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REVIEW ARTICLE

Mechanisms of comorbidity between Alzheimer's disease and pain

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ABSTRACT

Clinical studies have revealed a significant correlation between pain and neurodegenerative diseases, particularly Alzheimer's disease (AD). However, due to cognitive and speech impairments, AD patients, especially those in moderate to severe stages, are often overlooked in pain management. The challenges in obtaining pain-related information from this population exacerbate the issue. Although recent clinical research has increasingly recognized the comorbidity of AD and pain, the pathological alterations and interactive mechanisms underlying this relationship remain inadequately explored. This review provides a comprehensive analysis of the clinical features and pathological mechanisms of AD with and without pain comorbidity. It examines underlying processes, including neuroinflammation, peripheral-central immune interactions, and neurotransmitter dynamics. Furthermore, it highlights current pain assessment and management strategies in AD patients. By offering a theoretical framework, this review aims to support the development of effective pain management approaches and serve as a reference for clinical interventions targeting AD-associated pain.

KEYWORDS
Alzheimer's disease, Clinical studies, Mechanism, Pain, Treatment

Highlights

- The comorbidity between AD and CP encompasses multiple interrelated biological pathways, such as neurodegeneration and inflammatory responses.
- The damage to neurons and synapses in AD patients influences the brain regions responsible for processing pain, thereby reducing the pain response.
- Neuroinflammation plays a vital role in the development of both AD and CP. Enhanced inflammatory responses have an impact on the CNS and promote sensitization.
- Common neurotransmitter alterations exist in the comorbidity of AD and CP, influencing cognition, emotion, and pain perception.

Kaifang Yao contributed equally to this study.

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1 | INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder of the central nervous system (CNS) characterized by cognitive decline, memory loss, aphasia, apraxia, agnosia, and behavioral changes. With the rapid growth of an aging population, dementia affects approximately 50 million people globally, a number projected to double by 2050. As the most prevalent form of dementia, AD represents a substantial medical and societal burden.[1] Recent clinical research suggests shared risk factors between AD and chronic pain (CP), including aging, family history, depression, and social isolation. In addition to cognitive deficits, many AD patients experience CP, which significantly impairs their quality of life.[2–4] AD primarily affects older adults, with the majority of diagnoses occurring in individuals aged 65 years and older. Within this age group, the prevalence of AD ranges from 10% to 15%, increasing sharply with age. Similarly, CP is prevalent among the elderly population, with 25% to 50% of AD patients reporting CP. The concurrent rise in the prevalence of AD and CP highlights the need for targeted management strategies.[5,6] Cognitive decline in AD patients complicates the recognition and treatment of CP. Difficulties in accurately articulating the pain location and intensity often lead to underdiagnosis and undertreatment. Despite these challenges, CP remains a critical factor having a substantial negative impact on the quality of life of AD patients, emphasizing the importance of effective pain assessment and management strategies.[7]

Pain is a multidimensional experience encompassing sensory, emotional, and cognitive elements and results from actual or potential tissue damage.[8] In AD patients, the interplay between pain and cognitive dysfunction is particularly evident. Pain-related changes in emotion and cognition – such as anxiety, depression, and cognitive impairment – can significantly alter patients' pain perception and expression. These effects are particularly evident in AD patients with impaired cognitive function. High-order brain functions integrating emotional and cognitive responses to pain undergo substantial changes in AD, affecting CNS adaptive processes.[9,10] Research indicates that pain thresholds may vary in AD patients across disease stages. Pain perception and expression are affected by the stage of AD progression.[11] Early-stage AD patients are more likely to report pain than those in moderate or severe stages, where pain perception and expression diminish significantly. Moreover, the neural circuits through which AD mediates pain perception are different at different disease stages. The ventral striatum, a key structure in the brain's pain network, is severely affected by AD. In mild to moderate stages, pain activates the ventral striatum more intensely; however, the degree of this activation diminishes as AD progresses, and these behavioral changes become less pronounced.[12] Epidemiological data show that 24.9% of nursing home residents with severe cognitive impairment report pain, compared to 40.4% of residents without cognitive impairment.[13] These findings suggest a correlation between AD severity, pain tolerance, and the ability to communicate pain. As the disease progresses, patients exhibit higher pain tolerance and reduced ability to express pain. Neuropathological changes in AD, including neurotransmitter imbalances and heightened neuroinflammation, may directly or indirectly disrupt pain perception pathways and pain processing mechanisms.[14] Pain management in AD is particularly challenging because of patients' altered responses to medications compared with the general population. AD patients often require larger doses of analgesics to achieve comparable pain relief, increasing the risk of side effects. Therefore, selecting pain management strategies with greater caution is crucial to avoid any side effects. This poses additional challenges to pain assessment and management in AD patients.[15] Therefore, through a review of the pathogenesis and clinical characteristics of AD and pain comorbidity, the molecular mechanism and potential biological links between the two were explored from the perspectives of neuropathology, neuroinflammation, interactions between central and peripheral nervous systems, and neurotransmitters. We also summarize effective tools for pain assessment in AD and existing treatment options. The review aims to offer evidence-based strategies for pain management in AD patients, thereby elevating their overall quality of life.

2 | CLINICAL FEATURES OF AD AND PAIN COMORBIDITY

Pain is a common clinical manifestation of AD, affecting approximately 45.8% of the estimated 50 million individuals diagnosed with AD across the world. In AD patients, pain is frequently expressed through nonverbal behaviors such as frowning, sighing, groaning, and occasionally aggressive actions.[7] Pain sensitivity fluctuates across different stages of the disease, and its presence has been demonstrated to accelerate AD progression. Furthermore, pain perception in AD patients disrupts various cognitive domains, including memory and attention, which adds to the complexity of this disease's management.[16–18] CP occurs in approximately 50% of all AD patients, and those with CP are 2.2 times more likely to develop cognitive impairment compared to those without CP.[19,20] A past revealed that elderly patients without CP before hip replacement surgery scored higher on visual tests than those with CP, demonstrating that patients without CP had slow cognitive decline.[20] Aurélien Mulliez evaluated the impact of CP and the long-term use of analgesics on the incidence of AD and found a significant increase in AD incidence in the CP population.[3] A meta-analysis demonstrated that persistent pain conditions, such as headaches and migraines, were risk factors for cognitive decline.[21–25] New evidence indicates that patients with osteoarthritis (OA) have a higher incidence of AD compared to those without OA.[26,27] Chronic lower back pain also slows down information processing, delays memory, reduces problem-solving abilities, and decreases language fluency.[28,29] Fibromyalgia also causes progressive cognitive decline.[30] Zhao found that patients experiencing pain in multiple locations have a higher risk of dementia and cognitive deficits, with accelerated brain aging resulting in an increased risk of mortality.[31] When compared to early-stage AD, patients with late-stage AD exhibit higher pain thresholds.[32] The use of Mini-Mental State Examination (MMSE) and electroencephalography (EEG) to assess the severity of AD revealed that AD patients demonstrated increased pain tolerance to electrical stimulation and arm ischemia, indicating that the more severe the cognitive impairment, the greater

the pain tolerance.[33] Ronald et al. conducted a cross-sectional study in comparison with controls and found that AD patients require higher temperatures to feel warmth and pain, suggesting a reduced sensitivity to thermal pain detection in AD patients. Consequently, before injuries are recognized and reported, patients experience more severe pain and tissue damage.[34,35] These studies collectively indicated that, as AD progresses, patients' ability to recognize and self-report pain declines.

