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REVIEW

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Relationship between enriched environment and neurodegeneration: a review from mechanism to therapy

Yuan-qiao Xu[1,2,3†], Yanjiao Chen[4†], Jia-xin Xing[1,2,3*] and Jun Yao[1,2,3*]

Abstract

Enriched environment (EE), as a non-pharmacological intervention, has garnered considerable attention for its potential to ameliorate neurodegenerative diseases (NDs). This review delineated the impact of EE on the biological functions associated with NDs, emphasizing its role in enhancing neural plasticity, reducing inflammation, and bolstering cognitive performance. We discussed the molecular underpinnings of the effects of EE, including modulation of key signaling pathways such as extracellular regulated kinase 1/2 (ERK1/2), mitogen-activated protein kinases (MAPK), and AMPK/SIRT1, which were implicated in neuroprotection and synaptic plasticity. Additionally, we scrutinized the influence of EE on epigenetic modifications and autophagy, processes pivotal to ND pathogenesis. Animal models, encompassing both rodents and larger animals, offer insights into the disease-modifying effects of EE, underscoring its potential as a complementary approach to pharmacological interventions. In summary, EE emerges as a promising strategy to augment cognitive function and decelerate the progression of NDs.

Keywords Enriched environment, Neurodegeneration, Neuroplasticity, Anti-inflammatory, Cognitive function

Introduction

Neurodegenerative diseases (NDs), a heterogeneous group of conditions, are hallmarked by the relentless deterioration of neuronal function, culminating in significant cognitive and motor disabilities. Encompassing Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), Amyotrophic Lateral Sclerosis (ALS), and Multiple Sclerosis (MS), these disorders are underpinned by intricate pathogenic mechanisms. These include genetic predispositions, environmental triggers, and age-related factors, which converge on hallmark features such as protein misfolding, synaptic failure, and persistent inflammation. Despite their multifaceted origins, NDs are unified in their profound decrement in patients' quality of life and their considerable economic and societal impact, attributable to their chronic and currently incurable traits.

Enriched environment (EE) is housing condition that extends beyond the basic requirements of animal welfare to provide a complex and stimulating setting conducive to natural behaviors, play, motor activity, and new learning. These environments enhance sensory and motor stimulation, social interaction, and exploration. They promote neuronal plasticity and are associated with changes in neurochemistry and physiology, thereby

†Yuan-qiao Xu and Yanjiao Chen have contributed equally to this work and should be considered co-first authors.

*Correspondence:
Jia-xin Xing
jxxing@cmu.edu.cn
Jun Yao
yaojun198717@163.com
[1] School of Forensic Medicine, China Medical University, Shenyang, People's Republic of China
[2] Key Laboratory of Forensic Bio-Evidence Sciences, Shenyang, Liaoning Province, People's Republic of China
[3] China Medical University Center of Forensic Investigation, Shenbei New District, No.77, Puhe Road, Shenyang 110122, People's Republic of China
[4] Shanxi Provincial People's Hospital, Taiyuan, People's Republic of China

improving cognitive and motor performance. Furthermore, EE, a non-pharmacological intervention, can delay and alter the progression of diseases in various neurodegenerative disease models, offering a dynamic approach to enhance animal welfare and behavioral enrichment. By integrating a diverse array of sensory, motor, cognitive, and social stimuli, EE has demonstrated the capacity to augment neural plasticity, mitigate inflammatory responses, and ameliorate cognitive deficits. This review was poised to dissect the mechanistic linkages between EE and its effects on NDs, with a sharp focus on the modulation of neuroplasticity, anti-inflammatory activities, and cognitive enhancement. We delved into the molecular substrates underpinning the effects of EE, particularly the regulation of key signaling cascades, which were integral to neuroprotection and synaptic integrity. Additionally, we scrutinized the impact of EE on epigenetic modifications and autophagy, which processed pivotal to ND pathobiology.

Unraveling the intricate dynamics between EE and neurodegeneration is essential for devising innovative therapeutic strategies that may augment existing pharmacological treatments. This review endeavors to amalgamate the extant research, offering an exhaustive exposition on the potential of EE as a therapeutic adjunct in the management and amelioration of NDs.

Overview of enriched environment and neurodegeneration

Neurodegeneration

NDs are a group of conditions characterized by the progressive loss of nerve cells in the brain or peripheral nervous system, leading to a decline in function and ultimately cell death [1, 2]. These disorders encompass a range of diseases affecting the central nervous system, which are often closely associated with aging. Common examples include AD, PD. HD, ALS, and MS [3]. The loss of neuronal structure and function, including neuronal death and the imbalance of glial cells, can lead to cognitive impairments. The pathological hallmarks of NDs include the abnormal aggregation of pathological proteins, synaptic dysfunction, neuronal network disruption, protein homeostasis imbalance, cytoskeletal abnormalities, energy metabolism disorders, DNA and RNA damage, and chronic inflammatory responses [4]. These factors interact with each other, driving the progression of the disease, which can lead to brain and spinal cord dysfunction, affecting movement, cognition, and sensory functions [1].

Molecular mechanisms of neurodegeneration

The molecular mechanisms underlying NDs are complex and diverse, involving multiple biological processes. Pathological protein aggregation, neurofibrillary tangles, and mitochondrial dysfunction are among the factors that can contribute to the development of NDs. These processes can disrupt cellular homeostasis, leading to the progressive loss of neuronal function and structure [5]. For instance, in AD, the hyperphosphorylation of tau protein leads to the formation of neurofibrillary tangles, which are closely associated with cognitive decline and memory impairment [6]. Additionally, the accumulation of β-amyloid plaques is another hallmark of AD. In PD, the loss of dopaminergic neurons in the substantia nigra and the aggregation of α-synuclein are key pathological features, leading to motor dysfunction such as muscle rigidity, tremors, and gait changes [7]. Huntington's disease is caused by the expansion of the cytosine-adenine-guanine (CAG) repeat sequence in the huntingtin protein gene, leading to the aggregation of mutated huntingtin protein and negatively impacting mitochondrial function and metabolism as well as inhibiting the expression of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) [8]. In ALS, the degeneration of motor neurons results in progressive muscle weakness and atrophy [9]. Multiple Sclerosis is characterized by inflammation and demyelination in the central nervous system, causing impairments in neural signal transmission (Table 1) [10].

Pathogenesis of neurodegenerative diseases

The pathogenesis of NDs is multifactorial, involving genetic, environmental, metabolic, and age-related factors. Genetic predisposition plays a role in some forms of NDs, with certain mutations increasing the risk of disease development [11]. Exposure to toxins or pollutants, as well as protein metabolism abnormalities within the body, can also lead to NDs. Multiple sclerosis, for example, is an autoimmune disorder where the immune system attacks the central nervous system [12]. Dementia, a common consequence of neurodegenerative disorders, is characterized by a progressive and irreversible loss of cognitive function. Furthermore, many NDs are closely associated with aging, with the risk of developing these conditions increasing as one grows older [11].

At the molecular level, NDs involve the disruption of various cellular processes. Protein misfolding and aggregation lead to the formation of toxic species that can impair neuronal function [11]. Neuroinflammation, another key process in NDs, involves the activation of microglia and astrocytes in response to pathological stimuli such as protein aggregates, leading to a chronic inflammatory state that can exacerbate neuronal damage [13]. Altered cell signaling pathways, such as the Rheb/mTOR pathway, have been implicated in neuronal development, polarization, and network formation. These

Table 1 Comparison of several typical neurodegenerative diseases

The name of the disease	symptoms	Diagnostic methods	Treatment	Pathogenesis
Alzheimer's disease	Memory loss, cognitive decline, language impairment, mood changes	Cognitive tests, brain imaging tests, biomarker tests	There is currently no cure, and the main drugs are drugs to relieve symptoms and slow progression	β-Amyloid plaque formation, abnormal phosphorylation of tau protein leads to neurofibrillary tangles
Parkinson's disease	Motor dysfunction (e.g., muscle stiffness, tremor), gait changes	Clinical assessment of motor symptoms, dopamine transporter SPECT imaging	Dopamine replacement therapy, deep brain stimulation	Decreased dopaminergic neurons, particularly in the substantia nigra compacta
Huntington's disease	Chorea, cognitive decline, psychiatric symptoms	Genetic testing, neuropsychological evaluation, brain imaging	There is currently no cure, and the main treatment is symptom management	The huntingtin gene CAG trinucleotide repeat results in protein aggregation
Amyotrophic lateral sclerosis	Gradual weakening and atrophy of muscles, loss of motor function	Neuromuscular examination, electromyography, MRI of the brain and spinal cord	There is currently no cure, supportive care, and symptom relief	Upper and lower motor neurons are damaged, and the cause is not fully understood
Multiple sclerosis	Limb weakness, paresthesias, decreased vision, lack of coordination	Spinal tap, magnetic resonance imaging, evoked potential testing	Corticosteroids reduce neuroinflammation, disease-modifying therapies, stem cell transplants	Abnormalities in the immune system that attack the protective membrane (myelin) of nerve cells in the brain, optic nerve and spinal cord

pathways are also related to the pathogenesis of NDs [14]. The mTOR pathway is crucial for neuronal survival and dysfunction of this pathway can contribute to neurodegeneration. Additionally, the blood–brain barrier (BBB) plays a critical role in the pathogenesis of NDs by regulating the exchange of molecules between the central nervous system (CNS) and the periphery, and its dysfunction can contribute to neuroinflammation and neurodegeneration [15].

