Trends in Cognitive Sciences

CellPress

Review

Cognitive impairments in chronic pain: a brain aging framework

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Chronic pain (CP) not only causes physical discomfort but also significantly affects cognition. This review first summarizes emerging findings that reveal complex associations between CP and cognitive impairments, and then presents neuroimaging evidence showing aging-related brain alterations in CP and proposes a framework where accelerated brain aging links CP to cognitive impairments. This framework explains how CP-related multi-level factors, which either contribute to the onset of CP or arise as a result of CP, influence brain aging in linear and nonlinear ways, leading to cognitive impairments and increased dementia risk. Leveraging interpretable machine learning and molecular brain atlases, this framework enables the development of cognitive risk assessment indicators and elucidates the biological mechanisms underlying cognitive impairments in CP.

Highlights

The associations between chronic pain (CP) and cognitive impairments are complex, involving multi-level factors such as genetic predispositions, physiological and psychological alterations, and medication use.

CP patients often exhibit 'older' brains relative to their age, making them susceptive to cognitive decline and dementia.

CP-related factors can lead to brain aging through both independent and dependent pathways on CP onset, via linear and nonlinear processes.

A brain aging framework can integrate multi-level factors to explain the complex relationship, elucidate biological mechanisms, and guide clinical interventions for cognitive impairments in CP.

Understanding cognitive impairments in CP

CP, characterized by pain persisting for 3 months or longer, affects over 30% of the global population [1]. Its prevalence varies across age groups, with a high incidence among the elderly [2]. Persistent pain and associated disability frequently lead to emotional dysregulation and cognitive impairment. While the impact of CP on emotional dysregulation has been extensively elucidated [3], its impact on cognitive function has garnered comparatively less attention. With an aging global population, the intersection of CP and cognitive impairment warrants greater attention. Individuals with CP frequently report deficits in various cognitive domains, including attention, memory, executive functions, cognitive flexibility, and psychomotor skills [4]. One explanation for these impairments in CP is the **limited cognitive resource theory** (see Glossary), which posits that individuals with CP have limited cognitive resources available for processes beyond managing pain [4–9]. However, emerging findings suggest that the relationship between cognitive impairments and CP is more complex than this theory alone can explain. For example, cognitive deficits persist even after pain relief [10,11], and only certain CP conditions are associated with heightened cognitive decline and increased dementia risk [12–14]. Furthermore, CP involves multiple factors that can impact cognitive function, including genetic predispositions, physiological and psychological alterations, and medication use [15–20]. Although rodent studies have provided valuable insights into the neural mechanisms (see review in [4]), there is currently no unified framework that integrates these multi-level factors and explains the complex relationship between CP and cognition in humans.

Increasing evidence indicates that CP can lead to cognitive impairments by inducing structural and functional alterations in the brain [21,22]. Individuals with CP experience volume loss and dysfunction not only in regions that are usually activated in receiving nociceptive stimuli, such as thalamus, anterior cingulate cortex, and primary somatosensory cortices, but also in areas closely related to cognitive function like the prefrontal cortex and hippocampus [21,23–25]. Crucially, these changes are exacerbated by age, suggesting a connection between aging-related brain alterations (i.e., **brain aging**; see Box 1) and cognitive decline in CP. Emerging studies

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Box 1. Brain aging and its neuroimaging biomarkers

Brain aging can generally be seen as the time-related deterioration of the brain, accompanied by a progressive loss of cognitive function and an increasing vulnerability of neurodegenerative disorders. This process involves multi-scale biological transformations in the brain, including changes in molecules, cells or synapses, neural circuits, morphological structures, and large-scale functional networks. It is clear that humans do not experience brain aging at the same rate, with pronounced differences in both internal (i.e., biological changes) and external (i.e., neuropsychological changes) manifestations. The rate of brain aging can be influenced both positively and negatively by various factors, including genetic predispositions, psychological and psychosocial factors, lifestyle choices, and disease-related conditions, resulting in an older or younger brain. This has motivated extensive research efforts to measure aging from a biological perspective, aiming to identify 'aging biomarkers' that can accurately predict cognitive impairments.

Using neuroimaging techniques, substantial studies have unveiled aging-related changes in brain structure, function, and cerebral metabolic levels. The human brain shrinks with age, with significant volume loss found in the prefrontal cortex, inferior temporal cortex, hippocampus, and entorhinal cortices [21,124]. Older adults have decreased integration of brain white matter, particularly in the prefrontal white matter tracts [125]. Significant alterations in brain function with age include higher inter-network resting-state functional connectivity [126]. Furthermore, aging is also accompanied by decreased brain glucose metabolism across the whole brain [127]. These neuroimaging-derived changes have been associated with multiple domains of cognitive ability, suggesting their potential as 'aging biomarkers' that can inform the risks of cognitive impairments.

Large-scale biobank initiatives are driving the creation of brain charts [38]. These charts are designed to characterize the normative trajectory of human brain development and aging using neuroimaging data from large numbers of healthy individuals over their lifespan. This approach facilitates the comparison of an individual's brain to the expected benchmarks for their age and sex, enabling the assessment of whether their brain is developing or aging in a typical manner. Any deviations from the normative trajectory of brain aging warrant further investigation to potentially avert neurodegenerative conditions. Overall, brain charts not only mark neurodevelopmental milestones but also serve as a valuable resource for assessing individual's risk of cognitive impairments.

have demonstrated that individuals with CP have 'older' brains for their age [21,25,26], exhibiting characteristics typically seen in older individuals, making them more susceptible to memory loss and dementia. Therefore, brain aging may serve as a pivotal link between CP and cognitive impairments.

In this review, we propose an integrative framework in which altered brain aging connects CP and cognitive impairments. First, we summarize the complex associations between CP and cognitive impairments from recent research findings, which guide the development of our proposed framework. Second, we review emerging evidence from neuroimaging studies, indicating that the brain aging process in CP deviates from the normative trajectory and exhibits accelerated brain aging. Third, we present our brain aging framework, where CP accelerates brain aging through the multi-level factors, aiming to elucidate its complex associations with cognitive impairments. Finally, we discuss the biological and translational implications of the brain aging framework for CP.

Complex associations between CP and cognitive impairments

Although CP has been associated with cognitive impairments for decades, researchers increasingly recognize the complexity of their relationship. In addition to CP-related factors like pain intensity, coping strategies, medication use, and mental and physical health issues [9,15,17–20], recent studies have added further intricacy to the relationship between CP and cognitive impairments (Figure 1).