3 | MECHANISM OF AD AND PAIN COMORBIDITY

3.1 | Neuropathological changes of AD and pain comorbidity

AD patients experience significant and widespread changes in brain structure and function. A hallmark of AD is neuronal dysfunction in regions such as the cerebral cortex and hippocampus.[36,37] The brain regions affected during neurodegenerative changes in AD patients partially overlap with brain regions related to pain processing.[38,39] These changes not only lead to direct impairment of cognitive function but also lead to the development of abnormal responses to pain sensation in patients.[40] The hippocampus, a key component of the limbic system, plays an important role in regulating both cognitive and pain function. Enhanced hippocampal myelination can alleviate memory impairments in mice with CP.[41] AD rats with hippocampal injury display reduced responsiveness to continuous inflammatory chemical stimulation in the orofacial area.[42] CP in APP/PS1 mice accelerates cognitive impairment by reducing hippocampal neurogenesis through CCL2/CCR2 signaling.[43] The hippocampus also participates in the cognitive regulation of pain through its connection with the prefrontal cortex (PFC).[44] The PFC combines pain-related information with hippocampal memory imprinting to enable long-term storage of pain memories. Neuroimaging studies have revealed that the activity of the dorsolateral PFC (dlPFC) is related to the pain escape response in animals, and the pain areas, such as the dlPFC, are continuously activated.[45] CP is related to changes in the brain structure of the temporal lobe. Patients with CP have thinner cortical thickness and increased cortisol levels.

Temporal lobe cortical areas (such as inferior temporal gyrus and middle temporal gyrus) are sensitive to cognitive changes in AD and can predict mild cognition. Adults with mild cognitive impairment (MCI) and thin inferior temporal gyrus cortex have an increased risk of developing CP.[46,47] The periaqueductal gray (PAG) is crucial for pain processing and regulation. It is a component of the descending pain modulation system (DPMS) and a major source of endogenous opioids. There is an excessive accumulation of Aβ in the brains of AD patients. Pathological changes such as tau hyperphosphorylation and neuronal damage can easily lead to impairment of the PAG function, which can affect the ability of AD patients with pain to release endogenous opioids as well as affect exogenous opioid analgesia. Drugs play a role in amplifying pain in AD patients.[48] The anterior cingulate cortex (ACC) is involved in cognitive function, emotion, and pain regulation. Brain imaging studies have demonstrated that ACC plays a role in the perception of memory nociceptive pain, which alters the activity of neurons in ACC in CP patients.[49,50] Cui et al. found that an AD model mice had reduced pain responses after complete Freund's adjuvant (CFA) induction, and the neural mechanism involved the loss of vertebral neurons and dendritic spines in the ACC brain region of AD mice, indicating that defects in ACC synaptic neurotransmission in AD are mediated by neuronal activity and affects the pain response.[5]

The locus coeruleus (LC) is a nucleus in the pons that innervates noradrenaline (NE) nerves in the brain. It has multiple functions in regulating attention, learning, memory, pain, and brain metabolism.[51] The ACC receives extensive projections from the LC, and optogenetic activation or silencing of LC neurons projecting to the ACC can enhance or weaken the formation of learning and memory.[52] CP induces LC activation and increases the release of NE in brain areas, leading to the activation of neuroinflammatory response in microglia.[53,54] Aβ can regulate striatal-enriched protein tyrosine phosphatase (STEP). The deposition of Aβ inhibits the enzyme activity of the antioxidant enzyme system, inducing an oxidative stress effect, that when mediated by Aβ continues to increase. Activation of STEP signaling lowers the pain threshold, making patients more sensitive to pain.[5,55] The aggregation of metabolic wastes, including tau proteins, induces a series of neuroinflammatory events such as the phagocytic effect of microglia, which leads to changes in the structure and function of the patient's brain. The disrupted regions include those areas of the brain that are crucial for processing pain information, such as the basal forebrain and the medial temporal lobe.[56] The structural changes in the brains of patients with AD may impair their sensory and emotional responses to pain, resulting in a blunted pain sensation. These studies indicate that the same brain regions are involved in the development and modulation of both diseases, which is the structural basis for the comorbidity of AD and pain, and that there are comorbid neuropathological links between the two.

3.2 | Role of neuroinflammation in AD and pain comorbidities

Neuroinflammation plays a pivotal role in the comorbidity of AD and pain, with activated microglia serving as key drivers of inflammatory processes.[57] Under normal physiological conditions, microglia maintain immune surveillance in the CNS, sensing and responding to variations in the brain microenvironment. When exposed to lesions or pathological stimuli, microglia become activated, directly or indirectly influencing both peripheral and central sensitization, which can lead to hyperalgesia and synaptic plasticity.[58] Activated microglia can polarize into two phenotypes: M1, which releases pro-inflammatory mediators and causes neurotoxicity, and M2, which exerts anti-inflammatory and neuroprotective effects.[59,60] Across AD stages, microglial behavior varies substantially throughout AD progression. In the early stages, microglia remain relatively functional, exerting protective effects by attempting to engulf and clear Aβ deposist.[60] However, excessive microglial activation leads to an elevated inflammatory response, neuroinflammation, neuronal damage,

and progression of neurodegeneration.[61] In later stages, microglia may lose functional efficacy, failing to respond adequately to pathological changes such as Aβ deposition and neurofibrillary tangles, thereby accelerating neuronal damage death and cognitive decline.[62] Weiner et al. were the first to report that neuronal damage was associated with CP states and microglial activation.[63] CP exacerbates neuroinflammatory responses by activating the LC-norepinephrine (LC-NE) system, increasing NE release in brain regions such as the PFC and the hippocampus. NE triggers pro-inflammatory activation of microglia, promoting the expression of inflammatory mediators such as cyclooxygenase-2 (COX-2) and prostaglandin E2 (PGE2) mediated by β-adrenergic receptors, which aggravate inflammatory responses and pain hypersensitivity.[64]

