

Review

Harnessing BDNF Signaling to Promote Resilience in Aging

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ABSTRACT: As a key member of the neurotrophin family in the central nervous system, brain-derived neurotrophic factor (BDNF) plays a critical role in the maintenance and plasticity of the nervous system. Its innate neuroprotective advantage can also be shared with the brain when normal aging-dependent processes challenge neural circuits. The intricate relationship between BDNF and resilience during the aging process signifies the molecular mechanisms that underlie the maintenance and protection of brain function, such as cognition, movement and psychological well-being. As BDNF is crucial for neuronal growth and survival, it can also promote resilience against age-related functional decline and frailty, even if it fails to entirely prevent aging-related functional decline. In the present review, we discuss BDNF function from a neuroprotective perspective and how it may promote resilience in aging. We emphasize briefly the principal, well-known cellular hallmarks of brain aging and how BDNF may restrict such disabling molecular dynamics and enhance overall functional resilience in aging. Insight into the molecular pathways through which BDNF reduces age-related brain dysfunctions and/or improves resilience, provides a foundation for developing targeted interventions to promote mental well-being in an aging population.

Key words: Brain-derived Neurotrophic Factor, Brain, Aging, Resilience, Stress, Neurodegeneration, Neurodegenerative Disease, Alzheimer's Disease, Parkinson's Disease, COVID-19, Neurotrophins.

“This small, thatched roof hath a mighty spirit dwelling within”. *Hamlet* by W. Shakespeare (1564-1616).

The global aging population (defined as those aged over 60 years) is rapidly growing [1, 2]. Given the influence of unfavorable cultural and lifestyle factors (e.g. stress, poor social engineering, malnutrition) as well as adverse environmental conditions such as climate change, pandemics and social conflicts, extended longevity may not necessarily be linked to a prolonged period of good health and resilience. All these concerns represent just a snapshot of the multifaceted complications occurring within the field of aging research, which involves multiple disciplines ranging from social engineering and public health to psychology and sociology. For example, with the increasing frequency and intensity of natural disasters due

to climate change, attention to resilience building strategies is necessary to effectively mitigate the impacts of extreme weather events in aged individuals. Moreover, understanding how aged populations can recover from adversity, whether it is natural disaster, economic instability, or social conflict, is essential for fostering resilience at the grassroots level. These challenges explain why the UN declared 2021–30 as the *Decade of Healthy Aging*. Nevertheless, beyond the empirical level, it is essential to provide a conceptual framework for the dynamic processes of aging that enables actionable decision making for future interventions [3]. Whether aging is accelerated by damage accumulation over time, caused by disrupted homeostasis or linked to adverse developmental trajectories, there is still a chance that most interests in the field converge to a point of consensus:

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functional decline and deterioration that may compromise resilience. The brain, similar to various physiological systems, undergoes a gradual decline in functional capacities throughout the aging process, leading to impairments in cognitive domains such as learning, memory, attention, decision-making, sensory processing, and motor coordination. These manifestations are indicative of the progressive functional deterioration associated with aging [4]. For the present discussion, a time-dependent functional decline that is typically associated with progressive deterioration of physiological and cellular integrity may explain the aging process in different biological systems including the brain. More specifically, the normal aging process in the brain is accompanied by gradual molecular downregulation and cellular degradation, leading to cerebral atrophy and ultimately age-related brain dysfunction [5, 6].

Notably, aging is associated with a higher risk of neurodegenerative, inflammatory, and metabolic pathologies, which raises several intertwined conclusions. First, the impact of the aging process manifests heterogeneously among organ systems and individuals [*mosaic aging* [7]]. However, despite this variability, several shared mechanisms known as *hallmarks* [8] or *pillars* [9] of biological aging contribute to neuronal dysfunction in the elderly population. Second, the overt manifestations of brain aging are not uniformly exhibited across all brain structures. The specificity of these regional responses suggests selective vulnerabilities of certain functional networks to brain aging. For example, the hippocampus [10, 11] and cortical somatosensory and somatomotor areas [12] appear more vulnerable to neuronal aging than others. The molecular and cellular changes that occur during aging in these structures over time usually result in a poor functional profile, primarily in cognition (e.g. impaired spatial learning and memory) and movement (e.g. frailty and/or loss of balance). The region-specific aging of the brain along with physiological changes may also contribute to reduced resilience and lower adaptation to life adversities. Third, when people get older, the segregation of brain systems or specialization in brain function progressively decreases. The functional dedifferentiation in the aging brain ranges from the firing patterns of single neurons to the evoked activity of individual brain regions [13]. Interestingly, higher segregation of the brain's connectome into distinct functional networks serves as a modulating factor of cognitive decline and resilience in aging-related degenerative conditions [14]. Lastly, while aging is known to progressively contribute to disease and poor resilience, a reciprocal relationship between aging and disease can also occur; diseases and/or their treatments might also expedite the development of aging-associated pathologies [9]. This is specifically important when one is

concerned with understanding the aging process to recommend pathways as therapeutic targets or for preventative interventions, or even to employ this knowledge to extend healthspan in later life.