Two key properties of CP complicate its relationship with cognitive impairments: heterogeneity and co-occurrence (Figure 1A,B). CP is highly heterogeneous [27], with each type characterized by distinct variations in genetic predisposition, etiology, and pain locations. This variability suggests no universal associations between CP and cognitive impairments. For example, a study examining nine types of CP revealed discrepancies in cognitive decline, with limb pain showing more pronounced cognitive deterioration [14]. A prospective study indicated that chronic knee

Glossary

Biobank: a comprehensive database from a large number of participants, typically including demographic information, health record, lifestyle, neuroimaging data, multi-omics data, and genetic information.
Brain aging: refers to the gradual structural and functional deterioration of the brain with advancing age, accompanied by an increased risk of neurodegenerative diseases and cognitive declines across multiple domains, such as memory, attention, and decision-making speed. It can be accelerated or decelerated by genetic, lifestyle, and environmental factors, leading to individual differences in the rate of cognitive decline.
Cognitive Assessment Battery: assesses a wide array of cognitive domains, such as memory, attention, executive functions, and risk decision making. Different assessment batteries are specifically designed according to their intended purposes.
Feature space: refers to the vector space spanned by all the variables used to model a problem. In brain age studies, the feature space is typically defined as the vector space where each brain voxel or area is represented as an individual vector.
General genetic factor: a common genetic architecture underlying multiple phenotypes that provides profound insights into the intricate relationships among diverse phenotypes. This factor can be elucidated through the integration of genomic data and structural equation modeling.
Genetic pleiotropy: a pervasive phenomenon throughout the human genome, where a single gene or genetic variant influences multiple traits.
GWAS: a research approach involves identifying genetic variants that are statistically associated with the risk for a disease or a trait.
Limited cognitive resource theory: a theory hypothesizes that cognitive deficits in CP stem from pain competing with other attention-demanding stimuli for limited cognitive resources. Ongoing pain may disrupt top-down attentional control mechanisms that are essential for filtering out irrelevant stimuli, resulting in impaired task performance.
MCP: refers to the presence of persistent pain occurring in multiple sites of the body. Nearly half of individuals with CP report experiencing this condition. It

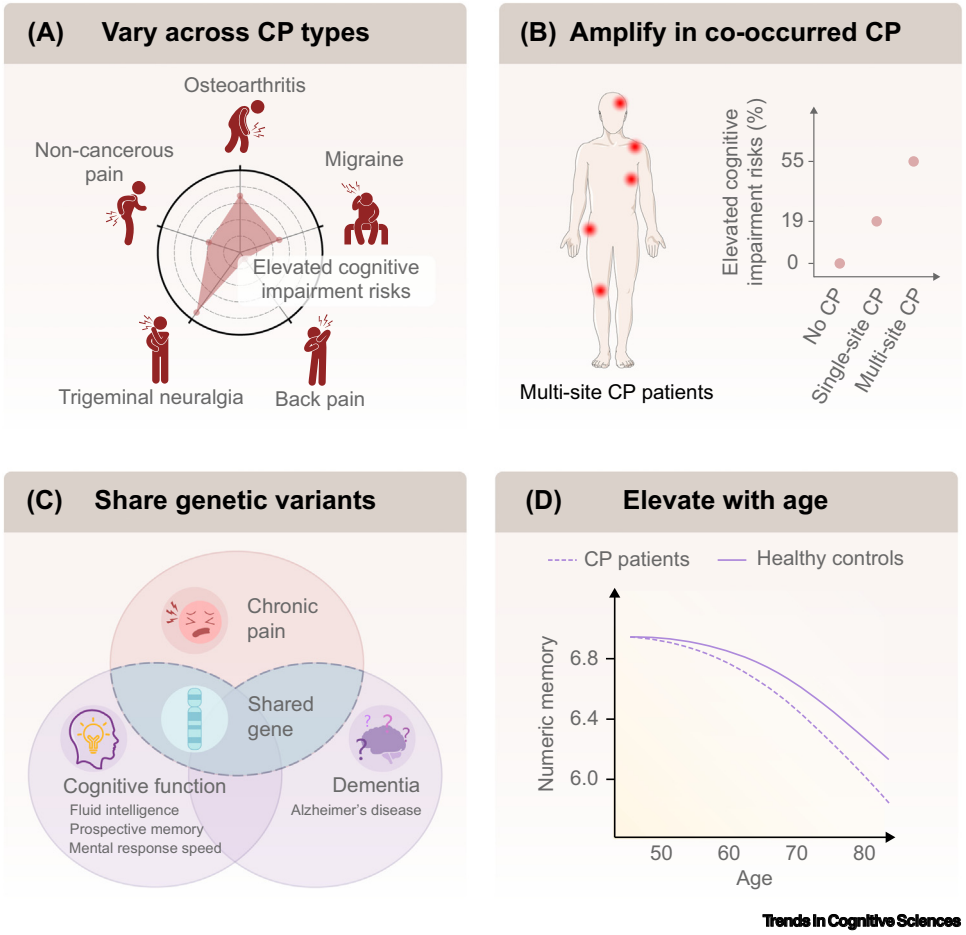

Figure 1. Complex associations between chronic pain (CP) and cognitive impairments. (A) Associations exhibit significant heterogeneity across different types of CP, both in their presence and in the magnitude of these associations. The heterogeneity displayed in the diagram references earlier studies on the associations between CP and dementia [12,13]. (B) The presence of multiple coexisting CP sites on the body amplifies these associations, with multiple co-occurring CP sites (MCP) cohorts displaying stronger links to cognitive impairments compared with single-site CP cohorts. The risk of dementia displayed in the diagram references an earlier study on the associations between MCP and dementia [21]. (C) The associations are inherently shaped by shared genetic variants. Some genetic variants/genes are linked to both CP and cognitive function or dementia. (D) The associations gradually elevate with the aging process, as CP cohorts demonstrate a nonlinear increase in the severity of cognitive impairments compared with healthy controls (HC) as they age. Accelerated memory decline in CP displayed in the diagram references an earlier study that models the trajectory of cognitive function with age [21].

pain, but not chronic back pain, was associated with an elevated risk of dementia [12]. Furthermore, a meta-analysis has shown that patients with trigeminal neuralgia have the highest risk of dementia, followed by those with osteoarthritis, migraine, and chronic non-cancer pain [13]. Additionally, individuals with multiple co-occurring CP sites (**MCP**) show more severe cognitive impairments across broader domains compared with those with single-site CP [21,28]. MCP significantly raises the risk of dementia, with each additional pain site further elevating this risk [21,29].