Glial cell activation and inflammatory factor release from macrophages can heighten neuronal excitability, increase pain sensitivity, and promote neuropathic pain (NP).[65,66] In a doxycycline-induced AD mouse model, in the late stages, microglia polarized to an M1 phenotype, leading to an increase in the expression of pro-inflammatory cytokines and pathological tau protein levels in neuronal soma, synapses, presynapses, and postsynapses. Treatment-inducing M2 microglia polarization alleviates AD-related NP in mice.[67] Moreover, activated microglia release inflammatory cytokines such as tumor necrosis factor α (TNF-α) and interleukin 1β (IL-1β), which in turn activate microglia to produce Aβ.[68,69] The inflammasome, an innate immune system sensor, regulates microglial activation to induce inflammation when exposed to risk signals. As a neuroinflammatory response, Nucleotide-binding oligomerization domain-like receptor pyrin domain-containing protein 3 (NLRP3) initiates an immune response after tissue damage.[70] Activating this inflammasome in AD induces IL-1β expression in the brain and a subsequent inflammatory response. NLRP3-related proteins can be inhibited to restore cognitive function in AD.[71] NLRP3 activation in animal CP models heightens inflammatory responses in local tissues, neurons, the spinal cord, and the brain, which are associated with pain initiation and transduction, amplifying pain perception.[72] Thus, NLRP3 is also an emerging therapeutic target for CP. For instance, NP is often accompanied by increased NLRP3 content in the spinal cord. Intrathecally injected NLRP3 inhibitors can relieve pain symptoms.[73] The brains of rats with trigeminal neuralgia (TN) exhibit degenerative changes, marked by increased NLRP3 inflammasome content in the cerebral cortex and hippocampus; an elevated microglial number; and heightened expression of NF-κB, p-NF-κB, and IL-1β in the cortical region. These pathological changes contribute to hyperalgesia, a condition characterized by heightened sensitivity to pain. Administration of the NLRP3-specific inhibitor MCC950 alleviates pain and memory deficits in TN rat models.[74] The NF-κB signaling pathway plays a key role in inflammation and pain. Its activation in microglia is associated with the propagation of tau protein pathology, exacerbating neurotoxicity and accelerating AD progression.[75]

Mouse models of AD have demonstrated that memory impairments and heightened nociceptive sensitivity induced by Aβ can be mitigated by treatment with 6-((4-fluorophenyl)selenyl)-9H-purine. This treatment decreased the expression of glial fibrillary acidic protein (GFAP) and NF-κB in the hippocampus, whereas it increased the levels of protective proteins, such as heme oxygenase-1 and peroxiredoxin-1. Additionally, it inhibited nuclear factor erythroid 2-related factor 2 (Nrf2) activity, thereby alleviating neuroinflammation and oxidative damage.[76] Tau protein, another key player in AD pathology, contributes significantly to neuroinflammation and synaptic loss. Under physiological conditions, tau functions as a cytoskeletal protein, supporting axonal transport, myelination, and synaptic plasticity. However, pathological accumulation of hyperphosphorylated tau is a hallmark of AD, driving neurodegeneration and impairing neuronal function.[77,78] Tau is also implicated in pain pathways. For example, studies comparing WT mice with tau-KO mice have found that the absence of tau reduces responses to acute painful stimuli. Excessive accumulation of hyperphosphorylated tau and microtubules disrupts neuronal development and connectivity, thus impairing pain sensitivity. In mice with nerve injury, hyperphosphorylated tau in the hippocampus worsens cognitive impairment and pain emotions.[79] In mice subjected to CFA-induced inflammatory pain, hyperphosphorylated tau in the spinal cord correlates with increased levels of IL-1β in the spinal cord and brain-derived neurotrophic factor (BDNF) in neurons. These changes contribute to heightened pain sensitivity. In such models, intrathecal administration of tau phosphorylation inhibitors, such as SSc, significantly alleviates pain, highlighting the link between tau pathology, cognitive deficits, and altered pain perception.[80] These findings underscore the interconnected roles of AD-induced neuroinflammation and neuronal damage in modulating pain transmission and processing of pain signals.

The experience of pain is often linked to nerve damage, the release of inflammatory mediators, and disruptions in neural circuits. Persistent pain typically triggers a neuroinflammatory cascade mediated by excessively activated microglia, which adversely affects brain function and exacerbates cognitive decline.[81,82] One significant player in this process is the P2 × 7 receptor (P2 × 7R), a member of the purinergic P2 receptor family. P2 × 7 is upregulated during inflammatory stimulation and has shown potential as a therapeutic target for AD.[83] In migraines, P2 × 7R activation promotes the formation of the NLRP3 inflammasome, initiating inflammatory responses by activating caspase-1. This results in glial cell proliferation, neuronal loss, and subsequent cognitive impairments.[84] Pretreatment of migraine mice with P2 × 7R antagonists alleviates migraine-associated cognitive deficits, highlighting the involvement of the P2 × 7R/NLRP3 signaling pathway in neuroinflammation-driven cognitive dysfunction.[85] IL-1β, a cytokine released by glial cells, is significantly elevated in the hippocampus of AD patients. Nerve damage further upregulates IL-1β in the sciatic nerve, plasma, and pain- and memory-related areas in the CNS, thereby activating microglia. In mice, intravenous neutralization of IL-1β or gene deletion of its products prevents hippocampal dysfunction, cognitive deficits, and pain behaviors induced by selective sciatic nerve injury (SNI). These findings suggest that IL-1β overproduction after injury is a shared mechanism underlying NP and memory deficits.[86] Moreover, elevated levels of plasma CXC motif chemokine 12 (CXCL12), pericerebral vascular macrophages, and hippocampal gliosis are observed in SNI mice. Blocking the CXCL12-CXCR4 signaling pathway restores memory and mitigates cognitive impairment in mice.[87]

Chronic stress also contributes to memory dysfunction in mice, as it disrupts the balance of Na/K-ATPase (NKA) in the CNS. Chronic stress reduces NKAα1 expression on microglial cell membranes while increasing free P2 × 7R levels, promoting potassium ion efflux. This activates the NLRP3 inflammatory signaling pathway, facilitating the release of IL-1β and leading to cognitive impairments and anxiety.[88] In mice with chronic constriction injury (CCI), decreased pain thresholds and increased expression of pro-inflammatory markers of microglia (eg, cluster of differentiation 68 [CD68], IL-1β, and TNF-α) in the hippocampus and spinal cord underscore the critical role of microglial activation and pro-inflammatory phenotype polarization in pain-induced cognitive dysfunction.[89] Toll-like receptors (TLRs) are widely recognized for their role in CNS neurodevelopment and cognitive function. For instance, TLR4 on hippocampal neurons binds to High Mobility Group Box 1 (HMGB1) ligands, activating the mitogen-activated protein kinase (MAPK) pathway. This induces phosphorylation of myristoylatde alaninerich C kinase substrate phosphorylation and mitochondrial calcium overload, which in turn increases Aβ levels.[90–92] TLRs are also key factors in pain mechanisms.[91,93] Similarly, Toll-like receptor 3 (TLR3) is involved in the neuroinflammatory responses of AD, where it senses Aβ to drive disease progression. In pain states, TLR3 activation is linked to memory loss after CP.[94] In CCI mouse models, TLR3 upregulation in the hippocampus exacerbates inflammation and apoptosis, while TLR3 knockout mice demonstrate reduced hippocampal inflammatory responses and apoptosis by inhibiting the Toll/IL-1 receptor-domain-containing adapter-inducing interferon-β/receptor-interacting protein 3/mixed lineage kinase domain-like protein signaling pathway. This suggests that pain-induced TLR3 activation disrupts synaptic plasticity and contributes to cognitive impairments after CP.[95] CP also triggers hyperphosphorylation and aggregation of the tau protein in the hippocampus, further damaging the structure and function of the hippocampus, ultimately leading to memory deficits.[96,97]