Chronological changes are not directly equivalent to the rate of biological alterations over time [15]. Thus, prior to any further discussion on how aging-related processes challenge overall resilience, it is necessary to distinguish between chronological and biological aging. While chronological aging refers to the actual number of years a person has been alive from the date of birth, biological aging (also known as physiological or functional aging), denotes the condition of a person's body and its systems relative to their chronological age. Accordingly, biological aging reflects how well or poorly an individual's body is functioning compared to the average person of the same chronological age. Biological aging is closely linked to experience-dependent patterns of epigenetic regulation of gene expression [16]. Undoubtedly, biological aging, as opposed to chronological aging, is correlated with substantial alterations in many hallmarks of health [17]. These changes reflect progressive deterioration of tissues and biological systems associated with the progressive senescence of organellar, cellular, organismic, and systemic functions. An optimal response to life-threatening factors in aging, therefore, is critically linked to the overall resilience that may be directly impacted by these pervasive incapacities. Additionally, reduced resilience in aging may in turn accelerate aging-dependent complications. This process may call for multi-level (systemic or lifestyle) therapeutic interventions that can properly address a set of influential factor (s) and their correlates. Further, the rate of biological aging typically varies among different tissues and systems within the body. However, compared to other systems, brain aging follows an entirely unique pattern of alterations, enabling it to profoundly affect the biological aging process in other body systems. This may occur through various interconnected pathways such as the autonomic nervous system, the hypothalamic-pituitary-adrenal (HPA) axis, and the endocrine system such as the hypothalamic-pituitary-gonadal (HPG) axis. However, the extent to which brain aging can influence or predict aging processes in other systems is still an area of ongoing research. Though controversial [18], neuroimaging measures indicate that brain age predicts mortality [19], and brain aging in return is reciprocally impacted by the biological aging seen in other organ systems [20]. For example, because the gut microbiome and its composition changes with age, the microbiome may contribute to the link between the aging gut and the aging brain [21, 22]. Thus, the brain's biological aging may predict the biological aging processes of other body systems [15].

It is promising to note that brain aging-dependent cellular impairments, which nearly consistently imply cellular senescence, and their subsequent cognitive decline can be restored to more youthful levels [5]. Therefore, any intervention that builds resilience (e.g. cognitive reserve) in the older population appears more constructive when it directly addresses specific brain functions at different levels of manipulation. Indeed, factors such as genetics, lifestyle, environmental

influences, and overall health status can also play a significant role in shaping the aging trajectory of different body systems. Hence, although the brain may contribute to the regulation and coordination of aging processes throughout the body, its ability to precisely predict these processes may be influenced by a complex interplay of multiple factors.

BOX 1: Overview: Resilience as a Process and its Practical Application to Aging

Resilience as a dynamic and multifaceted process involves the ability of organisms to recover from adversity, cope with stress, and adapt to challenges. The correlates of resilience as a process include: (i) *Exposure to adversity or challenge*. Resilience typically begins with the encounter of adversity, stress, or a significant life challenge. The nature and severity of the challenge can vary widely between individuals. Notably, individual differences determine heterogeneity of responses to challenges. In a practical approach, it is important to recognize that aging brings about various challenges, including physical, cognitive, emotional, and social changes. Practitioners should encourage their clients to embrace these challenges as opportunities for growth and learning rather than insurmountable obstacles. (ii) *Initial response*. When faced with adversity, individuals, including the elderly experience an initial reaction that may involve emotions such as frustration, fear, sadness, or anger. This initial response is a natural part of the process and can vary depending on factors such as personality, past experiences and learning history, and the specific nature of the challenge (see BOX 2). In a practical approach, it is critical to acknowledge and validate the emotions that arise in response to aging-related challenges. Practitioners should encourage their clients to practice self-compassion and remind themselves that it is normal to experience a range of emotions when facing transitions in life. (iii) *Coping mechanisms*. Resilience involves the use of coping mechanisms to manage the stress and emotions associated with adversity. Coping strategies can be both problem-focused (actively addressing the source of stress) and emotion-focused (regulating emotional responses to stress). Two fundamental psychological aspects of resilient behaviours are self-regulation and locus of control [26] which dictate both the direction and endurance of coping mechanisms. In a practical approach, it is important to develop adaptive coping strategies to effectively manage stress and navigate through aging-related challenges. This strategy may include seeking social support from friends and family, engaging in regular physical activity, and participating in social activities to find meaning and purpose in daily life. (iv) *Adaptation and adjustment*. As individuals navigate through adversity and apply coping mechanisms, they gradually adapt to the new circumstances and adjust their thoughts, behaviours, and emotions. This may involve developing new skills, changing perspectives, or finding alternative ways to meet demands, goals, and needs. In a practical approach, it is important to remind clients to remain flexible and open to adapting to changes in physical health, cognitive function, and lifestyle preferences as they age. Practitioners should encourage their clients to focus on what they can control and inspire creative solutions to overcome obstacles and maintain independence and autonomy. (v) *Learning and growth*. Resilience often leads to personal development. Through the process of overcoming adversity, individuals may gain new insights about themselves, build self-confidence, strengthen coping skills, and develop a deeper sense of purpose or meaning in life. These experiences can contribute to increased resilience in the face of future challenges. In a practical approach, it is critical to take advantage of opportunities for personal growth and development as individuals age. Practitioners may encourage clients to stay curious and engaged in lifelong learning activities, such as learning new skills or pursuing hobbies and interests that bring them joy and fulfillment. (vi) *Integration and maintenance*. Finally, resilience is an ongoing process that involves integrating the lessons learned from past experiences and maintaining adaptive coping strategies over time. This may even include achieving post-traumatic growth, which is a key component of resilience, as people transform distressing experiences into opportunities for personal development and deeper understanding [270]. Individuals who have developed resilience are better equipped to navigate future challenges, as they have built a repertoire of effective coping skills and have confidence in their ability to overcome adversity (Fig. 1). In a practical approach, it is important to encourage clients to integrate resilience-building practices into their daily routines to maintain emotional wellbeing and cope with the fluctuations of aging-related experiences. This may include practicing gratitude, staying connected with supportive social networks, prioritizing self-care activities, and maintaining a positive outlook on life. Social support also has a central role in building resilience [42]. Hence, it is important to spend quality time with family and friends and seek out meaningful community engagement.

Resilience, natural acumen of the organism

While resilience has recently been introduced into the natural science discourse, it is not a novel concept. Derived from the Latin root "resilire," meaning to spring back (or the ability to rebound), resilience was initially employed by physical scientists to signify the characteristics of a spring and explain the stability of materials and their resistance to external shocks. The contemporary psychobiological formulations of resilience uphold the core idea that there can always be a strategy to promote fortitude or resilience even in highly vulnerable biological systems. Thus, resilience from a natural science viewpoint is an end-product (not a dead end) of a counter-regulatory process that may modulate a system towards a more functional condition when challenged [[23], see also

[24] for further discussion]. Conceptually, resilience is not necessarily about the absence of vulnerability, however [25]. Instead, it refers to a dynamic process of adaptation (BOX 1) to adversity while a consistent, functional homeostasis or the maximum biobehavioural preparation is maintained. Even if we formulate resilience as a *capacity* or an *ability* [26, 27], the fact hidden behind it is a potentially well-orchestrated, productive dynamic that may support the process of adaptability to achieve a successful outcome in the face of adversity or stress. In the present discussion, therefore, we suggest that resilience is a condition that involves dynamic developmental, genetic, epigenetic, and neurochemical processes for optimizing adaptive biobehavioural responses to stressors or aversive experiences.