Genetic predispositions influence the association between CP and cognitive functioning (Figure 1C). The **general genetic factor** across 24 types of CP, which encapsulates their common genetic architecture, has been reported to be linked to cognition and intelligence [30].

is commonly associated with greater pain intensity, higher levels of disability, and a higher likelihood of developing associated conditions like depression and anxiety.

Mendelian randomization (MR): a method that infers the causal effects of an exposure (e.g., potential risk factors) on a health outcome by using genetic variants associated with the exposure.

Molecular brain atlases: a series of spatial distribution maps of molecules in the brain, derived from positron emission tomography scans, tissue samples from donated brains, or histological sections. These maps can be aligned into spatial patterns of macro-scale brain signatures derived from neuroimaging data for statistical comparison.

Specific CP types, like chronic musculoskeletal pain, are linked to genetic variants affecting fluid intelligence, prospective memory, and mental response speed [30,31]. **Genetic pleiotropy** analyses revealed numerous shared variants between migraine and intelligence [16]. Furthermore, genetic predispositions shape the impact of CP on neurodegenerative diseases. Evidence from **Mendelian randomization (MR)** analyses has revealed a genetic susceptibility of migraine patients to Alzheimer's disease (AD) [32].

Cognitive issues in CP vary with advancing age (Figure 1D) [21,28,33–36]. For instance, a 10-year longitudinal study found a 9.2% faster rate of memory decline and a 7.7% higher likelihood of developing dementia in CP cohorts [33]. Although cognitive decline in CP has usually been assessed by linear models, recent research suggests a nonlinear trend in change trajectory. A study modeling cognitive decline trajectories revealed that individuals with CP tend to exhibit accelerated declines in various cognitive domains, notably memory, around the age of 60 years [21]. Another study tracking pain persistence and cognitive function over 18 years showed that as the CP duration lengthens, the rate of cognitive decline initially speeds up, then decelerates, and eventually reaches a stable state [36]. These findings suggest that the adverse effects of CP on cognitive function accumulate gradually over time, particularly as individuals age.

Altered brain aging: a potential bridge between CP and cognitive impairments

Brain aging is well-documented to cause cognitive decline and is a major risk factor for neurodegenerative diseases [37–39]. Additionally, it mediates the effects of various risk factors on age-related cognitive decline and diseases [40]. CP also accelerates brain aging, with CP cohorts showing brain characteristics typically observed in healthy controls of advanced age across multiple neuroimage modalities, including reduced grey matter volume and white matter integration [21,23,41–43], diminished functional segregation [44], and decreased glucose metabolism [45]. These findings suggest that brain aging may connect CP with cognitive impairments, prompting extensive brain age research aimed at understanding accelerated brain aging in CP and precisely quantifying how individuals with CP deviate from the normative brain aging trajectory.

Brain age studies center on two key concepts: chronological age and brain age. Chronological age indicates the number of years a person lives, while brain age reflects the biological aging rate of the brain. The brain age model establishes the normative brain aging trajectory based on aging rate of a healthy population (see a recent review [46]). Specifically, it uses machine learning to encode chronological age into a neuroimaging-based brain **feature space** [46,47]. The model then predicts brain age in new individuals based on their brain features. By subtracting chronological age from predicted brain age, brain age gap (BAG) quantifies deviation degree from normative brain trajectory due to altered aging rate, with a positive BAG indicating accelerated brain aging compared with the healthy population.

Early studies identified accelerated brain aging in various types of CP, including knee pain, hip pain, low back pain, osteoarthritis, migraine, post-traumatic headache, and trigeminal neuralgia [25,26,48–57]. However, consistent findings have only been replicated in some types of CP, with mixed results in others. The most consistent accelerations have been observed in chronic knee pain and osteoarthritis [25,49–51,53,55–57]. Conversely, findings for chronic back pain have been less consistent, with some studies showing no significant acceleration [55]. Many factors contribute to this inconsistency, including variations in sample sizes, demographic differences, and the machine learning methods used. Large-scale **biobank** level data help overcome these limitations and suggest that acceleration is not CP-general but varies based on the type of CP. A recent study using over 5000 samples from the UK Biobank found significant brain aging

acceleration in chronic knee pain and knee osteoarthritis, but not in chronic back pain. Similarly, another study also found accelerated brain aging in individuals with chronic knee pain, but not in those with chronic back pain [49]. These results align with behavioral studies indicating that chronic knee pain, rather than chronic back pain, elevates the risk of dementia [12]. Additionally, although some brain age studies suggest variations in the level of accelerated brain aging across CP types, direct statistical comparisons among multiple types are limited, highlighting the need for further investigation [25,55].

The strong association between brain aging and CP is further highlighted by links between BAG and pain-related impacts. Individuals with CP who experience higher pain intensity, disability, and interference tend to exhibit elevated BAG levels [53,56,58,59]. Risk/protective factors for CP also intersect with BAG, as evidenced by findings that individuals with CP who have higher levels of pain catastrophizing, a key risk factor for CP, exhibited greater BAG [60]. In contrast, CP with strong projective factors demonstrated significantly lower BAG compared with those at higher risk [61]. Additionally, pain interventions also affect BAG. Both pharmacological and non-pharmacological pain treatments have been demonstrated to help slow down and even reverse the increased BAG in CP cohorts [26,50].

A robust connection between brain aging and cognitive function has been identified in CP. A recent study showed that an increased BAG was associated with poorer memory in knee osteoarthritis patients without obvious cognitive impairments [25]. Furthermore, a higher baseline BAG predicted faster memory decline and a higher risk of dementia over 5 years in knee osteoarthritis patients, suggesting that individuals with CP who exhibit older brains may be more susceptible to cognitive impairments. Although more evidence and external validation in varied settings are needed to explore the relationship between BAG and other cognitive deficits in CP, these findings highlight the contribution of accelerated brain aging to cognitive impairments in CP.

In summary, CP disrupts the natural trajectory of brain aging, leading to accelerated brain aging, with the rate influenced by CP heterogeneity, severity and disability, risk/protective factors, and pain management. Furthermore, accelerated brain aging predicts cognitive impairments in CP, including those without observable cognitive issues. Collectively, brain aging appears to serve as a bridge connecting CP and cognitive impairments.