3.3 | Peripheral-central neuro-immune interactions aggravate AD and pain comorbidity

AD is increasingly recognized as a systemic condition involving intricate interactions between peripheral and central immune responses.[98] These neuro-immune interactions exacerbate the comorbidity of AD and CP by propagating inflammatory mediators, causing neurotransmitter imbalances, increasing oxidative stress, and altering gut microbiota. Peripheral tissue injury or inflammation releases various inflammatory mediators and chemokines that can enter the CNS via a compromised blood–brain barrier (BBB) or neural pathways.[99,100] This process activates glial cells, intensifying neuroinflammation. Dysregulated peripheral inflammatory markers are prevalent in AD patients. A meta-analysis highlights that elevated levels of markers such as IL-6 and C-reactive protein (CRP) are significantly associated with AD onset.[101,102] Chronic periodontitis, characterized by local and systemic inflammation caused by microbial infections, demonstrates a strong connection to AD. Pro-inflammatory factors such as CRP, immunoglobulin G (IgG), and IL-1β can cross the BBB via neural pathways, aggravating neuroinflammation. This cascade promotes Aβ accumulation, cognitive dysfunction, and worsened pain symptoms, including toothaches.[103–106] OA, a condition involving chronic peripheral inflammation, is another significant risk factor for the development and progression of AD. The persistent inflammatory response associated with OA is strongly positively linked to the loss of perceptual memory. In a large cross-sectional study of American adults, adults with OA were more prone to AD than those without OA.[107] Inflammatory factors such as IL-1β and TNFα, which are released in response to inflammation in the knee joint, can cross the BBB and activate microglial cells in the brain, contributing to neuroinflammation.[108,109] In animal models of OA, these inflammatory factors have been shown to increase the levels of reactive oxygen species (ROS) in the brain and exacerbate Aβ deposition in the hippocampus and cortex. Additionally, OA-related inflammation leads to a reduction in myelin protein and a decline in the number of hippocampal neurons. These findings suggest that OA promotes local peripheral inflammation and accelerates AD progression through systemic inflammation that impacts the brain.[110] Yahyah et al. established an OA model using transgenic AD mice (TAS10xTPM). Compared with normal mice, 14–28 days later, OA-induced inflammation alters the microglia content and p38 mitogen-activated protein kinase (p-p38) in the dorsal horn of the spinal cord. Over time, this leads to reduced pain sensitivity, as indicated by behavioral changes. Behavioral weakening indicates that AD may affect pain processing and perception through alterations in the opioidergic system.[111] Furthermore, chronic inflammation in OA can trigger central pain processing pathways, exacerbating CNS hypersensitivity and contributing to the pain symptoms observed in AD patients.[14,112]

In mouse models of AD with nerve injury, macrophages tend to accumulate at the injury site and polarize toward the M2 phenotype, releasing enkephalins. This process alleviates mechanical allodynia, suggesting that opioid receptor activity plays a role in mitigating pain in AD-related pain models.[113,114] Additionally, peripheral pain and inflammation can also influence the gut microbiota composition, which in turn interacts with the CNS through the gut–brain axis. Disruptions in this axis may contribute to neuroinflammation, neurotransmitter imbalances, and cognitive dysfunction, further exacerbating the comorbidity of AD and pain.[115–117] Additionally, infection and inflammation resulting from surgical trauma can increase the risk of cognitive decline, particularly in patients with subjective cognitive decline (SCD) and MCI.[118] Postoperative systemic inflammation worsens the imbalance in the intestinal microbiota and disrupts intestinal barrier function disruption, leading to increased neuroinflammation, BBB destruction, and tau protein production, which intensifies both impairment and pain.[119–121] The aforementioned studies underscore the significant role of peripheral-central nerve-immune interactions in the comorbidity of AD and CP. Emotional and cognitive changes in AD patients, such as shifts in emotional set cognition, can modulate the immune response by activating the nervous system. Conversely, changes in immune system activity can feed back to affect nervous system function, influencing pain perception and behavioral outcomes.

3.4 | Dysregulation of neurotransmitters is involved in AD and pain comorbidities

AD is characterized by profound alterations in neurotransmitter levels in the brain, including the loss of cholinergic neurons, impaired glutamatergic function, reduced gamma-aminobutyric acid (GABA) levels, and degeneration of monoaminergic neurons. These changes contribute not only to cognitive deficits but also to disruptions in the perception and processing of pain signals in the brain, creating a complex interplay between cognitive decline and CP symptoms.[122–124] One of the earliest and most prominent changes in AD is the degeneration of the cholinergic system, which is critical for learning and memory. The decline in acetylcholine (ACh) levels (a cholinergic transmitter) correlates directly with cognitive deficits and memory loss.[125] In AD, damage to cholinergic neurons reduces ACh synthesis and release, impairing pain perception and regulation. Persistent pain stimulation further exacerbates damage to cholinergic neurons, creating a vicious cycle of reduced ACh release and worsening symptoms. For instance, ACh synthesis is decreased in AD patients. Acetylcholinesterase inhibitors (AChEIs) mitigate this decline by inhibiting the breakdown of ACh, thereby prolonging its activity.[126] ACh receptors play a vital role in mediating the central processing of pain. The ACh receptor α7 nicotinic acetylcholine receptor (α7nAChR) on the surface of microglial cells plays a vital role in the cholinergic anti-inflammatory pathway. It interacts with ACh and regulates glial activation and the release of pro-inflammatory cytokines, influencing both cognitive functions and CP modulation.[127] For instance, experimental studies demonstrated that selective destruction of cholinergic neurons in the basal forebrain increases pain sensitivity, suggesting a direct link between cholinergic dysfunction and altered pain perception in AD.[128] Further evidence shows that modulating cholinergic activity in specific brain regions can impact pain processing. For example, inhibiting cholinergic neurons in the medial septum through chemogenetic methods decreases pyramidal neuron excitability in the rostral ACC while increasing excitability in the ventral hippocampal CA1, potentially producing analgesic effects. Both these changes may exert analgesic effects. Therefore, cholinergic system degeneration in the basal forebrain of AD patients may interfere with pain attenuation.[129] Neuronal activity in the ACC is related to CP intensity and duration. Activating cholinergic receptors in the ACC can alleviate CP symptoms.[128,129]