Epigenetic modifications, particularly DNA methylation and hydroxymethylation, can significantly affect NDs. TET family proteins (TET1, TET2, and TET3) affect memory formation, hippocampal neurogenesis, and cognitive function in adult mice by regulating DNA methylation levels [16, 17]. Knockdown of TET1 can lead to impaired neuronal regeneration in the hippocampus of mice, resulting in abnormal learning, memory, and synaptic plasticity. Additionally, the loss or dysfunction of TET2 and TET3 can also affect cognitive function [18, 19].

Overall, NDs are characterized by a complex interplay of molecular mechanisms, including protein aggregation, synaptic dysfunction, and chronic inflammation, which contribute to the progressive loss of neuronal function and cell death. Neurodegenerative disorders pose significant challenges due to their progressive nature and impact on neurological function [20]. Understanding these mechanisms is crucial for the development of effective treatments and interventions aimed at improving the quality of life for individuals affected by these conditions (Fig. 1).

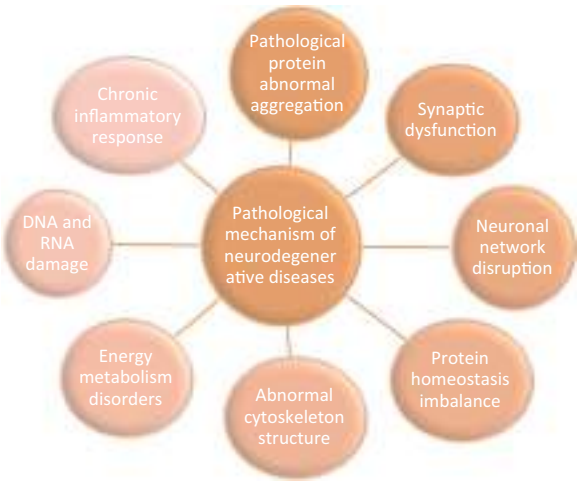

Fig. 1 Pathological mechanism of neurodegenerative diseases

Enriched environment

Definition and components of enriched environment

Enriched environment (EE) is a specialized living condition designed to promote the structural and functional development and recovery of an organism's brain, as well as enhancing cognitive behavioral performance, by increasing sensory, motor, cognitive, and social stimulation [21]. This multifaceted approach involves complex non-biological and social stimuli, playing a significant role in the plasticity of the central nervous system [22]. D. Shepherdson et al. further described EE as a method to alter the environments of captive animals for their benefit, with benefits including the enhancement of capillaries and the provision of additional energy to neurons and glial cells [23]. In experimental settings, EE was characterized by the collective housing of animals, such as rats, in cages with specific dimensions, offering a variety of engaging activities and stimuli. EE relies on the use of various individual and communal equipment for activities and is particularly related to the quality of life of captive animals, unrelated to the concentration of oxygen in the atmosphere [24].

The main components of sensory stimulation, cognitive activity, and physical exercise in EE are usually more effective in promoting neuroprotection and synaptic function [25]. These components improve the biological functions of experimental animals by increasing sensory, motor, and social stimuli.

Stimulating sensory perception is ultimately achieved by influencing synaptic activity or regulation. Researchers have provided a rich environment for rodent models that includes sufficient activity space, running wheels, and toys. In such an environment, the regulation of proteins and membrane lipids in the synapses of rodent hippocampal regions changes, depending on whether the animal has lived in a nutrient rich or relatively poor environment for a long time [26]. Especially, increasing physical activity, such as by providing exercise wheels, has been shown to induce a range of changes in the brain, including neuroprotection and enhanced synaptic function [27].

EE typically encompasses a variety of stimuli, including sensory, motor, cognitive, social, and environmental complexity (Fig. 2). Sensory stimulation within EE may involve exposure to diverse sounds, lighting, colors, and textures, which can promote the development and sensitivity of the senses by providing a range of sensory experiences. Motor stimulation refers to the provision of adequate space and facilities to encourage movement and physical activity, thereby fostering the development of physical coordination and motor skills. Cognitive stimulation often involves problem-solving and puzzles, learning new skills, or engaging in other activities that require thought and memory, which can enhance learning and

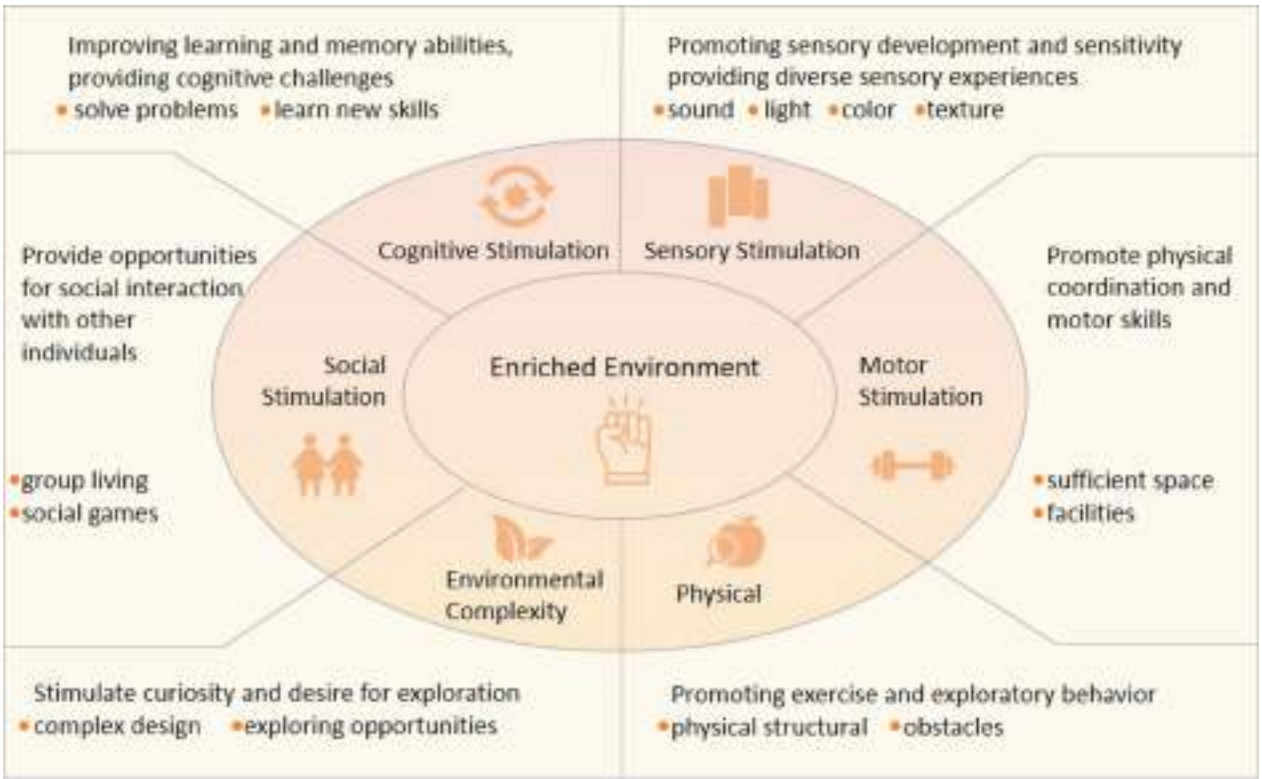

Fig. 2 Classification and role of enrichment environment

memory capabilities and provide cognitive challenges. These elements of EE are crucial in the context of studying its relationship with NDs, as they may contribute to the preservation and enhancement of cognitive functions [28, 29]. Socially enriched environment focuses on providing opportunities for social interaction with other individuals, which can be achieved through communication, cooperation, and competition with peers in social games and communal living. Therefore, these social behaviors serve as social stimulation. In terms of environmental complexity, enriched environment typically features more complex designs, offering a variety of experiences and opportunities for exploration to stimulate the curiosity and exploratory desires of the subjects. Moreover, physical activity in an enriched environment promotes the subject's movement and exploratory behavior by providing various physical structures and obstacles. Socially enriched environment has been implicated in studies exploring its relationship with NDs, suggesting potential benefits for brain health and function [22, 30]. The application of EE extends beyond animal research, as it has been found beneficial in the field of human rehabilitation, particularly in stroke recovery and the treatment of cognitive impairments [31]. By providing multisensory stimulation and social interaction, enriched EE contributes to the facilitation of the rehabilitation process and the enhancement of the quality of life.

Epigenetic and neurovascular effects of enriched environment

EE can cause chromatin remodeling and epigenetic markers to affect gene expression [32]. However, the long-term effects and specific mechanisms of these changes are still controversial, and some studies have failed to replicate these findings, suggesting that there may be other unknown factors regulating them [33]. Moreover, the improvement effect of EE was not always significant and in models of chronic cerebral hypoperfusion, the ability of EE to restore cognition depended on hippocampal synaptic plasticity. And it might vary depending on animal models and types of NDs [34].

Continuous exposure to EE has been shown to have neurovascular integration effects on chronic cerebral hypoperfusion rat models, indicating improvements in cognitive function and cerebrovascular health [28, 35]. Long term EE can alleviate brain tissue damage caused by chronic cerebral hypoperfusion (CCH) by enhancing autophagy and reducing inflammation, which is a common pathological state in AD and vascular dementia (VaD). Moreover, EE has been shown to alter DNA

methylation and histone acetylation, affecting gene expression through epigenetic modifications. For example, inducing Ca_2+ influx led to histone acetylation mediated by CREB binding proteins, which in turn increased the expression of pro regenerative genes [36].