Brain aging framework for cognitive impairments in CP

Building on the preceding findings, we introduce a brain aging framework that elucidates how CP-related multi-level factors may lead to cognitive impairments through their effects on brain aging processes. This framework holds promise in elucidating the complex relationship between CP and cognitive impairments, as well as enhancing understanding of the biological mechanisms underlying this association.

The effects of CP-related factors on brain aging

In the brain aging framework, accelerated brain aging mediates the detriments of a set of CP-related factors (Table 1) on cognitive function, leading to cognitive decline and elevated risk of dementia. These factors affect brain aging through different ways (Figure 2A and Box 2). Risk factors for CP, such as genetic predispositions, neuroinflammation, and early adversity, can directly accelerate brain aging, independently of CP itself. They begin to distort the brain aging trajectory before the onset of CP. Factors arising from persistent pain, which primarily include physiological changes, inappropriate coping strategies, medication use, and both mental and physical health issues, start to influence the brain aging trajectory following the onset of CP. Notably, certain factors serve both as risk factors and as dependent factors for CP (Table 1). For instance,

Table 1. Factors linked to both CP and brain aging, and how they affect brain aging[a]

Way	Factor	Manifestation in CP	Potential molecular mechanism influencing brain aging	Refs
Risk factor for CP (directly accelerate brain aging, independently of CP itself)	Genetic predisposition	CP shared risk SNPs and genes with brain aging CP shared biological processes with brain aging	Shared genes can influence brain aging by regulating cation homeostasis, neuronal development, neurogenesis, and synaptic plasticity	[25,30,31] [74,78,80]
	Brain-derived change	Decrease BDNF level Oxidation stress Dysregulated energy metabolism	Reduced BDNF levels weaken the capacity to support neuronal survival and differentiation, as well as to regulate synaptogenesis, synaptic transmission, and plasticity Excessive oxidation levels cause lipid peroxidation of neuronal cell membranes, protein inactivation, and DNA damage, accelerating the decline in neuronal function Dysregulated energy metabolism disturbs fuel supply and energy conservation necessary to support cell growth and differentiation, protein synthesis, and neuronal function	[100,101] [18,88] [18,102]
	Musculoskeletal injury	Elevated sclerostin secretion Bone marrow lesions	Osteocyte-derived sclerostin crosses the blood–brain barrier, impairing dendritogenesis and synaptic plasticity through dysregulation of Wnt–β-catenin signaling Bone marrow is pivotal in regulating systemic immunity that influences brain aging process. Lesions in the bone marrow contribute to immune senescence, hindering cerebral Aβ clearance and exacerbating neuroinflammation	[69] [70]
	Early adversity	Experiencing early adversity	Early adversity can undermine mitochondrial capacity to coordinate effective cellular stress responses, reducing the brain's resilience against accelerated aging	[103,104]
CP-dependent factor (influence the brain aging trajectory following the onset of CP)	Medication	Opioid use	Opioids can exacerbate oxidative imbalance, induce neuroinflammation, and impair neurogenesis	[17]
	Coping strategy	Smoking Alcoholism	Both smoking and alcoholism can exacerbate oxidative imbalance, compromise blood–brain barrier integrity, and promote neuroinflammation	[105,106] [106,107]
	Disease	Cardiovascular diseases Chronic fatigue syndrome	Cardiovascular diseases may induce deleterious pulsatile blood flow and compromise blood–brain barrier integrity, subsequently leading to tau upregulation, synaptic dysfunction, and neuroinflammation Chronic fatigue syndrome may induce decreased bioenergetics and increased oxidation due to mitochondrial dysfunction	[108,109] [110,111]
	Social participation	Lack of social participation	Reduced social participation may lead to feelings of isolation and chronic stress, thereby inducing neurotoxicity through hyperactivation of the HPA axis	[112,113]
	Endocrine change	Elevated cortisol level	Cortisol suppresses neurogenesis, inhibits synaptogenesis, and results in atypical dendritic branching	[114,115]

Table 1. (continued)

Way	Factor	Manifestation in CP	Potential molecular mechanism influencing brain aging	Refs
Risk factor for CP & CP-dependent factor	Neuroinflammation	Increased level of cytokine, inflammation, and glial overactivation	In neuroinflammation, microglia are primarily activated to release proinflammatory cytokines such as TNF-α, IL-1β, and IL-6, with astrocytes also contributing under certain conditions. These cytokines can induce neuronal dysfunction and cell death	[87,116]
	Lifestyle	Unhealthy diet Short sleep duration Insufficient physical activity	An unhealthy lifestyle can diminish the protective effects of BDNF secretion, antioxidant enzymes, and the cerebral glymphatic system, thereby increasing susceptibility to accelerated brain aging	[117,118] [117,119] [117,120]
	Psychological change	Depression Anxiety Psychological stress	Poor psychological health may induce dendritic retraction, inhibit neurogenesis, and promote neurotoxicity through hyperactivation of the HPA axis	[19,121] [19,121] [122,123]

[a]BDNF, brain-derived neurotrophic factor; HPA, hypothalamic-pituitary-adrenal; IL-1β, interleukin-1β; IL-6, interleukin-6; SNPs, single nucleotide polymorphisms; TNF-α, tumor necrosis factor.

neuroinflammation not only increases the risk of developing CP but also tends to worsen after the onset of CP, thereby magnifying its impact on brain aging.

Moreover, the brain aging process involves both continuous and step-wise changes [62]. Certain CP-related factors, such as poor sleep, may rapidly accelerate brain aging in a step-wise manner [63]. Continuous changes in brain aging are characterized by both linear and nonlinear influences [38,62], primarily driven by various factors that impact aging in a stage-specific manner [20,64]. Among CP-related factors, some continuously affect brain health. While their detrimental impact may be nearly linear within specific life stages, it varies across different periods of life. This variability is evident in factors like inflammation, depression, smoking, alcohol use, and some comorbidities [65–68]. To account for these observations, the framework decomposes the overall impact of CP-related factors into three types of acceleration effects (Figure 2B). The first is a continuous linear effect that consistently accelerates brain aging with a relatively stable rate. The second is a continuous nonlinear effect, marked by an unstable rate that may fluctuate due to age or specific life events. The third type is a step-wise effect that triggers a strong but not continuous acceleration in brain aging.

How does this framework explain the complex associations?

