quality and AD pathological lesions.[153] Glymphatic dysfunction may therefore represent a mechanistic link through which chronic sleep disruption promotes Aβ accumulation, creating a self-reinforcing cycle.

Emerging evidence suggests that elevated norepinephrine signaling and chronic sleep fragmentation can promote the formation of toxic Aβ and tau species within LC neurons themselves, potentially accelerating degeneration of wake-promoting circuits.[155] As these circuits deteriorate, sleep quality worsens and stress sensitivity increases, impairing negative feedback regulation of the HPA axis and promoting persistent neuroendocrine activation. Together, these processes may establish a positive feedback loop in which stress, sleep disruption, and degen-

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eration of wake-promoting circuits mutually reinforce one another, amplifying vulnerability to AD progression.

5 | CLINICAL IMPLICATIONS

Chronic stressors are clearly relevant in investigations of modifiable risk factors for AD. Stress's role as a risk factor for AD has been elucidated through mechanistic studies connecting neuroendocrine systems to AD pathophysiological processes. There is also evidence that AD increases stress neuroendocrine markers, potentially creating a positive feedback loop. It is unclear whether this pattern is a result of dementia due to AD acting to increase stress, AD pathological processes directly acting on stress neuroendocrine markers, or both.

5.1 | Stress system signaling in AD

Cross-sectional and longitudinal studies have shown that AD patients show significantly reduced HRV, reflecting decreased parasympathetic and increased sympathetic activity.[57,68–70] Further, lower HRV correlates with more severe cognitive impairment and disease progression.[68,70] Consistent with this increased sympathetic activity, AD patients have higher skin conductance levels compared to controls.[71]

Associations between HPA-axis hormone levels and AD severity and progression are mixed. Many studies have shown positive associations between HPA-axis hormone levels and AD risk, severity, and progression.[7,156–164] Some have shown null or even negative associations, though.[8–10,165–169]

Interpreting higher CORT level itself as a marker of higher stress should be taken with caution. A high CORT level can be indicative of a normal response to high stress exposure or hyperactivation of the HPA axis, and a low CORT level can be indicative of low stress exposure or hypoactivation of the HPA axis. HPA-axis stimulation tests (e.g., cosyntropin stimulation test, dexamethasone suppression/CRH stimulation test) are used to probe feedback loops for HPA-axis regulation. An inadequate CORT rise in the cosyntropin stimulation test indicates impaired adrenal responsiveness and supports a diagnosis of adrenal insufficiency. In contrast, escape of ACTH and CORT from suppression in the dexamethasone suppression/CRH stimulation test suggests impaired central HPA-axis feedback regulation, commonly associated with hippocampal hypofunction. The application of these tests in cohorts of AD patients compared to controls has reinforced the possibility that HPA-axis hypersecretion is due to impaired regulatory control rather than actual stress exposure.[170,171]

The collective body of literature surrounding CORT levels and AD must be interpreted in the light of CORT's native roles in the stress response. Hypoactivation of the HPA axis during and immediately following a stressor is associated with negative outcomes, including prolonged adrenergic arousal, suboptimal energy mobilization, exaggerated pro-inflammatory cytokine release, and PTSD incidence.[172] Altered HPA-axis regulation, including evidence for enhanced CORT negative feedback in PTSD, has been suggested to play a role in the increased burden of physical illness seen in affected individuals.[173] Hyperactivation or prolonged activation of the HPA axis is also associated with numerous adverse outcomes including immunosuppressive phenotypes, metabolic strain (e.g., insulin resistance, visceral adiposity), and increased hippocampal atrophy,[174,175] which are associated with greater cognitive decline.

5.2 | Selective vulnerability in AD and stress signaling measurement

A potential challenge in interpreting stress reactivity and associated biomarkers in the context of AD is the overlap between neurodegenerative patterns and stress circuitry. Over a dozen subcortical neuromodulatory structures, including noradrenergic, serotonergic, cholinergic, and orexinergic nuclei, show abnormal tau neuronal inclusions in AD prior to the entorhinal cortex.[176] In particular, the noradrenergic LC and lateral hypothalamic (LHA) orexin neurons feature significant neuron loss very early in AD progression.[63,64,147,177–179]