The role of the enriched environment in neurodegeneration

Neuroplasticity promotion

EE has been reported to promote neural plasticity, which can ameliorate neurofunctional impairments in NDs and facilitate the development of the central nervous system during early stages as well as post-injury repair [37]. The study indicates that EE increases the complexity of neural networks by enhancing the quantity and quality of synaptic connections, thereby promoting synaptogenesis and strengthening in the central nervous system, enhancing neural plasticity, and neural regeneration [38]. This, in turn, improves neurofunctional damage in various central nervous system diseases and achieves the restoration of impaired neural functions through synaptic remodeling [39].

The mammalian brain is highly plastic, and EE, as a non-invasive physical and psychosocial intervention, is widely used to enhance brain plasticity, providing new avenues for the study of therapeutic drugs for neuropsychiatric diseases. EE has been shown to significantly improve various brain functions, including brain development, brain aging, brain injury repair, and the brain's response to stress, thereby facilitating the treatment of brain development disorders and NDs [40].

The type 5 metabotropic glutamate receptor (mGluR5) has been shown to regulate neuroplasticity and function and a therapeutic target for neurological disorders, including stroke. In rodent models of focal ischemia, mGluR5 negative allosteric modulators (NAMs) such as MTEP, fenobam, and AFQ056 have been shown to restore sensory and motor functions post-stroke without reducing infarct size. Treatment with these NAMs, initiated at 2- or 10-days post-stroke for a duration of 12 days, led to a rapid and progressive recovery of functions. This recovery was mediated by mGluR5, as the activator VU0360172 counteracts the restorative effects of EE, highlighting mGluR5's role in EE-mediated recovery. Furthermore, mGluR5 inhibition in specific cortical regions could prevent the disruption of resting-state functional connectivity observed post-stroke. The findings suggested that mGluR5 inhibition reversed the maladaptive plasticity that suppressed neural circuits responsible for sensory and motor functions after stroke, offering a potential therapeutic approach for acute post-stroke treatment in combination with rehabilitation training [41].

The molecular mechanisms through which EE influences NDs are complex, with a focus on signaling pathways. For instance, recent studies have underscored the role of EE in modulating pathways associated with neuroprotection and synaptic function. Specifically, the extracellular regulated kinase 1/2 (ERK1/2) signaling pathway has been implicated in the neurorestorative effects of EE, with evidence showing that EE can activate the ERK1/2 pathway, leading to enhanced neurogenesis and synaptic plasticity following brain ischemia [42]. Additionally, the mitogen-activated protein kinases (MAPK) signaling pathway, which includes ERK1/2, JNK, and p38 MAPK, is closely related to the occurrence and repair of nervous system damage, with ERK1/2 and p38 phosphorylation activating rapidly in regions of nerve damage to mitigate the impact of nerve damage [43, 44]. Furthermore, the autophagy process, which is regulated by the ULK1-ATG14 complex, has been shown to be impaired in Huntington's disease models, indicating the importance of autophagy in neurodegenerative processes [45]. In the context of Parkinson's disease, the use of CRISPR-CasRx technology to convert astrocytes into dopaminergic neurons in animal models has shown promise, suggesting a potential therapeutic approach that could be influenced by EE [46].

A study has shown that the SIRT1 and MAPK/ERK signaling pathways interact to regulate neuronal apoptosis induced by traumatic brain injury (TBI) [47]. The inhibition of SIRT1 significantly promoted TBI induced apoptotic neuronal death and reduced ERK1/2 activation through pharmacological inhibitors salermide or SIRT1 siRNA. On the contrary, inhibition of ERK1/2 activation using PD98059 or U0126 (two mitogen activated protein kinase inhibitors) significantly reduced the expression of SIRT1 and Caspase-3, protecting neurons from TBI induced apoptosis. Another study showed that EE enhances autophagy flux by inhibiting mTOR and recruits Drp1 and Parkin through the network to enhance mitochondrial autophagy flux [48]. This indicated that EE promoted autophagy through the mTOR dependent pathway and might achieve this by inhibiting the PI3K-AKT and MAPK/ERK1/2 signaling pathways.

EE protected the brain from ischemia–reperfusion injury by enhancing autophagy flow and mitochondrial autophagy flow [48]. Specifically, compared to the standard condition (SC) group, mice in the EE group exhibited fewer neurological deficits, relatively reduced inflammation, higher expression of LC3 (a marker of autophagy), higher levels of mitochondrial Parkin, higher levels of mitochondrial fission factor Drp1, lower expression of p62 (a marker of autophagy inhibition), and lower expression of autophagy inhibitory factor mTOR. In addition, the SIRT1/MAPK pathway plays different roles

in the neuroprotective effects of cerebral ischemia in rats and humans [49]. In elderly experimental rats, activation of SIRT1 had a positive effect on the phosphorylation of JNK and ERK, and regulated neuronal survival in an AKT dependent manner. In young experimental rats, activation of SIRT1 reduced stress-induced phosphorylation of JNK, ERK, and caspase-3, and increased phosphorylation of AKT after cerebral ischemia. In human patients, the expression of SIRT1, phosphorylation of the JNK/ERK/MAPK/AKT signaling pathway, and expression of caspase-3 were upregulated [49].

Anti-inflammatory effect

In the study of PD, two proteins, β-arrestin 1 (ARRB1) and β-arrestin 2 (ARRB2), have been identified to exert opposing functions in microglial inflammatory responses. ARRB1 tends to promote inflammation, while ARRB2 tends to inhibit it [1].

Neuroinflammation is identified as a factor that may lead to cognitive dysfunction in patients. In a physiological context, inflammation represents a defensive response to stimuli. But sustained inflammatory challenges can inflict damage on tissues and cells, precipitating the development of chronic diseases. EE has been demonstrated to mitigate the progression of NDs by modulating microglial activity, whose function and state directly affect the level of inflammation in the brain. The regulatory influence of EE on microglia contributes to the downregulation of inflammatory factor expression, thereby exerting anti-inflammatory effects [50]. Microglia, as the resident immune cells of the central nervous system, are activated in the event of infection or injury, migrating to the site of insult to phagocytose infected cells and release a spectrum of cytotoxins to counteract invading pathogens [51]. Nevertheless, an overactive response from microglia can lead to the release of substances that are toxic to surrounding healthy tissues, thereby aggravating the progression of NDs.

EE works by reducing oxidative stress and inflammation. It can reduce oxidative stress and inflammation by inhibiting JNK and NF—κ B activation, which is particularly evident in Alzheimer's disease models. Rich hydrogen water inhibited the NF—κ B signaling pathway, which was central to regulating immune responses and inflammation. By inhibiting NF—κ B, hydrogen rich water reduced the transcription and expression of various inflammatory molecules. The antioxidant and anti-inflammatory actions of hydrogen-rich water were interconnected, as it alleviated oxidative stress and disrupts the vicious cycle between inflammation and oxidative stress [52].

Hydrogen-rich water also mitigated oxidative stress in conditions such as ischemia–reperfusion injury by selectively neutralizing excess reactive oxygen species (ROS), including hydroxyl radicals, which reduced oxidative tissue damage. It could inhibit the release of pro-inflammatory cytokines and exert anti-inflammatory effects. Additionally, hydrogen-rich water suppressed the activity of JNK, ERK1/2, and p38 in the MAPK signaling pathway, curbing inflammation and apoptosis, which can alleviate acute liver injury in severe pancreatitis.

EE exerts anti-inflammatory effects by reducing gut microbiota associated with metabolic syndrome, such as Tepidimicrobium, Acidaminobacteraceae, and Fusibacter, while promoting microbiota associated with healthy physiology, including Syntrophococcus sucrumutans, Dehalobacterium, Prevotella, and Butyricimonas. Under the influence of EE, the integrity of the intestinal barrier is enhanced, the number of mucus-producing goblet cells is increased, and the expression of Muc2 in the colon is upregulated, leading to a reduction in systemic lipopolysaccharide (LPS) levels and alleviation of colonic inflammation [53].

Additionally, studies have shown that the AIM2 protein, a component of the inflammasome, inhibits the onset of multiple sclerosis through non-inflammatory functions, elucidating the immunological mechanisms by which antiviral inflammatory pathways mediate the development of multiple sclerosis [14]. The expression of AIM2 protein is increased in the central nervous system of patients with multiple sclerosis. In both inflammasome-dependent and -independent multiple sclerosis mouse models, AIM2 knockout was shown to accelerate disease progression, indicating that it exerts a negative regulatory effect on disease pathogenesis, independent of inflammasome function [54, 55].

Currently, neuroinflammation is considered a potential therapeutic target due to the emerging roles of peripheral and central immune systems in NDs. The immune system exhibits interactions in NDs. The cytokines released from the periphery can penetrate the blood–brain barrier, induce direct neurotoxicity, and activate microglia and astrocytes. Peripheral immune cells can infiltrate the brain and participate in the progression of neuroinflammation and NDs [56].