RESILIENCE: A DYNAMIC PROCESS

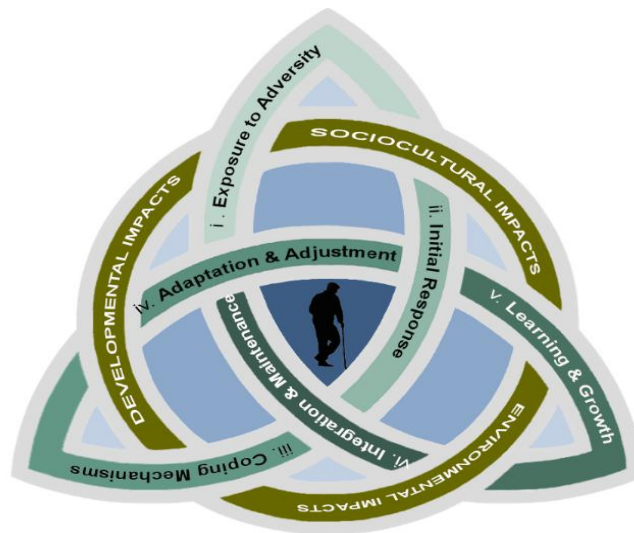


Figure 1. Resilience as a process. Resilience is often described as the capacity to recover quickly from difficulties (e.g., developmental and environmental impacts); however, understanding resilience as a process rather than a static trait or outcome offers a deeper and more dynamic perspective. Viewing resilience as a dynamic process offers a nuanced and holistic understanding of how individuals navigate adversity. It highlights the dynamic interplay between personal attributes and external resources/impacts, emphasizing growth, adaptation, and continuous development.

This viewpoint requires that resilience modalities be expanded from a mere biobehavioural domain to also consider the psychology of resilience [28] where the stability or disruption in psychological functioning is addressed (BOX 2). However, when *development* becomes a factor in the equation [29], a practical approach is also encouraged to promote lifetime health trajectories. For example, development appears to influence the heterogeneity of responses to adversity throughout a

lifetime through an interplay with environmental or contextual factors, such as lifestyle. While some individuals may wilt under pressure, others may bloom and thrive, exhibiting empowerment over environmental susceptibility. Hence, slightly- and highly-reactive phenotypes do not simply represent two alternative states of calmness and overarousal in neurobiological pathways. Instead, they refer to sensitivity to both protective and harmful contextual effects, known as the developmental

dichotomy of *orchid* versus *dandelion* metaphor of resilience [30]. This metaphor refers to two distinctive patterns of responses in which orchids represent those individuals who do exceptionally well in ideal conditions but who also respond more strongly to poor conditions. By contrast, dandelions are less sensitive to environmental quality, i.e. they are more resilient, adapt readily to environmental changes and thrive [30]. In the context of aging, where it is seen in the continuum of development and as an environmental susceptibility, not only the biobehavioural resilience, but other concerns arise about psychological resilience, such as cognitive

aging and mental health in the elderly. These include, for instance, how older individuals cope with loss (e.g. loss of independence), the strategies by which they adapt to health changes (e.g. cognitive and motor decline), how they face existential challenges (e.g. sense of acceptance and gratitude), and more importantly, how to promote resilience in the elderly in this context. Hence, regardless of how elderly individuals respond to adversities, and how varied these responses are, the existing conceptual frameworks of resilience are expected to identify a way to how resilience can be built and optimized.

BOX 2: Outlook: From Conflict to Growth

Resilience, the dynamic process of adaptation to adversity, represents two major intertwined responses (1) *during* a challenge, and (2) when the challenge is *over*.

Resilience during a challenge (*resilience in a confrontation*) refers to the ability to remain composed, adaptable, and effective when facing challenging or adversarial situations. This involves maintaining mental strength, emotional stability, and strategic thinking during conflict or confrontation. As confrontation deepens, the resilience process requires an organism to be more purposeful and goal-directed until the challenge is terminated. Resilient individuals, therefore, can withstand pressure, criticism, or hostility without losing their sense of self-control or purpose. They also tend to approach stressful situations with a sense of agency, actively seeking solutions and taking steps to manage and cope with difficulties. This sense of control empowers them to take effective action and maintain a sense of mastery over their circumstances. Such individuals are capable of bouncing back from setbacks, learning from experience, and even using confrontation as an opportunity for growth or positive change. The ability to express personal thoughts, feelings, and needs confidently and respectfully (assertiveness) and maintaining personal perspective during confrontations are the most representative aspects of psychological resilience. Taken together, resilience in a confrontation is about facing difficult circumstances and stressful situations with courage, commitment, control, and a constructive mindset.

Resilience when a challenge is over (*resilience in restoration*) implies the ability of individuals to recover, adapt, and thrive in the face of adversities or stressors. This response can also be applied within a broader framework when the ability of ecosystems, habitats, or communities is addressed to recover and persist following adversities, disturbances, or environmental stresses. However, if it is applied in the context of psychobiological restoration, the response entails the capacity of an organism to be fully restored after being disturbed. The process pertains to the capacity of the organism to recover and regain its optimal functionality (or the maximum biobehavioural preparation) following disturbances. It encompasses factors such as physiological function, organismal homeostasis, psychophysiological integrity, and behavioural stability. Further, resilience in restoration can extend to social and economic aspects of adaptation, focusing on the ability of individuals to recover and rebuild in the aftermath of interpersonal crises or disruptions, such as social conflicts and rejections as well as economic downturns. Overall, resilience in restoration emphasizes the importance of building and maintaining systems that can survive and recover from adversities, trauma, and stresses while sustaining their essential functions and services. During restorative response, resilient people also exhibit stability in the face of new disturbances up to a certain threshold. Beyond this threshold, they may undergo abrupt changes or collapse into an alternative state, leading them to suboptimal or nonoptimal resilience.