The LC is the brain's main source of norepinephrine and is central to arousal, attention, and physiological and behavioral response to stress. In response to stressors, the LC noradrenergic system is activated by CRH inputs from the paraventricular hypothalamus, amygdala, and medial prefrontal cortex projections.[81] Its activation increases arousal, vigilance, and primes the body for adaptive responses.[66,67] LC activity is tightly linked to threat perception, emotional intensity, and the regulation of anxiety and stress reactivity. The early loss of LC neurons in AD would blunt the brain's ability to mount normative arousal and stress responses. This could manifest in diminished autonomic and subjective stress responses.[180] LC degeneration can also associate with decreased adaptive stress responses (i.e., resilience) due to the reduced functional coupling with the amygdala.[66,67,180]

LC degeneration may confound the interpretation of stress using stress biomarkers in AD. Acute stress is associated with decreased HRV and increased skin conductance. Because of the reduced sympathetic outflow and suppression of parasympathetic tone due to LC degeneration, AD patients would be expected to exhibit blunted HRV and skin conductance responses. Studies in older adults using LC imaging have supported this relationship.[181,182] Blunted HPA-axis activation has also been associated with the loss of LC neurons.[126,183]

LHA degeneration similarly may blunt stress perception and reactivity. The LHA integrates signals related to arousal, motivation, and homeostasis for stress response orchestration. The loss of LHA orexinergic and CRH-responsive neurons reduces the anxiety and stress-induced behavioral changes.[184–186] LHA degeneration would, like the LC, impair activation of the HPA axis.

Curiously, despite the early LC and LHA degeneration established in AD, CORT levels tend to be higher in AD patients compared to controls. While acute HPA-axis activation may be blunted by their degeneration, there is less control over baseline secretion levels. The elevated average CORT levels in AD patients likely reflect tonic disinhibition that may wash out the effects of LC- or LHA-associated phasic

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dysregulation. This tonic disinhibition may instead be attributable to degeneration of other systems, particularly in more advanced AD clinical stages.

Hippocampal degeneration is the main correlate of episodic memory decline – the primary clinical feature of AD. Its degeneration is also associated with impaired emotional regulation, often resulting in increased anxiety-like behaviors.[187–189] The impaired memory formation and recall resulting from hippocampal degeneration can further affect the perception and processing of stressful experiences.[187,190,191] Critically, the hippocampus acts through GABAergic relays to shut down HPA-axis activation via top-down negative feedback.[192] As an inhibitor of the HPA axis, degeneration of the hippocampus leads to impaired feedback, which, unlike the LC and LHA, results in prolonged and exacerbated CORT secretion in response to stress.[187,189]

Structural atrophy changes in the medial prefrontal cortex can precede overt dementia symptoms in AD.[193,194] Medial prefrontal cortex degeneration would shift autonomic signaling toward sympathetic dominance and diminish inhibition over the basolateral nucleus of the amygdala and the paraventricular nucleus CRH neurons, thereby prolonging ACTH and CORT secretion.

Given the overlap between AD degenerative patterns and stress circuitry, stress researchers are confronted by a unique challenge in the dementia population. While thought to be objective measures of stress, certain stress biomarkers (e.g., CORT) are poorly representative of stress severity and stress experiences due to the degeneration of stress regulatory structures. At the same time, anosognosia, impaired self-appraisal and lack of insight in certain dementia populations, diminishes a person's ability to both perceive stress and report on it.[195] Given the challenges in measuring both perceived stress and stress responses, extra care should be exercised in structuring research studies and clinical care focused on stress in dementia populations.

5.3 | Interventions

Public health approaches mitigating certain kinds of stressors – especially social isolation and ACEs – may measurably decrease AD incidence.[34,39–41] Especially in early AD clinical stages, stress-lowering approaches may improve quality of life for patients and caregivers. Research on stress-lowering approaches have included mindfulness practices,[162,196,197] music therapy,[198] and cognitive behavioral therapy.[199] During advanced AD stages, there is some evidence for benefits from stress-lowering interventions on quality of life and mood, but there is less evidence for cognitive benefits.[200,201]

Epidemiological models incorporating stress biomarkers have supported the hypothesis that high circulating CORT is tied to cognitive decline.[202,203] Based on this hypothesis, elevated CORT has been targeted in clinical trials as an AD treatment. Specifically, trials have sought to inhibit 11β-HSD1 activity, focusing pharmacological effects on cortisol resynthesis from cortisone in the brain instead of inhibition of the HPA axis. The primary outcomes for these trials include cognitive performance and AD biomarkers (e.g., Aβ, tau, brain atrophy). Some programs have been halted due to futility analysis, while others remain in trials.