Activating central α7nAChR in the hippocampus also reduces neuroinflammation by downregulating glial activity and pro-inflammatory cytokines via the p-JNK-MAPK pathway, alleviating symptoms in chronic migraine models.[130] Glutamate, the brain's primary excitatory neurotransmitter, is essential for synaptic signaling and cognitive functions. However, excessive glutamate stimulation results in neuronal damage, a phenomenon known as excitotoxicity. This excitotoxicity can result in calcium overload, mitochondrial dysfunction, and neuronal apoptosis, contributing to AD pathogenesis.[131] Glutamate also plays a central role in transmitting pain signals from the periphery to the CNS. CP stimulation leads to heightened glutamate release in the CNS, increasing neuronal excitability and establishing central sensitization. This state amplifies and prolongs pain perception, which is often observed in AD patients.[132] Mice carrying two familial amyloid precursor protein (AβPP) CRND8 mutations exhibit significant neuropathological changes, including diffuse Aβ deposition, cognitive impairment, and altered pain sensitivity. These mice demonstrated reduced responses to acute noxious thermal and peripheral inflammatory stimuli but exhibited heightened sensitivity to persistent formalin-induced inflammatory pain. This hypersensitivity has been linked to a reduced expression of beta-endorphin precursors in the brain during chronic inflammation.

Electrophysiological studies have revealed increased glutamate release from nociceptive neurons in the spinal cord's dorsal horn of 11-week-old inflammatory mice, resembling the reduced pain sensitivity observed in AD patients to mild and moderate pain stimuli.[14,133,134] BDNF, highly expressed in the hippocampus, interacts with its receptor, tyrosine-protein kinase B (TrkB), to support neuronal growth, maintenance, and survival.[135] However, aggregated Aβ and tau proteins in AD brains lead to a decline in BDNF expression, impairing learning, memory, and pain modulation. BDNF is not only a critical mediator of cognitive function but also a key modulator of pain, particularly in response to peripheral inflammation. Inhibition of the BDNF/TrkB pathway disrupts neuronal function, affecting animal behavior, such as learning and memory impairment, pain perception, and movement disorders.[136–138] GABA, the primary inhibitory neurotransmitter, plays a pivotal role in modulating cognitive and pain processes. In AD, inhibition of hippocampal GABAergic neurons leads to memory impairment, with increased synaptic output observed in the CA1 and CA3 pyramidal cell layers of AD mouse models.[139] BDNF regulates GABAergic activity, but in AD, disrupted BDNF maturation in the hippocampus compromises GABAergic transmission, impairing memory and pain regulation.[140] In peripheral pain models, enhancing GABA receptor activity alleviates CP and mitigates AD symptoms, suggesting therapeutic potential.[141]

Inflammatory conditions trigger the release of nerve growth factor (NGF) from tissues, stimulating tropomyosin receptor kinase A (TrkA) receptors on neurons and contributing to pain. Pharmacological inhibition of NGF alleviates pain and has shown potential in reversing AD-related cognitive and pain symptoms.[142] Neuropeptide Y (NPY), a neurotransmitter predominantly found in sensory systems, is significantly reduced in the plasma of AD patients compared with controls.[143–145] NPY counteracts excitotoxicity, regulates calcium homeostasis, mitigates CNS inflammation, and treats pain by activating microglial NPY receptor signaling pathways.[146] The serotonergic system, vital for learning and memory, is compromised in AD, with reduced 5-hydroxytryptamine (5-HT) receptor expression in the hippocampus and frontal cortex.[147] Activation of 5-HT receptors, such as through systemic administration of TCB-2, enhances potassium chloride co-transporter 2 (KCC2) function, reducing NP, improving cognitive function in rats, and treating AD.[148] This finding supports the potential use of 5-HT modulation in treating both pain and neurodegenerative diseases. LC, a major source of NE, exerts descending inhibitory control over pain. In AD, severe neuronal loss

in the LC impairs this modulatory pathway, exacerbating pain and neurodegenerative processes.[149,150]

Opioid receptors are members of the G protein-coupled receptor (GPCR) superfamily and modulate neurotransmitters such as glutamate, serotonin, and neuropeptides, which are dysregulated in AD and accelerate the condition. The GPCR ligand enkephalin is involved in Aβ generation.[151,154] These receptors also regulate analgesia, synaptic activation, and neuroimmune responses, contributing to pain and memory mechanisms.[152] Synaptic plasticity is central to both memory formation and pain perception.[153] Synaptic loss is a hallmark of AD, contributing to memory deficits.[154] Dendritic spine morphology and density, which influence synaptic function, are altered by microglial activation, Aβ accumulation, and tau phosphorylation. These changes disrupt synaptic dynamics and exacerbate pain and cognitive decline.[50,155] Kim et al. discovered that physical injuries increased peripheral and central nerve excitability, activating signaling pathways such as mGluR5-Ca^{2+}-TSP-1, which enhance synapse formation and transmission efficiency, contributing to central sensitization.[156] Eto et al. demonstrated that in layer 2/3 neurons of the S1 cortex, synaptic remodeling in mice influenced the activity of neurons in the ACC, intensifying pain responses.[12] Diazepam, a GABA receptor modulator, produces analgesic effects, supporting the therapeutic overlap between AD and CP management. Aβ promotes glutamate and ATP release from astrocytes, and reduces synaptic molecules and dendritic spine density in adjacent areas. These alterations lead to a weakened upward facilitation of pain.[157] These studies have suggested pain and learning and memory mechanisms in the hippocampus and cerebral cortex at the neurotransmitter level are similar.