Resilience needs to be considered in light of the degree or dose of exposure to adversities over time [23, 29, 31], whether it is a single highly traumatic incident or cumulative effects of repeated or enduring stressors. Both short-term traumatic experiences and persistent stress appear to significantly influence physiology and health outcomes, especially in aging when most coping systems are more vulnerable and at higher risk of failure. Chronic stressful experiences in older adults may contribute to

accelerating immune aging by decreasing naïve and increasing terminally differentiated T-lymphocyte percentages [32]. Thus, the accumulation of adversities and stressful events across the life course has a significant impact on age-related activation of the immune system. At a mechanistic level, however, reduced immunological resilience to stress in the elderly is entangled with a common point of convergence across various biological

systems that fail to optimally function in the face of stress or have difficulty to recover from adversity.

A conceptual framework that considers aging of multiple systems linked to cumulative lifetime stresses is allostatic load [33]. The study of allostatic load has become valuable in providing sets of biomarkers that assess multi-system “wear and tear” and pathological risk over time - allostatic load increases as the body attempts to cope with stressors, and a high allostatic load predicts a higher risk of aging-associated diseases. Various types of allostatic load indices with measurements from the endocrine, immune, metabolic, and genomic domains have been adopted by clinical studies [34-36] but lately also introduced to animal models to facilitate knowledge translation [37, 38]. These approaches, together with epigenetic aging clocks [39-41], have become robust tools in assessing biological aging and prognosticating future health- and lifespan trajectories.

Resilience from a developmental and immunological perspective

Mere biological approaches to resilience fail to fully explain sociocultural and environmental impacts if developmental inputs are underestimated. The developmental dynamics, in turn, reflect the impact of social interactions and environmental influences on overall biological resilience [23, 42]. Resilience in aging also follows a similar trajectory. That is, developmental components including social relationships, ecosystems, and organizations may shape the nature of the adaptive biological systems such as immune system function later in life. Developmental trajectories of resilience also involve time-dependent milestones and critical periods that along with sociocultural inputs may drive biological systems to either flexibility or vulnerability [43]. Perinatal influences can change physiological systems in children, potentially affecting childhood health and overall resilience [44]. For example, childhood self-control predicts physical health, and children with lower self-control have poorer biobehavioural outcomes [45].

In addition, aging is typically associated with profound physiological alterations that affect the immune system. The aging immune system is prone to immunosenescence, a condition that mainly involves profound changes in immune parameters such as a reduction in the number of peripheral blood naïve cells and a relative increase in the frequency of memory cells when compared to young healthy individuals [46, 47]. Cellular aging-induced deterioration of immune cells and programmed cell death (apoptosis), such as observed in thymus and spleen, are regulated by epigenetic processes [48]. Also, immunosenescence coupled with chronic low-grade inflammation in aging known as inflamm-aging

[49, 50], is the underlying cause of many diseases and reduced resilience in older individuals. Therefore, the aging-related immune decline represents a normal gradual deterioration, profound remodeling, and significant changes in immune function with a profound impact on immune resilience [51]. It appears that an immunologically resilient phenotype (high immunocompetent) aligned with a specific immunocompetence-inflammation balance is linked to favorable immunity-dependent health outcomes [51]. Conversely, failure to preserve and/or restore optimal immune resilience when aged individuals experience immunoinflammatory stressors is a key to health-related challenges. Though developmentally dictated, immunosenescence has not yet been extensively explained in terms of its molecular and cellular foundations. Nevertheless, it is associated with the overproduction of proinflammatory cytokines such as interleukin 1 β (IL-1 β), interleukin 6 (IL-6), interleukin 18 (IL-18), C-reactive protein (CRP), and tumor necrosis factor alpha (TNF α) in the innate immune system [52-54]. In the central nervous system (CNS), these alterations may result in reduced levels of brain-derived neurotrophic factor (BDNF), leading to glutamatergic activation and consequently triggering three major pathways of neuronal death: excitotoxicity, oxidative stress, and the induction of apoptosis [6, 55, 56], all of which contribute to cognitive decline in the aging brain. For instance, BDNF levels predict the need for intensive care in elderly with COVID-19, suggesting that lower BDNF levels may serve as a biomarker for more severe disease progression and poorer clinical outcomes in an age- and sex-specific manner [57, 58], especially when infection leads to severe pro-inflammatory cytokine responses. It appears that older men respond to COVID-19 infection with lower concentrations of BDNF [57]. Thus, BDNF may be a critical determinant of severe COVID symptoms and a key component in long COVID syndrome [59].

Although this topic falls beyond the scope of the present review, it is worth noting that the immune system acts in close dialogue with the neuroendocrine system including the HPA axis, where its optimal resilience is regulated by the release of glucocorticoids (GC) [46, 60]. GCs normally inhibit the release of proinflammatory cytokines such as IL-6. However, when the HPA axis experiences chronic dysregulation influenced by persistent adversities, the ability to restrict proinflammatory cytokine production may diminish, leading to heightened inflammation and consequently suboptimal or even nonoptimal immune resilience [61]. Unsurprisingly, BDNF was shown to be highly involved in HPA axis regulation [62-64] indicating that it is a key player in the maintenance of homeostasis, one of the hallmarks of optimal resilience at different levels of

cellular function. Prolonged HPA activity, on the other hand, may reduce BDNF signaling and its receptor TrkB in the CNS [65]. It appears that BDNF downregulation critically contributes to the loss of resilience in the elderly,

although the primary causes that perturbate optimal resilience process in aging have not been fully elucidated yet.