By integrating various factors, the framework can explain many of the complex associations between CP and cognitive impairments. First, it accounts for the effect of the heterogeneity of CP. The rate of brain aging is determined by the combined influence of CP-related multi-level factors, which vary across different CP types. Genetic predispositions and other risk factors show a high degree of specificity to particular types of CP. Consequently, CP types with greater overlaps with these factors tend to exhibit a faster rate of brain aging and more severe cognitive decline. For instance, knee osteoarthritis patients have substantial risk genes, musculoskeletal injury, and dysregulated energy metabolism, which can accelerate brain aging and make patients particularly susceptible to cognitive decline [18,25,69–71]. Factors arising from persistent pain, such as mental health problems, inappropriate strategies to relieve pain, and opioid medications, are common across CP types, since pain sensation is a primary trigger for them. However, the prevalence of these factors varies [17,72], with CP types associated with higher prevalence tending to show a greater degree of accelerated brain aging. For example, neuropathic CP leads to more

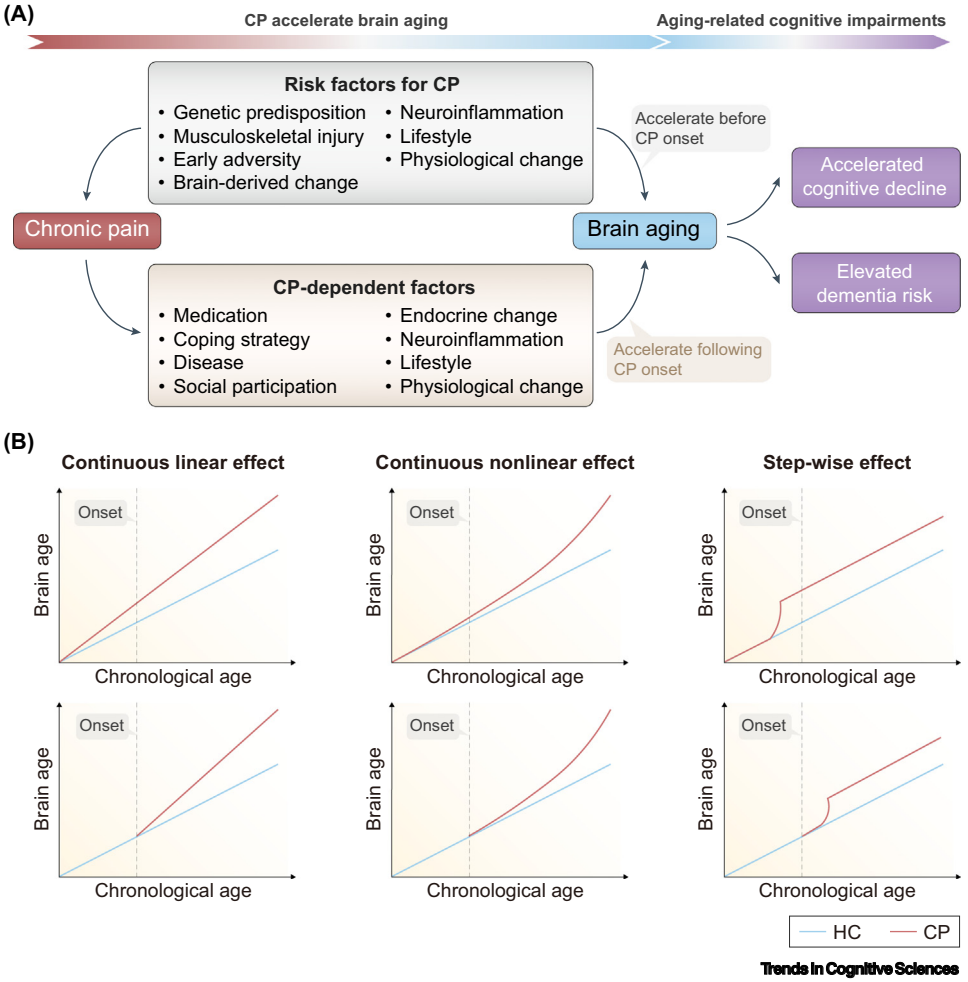

Figure 2. Schematic representations of how the brain aging framework links chronic pain (CP) and cognitive impairments. (A) The framework posits that brain aging bridges CP and cognitive impairments, supported by evidence that various CP-related factors can accelerate brain aging, leading to higher brain age gap (BAG) in CP cohorts compared with healthy controls (HC). These factors are categorized into two sets: one accelerating brain aging before the onset of CP, independently of CP itself, and the other, triggered by CP, accelerating brain aging after the onset of CP. (B) Three types of acceleration effects of CP on brain aging. CP-related factors can induce continuous linear (left), continuous nonlinear (middle), or step-wise acceleration effects (right) on brain aging before (top) or after (bottom) the onset of CP.

pronounced brain aging compared with non-neuropathic CP types [55]. This could be associated with higher pain intensity, increased incidence of comorbid depression, and reduced physical activity in neuropathic CP relative to non-neuropathic types [72,73].

The framework also explains why MCP is related to more severe cognitive impairments. Hippocampal aging has been shown to mediate cognitive decline in MCP [21]. Importantly, each additional pain site accelerated hippocampal aging by over a year, linking more pain sites to greater hippocampal atrophy and faster cognitive decline. The reasons for accelerated brain aging in MCP may be multifaceted. First, with an increase in the number of pain sites, individuals are subjected to a greater array of factors that accelerate brain aging. Second, compared with single-site CP, risk genes of MCP are more extensively expressed in the brain, providing a greater number of genes potentially involved in regulating brain aging [74]. Third, MCP exacerbates the adverse

Box 2. Two ways that CP-related factors affect brain aging

Several factors influencing CP can also accelerate brain aging before the onset of CP. Genetic predispositions play a significant role, as certain genes can affect neural plasticity, inflammation, and pain sensitivity. These genetic factors can predispose individuals to both CP and accelerated brain aging [25,89]. For instance, the RUNX2 gene, crucial in osteoarthritis development, also regulates the acceleration of brain aging [89]. Neuroinflammation is another critical factor. Chronic low-grade inflammation in the brain can precede the onset of CP. Proinflammatory cytokines and activated microglia can damage neural tissues, leading to both pain sensitization and cognitive decline [87,116]. Musculoskeletal injuries serve as a source of CP, and recent studies suggest that the molecular determinants of bone injury also regulate the brain [69,70]. Brain-derived neurotrophic factor (BDNF) is crucial for synaptic plasticity and neuroprotection. Altered levels of BDNF can lead to maladaptive neuroplasticity, increasing the risk of both CP and cognitive impairment [100,101]. Early adversity can have long-lasting effects on the brain, altering the development of neural circuits involved in pain processing and cognitive function. This can increase susceptibility to both CP and accelerated brain aging [103,104]. Additionally, lifestyle factors such as inadequate physical activity, poor diet, and insufficient sleep can negatively impact brain health and increase the risk of both CP and brain aging [117,119,128].