Cognitive function improvement

EE has a significant positive effect on cognitive function, so we hope to provide various EEs as a condition to assist in the treatment of NDs. Animal experiments have found that in an enriched environment, animals exhibit enhanced spatial learning and memory abilities, which we speculated maybe related to increased neurogenesis in the hippocampus. Study has shown that EE has a neuroprotective effect on cognitive impairment induced by chronic cerebral hypoperfusion [28]. Chronic cerebral

hypoperfusion (CCH), also referred to as Chronic Cerebral Ischemia (CCI), is a condition in which the brain is chronically subjected to hypoperfusion, leading to cortical or subcortical infarctions, leukoaraiosis, blood–brain barrier disruption, and hippocampal damage, resulting in cognitive deficits. This is a prevalent pathophysiological state in patients with AD and VaD [57–59]. EE mitigates brain tissue and neurological functional damage caused by chronic cerebral hypoperfusion through the regulation of autophagy and epigenetic mechanisms, suppression of oxidative stress, maintenance of the blood-cerebrospinal fluid barrier, promotion of neurovascular remodeling, and enhancement of synaptic plasticity, among other mechanisms. It promotes nerve growth and functional recovery in ischemic brain regions, providing relief for NDs [60].

Studies have shown that EE may improve cognitive function in Alzheimer's disease mouse models by potentially regulating DNA methylation and histone acetylation. This study has identified for the first time a highly expressed serine/threonine protein kinase FAM69C in the brain, which can regulate synaptic plasticity and complete memory processes. Abnormal expression of FAM69C is associated with a significant decline in biological pathways regulating neuronal and glial synaptic structure and function as well as the process of memory decline in Alzheimer's disease [61].

Different environmental conditions affect hippocampal inflammatory response and cognitive dysfunction in stroke mouse models. EE can improve cognitive dysfunction after stroke by upregulating the expression of miR-146a-5p and reducing inflammatory response. MiR-146a-5p may regulate TXNIP expression through the PRKAA/mTOR signaling pathway, regulate neuroinflammation and inhibit autophagy, alleviate intestinal ischemia–reperfusion injury, and thus affect NDs [62, 63]. Compared with mice raised in standard environments, mice raised in EE showed significantly reduced pathological damage in the hippocampal CA1 region and improved cognitive impairment. The expression levels of nuclear factor kappa B p65, interleukin-6 and other proteins, as well as the mRNA expression level of tumor necrosis factor receptor associated factor 6 (TRAF6), were significantly reduced, while the expression level of miR-146a-5p was higher [62].

Recent studies on the treatment of vascular dementia have shown that activation of the AMPK/SIRT1 signaling pathway by enkephalin can improve pathological changes in the hippocampus of dementia rats, promote myelin regeneration, inhibit the expression of inflammatory factors, and alleviate cognitive impairment in patients with cerebral hemorrhage [64]. The AMPK/SIRT1 pathway can also mediate the overexpression of serum complement C1q/tumor necrosis factor related protein-3, playing an anti-inflammatory role and improving postoperative cognitive dysfunction (POCD) induced by sevoflurane anesthesia [65].

EE may indirectly improve cognitive function by reducing biomarkers associated with obesity and metabolic syndrome. It is speculated that EE can alleviate cognitive decline by reducing inflammatory mediators and enhancing the insulin signaling pathway. It may also increase the abundance of gut microbiota associated with health status, increase the production of neuroactive metabolites in the gut, and may help improve cognitive function [53].

Neuron protection

The blood-cerebrospinal fluid barrier (BCSFB) is an important defense line of the central nervous system. EE can protect neurons from damage and delay the process of neurodegeneration by increasing the expression of neurotrophic factors, such as BDNF [66]. However, studies showed that the increase of BDNF was not always associated with the positive effects of EE in different brain regions and developmental stages [28]. In studying the protective mechanisms of environmental factors on the nervous system and the improvement of NDs by EE treatment, researchers used electron microscopy to observe the changes in the ultrastructure of the blood cerebrospinal fluid barrier under EE conditions, and used immunohistochemical techniques to detect the expression of tight junction proteins such as Occludin. EE also promotes the integrity of the blood cerebrospinal fluid barrier and enhances barrier function by activating the Wnt/β-catenin signaling pathway [67, 68]. In AD, WNT proteins, low-density lipoprotein receptor-related protein 6 (LRP6), and Frizzled (Fzd) were downregulated, while WNT antagonists glycogen synthase kinase-3 beta (GSK3β) and Dickkopf-1 (DKK1) were upregulated. These changes affected the control of neurodegeneration and neurorestoration. Pharmacological activation of the WβC signaling can inhibit tau phosphorylation, Aβ production, suppress DKK1, inhibit GSK3β, enhance the integrity of the BBB, suppress beta-site amyloid precursor protein cleaving enzyme 1 (BACE1), increase the expression of surviving and neuronal markers, and inhibit neuroinflammation, thereby enhancing synaptic plasticity in animal models and AD patients [69]. When studying the role of environmental factors in the common neurodegenerative disease in clinical practice, the expression of amyloid precursor protein and Aβ deposition are evaluated by immunohistochemistry techniques. The study found that EE can reduce Aβ load in AD model mice, enhance neural plasticity, and improve cognitive function [67].

Zamanian et al. provided a comprehensive review of the role of quercetin in targeted activation of the Nrf2 signaling pathway, which was implicated in the antioxidant response and neuroprotection. Their review emphasized that quercetin could enhance the expression of antioxidant genes and inhibit pro-inflammatory cytokines to affect neuroprotective mechanisms. As discussed in our section on the BCSFB, this pathway was crucial in neurodegeneration. Zamanian et al.'s comments added to our understanding of how quercetin affected epigenetic modifications and antioxidant responses: regulation of Nrf2 signaling might be a key therapeutic strategy [70].

EE activates Activin A in the hippocampus and cortex through the NMDAR-Ca2+-ActA pathway [25]. Activated ActA not only up-regulates the expression of NMDAR, NR2A, and NR2B in the hippocampus and cortex but also activates the Wnt/β-catenin signaling pathway, increasing the expression of synaptic-related proteins such as GAP43, SYN, PSD-95, and MAP-2, thereby regulating synaptic structure and neural plasticity [71, 72]. Concurrently, EE can block the activation of the TLR4-p38MAPK pathway, inhibiting the expression of toll-like receptor 4 (TLR4), myeloid differentiation factor 88 (MYD88), phosphorylated p38 mitogen-activated protein kinase (p-p38MAPK), and pro-apoptotic protein Bax, reducing the secretion of tumor necrosis factor α (TNF-α) and interleukin-1β (IL-1β), and alleviating the damage to the nervous system caused by inflammation and apoptosis.

In NDs with motor dysfunction such as PD, EE can also improve motor coordination and balance through the co-transplantation of dopaminergic neurons [46]. In some models of NDs, commonly AD and PD, EE has been demonstrated to mitigate the accumulation of pathological markers, such as β-amyloid plaques and α-synuclein [73]. EE can also promote neural regeneration and repair damaged neural tissue by activating endogenous neural stem cells [42].

Molecular mechanisms of the interaction between enriched environment and neurodegeneration

The etiology of NDs is complex, involving multiple molecular mechanisms. For instance, the abnormal aggregation of β-amyloid forms plaques in the brain. The abnormal phosphorylation of tau protein results in neurofibrillary tangles. Mitochondrial dysfunction impairs energy production, causing cell death. Neuroinflammation, due to abnormal immune responses, induces neuronal damage. Oxidative stress disrupts the balance of reactive oxygen species production and clearance, thereby damaging cells.

Enriched environment promotes neurogenesis

EE can promote neurogenesis and synaptic plasticity, involving multiple levels of biological processes. Neurogenesis is the process of generating new functional neurons from endogenous neural stem/progenitor cells, which is crucial for repairing damaged brain tissue. EE increases the expression of phosphorylation signal sensor and transcription activator 3 (p-STAT3) in ischemic brain regions by inhibiting the activity of calpain 1, thereby activating the hypoxia inducible factor-1α (HIF-1α)/VEGF signaling pathway and promoting the production and secretion of high mobility group 1 protein (HMGB1) in activated astrocytes [74]. Astrocytes HMGB1 can promote the proliferation of neural precursor cells and neuronal differentiation, ultimately promoting the recovery of various neurological functional disorders after ischemia [75].

EE promotes the proliferation and differentiation of neural stem cells by increasing physical and social stimuli. In brain regions such as the hippocampal dentate gyrus, EE has been shown to increase the number of neural progenitor cells, thereby promoting neurogenesis [28]. During this process, EE may enhance neurogenesis by activating specific signaling pathways, such as the Wnt/β-catenin pathway [76]. The facilitatory effect of EE on synaptic plasticity is closely related to its regulation of postsynaptic protein expression. For instance, EE increases the expression of postsynaptic density protein 95 (PSD-95) and synaptophysin. These proteins are key molecules in synaptic plasticity and memory formation. EE also enhances synaptic stability and function by upregulating the expression of brain-derived neurotrophic factor [28].

In the molecular realm, EE plays a significant role in neurogenesis through the regulation of histone acetylation and DNA methylation. Histone acetylation is an epigenetic modification that modulates gene expression. EE can enhance neurogenesis by increasing the activity of histone acetyltransferase, thereby promoting the transcription of specific genes. Additionally, EE influences neurogenesis by affecting the expression of microRNAs [77]. EE can also regulate neurogenesis by affecting the expression of microRNAs. For example, miR-132 is a key miRNA that plays a crucial role in the regulation of neural plasticity within the nervous system. It can suppress the expression of Histone deacetylases (HDACs), thereby promoting neurogenesis and synaptic plasticity [78].