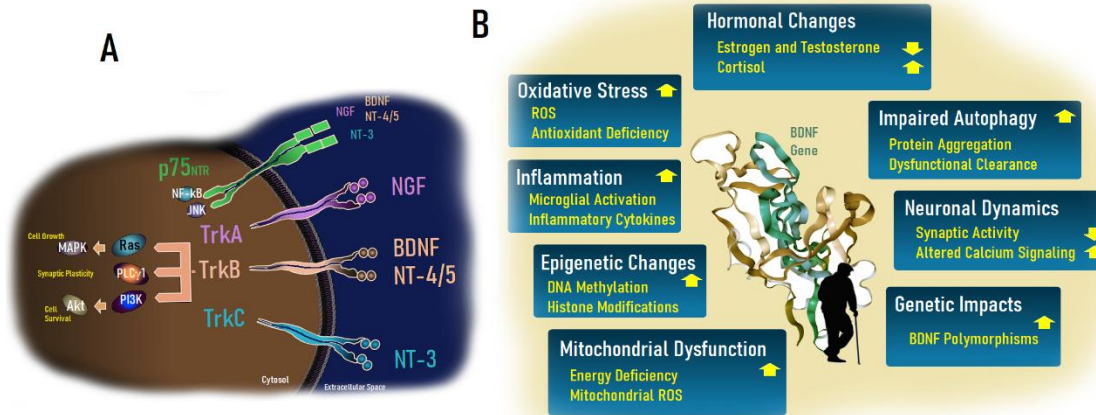


Figure 2. BDNF signaling and the aging brain. (A) *Neurotrophins, neurotrophin receptors and their downstream signaling pathways.* Neurotrophins are a family of proteins that play crucial roles in the development, maintenance, and survival of neurons in the nervous system. BDNF is one of neurotrophic proteins that supports the survival, growth, and differentiation of neurons in the central nervous system. It is crucial for synaptic plasticity, which underlies learning and memory processes. Note that mature BDNF and NT-4/5 bind to the TrkB receptor. Also, all members of the neurotrophin family are capable of signaling through a low-affinity receptor, referred to as the p75 (p75^{NTR}) receptor, which is structurally distinct from the Trk receptors. NGF, *nerve growth factor*; NT, *neurotrophin*; BDNF, *brain-derived neurotrophic factor*; Trk, *tropomyosin receptor kinase*; PLCγ1, *phospholipase Cγ1*; PI3K, *Phosphatidylinositol-3-kinase*; MAPK, *mitogen-activated protein kinase*; NF-κB, *nuclear factor-κB*; JNK, *Jun kinase*. (B) *Principal mechanisms of BDNF decline in the aging brain.* The decline of BDNF in the aging brain is multifactorial. BDNF levels tend to decrease in the aging brain, contributing to increased susceptibility to neurodegenerative diseases, cognitive decline, reduced overall resilience and lower adaptation to life adversities.

Neurotrophins, guardians of nervous system function

Neurotrophic proteins are among the most structurally complex and functionally sophisticated molecules critical for the proper functioning of the nervous system. They are involved in a wide range of processes, including neuronal growth and differentiation, synaptic plasticity, mood regulation, and the brain's response to injury and disease [66-69]. The most well-known neurotrophins include nerve growth factor (NGF), BDNF, neurotrophin-3 (NT-3), and neurotrophin-4/5 (NT-4/5). Each of these neurotrophins interacts with specific receptors on the surface of neurons to exert their supportive effects. For instance, NGF primarily binds to the tropomyosin receptor kinase A (TrkA) receptor, while mature BDNF and NT-4/5 bind to the tropomyosin receptor kinase B (TrkB) receptor. NT-3, on the other hand, specifically recognizes TrkC receptors [70]. It is also important to note that all members of the neurotrophin family are capable of signaling through a low-affinity receptor, referred to as the p75 (p75^{NTR}) receptor, which is structurally distinct from the Trk receptors [see [71] for further discussion] (Fig. 2A). Although p75^{NTR} exhibits lower affinity

compared to the Trk receptors, it is a multifunctional protein that intimately interacts with neurotrophins and other ligands to regulate various aspects of neuronal development, survival, and function, especially in aging. When comparing BDNF with other neurotrophins such as NGF, NT-3, and NT-4/5, several key differences and similarities emerge, especially concerning their effects on neural resilience and aging. For instance, NGF levels, although decreasing with age, particularly affect basal forebrain cholinergic neurons, which are recognized as an NGF-sensitive cell population. Hence, NGF loss may lead to cognitive impairments, especially in Alzheimer's disease (AD) [[72]; see also [73] for more discussion]. Specifically, the NGF signaling system, in which TrkA or NGF-specific receptors are expressed, appears to be dysfunctional during the prodromal stages of AD, contributing to the selective degeneration of nucleus basalis cholinergic cortical projection neurons in AD [74]. Unlike BDNF and NGF, the role of NT-3 and its receptor TrkC in aging is less understood, although its expression seems to be higher in the CNS during the intrauterine period than in the adult brain [75], thus promoting survival of several neuronal populations in early

development. NT-3 has also been shown to be involved in the survival of motor peripheral nerves [76] and proprioceptive neurons [77, 78]. NT-4/5, however, has a more limited distribution compared to BDNF, even though it still plays a role in synaptic plasticity and neuron survival. Like NT-3, the effects of NT-4/5 on aging are also not as well studied as those of BDNF or NGF. However, its decline with age could potentially contribute to memory deficits [79] and specific forms of neural degeneration, particularly in the sensory systems [80]. It appears that NT-4/5 expression is more region-dependent and exhibits differential effects depending on the timing and location of its co-expression with BDNF [81]. Moreover, it is noteworthy that in the realm of neurotrophins, BDNF emerges as particularly paramount due to its diverse and impactful function, especially in the context of experience-dependent aging and associated changes in the brain.