Once CP has developed, several factors can exacerbate brain aging. Mental health issues such as depression and anxiety commonly co-occur with CP and can accelerate brain aging [121]. Depression and anxiety can also exacerbate pain perception and contribute to cognitive decline [129]. Coping strategies also play a crucial role. Ineffective coping strategies, such as alcohol abuse, smoking, or catastrophizing, can worsen CP and contribute to stress, further accelerating brain aging [105,107]. Social factors are also important. Lack of social participation can increase the risk of both CP and cognitive decline. Social isolation can lead to mental health issues and reduced physical activity, both of which are detrimental to brain health. Also, CP has the potential to change brain aging trajectory by disrupting the endocrine system and hormones, such as by increasing cortisol levels [114,115]. Comorbid conditions, such as cardiovascular disease [108], could serve as a mediator between CP and brain aging. These disorders can lead to systemic inflammation and vascular issues, affecting both pain and brain health [109].

effects of factors arising from persistent pain, such as more severe depressive symptoms and higher prevalence of cardiovascular diseases [75–77]. These factors lead to each additional pain site not only increasing the rate of brain aging acceleration before CP onset but also enhancing the rate after onset, seriously distorting the brain aging trajectory.

The genetic association between CP and cognitive impairments may also be explained by brain aging. Many genetic loci associated with CP are expressed in the brain, influencing its structure and function [25,30,31]. These genetic loci can impact cognitive function by regulating the brain aging process, which is also highly heritable [78]. For example, the gene DCC, crucial in nervous system development, has shown a strong association with MCP [74]. DCC expression regulates synaptic function and plasticity in the adult brain, influencing not only CP but also brain aging and cognitive functions such as memory formation [79]. In addition to synaptic plasticity, the risk genes for CP are also involved in several other biological processes that influence cognitive function via regulating brain aging, such as neurogenesis and neuron differentiation [74,78,80].

This framework further clarifies the impact of the aging process on the relationship between CP and cognitive impairments. The gradual increase in cognitive impairments with age in CP can be attributed to the persistent acceleration effect of CP on brain aging, as some CP-related factors that impact cognitive function consistently exert detrimental effects on the brain [65–67]. This is evidenced by brain age studies showing a significant increase in BAG during follow-up in CP cohorts [25]. Further support comes from MR studies indicating that accelerated thalamic atrophy with age mediates the detrimental effects of CP on AD [32]. Additionally, a study characterized the brain aging trajectories of CP and demonstrated a continuous yet nonlinear detrimental effect of CP on hippocampal aging [21].

Biological insights from the framework

In addition to its clinical relevance (Figure 3A, see ‘Future study directions guided by the framework’), the proposed brain aging framework offers biological insights beyond merely