In NDs, this mechanism is disrupted, and the inflammation and immune responses regulated by miRNAs are affected. EE has been shown to enhance neural plasticity, maintain memory and learning by modulating the balance between the activities of Histone Acetyltransferase and Histone deacetylases. Disruption of this

balance can lead to the accumulation of pathological proteins and impaired axonal transport. The interplay between DNA methylation and histone modifications, including acetylation, also produce effect in the context of NDs [79, 80]. Altered gene expression can result in abnormal methylation patterns, affecting neurodevelopment and contributing to the onset of NDs. In Alzheimer's disease, the expression of risk genes such as apolipoprotein E (APOE) leads to DNA methylation. Meanwhile, Tet proteins influence neurogenesis by regulating DNA demethylation in various neural cell types. In Alzheimer's disease patients, cognitive ability in the neurodegenerative brain is hindered by epigenetic blockade of gene transcription, which is mediated by histone deacetylase 2 (HDAC2). HDAC2 enhances the neurotoxic damage associated with AD by enhancing its inhibitory effect. Histone deacetylase 2 binds to histones associated with genes that are crucial for learning and memory, reducing histone acetylation, which consequently results in decreased expression levels of these genes [81].

EEs are acknowledged for their capacity to stimulate neuroplasticity and facilitate recovery in NDs, such as stroke and Huntington's disease. Recent studies highlight the role of EE in modulating molecular mechanisms that are essential for neural repair and synaptic function [30]. Specifically, our study has revealed that UNC-51-like kinase 1 (ULK1) promotes autophagy by phosphorylating autophagy-related gene 14 (ATG14) at Serine 29, a process that is crucial for the activity of the ATG14-Vps34 lipid kinase complex in a manner dependent on mammalian target of rapamycin (mTOR), thereby controlling autophagy levels [45]. In the Q175 mouse model of Huntington's disease, we observed impairments in Vps34 activity associated with ATG14 and in the phosphorylation of ATG14 and Beclin 1 mediated by ULK1. In addition, during general protein toxicity stress induced by proteasome inhibition, the phosphorylation of ATG14 was reduced, a decrease that was partly mediated by the sequestration of ULK1 to insoluble cellular fractions induced by p62 [82]. Our study indicated that increasing ULK1 levels and phosphomimetic mutations of ATG14 could aid in the clearance of polyglutamine (polyQ) aggregates within cells. These findings suggested that EE might exert its beneficial effects, in part, by influencing the ULK1-ATG14 signaling axis, which was implicated in the regulation of autophagy—a process critical for the clearance of aggregated proteins associated with NDs [30]. By enhancing the activity of the ULK1-ATG14 complex, EE can potentially promote the clearance of toxic protein aggregates and support synaptic plasticity, thereby facilitating functional recovery in the context of neurodegenerative processes. This approach may provide new therapeutic targets for amplifying the restorative effects of EE.

Enriched environment inhibits inflammatory responses

EE exerts anti-inflammatory effects in Alzheimer's Disease potentially through modulation of the β-adrenergic signaling pathway. EE may enhance the activity of β-adrenergic receptors in the brain, which are linked to the cAMP signaling pathway [83]. Activation of β-adrenergic receptors leads to the activation of adenylyl cyclase, increasing cAMP levels and thereby activating protein kinase A (PKA). PKA activates cAMP response element-binding protein (CREB) by phosphorylating various substrates, and phosphorylated CREB (p-CREB), acting as a transcription factor in the nucleus, enhances the expression of BDNF, increasing BDNF levels and synaptic plasticity, thereby improving cognitive function [84]. Neuroinflammation is identified as a factor that may lead to cognitive dysfunction in patients. In a physiological context, inflammation represents a defensive response to stimuli. However, sustained inflammatory challenges can inflict damage on tissues and cells, precipitating the development of chronic diseases. Microglia, as the resident immune cells of the central nervous system, are activated in the event of infection or injury, migrating to the site of insult to phagocytose infected cells and release a spectrum of cytotoxins to counteract invading pathogens. Nevertheless, an overactive response from microglia can lead to the release of substances that are toxic to surrounding healthy tissues, thereby aggravating the progression of NDs [85]. In short, although activated microglia can engulf and clear necrotic cells and Aβ deposits, providing some protective effect, the activation of microglia can also lead to abnormal release of iron ions, activation of the Aβ pathway, and other conditions, which overall promote the progression of Alzheimer's disease.

In the context of NDs, pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α are implicated in the pathogenesis by modulating cellular signaling pathways that interfere with synaptic plasticity and long-term potentiation, culminating in cognitive dysfunction [86]. TNF-α, a significant pro-inflammatory cytokine, is known to activate immune cells, increase vascular permeability, and elicit inflammatory responses, thereby participating in the activation of immune cells and the generation of inflammatory mediators. Similarly, IL-1 β and IL-6 modulate the proliferation and differentiation of immune cells, and sustain the inflammatory response.

TNF receptor-associated factor 6 (TRAF6) serves as a salient adaptor protein within inflammatory signaling cascades. Upon activation by upstream inflammatory stimuli, TRAF6 engages in interactions with interleukin-1 receptor-associated kinase 1, which results in the

nuclear translocation of NF-κB p65. This translocation subsequently upregulates the expression of pro-inflammatory cytokines, such as IL-6 and TNF-α, intensifying neuroinflammatory responses [87]. Consequently, TRAF6 emerges as a potential therapeutic target for the treatment of NDs.

The activation of the AMPK/SIRT1 pathway has been implicated in the amelioration of cognitive dysfunction through its anti-inflammatory effects. AMPK, acting as an activator of SIRT1, upregulates the expression of SIRT1, thereby modulating the acetylation status of downstream molecules and exerting anti-inflammatory effects. The precise molecular mechanisms through which SIRT1 exerts its anti-inflammatory actions are not yet fully elucidated, but it is hypothesized to involve interactions with NF-κB, transcription factors, and histones [64].

Resveratrol is an activator of SIRT1 and has been found to reduce the release of pro-inflammatory cytokines in microglia, possibly by inhibiting downstream molecules involved in inflammation and protecting cells from inflammatory damage [88]. Natural products, such as astragaloside and matrine, have been shown to improve cognitive impairment, neuroinflammation, and neuronal damage by inhibiting the activation of microglia and the production of TNF-α, IL-6, and IL-1β. A study by Chen et al. demonstrated that astragaloside improved cognitive impairment, neuroinflammation, and neuronal damage induced by oligomeric Aβ (oAβ) in an AD mouse model by inhibiting microglial activation and the production of TNF-α, IL-6, and IL-1β [89]. Similarly, Li et al. reported that matrine improved learning and memory deficits in oAβ-induced AD mice by inhibiting the activation of microglia and the expression of NADPH oxidase, thereby reducing the levels of TNF-α, IL-6, and IL-1β, which are key inflammatory mediators in neuroinflammation.

In Parkinson's disease mouse models, ARRB1 and ARRB2 exhibit opposing regulatory patterns. Specifically, the genetic ablation of ARRB1 ameliorates pathological features of PD, involving the loss of dopaminergic neurons, neuroinflammation, microglial activation, and microglial-mediated neuronal damage. There is a strong correlation between chronic inflammatory reactions caused by glial cells and NDs of the nervous system. In various acute and chronic NDs, activated glial cells secrete inflammatory factors such as cytokines, which have toxic effects on neuronal survival [90]. In contrast, the genetic knockout of ARRB2 exacerbates these pathological features. Studies reveal that Nitrogen permease regulator-like protein 3 (Nprl3) is a key effector molecule in the differential regulation of microglial neuroinflammation by ARRB1 and ARRB2. It plays a mediating role in the inflammatory response of microglia, with its expression levels participating in the modulation of inflammatory pathways, affecting neuroinflammation and neuronal activity [1].

In addition to the discussed mechanisms, Ivraghi et al. demonstrated that gemfibrozil, a fibric acid derivative, exerted neuroprotective effects by modulating the expression of pro-inflammatory molecules such as iNOS and by inhibiting the activation of transcription factors like NF-κB and AP-1. This study provided evidence for the role of gemfibrozil in attenuating neuroinflammation and promoting neuronal survival, which was in line with our discussion on the molecular mechanisms of neuroprotection induced by EE [91].

Enriched environment inhibits apoptosis

EE treatment may decrease the levels of glial fibrillary acidic protein (GFAP), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) in the hippocampal CA1 area, suppress the activation and multiplication of astrocytes in this region, lower the secretion of pro-inflammatory factors, and mitigate inflammatory reactions, potentially enhancing brain function in Alzheimer's disease [92]. According to a study, GFAP is a biomarker for Alzheimer's disease, and its overexpression can reflect disease progression. EE exposure in the SAMP8 mouse model has been shown to diminish β-amyloid plaque accumulation in the hippocampal CA1 region, reduce neuronal apoptosis, ameliorate synaptic plasticity, and bolster cognitive performance [93, 94]. In neuroinflammation, EE therapy has been shown to downregulate the expression of pro-inflammatory cytokines (such as TNF α and IL6) in the hippocampus of SAMP8 mice, exerting anti-inflammatory properties. In spinal cord injury models, exposure to a enriched environment can regulate synaptic vesicle cycles and promote axonal regeneration, leading to neural recovery.