BDNF, tiny but mighty

BDNF [82], a small secreted protein, is the brain's fertilizer, nurturing growth, adaptation and resilience [83]. The factual rationale that supports such impressions is that neurotrophins such as BDNF control numerous cellular functions, including proliferation, differentiation, migration, and survival in the brain. Interestingly, BDNF is synthesized and released constitutively [84] and in an activity-dependent manner suggesting that endogenous extracellular BDNF levels are extremely low [82] and its release and regulation is highly dependent on exogenous stimulus patterns [85]. The synthesis of BDNF within the CNS occurs in the form of its precursor, proBDNF, which exhibits the capacity for storage within dendrites or axons. The precursor proBDNF subsequently undergoes cleavage processes, both intra- and extracellularly, to generate the mature BDNF protein [86]. Notably, proBDNF and mature BDNF represent two different functional states of the BDNF protein with distinct roles [87-89] in regulating neuronal structure and function. For example, proBDNF exhibits a preference for binding to the p75^{NTR} receptor, which can be associated with facilitating long-term depression (LTD) [90] and apoptosis [91], whereas mature BDNF binds selectively to TrkB receptors which promote cell survival, facilitate long-term potentiation (LTP) and increase spine complexity [86]. In the aging brain, there tends to be an imbalance between proBDNF and mature BDNF levels, with an increase in the ratio of proBDNF to mature BDNF, a pathogenic process which is thought to contribute to aging-related cognitive decline and neuronal dysfunction [92].

At the genetic level, the BDNF gene in humans is localized on chromosome 11p14.1 [93]. A single-

nucleotide polymorphism in the proregion of BDNF, known as the *Val66Met* polymorphism, involves a substitution of methionine (*Met*) for valine (*Val*) at position 66 in the BDNF protein. This change can affect the intracellular processing and the activity-dependent secretion of BDNF [94]. Specifically, the presence of the *Met* allele is associated with impaired trafficking of BDNF-containing vesicles to the synaptic site, leading to reduced release of BDNF during neuronal activity. Individuals with the *Met* allele generally exhibit reduced BDNF secretion in response to neuronal activity, which affects synaptic plasticity and cognitive function [95, 96]. Consequently, lower levels of BDNF in *Met* allele carriers may be associated with decreased resilience to age-related cognitive decline, increased susceptibility to stress, diminished psychological resilience, and a higher risk of developing neurodegenerative conditions such as Alzheimer's disease in the elderly. Hence, the *Val66Met* polymorphism affects the production and release of BDNF, and may represent a key factor in understanding individual differences in aging trajectories and susceptibility to age-related cognitive and mood disorders ([97]; see also [98] for further discussion).

BDNF, resilience, and challenges of brain aging

Brain aging is accompanied by several challenges to resilience. As explained earlier, resilience represents a dynamic process that involves the existing neurobiological potentials for optimizing adaptive responses to aversive experiences over the life course. Both development and lifetime adaptation to a dynamically changing environment are directly linked to BDNF activity in the brain. BDNF levels in the brain fluctuate throughout postnatal development. However, the regulation of BDNF in the aging brain appears to vary depending on the region and species [99], with some regions showing upregulation while others displaying downregulation. Since the brain serves as the central hub for perception and response to adversities, it is highly susceptible to the effects of allostatic load, with a similar level of vulnerability observed also in other biological systems (or organs) in response to stressors [100]. The region-dependent alterations in BDNF and the vulnerability of brain aging to the cumulative wear and tear (i.e., allostatic load/overload) can be traced through the neuroendocrine-immune, metabolic, and behavioural phenotypes in the elderly. Here, we briefly survey the most influential, deleterious neurobiological events in the brain that proactively play as drivers of brain aging. In this section, we also discuss how changes in BDNF deal with the destructive neuronal dynamics to support neuronal repertoires in favor of an optimal function. Three major domains of experimental observations related to brain

aging and reduced resilience in the elderly, i.e. neuronal events and dynamics, inflammatory processes and neuroinflammation, and blood-brain barrier dysfunction and morphological changes, will be discussed. Indeed, aging is a complex biological process that should be examined comprehensively. Yet, delving into individual cellular and/or molecular events that accelerate brain aging or affect overall resilience in older individuals is crucial for gaining insight into aging and initiating innovative anti-aging strategies.

1. Neuronal events and dynamics. Brain aging is characterized by shifts in the functional properties and dynamics of neurons, which may have maladaptive consequences. Typically, the brain encounters neuronal dysfunctions such as neurodegeneration, decreased neuroplasticity, and the accumulated impacts of oxidative stress as it ages, which coincide with disruptive inter-neuronal dynamics within the connectome. These changes closely contribute to declines in cognitive abilities, impaired mobility, and unfavorable mood alterations [5, 101]. Importantly, age-related alterations in neuronal function can diminish resilience [102, 103]. While not within the immediate focus of this review, it still remains essential to address these cellular changes, particularly when examining the beneficial impact of BDNF on optimizing resilience during aging. Numerous abnormal processes (Fig. 2B) lead to neuronal dysfunction in aging, which can potentially be modulated by BDNF and BDNF-mediated regulatory mechanisms:

1.1. Neurodegeneration (gradual loss of neurons). Neurodegeneration is one of the biological hallmarks of brain aging. Two observations regarding aging, neurodegeneration and resilience are of significance. One, neurodegeneration occurs over time; that is, some degree of neuronal loss and decline in brain function is considered a normal part of aging [104]. Second, neurons are selectively vulnerable in different neurodegenerative diseases [105]. However, excessive or accelerated neurodegeneration can lead to region-dependent neuropathology, which is typically associated with cognitive decline and/or motor dysfunction, and ultimately neurodegenerative diseases. Notably, neurodegeneration in the aging brain can be accelerated by several mechanisms.