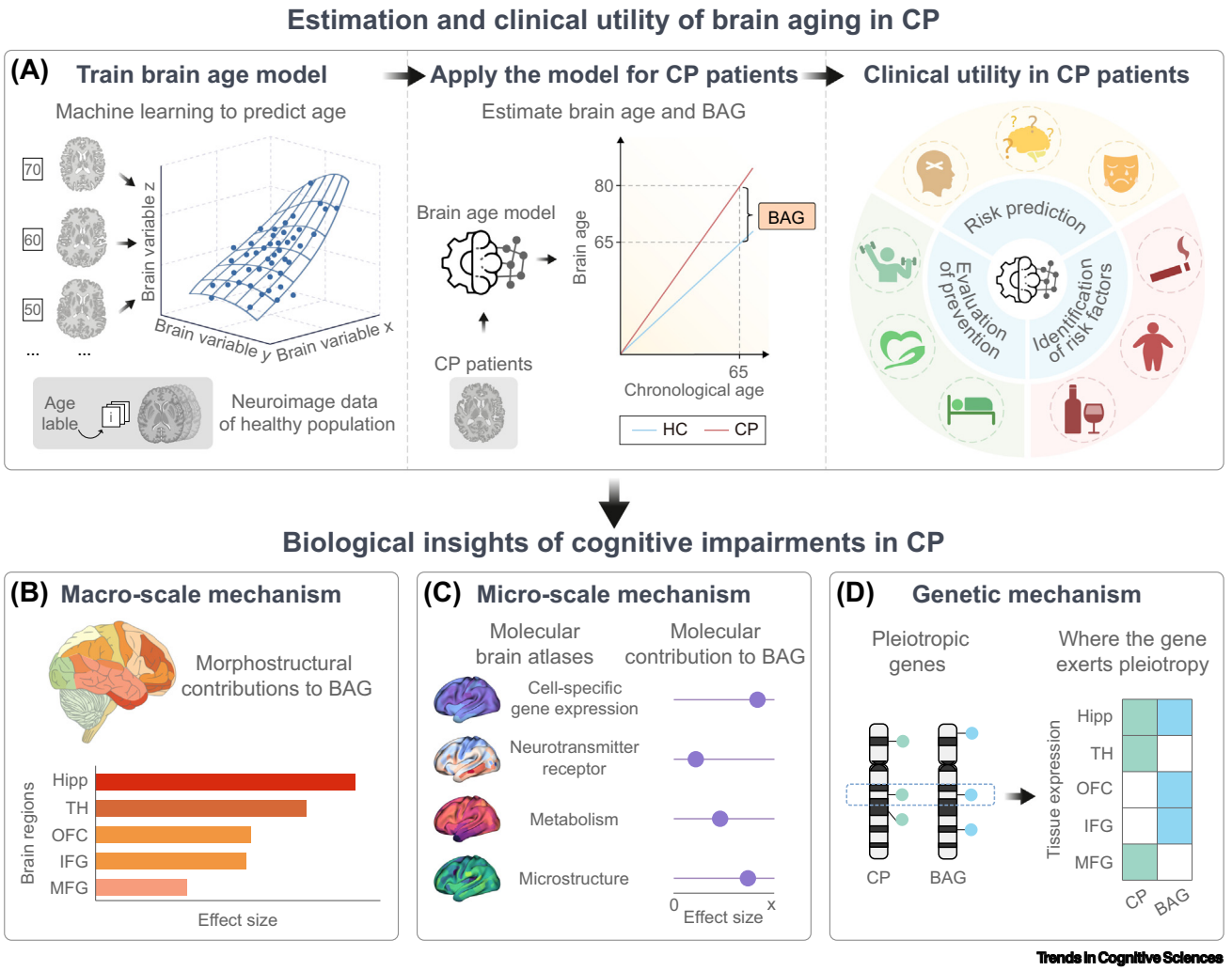

Figure 3. The brain aging framework facilitates understanding of cognitive impairments in chronic pain (CP) from multiple scales. (A) Estimate and clinical utility of brain aging in CP. Brain age gap (BAG) proves valuable in predicting cognitive risks, identifying unknown risk factors for cognitive impairments, and assessing the efficacy of cognitive decline prevention strategies in CP. Decoding (B) macro-scale, (C) micro-scale, and (D) genetic mechanism of cognitive impairments in CP. Interpretable machine learning is used to decode the macro-scale mechanism that characterizes morphological or functional contributions of the brain to BAG. Molecular brain atlases detailing the spatial distribution of molecules in the brain are leveraged to characterize micro-scale mechanism by annotating macro-scale regional contributions. Pleiotropic genes that influence both CP and BAG can be identified based on their genetic architecture. Then, the locations where pleiotropic genes exert their effects can be further elucidated using the expression data of these genes across various tissues. As shown in the diagram, a pleiotropic gene associated with CP and BAG affects CP through its expression in the hippocampus, thalamus, and middle frontal gyrus, and impacts BAG through its expression in the hippocampus, orbitofrontal cortex, and inferior frontal gyrus. Figure created with BioRender.com. Abbreviations: Hipp, hippocampus; IFG, inferior frontal gyrus; MFG, middle frontal gyrus; OFC, orbitofrontal cortex; TH, thalamus.

explaining the complex associations between CP and cognitive impairments (Figure 3B–D). Brain aging spans multiple spatial scales, allowing the framework to deliver insights on both macro- and micro-scale levels, thus enhancing the understanding of cognitive impairments in CP and contributing to its prevention.

Interpretable machine learning is increasingly used to estimate macro-scale BAG spatial patterns that quantify the neuroimaging-derived (e.g., grey matter volume) contribution of various brain areas to BAG [46]. Identifying brain areas with strong contributions to BAG helps predict cognitive

decline and implement early and targeted interventions (Figure 3B). Interpretable machine learning has revealed distinct macro-scale BAG spatial patterns across CP types, highlighting their heterogeneous aging patterns [25,52]. For example, a spatial pattern, including the orbitofrontal cortex and superior frontal gyrus, was found to significantly contribute to the increased BAG in migraine patients [52]. Another study identified a distinct spatial pattern in knee osteoarthritis patients, revealing significant contributions of the hippocampus, thalamus, orbitofrontal cortex, inferior frontal gyrus, and middle frontal gyrus to the increased BAG [25].

Micro-scale biological insights can be further obtained by annotating macro-scale BAG spatial patterns using various categories of **molecular brain atlases**, such as 'Neuromaps' and 'Allen Brain Map' repository (Figure 3C) [81,82]. These repositories allow researchers to link variations in regional contributions to BAG with variations in the distribution of various molecular components in the brain, such as gene expression, cell types, myelination, cytoarchitecture, metabolism, neurotransmitter receptors, and transporters [83]. This enables the identification of specific molecular mechanisms underlying brain aging and provides a comprehensive understanding of how different biological factors contribute to cognitive decline in CP. For example, using the Allen Brain Map repository, a study found that microglial cells, astrocytes, synaptic structures, and neurodevelopment-related biological processes played key roles in accelerated brain aging in knee osteoarthritis patients [25]. Importantly, the associations between these molecular mechanisms and cognitive impairments have been confirmed by previous preclinical studies [84], underscoring the potential of multi-scale decoding to uncover the underlying mechanisms of cognitive impairments in CP based on the brain aging framework.

With the increasingly available genome-wide association studies (**GWAS**) of different CP types [30,74], decoding genetic determinants of accelerated brain aging in CP is also beneficial for understanding the biological mechanisms as well as identifying potential drug targets that can both reduce CP symptoms and prevent cognitive impairments (Figure 3D). For example, genetic pleiotropy analysis identified the risk gene SLC39A8 shared by knee osteoarthritis and BAG [25]. This gene aids in bone formation and cartilage catabolism and also affects brain deterioration, explaining why knee osteoarthritis patients exhibit accelerated brain aging and positioning SLC39A8 as a potential intervention target for both knee osteoarthritis and related cognitive impairments. A previous study demonstrated accelerated hippocampal atrophy in MCP, yet the underlying causes remain unclear [21]. Using GWAS data, recent research has linked MCP to the upregulation of the *ECM1* gene in the hippocampus [85]. This gene's ability to disrupt the blood–brain barrier, a crucial factor in brain aging, positions it as a potential risk gene for both MCP and accelerated brain aging.

In summary, the brain aging framework holds great promise for understanding cognitive impairments in CP by offering an integrative biological profile that links genes, molecular mechanisms, and morphological changes with BAG.

Framework rationale and justification: specificity, necessity, and falsifiability

While accelerated brain aging has been observed also in other condition [86], the proposed framework targets CP for key reasons. First, CP prevalence increases with age [2] and shares biomarkers with brain aging, such as neuroinflammation [87], oxidative stress [88], and genetic risk factors [25,89]. This supports the exploration of CP and cognitive impairment through the lens of brain aging. Second, brain aging is a heterogeneous process [90]. Phenotypic and genetic evidence suggests that although accelerated brain aging is present in multiple disorders, the underlying mechanisms vary [86]. By integrating machine learning, molecular brain atlases, and genetic data, the framework can identify CP-specific mechanisms (e.g., a distinct brain aging

pattern with molecular and genetic basis) underlying cognitive impairments. While brain aging mediates the relationship between CP and cognitive impairment, it might also indicate a general susceptibility to various brain disorders. Future research is needed to support this broader hypothesis.

In addition to the limitations of existing theories, the significant heterogeneity within CP also underscores the necessity of the brain aging framework. The substantial heterogeneity across types of CP suggests that similar cognitive impairments may arise from diverse patterns of brain alterations [27]. By integrating machine learning algorithms and large-scale neuroimaging datasets, brain age offers a single quantifiable measure suitable for investigating such heterogeneous conditions, serving as a biomarker for risk prediction and prevention evaluation. Moreover, CP involves numerous psychological and physiological factors that lead to cognitive impairment [15–20]. Any suitable alternative framework would need to integrate them. Given that most of these factors are closely associated with accelerated brain aging (as shown in Table 1), a brain aging-centered framework is essential for capturing the complex impact of CP on cognition.