EE can activate multiple molecular pathways to inhibit apoptosis, exerting neuroprotective functions. In NDs such as Alzheimer's disease, the infiltration of CD8 + T cells exacerbates microglia-driven neuroinflammation [95]. Studies indicate that CD8 + T cells within the brain interact with microglia through the expression of CXCR6 and PD-1, inhibiting inflammatory responses and restricting the pathological progression of AD. The CXCL16-CXCR6 axis can promote the accumulation, tissue retention, and clonal expansion of PD-1 positive CD8 + T cells in the brain. The absence of Cxcr6 or CD8 + T cells intensifies the pro-inflammatory effects of microglia [96]. EE mitigates oxidative stress by bolstering the antioxidant defense system, which includes the upregulation of superoxide dismutase (SOD) and glutathione peroxidase (GPx), key enzymes in neutralizing

reactive oxygen species and reactive nitrogen species. The activation of the Nrf2 ARE signaling pathway further promotes the enhancement of antioxidant capacity, which drives the expression of downstream antioxidant genes such as SOD, GPx, and glutathione to enhance cell resistance to oxidative challenges [97, 98].

EE can inhibit the activation of the NF—κ B/NLRP3 inflammasome pathway, perform anti-inflammatory effects, and reduce the production of pro-inflammatory mediators such as IL-1 β [99]. It also improves cognitive decline by regulating the accumulation of beta-amyloid peptide (Abeta), a marker of Alzheimer's disease, regulating their production, clearance, or neurotoxicity [100]. EE can also inhibit neuronal apoptosis and further promote its neuroprotective effect by regulating the expression of apoptotic proteins such as Bcl-2/Bax and Caspase-3. These findings indicate that microenvironment specific intercellular communication is beneficial for maintaining tissue homeostasis and resisting neuroinflammation, exerting neuroprotective effects, supporting the ability of EE to improve cognitive function, and providing new possibilities for the prevention and treatment of NDs such as Alzheimer's disease [99].

Post stroke EE regulates cognitive impairment through a series of molecular pathways and receptor expression. EE upregulates the expression of α 7-nicotinic acetylcholine receptors (α 7-nAChRs) [101], a pathway that intersects with key signaling cascades. For example, the Nrf2 ARE pathway is the core of coordinated expression of antioxidant and detoxifying enzymes, while the JAK-STAT3 and PI3K Akt pathways also play a role in neuroprotection and inhibition of inflammatory responses [102, 103]. EE enhances the expression of Netrin-1 and its receptor DCC in the infarcted area of stroke rats, indicating that EE can play a role in axonal guidance and nerve regeneration. EE also regulates the expression of apoptosis related genes such as XIAP, P53, and QSER1, inhibits cell apoptosis, and promotes neuronal survival [104–106]. Due to the impact of miR-146a-5p microRNA on innate immunity and inflammation, EE regulation of its downregulation can also assist in reducing neuroinflammation [107]. These indicate that axonal guidance signals may be involved in the rich environment induced angiogenesis and neurogenesis after cerebral ischemic injury, which can alleviate cognitive impairment and promote nerve regeneration after stroke [108, 109].

Methods of enriched environment and neurodegeneration

Large animal models, such as primates, provide unique insights into the pathogenesis of NDs, which are not always evident in rodent models. Compared with rodents, primates have differences in the expression and function of proteins such as PINK1 in their brains. Mutations in the human PINK1 and PRKN genes can easily lead to neurodegeneration and mitochondrial dysfunction, resulting in Parkinson's disease. Genetic based amyloid pathology models in rodents may not fully replicate the complexity of human NDs. Larger animal models can be closer to human responses in order to understand the impact of EE [110]. A study using CRISPR/Cas9 to target large animals such as pigs and monkeys has found pathological events similar to neurodegeneration in patients' brains, which cannot be replicated in small animal models. The genome editing of non-human primates is performed by introducing the CRISPR/Cas9 system into fertilized eggs. Although large animals have unique properties for modeling NDs, there are also limitations in testing treatment efficacy [111]. Moreover, EE research has major limitations such as inter laboratory variability, difficulty in separating different components of EE, and differences in individual responses to EE [112]. EE may trigger neuroprotective effects as well as neurogenic transcription and translation events [27]. In various neurodegenerative disease mouse models, specific changes targeting the underlying pathological mechanisms of the diseases can be observed.

Enriched environment therapy in neurodegeneration

Challenges in translating animal models to humans

One of the main challenges in translating research results from animal models into humans is the variability of responses due to species-specific biological differences [113]. Although EE has shown promising results in enhancing neurogenesis and cognitive function in animal studies, the same effect may not be as apparent in humans due to differences in brain structure and function. In addition, ethical considerations and the complexity of human diseases pose significant obstacles to effective translation. In the future, it is necessary to develop large-scale animal models that are closer to human anatomy and physiology, as well as integrate advanced technologies such as imaging and biomarker analysis, to improve the predictive effectiveness of animal research [114].

In AD research, the 5xFAD mouse model emulated the pathological hallmarks of the disease, including β-amyloid plaques and tau protein neurofibrillary tangles, by expressing human genes harboring mutations associated with familial Alzheimer's disease [27, 115]. Cognitive function in these mice was evaluated using behavioral assays such as the Morris water maze, which measured spatial memory and learning capabilities. Pathological alterations were quantified through immunohistochemical and Western blot analyses [27]. For PD, the MPTP-induced mouse model simulated the disease's pathological characteristics by selectively

targeting dopaminergic neurons. Motor function was assessed using the rotarod test and the pole test, which evaluated balance, strength, coordination, and bradykinesia, respectively. And the number of dopaminergic neurons in the substantia nigra was determined using immunohistochemical quantification [116]. In amyotrophic lateral sclerosis study, the SOD1 mutant mouse model replicated the disease's pathological features, such as the degeneration of motor neurons, by expressing mutated human SOD1 genes. Muscle strength was assessed through grip strength tests, while the health of motor neurons was indicated by nerve conduction velocity, as evaluated by neurophysiological testing [117]. In recent decades, significant progress has been made in PD modeling, but the elderly population still lacks effective treatment for PD. The PD model, from cellular to toxicity and genetic animal models, replicated almost all the features of the disease and was capable of identifying specific events and testing new neuroprotective strategies. Classic and new models effectively supplemented PD feature modeling and enhanced current understanding of disease molecular mechanisms [118].

In the R6/1 HD mouse model, EE may promote the recovery of brain-derived neurotrophic factor transport in the striatum. In Alzheimer's disease models, EE may enhance the levels of the amyloid-degrading enzyme Carboxypeptidase E (CPE) [119]. These findings reveal the potential role of EE in modulating microglial responses and inflammation, potentially providing new therapeutic targets for the intervention of NDs in the future [50, 120].

Traditionally, rodent models have been the cornerstone of neurodegenerative disease research, but they still have certain limitations in summarizing human brain structure and disease pathology. Therefore, some people also use large animal models for study [111]. The CRISPR/Cas9 gene editing technology provides a foundation for the creation of large animal models, such as pigs and monkeys, which are more similar to human neuroanatomical and physiological features. A Huntington's disease pig model has been developed that exhibits selective neurodegeneration and motor dysfunction similar to human HD patients [111]. The latest progress also emphasizes the role of fruit fly models in drug discovery for NDs. Drosophila provides a genetically tractable system with clear neuroanatomical structures that can quickly identify new therapeutic targets and evaluate drug efficacy. The key molecular pathways between fruit flies and humans are highly conserved, making the simulation of human NDs more reliable [121].

Influences of environment and individuals on enriched environment

In the study of EE, potential confounding factors such as variations in environmental conditions and individual differences in animals can lead to different effects of EE therapy. The same differences also exist in human. A study found a causal relationship between exposure to common environmental factors and major NDs, and multiple environmental factors have overlapping effects on NDs [122]. Variations of environmental conditions such as environmental toxins can also increase the risk of developing major NDs. Neurotoxic metals can produce senile plaques or amyloid plaques and neurofibrillary tangles, leading to neurological dysfunction [123].

The effect of EE on NDs may vary depending on the gender, genetic background, or environmental factors of the subjects [124]. Studies have shown that most of the clinical differences reported in NDs appeared to be closely related to gender, which might be evidenced by significant changes in female/male autoimmune mechanisms, reflecting the impact of gender differences on EE efficacy [125]. The impact of social and physical EE on brain plasticity and cognition varied, resulting in different outcomes due to the types of environmental enrichment that affected disease efficacy [125].

Adult neurogenesis is a potential target for extending cognitive health lifespan, but it decreases with age. Based on this, EE may be more effective in the early stages of NDs before significant cognitive decline [126]. There has also been study discussing that the complexity of electroencephalogram (EEG) signals might be influenced by EE, showing a U-shaped pattern with age, increasing from late adolescence to adulthood and decreasing in old age. This pattern suggests that EE may have different impacts throughout the entire lifecycle, and middle-aged individuals may be more effective compared to older age [127]. Considering the progression stage of the disease, EE is generally more effective in the preclinical stage of NDs [128].

Epigenetic modifications enriched by environmental influences can promote long-term neuroprotection and disease progression in NDs. There are differences in epigenetic modifications between individuals, which may affect the impact of NDs on individuals and lead to differences in the response of different individuals to EE [129]. A study found that the intrinsic activity intensity of brain functional networks had a high heritability, while the functional connections between brain networks were influenced by environmental factors. This indicated that in EE research, an individual's genetic background might affect their response to environmental stimuli, resulting in individual differences [16].