The aging brain experiences compromised protein clearance mechanisms [106]. Normally, the brain employs mechanisms for the degradation of cellular proteins to remove damaged or misfolded proteins. These mechanisms include the ubiquitin-proteasome system (UPS) [107, 108] and autophagy-lysosomal pathways (ALP) [109, 110]. Aberrations in either mechanism may result in disruptions to protein quality control and homeostasis, thereby contributing to neurodegenerative conditions [111]. Notably, both protein degradation

systems involve the BDNF/TrkB neurotrophic signaling in various functional aspects within the aging brain, particularly through neuroplasticity-related processes (see section 1.2). In many neurodegenerative diseases, abnormal amounts or misfolded proteins accumulate within or between neurons, predominantly due to the loss of proteostasis (i.e., protein homeostasis) [104, 112]. The accumulation of toxic proteins may include existence of extracellular amyloid- β (A β) plaques and intraneuronal neurofibrillary tau tangles in AD [113-115], aggregation of alpha-synuclein (α -syn) in nigrostriatal neurons in Parkinson's disease (PD) [116, 117], and accumulation of huntingtin protein in Huntington's disease (HD) [118, 119]. These protein aggregates may disrupt normal cellular function and lead to neuronal damage at different levels of neuropathological events such as DNA damage, and mitochondrial and lysosomal dysfunction. It is important to note that aging-related protein abnormalities, especially in the phagolysosomal system within the aging brain, result in blurred distinctions between aging and neurodegenerative disorders. Consequently, elderly individuals may have pathological abnormalities in the brain that do not necessarily correlate with their cognitive disabilities or go undiagnosed [104].

AD patients typically suffer from reduced BDNF [120]. Notably, neurotrophin replacement therapy to the brain is challenging. Drug delivery to the CNS through peripheral administration is associated with complications in part because only minimal quantities of BDNF can cross the blood-brain barrier (BBB) due to its charge and molecular dimensions [121]. Using an alternative procedure known as adeno-associated virus (AAV) injection carrying the BDNF gene [122], several studies paved the way for AAV-based gene therapies that are associated with minimal complications and maximal efficacy [123, 124]. An alternative procedure has been recently suggested for targeted delivery of the BDNF gene to the brain using liposome nanoparticles to increase BDNF protein levels and reverse AD pathophysiology [125]. Of note, BDNF gene delivery involves several delivery vectors with different advantages and disadvantages. Subclinical manipulations aimed at infusing AAV-BDNF gene into the intralateral ventricle of the brain resulted in the restoration of the BDNF level, along with alleviated synaptic degeneration and attenuated behavioural deficits [122]. However, the gene delivery of BDNF did not affect tau hyperphosphorylation levels in AD. It appears that BDNF itself does not directly degrade or remove toxic proteins, such as the tau protein, from the brain [126]. Yet, the efficacy of BDNF manipulations in AD suggests that BDNF-involved mechanisms such as the BDNF/TrkB signaling pathway can modulate A β -induced neurotoxicity in AD and other

neurodegenerative conditions with tauopathy [see [127] for more discussion].

Furthermore, α -syn protein overexpression is associated with the downregulation of BDNF mRNA and protein in the pars compacta (SNpc) of the substantia nigra in patients with PD, and lower levels of BDNF can increase vulnerability to degeneration in nigral neurons [128, 129]. On the other hand, selective α -syn overexpression may negatively impact BDNF signaling and/or reduce BDNF gene and protein expression [130]. Using an α -syn-HDO that specifically targets α -syn abnormal overexpression, it has been recently shown that α -syn silencing protects dopaminergic neurons from degeneration via activation of BDNF transcription [129]. α -syn silencing may also upregulate BDNF mRNA expression [131], increase TrkB protein levels, and BDNF/TrkB neurotrophic signaling along with restoring motor function [85, 132]. If the pathological accumulation of α -syn protein leads to a reduction in BDNF levels, it suggests that BDNF may potentially influence disease progression in PD by regulating α -syn levels.

Criticism has recently been raised against neuroprotective approaches to PD due to their limitations in addressing the multifaceted nature of this condition, constraining it within the framework of a single pathogenic disease entity [133]. Therefore, it is recommended that interventions targeting PD pathogenesis be tailored to accommodate potential efficacy according to the distinct biological processes evident in various subgroups of PD patients. However, BDNF-centered interventions may still offer opportunities for exemption from these limitations, owing to BDNF's wide-ranging biological effects. Indeed, BDNF may indirectly influence α -syn clearance mechanisms in PD. BDNF may slow apoptotic processes in dopaminergic neurons in SNpc and enhance protein degradation pathways, including autophagy, which plays a role in clearing misfolded proteins [134, 135]. Although not specific to PD, BDNF-involved neuroprotective interventions provide insights into potential mechanisms by which BDNF induction may confer neuroprotection and modulate protein aggregation pathways.

Brain aging is also associated with an increase in oxidative stress, which can damage neurons and impair their function over time [136]. The free radical theory of aging [137] suggests that aging and associated diseases are caused by damage accumulated over time from free radicals or reactive oxygen species (ROS) in the body. In fact, ROS are the natural byproducts of cellular metabolism that can impair various neuronal components such as DNA, proteins, and lipids if not adequately neutralized by antioxidants. This damage, known as oxidative stress, can lead to impaired cellular function and

eventually contribute to aging and age-related diseases like neurodegenerative disorders, which usually result from the disruption of oxidant-antioxidant balance in neurons or an excess of ROS accompanied by a compromised intrinsic antioxidant defense [138]. Accordingly, the decline in antioxidant defenses drives the aging brain to increased oxidative stress and damage to neuronal architecture. BDNF, however, may counteract this process [6, 55]. For instance, BDNF/TrkB signaling attenuates oxidative stress by enhancing mitochondrial function and biogenesis through the upregulation of thioredoxin and peroxiredoxins [56], which are involved in maintaining cellular redox balance, and by activating peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 α) [139]. This reduction in oxidative stress is critical for maintaining cellular homeostasis and protecting against age-related neurodegeneration. More importantly, BDNF shares overlapping roles with sirtuins (SIRT1–SIRT7) in regulating cellular processes in brain aging. SIRT proteins are histone deacetylases (HDACs) whose activity depends on the cellular metabolic status and regulate energy metabolism and mitochondrial function [140]. SIRT1 activation may upregulate BDNF expression, potentially mitigating aging-related cognitive decline [[141, 142], See [143] for further discussion]. In humans, the overactive allele of SIRT6, which is known to regulate both longevity and progeria through the control of oxidative homeostasis [144, 145], is associated with longer life [146]. SIRT6 also plays a critical role in DNA repair, telomerase function, genomic stability, and cellular senescence [147], all of which involve BDNF function. Interestingly, caloric restriction that stabilizes mitochondrial function and reduces oxidative stress [148–150], has a potent antioxidant correlate: BDNF [151].