It is important to acknowledge that the framework, though based on multi-faceted evidence, does not imply that accelerated brain aging is the sole explanation for cognitive impairments in CP. The question remains whether significant cognitive deficits could persist in CP patients even after reversing brain aging acceleration. If such conditions do exist, further exploring other factors, independent of brain aging, that contribute to these persistent cognitive impairments is vital.

Future study directions guided by the framework

By leveraging advanced imaging techniques, computational approaches, and multidimensional datasets, the framework can guide future studies to better understand biological mechanisms and improve clinical practice.

Biological aging across organs

Most types of CP, probably except for headaches and trigeminal neuralgia, receive signals (e.g., nociceptive signals, molecules) from outside the brain [91] and are often comorbid with diseases affecting other organs [92]. The brain is regulated by various messengers from other organs, with homeostasis maintained through stable interactions between organs [93,94]. Recent studies on multi-organ interactions suggest that this regulatory effect may manifest during the aging process. Dysfunctions in other organs, such as accelerated aging, can influence the brain's aging trajectory, with these effects potentially emerging several years beforehand [95,96]. Therefore, future research should assess the interaction of the aging processes between the brain and other organs in CP to better understand the mechanisms underlying cognitive impairments.

Reverse translation opportunities for cognitive impairments

The framework creates valuable opportunities for reverse translation. Brain aging-related regions, cells, neurotransmitters, and genes identified by the framework (Figure 3B–D) can inspire animal studies to elucidate the detailed biological mechanisms underlying cognitive impairments in CP and discover new therapeutical targets or repurpose existing drugs to mitigate cognitive decline. For example, the identification of SLC39A8 as a shared risk gene between knee osteoarthritis and BAG [21] can drive animal studies to investigate the causal role of SLC39A8 in cognitive impairments associated with CP using gene editing techniques. Additionally, animal models could assess whether drugs targeting downstream proteins of SLC39A8 might have therapeutic effects on cognitive impairments.

Brain age model-inspired interventions of cognitive impairments

Future research can leverage this framework to inform the development of effective interventions aimed at mitigating and preventing cognitive impairment in CP. Currently, research in this field, especially longitudinal studies, remains limited [50]. Longitudinal studies are essential for assessing the efficacy of lifestyle interventions and pharmacological treatments in reducing BAG and monitoring changes in brain age biomarkers. Many commonly prescribed medications for CP have been shown to negatively impact cognitive function [17,97]. Future longitudinal studies may assess their long-term impacts on brain aging, informing their use, or focus on developing new pharmacological treatments for CP with fewer adverse effects on brain aging and cognitive function. In addition, the rapid advancement of machine learning presents further opportunities for brain age model-inspired interventions of cognitive impairments. For instance, generative learning has shown effectiveness in mapping multiple progression pathways through which the brain transitions from an initial state (e.g., healthy) to a target state (e.g., dementia) and in evaluating how combinations of these pathways contribute to reaching the target state at an individual level. This provides a technological foundation for developing brain age models that can guide personalized interventions in CP management.

Concluding remarks

As the global population ages, cognitive impairments in CP have gained increasing attention. Recent research has uncovered association patterns that are notably more complex than previously recognized. The framework we present positions accelerated brain aging as a critical pathway bridging CP and cognitive impairments, thereby enhancing our understanding of their complex associations. This framework incorporates CP-related multi-level factors that influence the brain aging process, operating either before or after the onset of CP, in linear or nonlinear ways. The advancement of brain age models, interpretable machine learning approaches, and molecular brain atlases equips this framework with the tools to develop quantifiable cognitive risk assessment indicators and elucidate their biological mechanisms across multiple scales.

Some questions still remain to be explored. While accelerated brain aging has been associated with multiple cognitive domains in the general population, its connection in CP has so far been explored and identified mainly in the memory domain. CP involves cognitive impairments across multiple domains, yet it remains unclear whether accelerated brain aging accounts for a general factor or is specific to certain domains (see Outstanding questions). Future research would benefit from integrating brain age models with cognitive assessments that span a broader range of cognitive domains, such as the **Cognitive Assessment Battery**, with rigorous validation to avoid inaccurate inferences arising from insufficient reliability and validity [98].

Our proposed framework focuses on CP-related factors that may accelerate brain aging. However, this does not rule out the possibility that some CP-related factors could potentially decelerate brain aging (see Outstanding questions). For instance, a recent study identified the APOE2 allele, known for its protective effects against dementia, as a risk factor for chronic back pain [99]. This could explain why chronic back pain, despite numerous factors that could accelerate brain aging, does not show significant accelerated brain aging and increased dementia risk. This emphasizes the importance of future brain age studies conducting stratified assessments on CP to identify high-risk subgroups.

Acknowledgments

The study was supported by the STI2030-Major Projects by the Ministry of Science and Technology of China (2022ZD0206400), National Natural Science Foundation of China (32322035, 32171078), the Scientific Foundation of the Institute of Psychology, Chinese Academy of Sciences (E0CX52, E2CX4015), and Young Elite Scientist Sponsorship

Outstanding questions

Which cognitive domains, aside from memory, are associated with BAG in CP? Does BAG elucidate changes in CP as a general factor across all cognitive functions, or is it linked to alterations in specific cognitive domains?

Are there factors that both elevate the risk of CP and delay brain aging, leading to certain types of CP, such as chronic back pain, not being linked to accelerated brain aging and elevated dementia risks?

Compared with brain age models that rely on unimodal neuroimaging, can models based on multimodal neuroimaging capture a broader range of cognitive domains and more accurately predict the risk of cognitive impairments in CP?

Early studies have highlighted the effects of pain treatment, psychological interventions, and lifestyle modifications in slowing brain aging in CP. Could brain aging be slowed by directly modulating the brain, such as through neuromodulation techniques that deliver stimulus with biological significance to the brain?

Gender differences not only intersect various aspects of CP but also play a significant role in the aging process. Does gender moderate the impact of CP-related factors on brain aging? Additionally, which CP-related factors that influence brain aging are most sensitive to gender modulation?

Program by the China Association for Science and Technology (E1KX0210). We thank Zhiguo Zhang, Weiwei Peng, and Li Hu for their valuable comments during the preparation of this manuscript. We also appreciate Jie Chen's assistance in creating the figures.

Declaration of interests

The authors declare no conflicts of interest.

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