The epigenetic modification mechanisms influenced by EE also vary among different types of diseases. In Alzheimer's disease, the levels of H3K27ac and H3K9ac histone modifications in the patient's brain were elevated. These modifications affected the regulation of disease-related genes. The RNA methylation patterns between animal models of Alzheimer's disease and Parkinson's disease were also different, indicating that the epigenetic profiles of each disease are different. In addition, elevated DNA methylation could inhibit the expression of genes involved in DNA repair, which was one of the factors contributing to the development of Huntington's disease [16]. A systematic review indicated that EE could modulate epigenetic processes in the central nervous system under adverse conditions. The benefits of EE on animal brains and behavior are directly linked to distinct epigenetic mechanisms, which are reflected in cellular growth and neuroplasticity. After exposure to EE, an increase in the expression of miR-221 and miR-483 was observed in the prefrontal cortex, while a decrease in the expression of miR-92a-3p and miR-134 was noted in the hippocampus. In terms of DNA modifications, a reduction of DNMT levels in the hippocampus was reported. EE may serve as a non-pharmacological and easily applicable alternative to prevent symptoms affecting brain tissue diseases [130].

Variability and standardization in enriched environment studies

There is variability and standardization in EE across different studies, and differences in protocol settings can affect the results and reproducibility of experiments. EE components can be variable. The size of the cage, the number of animals raised, the type of experimental animals, the age of the animals at the beginning of EE, the duration of different feedings, the type of control used, the rat strain used, and the gender of the rats may all serve as differences in the experimental protocol. These differences may lead to different behavioral and neurochemical outcomes [16], as the complexity and social interaction opportunities provided by EE can affect cognitive function and neural plasticity.

Different environmental settings have an impact on experimental results, including enhancing synaptic plasticity in the nervous system, improving learning and memory abilities, and slowing down the progression of NDs [76]. Therefore, when designing and conducting EE studies, careful consideration and standardization of environmental settings must be given, including the use of standardized operating procedures between patients and controls, inclusion of the same pre analysis protocol, to ensure the reliability and reproducibility of research results.

The differences in EE schemes and the effects of EE on individuals of different periods or ages can lead to variations in research results. Some studies showed that early postpartum EE could alter the neurodevelopmental program of stress neuroendocrine responses, as well as the volume and morphology of the hippocampus and prefrontal cortex [131]. In addition, EE induced changes in oxidative metabolism capacity and connectivity in brain regions, as measured by cytochrome c oxidase (CCO) activity. There were also studies indicating that anxiety or depression like behaviors decreased and enhanced learning and memory in certain situations, while others reported an increase in anxiety or no significant impact. These differences might be due to variations and changes in the EE plan and period, which could affect the generalizability of the research findings [131].

Synergism of enriched environment with clinical therapies

EE has become a promising non-pharmacological approach that can synergize with other therapeutic methods such as drugs and cell therapies in promoting human brain repair [27]. For instance, studies have manipulated autophagy to investigate how EE influences this process, which is a significant protective mechanism against NDs [132]. Autophagy is an intracellular degradation process that is crucial for maintaining cellular homeostasis. In NDs, disturbances in autophagy may lead to cellular dysfunction and disease. The accumulation of abnormal protein aggregation, as a common cause of NDs, can be reduced through autophagy degradation [133]. Autophagy facilitates the clearance of impaired and senescent organelles, thus preserving cellular equilibrium. The impact of EE on AD was mainly concentrated in the hippocampus and entorhinal cortex, which were associated with memory formation, spatial navigation, and motor behavior. Researchers have developed animal models of NDs, such as Alzheimer's disease mouse models, and subjected these models to EE [134]. By quantifying the levels of autophagy-associated proteins in the hippocampus, like LC3-II and p62, the effects of EE on autophagy were evaluated. Study indicates that EE can up-regulate the expression of autophagy-related proteins in the hippocampus of rats, and reduce neurodegeneration induced by oxidative stress [35, 134]. Moreover, EE could promote the recovery of limb motor dysfunction after cerebral ischemia through neuroprotection. This recovery might be achieved by regulating the expression of GAP-43, SYN, and Bcl-2/Bax, and depended on neuroprotection of the ischemic penumbra [135].

NDs exhibit heterogeneity in clinical manifestations, with alpha synucleinopathy and tau proteinopathy being the most common disease categories. Due to the different pathophysiological mechanisms of NDs, the application

of EE needs to consider disease specificity. For example, in Alzheimer's disease, EE may play a role by improving spatial learning and memory consolidation, while in Parkinson's disease, it may affect the course of the disease more by reducing behaviors related to depression and anxiety [99].

EE has been demonstrated to reduce biomarkers of oxidative stress within the rat brain and bolster the efficacy of antioxidant enzymes, suggesting their potential in mitigating oxidative stress-related neuronal damage [136]. This study assessed the effects of EE on oxidative stress through quantification of malondialdehyde (MDA) and superoxide dismutase (SOD) levels within brain tissue, providing insights into their neuroprotective properties. Oxidative stress is a pivotal factor in neuronal damage and demise, prompting examination of the influence of EE on neuronal health and the progression of NDs. Techniques in molecular biology, including Western blot, are employed to evaluate the activation of pathways implicated in antioxidant stress response, particularly focusing on the Nrf2-ARE pathway. Notably, the Nrf2-ARE signaling pathway, when activated, has been shown to ameliorate neural damage induced by oxidative stress, demonstrating its role in neuroprotection [137], and concurrently initiate the NF-κB inflammatory signaling cascade, dampening inflammatory reactions, which may contribute to neurorestoration. The BCSFB serves as a vital protective mechanism within the central nervous system, safeguarding against the infiltration of harmful xenobiotics by preserving barrier integrity. Researchers utilized electron microscopy to assess the effects of EEs on the ultrastructure of the BCSFB and employed immunohistochemical methods to quantify the expression of tight junction proteins, including Occludin, to elucidate the protective mechanisms of environmental factors on the nervous system to delineate the neuroprotective effects of environmental factors and the therapeutic potential of EEs in neurodegenerative disorders.

Additionally, EEs stimulate the Wnt/β-catenin signaling pathway, reinforcing the integrity of the BCSFB and subsequently enhancing its barrier function, which may offer additional neuroprotection [71, 138]. In PD, downregulation of the WβC signaling pathway led to degeneration of dopaminergic neurons, causing motor and cognitive impairments. Pharmacology and stem cell-based therapies that activated WβC signaling improved alpha synuclein accumulation, Lewy activation mutations, and promoted neurogenesis of dopaminergic neurons. In NDs such as HD, ALS, and MS, the WβC signaling pathway was upregulated, but the reasons for this remained to be studied [69].

In examining the role of environmental elements in neurodegenerative disease therapeutics, with a focus on AD, immunohistochemical assays are routinely applied to evaluate the expression levels of Amyloid Precursor Protein (APP) and Aβ plaque deposition, subsequently gauging the influence of EEs on AD's pathological hallmarks [139]. By employing this evaluative approach, one might deduce that EE could diminish Aβ aggregation and augment synaptic plasticity, consequently advancing cognitive performance in murine models of AD [28, 140]. Androgen deprivation therapy (ADT) for treating prostate cancer (PCa) is associated with cognitive impairment, which may exacerbate AD related dementia in elderly men. Androgens may protect cognitive function by inhibiting tau protein phosphorylation. Androgen levels can disrupt the balance of genes sensitive to androgen levels, especially in memory and emotional regions such as the hippocampus and amygdala. This hormone manipulation may lead to long-term cognitive problems and AD through processes such as Aβ aggregation and neurofibrillary tangles (NFT) formation. Animal studies have shown that androgen deprivation can reduce synapses in the hippocampus by 40%, increase the deposition of Aβ, alter neural conduction in the frontal cortex, and impair normal neuronal function [141].

Within the domain of neurovascular restoration, the fluorescent gold neurotracing method is harnessed to track pivotal biomarkers influenced by EE, encompassing the expression levels of Nerve Growth Factor (NGF) and Vascular endothelial growth factor (VEGF). Study showed that EEs facilitate the process of neurogenesis [76, 142]. Using a EE for adjuvant therapy can aid in the reconstruction of nerves and blood vessels, promoting repair after brain injury.

Enriched environment in combination with drugs

In clinical applications, the combination of EE and existing therapies can have greater potential for the treatment of current NDs. Research has shown that stem cell extracellular vesicles have the potential to improve symptoms and quality of life in the clinical treatment of diseases such as Alzheimer's disease, stroke, and Parkinson's disease. These extracellular vesicles are rich in neurotrophic factors, which can promote the survival and regeneration of neurons, activate intracellular signaling pathways, promote neuronal growth and synapse formation [143]. Research has shown that EE can promote the generation, stabilization, and strengthening of synapses to alter perceptual and behavioral outputs, which at the level of neuronal characteristics determine whether connections are strengthened and maintained, or eliminated. Early stress conditions, such as maternal care, can lead to long-term emotional and behavioral changes in clinical practice. EE has been shown to alleviate these effects, prevent damage to hippocampal synaptic plasticity caused by

early stress, and improve cognitive function, with positive effects on the central nervous system. EE and physical exercise enhance the plasticity of the adult brain by increasing the expression of neurotrophic factors such as BDNF. These activities can improve cognitive function, reduce anxiety and depressive like behaviors, and promote neuroprotection.