4 | PAIN ASSESSMENT IN AD PATIENTS

Due to cognitive and communication impairments, AD patients often struggle to self-report pain, making it challenging to evaluate and manage their pain effectively.[158,159] Studies have shown that individuals with better cognitive function report higher pain interference and more depressive symptoms, indicating that as AD progresses, pain is increasingly overlooked. To improve treatment outcomes and slow disease progression, accurately assessing both cognitive function and pain is essential.[160–162]

There are two primary categories of clinical pain assessment tools for AD patients, self-descriptive pain tools and observer pain assessment tools. Self-descriptive pain tools for AD patients comprise the Visual Analog Scale (VAS), which is suitable for young people, and the Numeric Rating Scale (NRS) and the Verbal Description Scale (VDS), which are more applicable to elderly people.[163] The VAS is a tool comprising a 10-cm horizontal line, with one end labeled "no pain" (usually scored as 0) and the other end marked "worst pain" (scored as 10). Patients are asked to mark their pain level along this line. It is simple and intuitive, allows continuous quantification, and is widely applicable across various pain types. However, its disadvantages include high subjectivity, limited usability for patients with cognitive impairments or communication difficulties, and difficulty in clarifying the clinical significance of minor changes. The NRS uses a scale of 0 to 10, where 0 represents no pain and 10 indicates the most severe pain. Patients select a number that corresponds to their pain level.[164] It is convenient to use, easy to understand and record, reflects pain severity relatively accurately, and can be used for various pain types. However, it does not adequately capture the nature of pain or the reasons for its variability and is subject to individual bias. The VDS uses descriptive words (eg, "no pain," "mild pain," "severe pain") to indicate pain intensity. This tool is particularly preferred by elderly people and can be used accurately in patients with mild to moderate cognitive impairment. It is easy for patients to understand and use and useful for distinguishing pain severity. The disadvantages of VDS are limited descriptive options, high subjectivity, and not sufficiently sensitive to changes in pain levels. The Iowa Pain Thermometer (IPT) is a modified version of the VDS, featuring seven descriptors of pain levels combined with the evaluator's input. AD patients often select IPT level 4. However, the IPT does not provide numerical values to assess sensitivity to changes in pain.[165] The Facial Pain Assessment Scale (FPS) uses a sequence of facial expressions to represent different levels of pain intensity. However, AD patients may struggle with facial expression recognition, leading to inaccurate assessment.[166]

Through a systematic search, 24 observer pain assessment tools were identified for AD patients,[163] of which the Pain Assessment in Advanced Dementia Scale (PAINAD) and the Doloplus-2 scale are commonly used clinically.[167] PAINAD, designed by American medical staff, is used for patients with cognitive dysfunction and limited expression ability. With this tool, the assessment is completed by family members or caregivers. The observations include pain-related aspects: breathing, abnormal sounds, facial expressions, and body postures, and higher scores on the assessment indicate more severe pain. This scale has strong reliability, is tailored to effectively assess the pain of patients with advanced dementia, and includes comprehensive assessment indicators. The disadvantages of PAINAD are the relatively narrow application range and the requirement for higher assessor proficiency.[168] The Doloplus-2 scale, designed by French geriatric experts, is a tool designed to evaluate pain in patients with limited communication abilities. Its score is directly proportional to the pain level, offering a structured approach to pain assessment. Another widely used tool, the Pain Assessment Checklist for Seniors with Limited Ability to Communicate (PACSLAC), consists of 60 detailed items, including expressions of pain and physical behaviors such as limping. This checklist is particularly effective for detecting pain in cognitively impaired patients due to its comprehensive coverage. However, its complexity and time-consuming nature can limit its practicality in certain clinical settings.[169] Functional MRI (fMRI) has emerged as a valuable tool for assessing pain in patients with mild to moderate AD. By identifying activity in pain-related brain regions, fMRI allows clinicians to pinpoint the location and intensity of pain in AD patients, offering insights that traditional observational methods might miss.[170] Wearable devices equipped with biosensors represent a promising innovation in pain assessment for AD patients. These devices monitor physiological

signals such as heart rate, respiratory rate, and skin temperature in real time, often integrating these data into smartphone program applications for easy access and analysis.[171] One example is an electronic textile (e-textile) tool, which employs multisensory stimulation interventions to assess and communicate pain non-verbally. With features like soft fabric for comfort and high sensor accuracy, these wearable technologies offer an alternative means of two-way communication between AD patients and caregivers.[171,172] They are particularly beneficial for individuals with severe cognitive or verbal limitations.

5 | TREATMENT OF AD AND PAIN COMORBIDITY

5.1 | Application of drugs in AD pain treatment

Opioid analgesics are commonly prescribed to treat AD-related pain. In the United States, opioid use for pain management in community-dwelling older adults with AD and related dementias increased from 15% in 2005 to 45% in 2015.[173–176] Similarly, in Finland, research has shown that potent opioids, including fentanyl, effectively alleviate both pain and pain-induced symptoms in AD patients.[177] Cannabinoids are emerging as promising therapeutic agents for elderly individuals with AD and CP. Clinical studies have demonstrated that cannabidiol, nabilone, and cannabis oil can significantly improve AD-related other physiological aspects and neuropsychiatric symptoms.[178] During pain transmission, peripheral noxious stimuli in the periphery (such as tissue damage or inflammation) activate peripheral nerve endings, generating pain signals that travel to the spinal cord and the brain through nerve fibers. This process, known as ascending pain transmission, can be modulated by cannabinoids. They not only inhibit the ascending transmission of pain signals but also enhance the DPMS in the CNS, further alleviating pain. Cannabinoids exert their analgesic effects primarily through CB1 and CB2 receptors.[179] When a CB1 receptor agonist binds to the CB1 receptor, it disrupts the transmission of pain signals and modulates the descending pain pathways, ultimately leading to pain relief. The amygdala, involved in emotional processing, and the PAG, a key component of the descending pain control system, both play critical roles in this process. CB2 receptor agonists, in particular, have been shown to inhibit pain circuits within these two regions and suppress pro-inflammatory pathways, reducing inflammation.[180] Additionally, CB1 receptor agonists can reduce Aβ accumulation in AD patients, which helps diminish neuroinflammation. The CB2 receptor agonist JWH-133, for example, reduces microglial reactivity and decreases the expression of the pro-inflammatory cytokines IL-1β, IL-6, TNFα, and gamma (IFNγ) in AβPP/PS1 transgenic mice. It also reduces the Thr181 site near Aβ plaques. These effects contribute to a reduction in tau hyperphosphorylation and improvements in cognitive function.[56,181,182]

Nonsteroidal anti-inflammatory drugs (NSAIDs), including COX-1 and COX-2 inhibitors such as diclofenac, ibuprofen, naproxen, and rofecoxib, are also integral in managing AD-related pain and cognitive decline.[183] NSAIDs work by inhibiting the synthesis of peripheral and central prostaglandins and lipoxygenase, as well as activating descending serotonin pathways to alleviate pain.[184] Epidemiological studies have reported that long-term use of NSAIDs in OA patients is associated with a slower progression and less severe cognitive decline in AD, compared with individuals who do not use NSAIDs.[185–188] In one study, AD patients used paracetamol more frequently. A prospective study in the UK involving 194,758 participants with CP, followed over 13.7 years, found that regular use of aspirin and paracetamol was associated with a higher risk of AD in individuals with CP.[189,190] NSAIDs are believed to influence the pathological progression of AD through their anti-inflammatory effects, such as reducing inflammation in the brain, inhibiting amyloid beta (Aβ) deposition, and preventing the formation of neurofibrillary tangles.[191] For example, diclofenac alleviates pain hypersensitivity and inflammation caused by CFA-induced arthritis in rats. It also reduces the levels of phosphorylated/total extracellular signal-regulated kinases 1 and 2 (pERK1/2) in regions of the brain, such as the spinal cord, LC, and PFC, and mitigates anxiety- and depression-like behaviors.[192] Furthermore, diclofenac inhibits the release of pro-inflammatory mediators from microglial cells, suppresses the NLRP3/IL-1β pathway, and reduces both peripheral and systemic inflammation, which in turn lessens the pathological manifestations of AD.[193]