Because of the degenerating regulatory structures that control stress neuroendocrine systems, stress-lowering approaches alone might not mitigate phenotypes such as high circulating CORT. While elevated CORT levels in AD may not be entirely explained by high stress exposure or experience, it should not be ignored. High circulating CORT levels can have additional adverse effects in older adults including metabolic complications, sarcopenia, and impaired immune defense.[204,205] Clinical studies should evaluate whether monitoring and pharmacologically addressing CORT hypersecretion might benefit these comorbidities of AD.

Additionally, pharmacological targeting of neuromodulatory systems that degenerate in early AD stages may influence stress neuroendocrine systems. Despite the early vulnerability of LHA orexinergic neurons in AD, there is paradoxically increased orexin activity.[206] Dual orexin receptor antagonists (DORAs) are currently being evaluated to stabilize sleep dysfunction due to orexinergic signaling dysregulation in AD. A randomized controlled trial demonstrated that acute suvorexant administration decreased phosphorylated tau-181 by approximately 10% to 15% and Aβ concentrations by approximately 10% to 20% in cerebrospinal fluid compared to placebo, providing early evidence that DORAs may modulate AD biomarkers.[207] Atomoxetine, a noradrenaline reuptake inhibitor, is also being evaluated in early clinical AD stages to recover lost noradrenaline signaling due to LC degeneration.[208] Because orexin and noradrenaline can stimulate the HPA axis,[206] follow-up trials should include monitoring of diurnal CORT secretion.

6 | FUTURE DIRECTIONS

Future research addressing the role of stress in AD must confront the fundamental measurement constraints inherent in studying stress in AD. In the context of progressive degeneration of stress-regulatory circuits, single biomarkers cannot be assumed to comprehensively index stress exposure or severity. Accordingly, studies should adopt multimodal, disease stage-aware approaches that integrate subjective measures, longitudinal endocrine profiling with diurnal resolution, autonomic physiology, and neuroimaging markers of circuit integrity.

There is a remaining need to clarify the temporal and causal relationships between stress and AD. Stress and stress neuroendocrine systems may function as risk factors, emerge because of early neurodegenerative changes, and act as an amplifier of downstream pathological processes. Disentangling these possibilities will require longitudinal studies that jointly track stress-related measures and AD biomarkers throughout healthy aging into AD. Future work should also explicitly test whether stress primarily lowers resilience within selectively vulnerable circuits or instead engages distinct pathological pathways such as tau and Aβ modulation, neuroinflammation, or BBB dysfunction.

Mechanistic investigations would also benefit from greater circuit- and cell-type specificity. Given early involvement of the LC, LHA, hippocampus, and medial prefrontal cortex, stress-related neuroen-

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docrine phenotypes in AD may reflect degenerating neuromodulatory control and feedback regulation rather than actual stress exposure. Experimental models should therefore move beyond simple hormone application paradigms toward approaches that incorporate partial loss or dysfunction of stress-regulatory circuits and examine downstream effects on neuronal, glial, and vascular processes relevant to AD. Interventions must also carefully consider relevant outcomes to test in clinical trials.

Finally, translational and clinical studies should treat stress biology as a stratification dimension rather than a uniform therapeutic target. Behavioral stress-reduction interventions may improve quality of life without normalizing underlying endocrine dysregulation, whereas pharmacological approaches targeting CORT, orexinergic, or noradrenergic systems may have stage-dependent and circuit-dependent effects. Given the challenges in measuring both perceived stress and stress responses, it is prudent to understand the unique effects of neurodegeneration on stress and stress measures. Extra care should be taken in structuring research studies and clinical care programs focused on stress in dementia populations.

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CONFLICT OF INTEREST STATEMENT

CEM sits on the executive committee for the Neuropsychiatric Syndromes PIA for the International Society to Advance Alzheimer's Research and Treatment (ISTAART). AJE is the chair of the executive committee for the Neuromodulatory Subcortical Systems PIA for ISTAART and serves as the guest editor for the Neuromodulatory Subcortical Systems special issue for *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*. AJE also sits on the advisory board for the Genomic Answers for Children's Health Alliance under the organization of Leavitt Partners. Further, AJE has patents pending for methods related to histological labeling of epitopes and a method for RNA aptamer-based therapeutics. SGE, JP, TCN, and DAK have no relevant conflicts to disclose. Author disclosures are available in the Supporting Information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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