EE has been found to improve the behavior, cellular and molecular defects of animal models of various neurological and NDs, and provide potential new targets for NDs treatment interventions by regulating molecular and cellular mechanisms. For example, EE has been shown to regulate iron metabolism, reduce iron death, and exert neuroprotective effects in models of cerebral ischemia/reperfusion injury [144]. "Mosquito like drug", an EE mimetic drug, can simulate or enhance the beneficial effects of cognitive activity and physical exercise on the brain. This drug utilizes the therapeutic effects of cognitive stimulation and physical activity to enhance experience dependent plasticity, targeting the molecular and cellular mechanisms of positive effects of EE. This method proposes a new non-invasive treatment strategy to address CNS developmental defects and neurological disorders [145].

Synergy with clinical drugs

EE can have a synergistic effect with clinical drugs, improving the treatment effectiveness of NDs. When used in combination with anti-inflammatory drugs, EE can amplify and alleviate neuroinflammatory effects. Dexamethasone, as a key participant in neuroinflammation, is a glucocorticoid with anti-inflammatory effects that can inhibit NF—κ B activation [146]. This type of medication can be used in combination with EE to alleviate drug use and predict phenotypes associated with addiction and stress, significantly reducing inflammation [147]. When combined with neurotrophic factors, EE can promote neurogenesis. BDNF promotes neuronal growth and survival, and EE has been shown to increase BDNF expression. By administering drugs such as 7,8-dihydroxyflavone (7,8-DHF), which are TrkB agonists, this upregulation can be further enhanced, activating the BDNF TrkB signaling cascade and improving cell survival and neuroplasticity [148]. The NF—κ B pathway associated with neuroinflammation can be inhibited by EE, reducing NF—κ B activation. Meanwhile, pathways related to neuroprotection and regeneration, such as the Phosphoinositol-3 kinase (PI3K) Protein Kinase B (Akt) pathway, can be activated by EE to increase BDNF TrkB signaling and promote neuronal growth and survival [148]. This dual regulation leads to a synergistic effect between anti-inflammatory and neuroprotective mechanisms. Targeting the PI3K/Akt and extracellular signal-regulated kinase (ERK) pathways has the potential to inhibit the progression of ND. The disruption of these signaling cascades significantly promotes the pathogenesis of ND, including PD, AD and HD. The Akt pathway regulates neuronal toxicity and survival by interacting with substrates such as FOXos, GSK3β, and caspase-9, typically binding to PI3K. ERK is another key kinase that regulates the proliferation, differentiation, and survival of nerve cells, playing a role in maintaining neuronal health [149].

EE reduces susceptibility to epileptic seizures by enhancing adult neurogenesis in the olfactory cortex (EC) circuit [150]. EE increases hippocampal neurogenesis in adults and significantly reduces susceptibility to epileptic seizures after EE exposure. EE enhanced adult new granulocytes (abDGCs) are activated during epileptic seizures, and the activation of these cells simulates the antiepileptic effect of EE. In addition, whole brain c-Fos mapping showed an increase in the activity of EC CaMKIIα+neurons projected by DG in EE response. These neurons bidirectionally regulate the proliferation and maturation of abDGCs, activate local GABAergic interneurons, and are an important component of EE mediated antiepileptic effects.

In the role of EE in Alzheimer's disease, EE can promote the conversion of proNGF to mNGF by increasing the level of mature NGF (mNGF), thereby activating the PI3k Akt and MAPK/ERK pathways, promoting neurogenesis, cell survival, cell proliferation, and increased synaptic plasticity [99]. EE also indirectly reduces the activation of the JNK pathway by reducing proNGF levels and directly reducing p75NTR levels, leading to excessive phosphorylation of tau protein, decreased APP phosphorylation, and reduced cell death. EE, along with physical activity, can improve spatial and working memories, and reduce the levels of pathological markers of neurodegeneration such as amyloid beta and tau protein, thereby exerting a synergistic effect on drug therapy. One study investigated the effects of EE and drug intervention (such as metformin) on hippocampal neuronal survival and hippocampal dependent memory in type 2 diabetes rats [151]. The results showed that the combined intervention of EE and EE with metformin improved hippocampal neuron survival and hippocampal dependent memory under stress in T2D rats by enhancing gene expression regulation of neurogenesis and synaptic plasticity. These findings support the view that EE and combined interventions have neuroprotective properties. In a study of AD rats receiving both EE and donepezil (a acetylcholinesterase inhibitor) simultaneously, the performance of the Morris water maze test was significantly improved compared to using EE or donepezil alone or neither [152]. This indicates that EE has the potential to enhance the efficacy of drug therapy.

The drug therapy targets for AD involve multiple key pathophysiological processes, including Aβ aggregation, tau protein hyperphosphorylation, neuroinflammation, oxidative stress, and cholinergic dysfunction. In terms of traditional medicinal plants, such as ginkgo leaves, fir, turmeric, and ginseng, they contain bioactive compounds that can regulate the above targets. For example, flavonoids and terpenoids contained in ginkgo leaves can reduce Aβ deposition and enhance cerebral blood flow, thereby exerting neuroprotective effects. Huperzia serrata is known for its natural source of huperzine A, which can be used as an acetylcholinesterase inhibitor to improve cholinergic function. Turmeric is rich in curcumin, which has anti-inflammatory and antioxidant properties, and can alleviate neuroinflammation and oxidative stress. Ginseng contains ginsenosides, which have shown neuroprotective effects and the ability to counteract amyloidosis [153].

Limitations and challenges

At present, EE still has some limitations in alleviating NDs. Due to the lack of effective biomarkers, the detection efficiency of AD and PD is not high, and currently available biomarkers can often only be diagnosed in the late stages of the disease [154]. This increases the difficulty of disease prevention and limits the effectiveness of early assessment and monitoring of EE. The EE effect is age dependent. In a study, the neuroprotective strategy of EE depended on its early exposure, which limited the effectiveness of EE intervention until later adulthood [155]. In addition, the biomarker detection methods based on cerebrospinal fluid (CSF) and blood also have shortcomings, such as the extremely low concentration of protein biomarkers and the invasive collection process of CSF [154]. These factors affect the application of EE in early disease intervention.

It is difficult to achieve consistency and reproducibility of results through standardization in EE studies and clinical translation. The main obstacle at present is the lack of methods to quantify the degree of EE. Physical motion is considered a key component of EE, but there is currently a lack of evidence to prove a direct relationship between the inanimate and social stimuli generated by EE and the motion induced by EE [156]. All environmental conditions, whether known or unknown, may affect the research results. For example, David et al. found that mice in independent ventilated cages lacking shelter exhibited histological signs of chronic cold stress and altered experimental results (as measured by adrenal gland weight, tumor growth, and adipose tissue) [157].

Even under standardized conditions, differences between laboratories and interactions between genotypes and laboratories may still affect experimental results. The true standardization of all environmental variables is almost impossible to achieve between laboratories, which may result in variations in the results [157]. Moreover, there are challenges in the clinical translation of EE. For outpatient patients, not only is the shared environment diverse, but the non-shared environment is also varied, which is one of the difficulties in EE conversion. In addition, there are technical and feasibility limitations in aligning the feeding conditions in animal experiments with the treatment mode and environment in clinical practice, as well as achieving standardized environmental conditions between hospitals or hospital departments [37].

The use of EE in clinical or experimental settings may result in potential side effects and limitations. Although EE has shown positive effects in the short term, its long-term impact and stability are not fully understood. Some studies suggested that early life experiences led to persistent individualized changes, including behavior, brain plasticity, and epigenetics [158], but the duration of these changes was unknown and might have side effects such as long-term health impacts. Additionally, due to individual differences in response to environmental stimuli, the implementation of EE is limited by individual differences in order to ensure that each subject can achieve optimal results [158].

The emerging treatment strategies currently include the use of stem cell-derived exosomes, which have shown potential to improve cognitive function and reduce Aβ deposition in preclinical models of Alzheimer's disease. The PI3K pathway is beneficial for neuronal regeneration after stroke, and activators of this pathway can enhance the survival and differentiation of neuronal cells [159]. Digital therapy (DTx, which may include EE) has limitations in addressing drug non-compliance, adverse reactions, toxicity, and inadequate efficacy of drugs and biologics for chronic diseases. In animal disease models, preclinical studies on EE and other non-pharmacological modes such as physical activity, social interaction, learning, and music have shown improved results and can serve as alternatives to the "active ingredients" in DTx [152].These findings suggest that the combination of EE with such novel therapies may provide a new therapeutic approach for treating NDs.

Summary

In this review, we delved into the role of EE on NDs and underlined the potential of EE for ameliorating NDs through the promotion of neuroplasticity, anti-inflammatory actions, and cognitive function enhancement. We explored the molecular mechanisms with a focus on the modulation of key signaling pathways including promoting neuroplasticity, exerting anti-inflammatory effects,

and enhancing cognitive function. Additionally, we summarized animal models related to NDs and discussed the therapeutic effect of EE on improving NDs.

Author contributions
J.Y. conceived and designed the project. Y.X. collected the literature and wrote the draft. Y.X. wrote the paper. J.Y., JX.X., and Y.C. revised the paper. All authors reviewed and approved the final manuscript.

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Availability of data and materials
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Declarations

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The authors declare no competing interests.

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