Minocycline is a neuroinflammation inhibitor that suppresses microglial activation. Minocycline improves inflammatory pain and postoperative cognitive dysfunction in elderly patients following cardiac surgery.[194] In a mouse model of surgery, minocycline alleviated postoperative cognitive impairment and inflammatory pain by inhibiting IL-1-induced microglial activity.[195] TNF-α inhibitors, such as etanercept and infliximab, used in a phase I clinical study led to a 40.6% reduction in arcuate fasciitis-associated inflammation in AD patients treated with the drug XPro1595.[196] Activation of the glucagon-like peptide-1 receptor ameliorates NP-induced memory impairment, and its agonist Ex-4 inhibits NF-κB p65 by increasing the p-AMPKThr172/AMPK ratio, which reduces the expression of IL-1β and TNF-α. This not only reduces neuroinflammation but also protects neuronal plasticity in NP mice.[197] Transient receptor potential vanilloid type 1 (TRPV1), an ion channel protein involved in CP, can be activated by capsaicin, which desensitizes peripheral TRPV1 channels, exerting analgesic effects. In addition to its role in pain modulation, TRPV1 also influences synaptic plasticity, microglia-to-neuron communication, and brain development. Modulating TRPV1 can have therapeutic effects for both AD and pain.[198–202] TRPV1 also contributes to cellular energy metabolism by activating the mammalian target of rapamycin (mTOR)-AKT-hypoxia-inducible factor 1-alpha (HIF-1α) pathway, elevates the expression of the anti-inflammatory cytokine IL-10 in brain tissue, augments microglial immune function, reduces Aβ deposition, and improves cognitive function.[203,204] These studies collectively highlight the potential for a diversified approach to drug targeting in the treatment of both AD and pain comorbidities.

5.2 | Non-pharmacological treatment of AD with pain comorbidities

Non-pharmacological interventions hold significant promise in alleviating cognitive dysfunction, mood disturbances, and pain behaviors in AD patients.[7,205] Relevant clinical trials have revealed the positive effects of lifestyle interventions, such as balanced diets and improved sleep quality, particularly in patients with MCI.[206,207] For instance, the Mediterranean ketogenic diet has been found to promote changes in the serum microbiome and metabolites through the vagus nerve and immune system pathways. This diet boosts the levels of neuroprotective receptors, namely, glutamate and GABA in the hippocampus, thereby improving brain function.[208] Hypnosis has also proven effective in reducing uncomfortable symptoms such as pain and anxiety in AD patients undergoing procedures such as lumbar puncture.[209] Furthermore, sleep plays a crucial role in cognitional health. During sleep, neurons in the lateral hypothalamus produce melanin-concentrating hormone (MCH), which reduces CA1 neuron excitability in AD mice, helping to restore hippocampal function.[210] Both clinical and animal studies have reported that sleep disorders can exacerbate pain perception in AD patients.[211] Physical exercise has emerged as another promising lifestyle intervention. It inhibits microglial activation and the production of inflammatory mediators, such as TNF-α and IL-1β, in AD patients. Exercise also increases the serum and muscle levels of the anti-apoptotic factor miR-129-5p and the CNS anti-inflammatory factor IL-10, while promoting the expression of BDNF and remodeling brain neural circuits. By contrast, sedentary behavior has been linked to increased IL-1β concentrations and reduced BDNF in both humans and animals.[212–214]

Music therapy also exerts beneficial effects on the cognitive function of MCI patients to varying degrees, suggesting that it can promote analgesia through corticothalamic circuits.[215] In a randomized controlled trial, music intervention reduced pain and improved anxiety and depression in AD patients. Neuroimaging imaging studies have revealed that music activates regions in the left frontal lobe and cerebellum, which helps improve recall and memory.[216,217] Dance therapy, too, has been known to significantly improve cognition and memory in MCI and AD patients, thereby enhancing emotional well-being.[218,219] Among other therapies, repetitive transcranial magnetic stimulation (rTMS) has gained attention as a non-invasive treatment. It works by delivering a series of pulses rhythmically and repetitively, thus modulating neural activity and cortical excitability. rTMS is widely used in the clinical auxiliary treatment of various neuropsychiatric diseases.[220,221] High-frequency rTMS applied to the left parietal lobe has been shown to enhance visual recognition memory in AD patients by reducing oxidative stress and protecting mitochondrial function.[222] High-frequency rTMS also reduces microglial proliferation in AD mice, decreases pro-inflammatory factors, and activates signaling pathways, such as PI3K/AKT/GLT and BDNF/TrkB, thereby playing a pivotal role in neuroinflammation and improving the cognitive function of mice.[223–227] This technique also downregulates the overexpression of neuronal nitric oxide synthase in the ipsilateral DRG of NP rats, reduces hyperalgesia, and modulates neuroinflammation and neural plasticity.[228,229] Acupuncture and electroacupuncture (EA) exert positive effects on cognition and pain management in AD patients. The side effects of these treatments are mild and significantly less than those of drug treatment.[230–235] In mice, acupuncture suppresses inflammatory responses in the peripheral system and CNS by balancing the intestinal flora, improves cognitive ability, and reduces pain.[236–238] EA intervention in particular helps alleviate cognitive impairment by inhibiting hippocampal neuron apoptosis through activation of the PI3K/Akt signaling pathway, upregulating B-cell lymphoma 2 (Bcl-2) protein expression, and reducing Bcl-2-associated X (Bax) expression, thereby alleviating CFA-induced CP.[239] EA improves chronic inflammatory pain(CIP) while at the same time regulating 5-HT/GABA/Glu levels in the hippocampus by activating the BDNF/TrKB/cAMP-response element binding protein signaling pathway to prevent damage to neuronal synaptic plasticity.[240] In summary, non-pharmacological treatments for AD and pain comorbidities are becoming increasingly recognized and integrated into clinical practice.

6 | DISCUSSION

This review examines the factors contributing to pain sensitivity in the early stages of AD and the slowed pain response observed in its middle and late stages. In the early phase of AD, neuroinflammatory responses are triggered, leading to the activation of microglia in the brain of AD patients, which causes inflammation in the CNS. The subsequent release of pro-inflammatory cytokines and other mediators exacerbates both neurodegeneration and pain perception. Concurrently, peripheral and central inflammatory responses are heightened in CP conditions, further impacting the CNS through alterations in the BBB, which promotes central sensitization and accelerates AD progression. As AD progresses, the degeneration of the cholinergic system impairs both cognitive function and pain perception. Additionally, disruptions in the balance of other neurotransmitters such as serotonin, glutamate, NE, and dopamine can affect mood regulation and pain thresholds. CP may further disrupt these neurotransmitter systems, intensifying the amplification of pain signals. In the middle and late stages of AD, the over-phosphorylation of tau proteins and accumulation of Aβ plaques lead to widespread damage in brain regions involved in processing pain, particularly those responsible for emotional and cognitive functions such as the PFC and hippocampus. These alterations disrupt the brain's ability to receive and interpret pain signals accurately. Neuronal loss, synaptic dysfunction, and the presence of neurodegenerative pathological markers significantly impair the brain's capacity to regulate pain in AD patients, resulting in a blunted or diminished response to pain stimuli (Figure 1).

The comorbidity of AD and CP represents a critical area of both neuroscience and clinical research, especially given the high prevalence of these conditions in the elderly population. Although clinical attention paid to the pain assessment and management of AD patients has been increasing, the exploration of biomarkers associated with the comorbidity of AD and CP, such as inflammatory mediators, neurodegenerative markers, and neuroplasticity-related proteins, is still in its

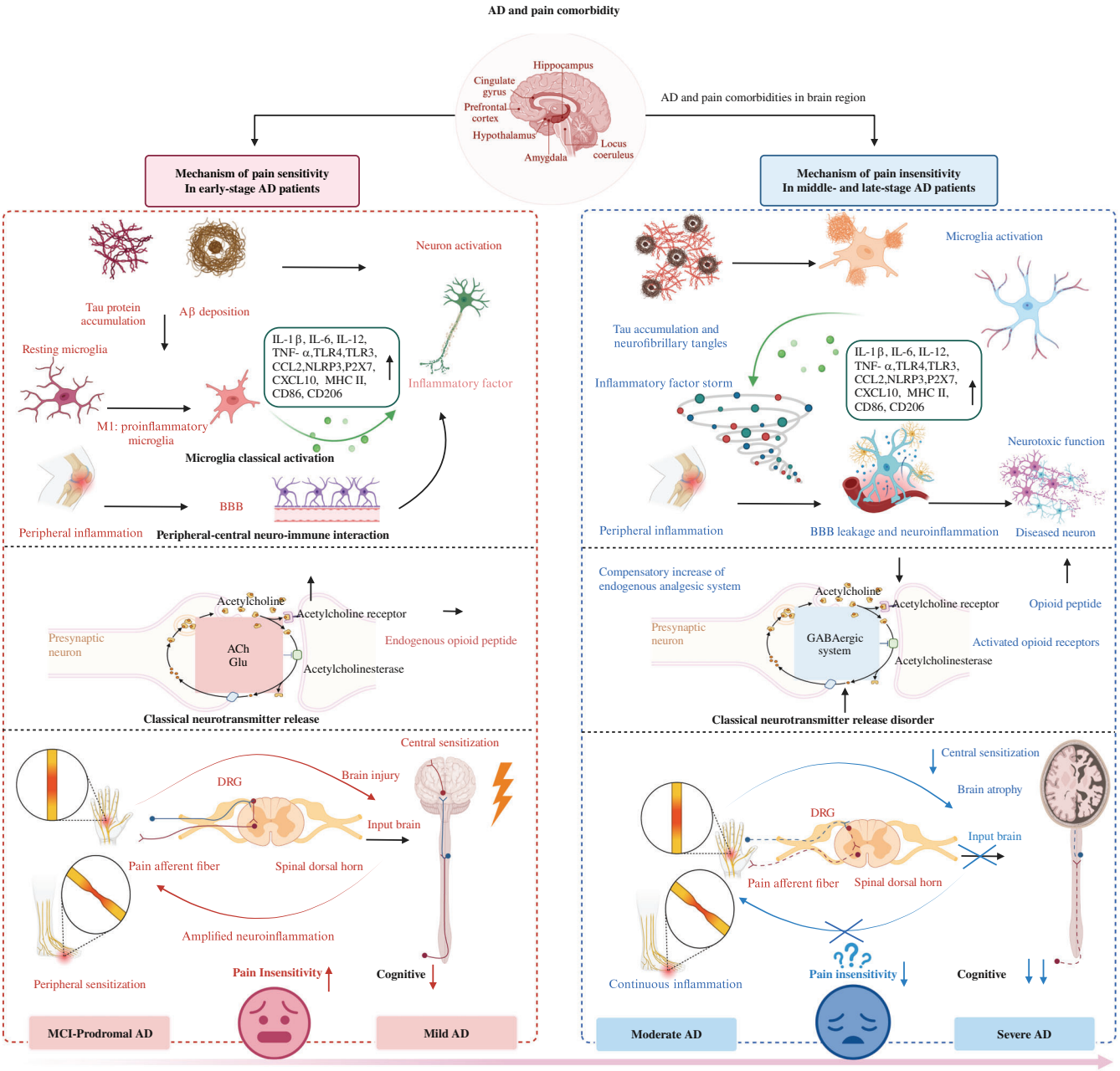

FIGURE 1 AD and pain comorbidity.

early stages. The complex interactions within neural pathways common to both AD and CP, particularly those involving inflammation, neurodegenerative changes, and central sensitization, are beginning to be understood. However, challenges remain because of the difficulties AD patients face in accurately expressing pain sensations, complicating pain assessment and management. Currently, a standardized pain assessment tool specifically for AD patients is lacking. Moreover, treatment strategies for AD and CP often conflict, especially with pharmacological treatments. Certain drugs used to manage pain may exacerbate cognitive decline or cause adverse side effects in AD patients, further complicating therapeutic interventions. Moreover, unified standards for evaluating the interplay between CP and AD are lacking. Most studies in this field rely on animal models or small-scale clinical trials, limiting the generalizability and applicability of findings.

To address these issues, more comprehensive and detailed experiments using animal models are required to better understand the underlying mechanisms of AD and CP comorbidity. Basic research findings should be actively translated into clinical practice, incorporating technologies such as neuroimaging to classify pain at various levels and improve diagnostic accuracy. Further investigation into the cellular and molecular complexities of brain adaptation during aging is essential. By combining dietary interventions, physical exercise, non-invasive brain stimulation, and pharmacological treatments, it may be possible to

engage multiple adaptive mechanisms that protect and maintain brain functions during aging. Additionally, a deeper understanding of these cellular and molecular mechanisms of adaptation and their application in clinical settings is crucial. Large-scale, multicenter clinical trials are necessary to validate the efficacy and safety of current treatment methods. These trials should explore differences across diverse patient populations, including variations in race, gender, and age, to facilitate a more comprehensive approach to AD treatment and management.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. 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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