Dysregulation of mitochondrial function and dynamics in the aging brain [152] signifies diminished energy metabolism within the neurons. Mitochondrial dysfunction can impair energy production, induce lipid peroxidation and heighten oxidative stress [137, 153, 154], thus exacerbating neuronal damage and precipitating cognitive decline in aged individuals. BDNF modulates mitochondrial physiology by enhancing mitochondrial biogenesis (i.e., the generation of new mitochondria) [155]. The neuroprotective effects of BDNF on mitochondrial function were also shown to be associated with increased resistance of neurons to oxidative stress [156]. BDNF is a key player to regulate mitochondrial dynamics by influencing the expression and activity of proteins involved in fusion (e.g., mitofusins) and fission (e.g., dynamin-related protein 1). Of note, such functional dynamics are essential for maintaining a healthy mitochondrial network and optimal cellular function. BDNF can influence the transport of

mitochondria within neurons along axons and dendrites (see 1.2). Therefore, dysregulated communication between BDNF and mitochondria may severely disrupt cellular energy metabolism and contribute to the pathogenesis of neurological disorders, especially neurodegenerative diseases.

The process of brain aging is also associated with complex changes in hormonal and neurotransmitter systems. Alterations in the concentrations and functioning of various neurotransmitters, e.g., dopamine [157], serotonin [158], and acetylcholine [159], see [160] for more discussion] impact mood, cognition, and behaviour in the elderly. However, excessive activation of excitatory neurotransmitters, primarily glutamate [161], through excitotoxicity can specifically lead to neurodegeneration and neuronal death by increasing intracellular calcium concentrations in neurons [84, 162]. Aging-related changes in neurotransmitter systems and receptor sensitivity may increase susceptibility to excitotoxicity. It appears that regulation of glutamate homeostasis (release, uptake, and metabolism) to some extent depends on the BDNF/TrkB neurotrophic signaling in the brain. This signaling pathway regulates the expression of glutamate transporters and receptors, ensuring proper clearance of glutamate from the synaptic cleft and preventing its accumulation to toxic levels [163]. The multifaceted nature of neurodegeneration in aging brains underscores the intricate interplay between various biological processes and pathological mechanisms. While challenges remain in tailoring interventions to accommodate the heterogeneous nature of neurodegenerative conditions, the wide-ranging biological effects of BDNF provide hope for therapeutic strategies that address the complex underlying mechanisms of aging-related neurodegeneration and reduced resilience in the elderly.

1.2. Decreased Neuroplasticity. Neuroplasticity enables the brain to learn, adapt, and change (e.g., recover) in response to experiences and environmental influences [42, 164]. As people age, neuroplasticity tends to decline, making it more difficult for the brain to form new connections and reorganize neural pathways. Like neurodegeneration, diminished neuroplasticity in older adults may compromise cognitive functions such as learning, memory, and other cognitive processes linked with cognitive aging [165]. The mechanisms through which the BDNF/TrkB neurotrophic signaling preserve optimal neuroplastic processes during aging seem to involve several key neurobiological dynamics. However, the most important domains of reported observations include synaptic plasticity (synaptic transmission, and changes in spine number, size, and shape), neurogenesis, and neuronal survival and anti-apoptotic mechanisms.

Synaptic plasticity. In addition to its neuroprotective function, BDNF serves as a biomarker for neuronal plasticity [84]. It promotes synaptic plasticity by enhancing the formation and strengthening of synapses [166], thereby maintaining cognitive function and memory as the brain ages. Conversely, reduced BDNF signaling was shown to directly contribute to low synaptic function through altered expression of markers for inhibitory and excitatory neurons in human brain aging and synaptic function-related genes [167]. The BDNF signaling in regulating synaptic transmission and dendritic integrity holds significance due to two distinct findings. Firstly, it manifests in both presynaptic and postsynaptic neuronal compartments. Secondly, BDNF mRNA can be transported in neuronal dendrites in an activity-dependent manner [168, 169]. Accordingly, age-dependent decrease in BDNF signaling may cause synaptic alterations, the most consistent plasticity-related deficits associated with poor cognitive resilience [e.g., cognitive flexibility and perspective-taking [26]] and other forms of cognitive performance such as learning and memory in the elderly. For example, BDNF-LTP in different cerebral regions is impaired in the aged brain, and can be restored by endogenous BDNF induction through pharmacological approaches [168, 170] and physical exercise regimens [171].

LTP and LTD, two models of synaptic plasticity, represent the ability of synapses to strengthen or weaken over time in response to activity. LTP involves the strengthening of synaptic connections between neurons when two neurons are stimulated simultaneously, leading to enhanced interneuron communication. LTD, on the other hand, is the long-lasting decrease in synaptic strength, and involves the weakening of synaptic connections between neurons [16, 172]. In a neurofunctional perspective, LTP is typically induced by high-frequency stimulation of the presynaptic neuron, causing a significant influx of calcium ions into the postsynaptic neuron. Consequently, the influx of calcium triggers various molecular mechanisms, including the activation of calcium-calmodulin-dependent protein kinase II (CaMKII), the insertion of additional the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors into the postsynaptic membrane [173, 174], and an increase in the transcription of postsynaptic BDNF mRNA [175] as a retrograde messenger [173]. However, LTD results in a decrease in the number or efficacy of postsynaptic receptors, such as the removal of AMPA receptors from the postsynaptic membrane, thus refining neural circuits and eliminating unnecessary connections. Both processes can last for extended periods of time and have been shown to optimize synaptic transmission and cognitive function through increased synaptic plasticity. However, biological age dramatically

determines LTP and LTD functions in the brain through dysregulating p75^{NTR} [176]. It appears that the aging neurons display an increased tendency to induce LTD and reverse LTP, driving the decrease of synaptic transmissions [177]. Nevertheless, when locally microinfused, BDNF can trigger long-lasting synaptic strengthening in a region-dependent manner within the hippocampus, and selective induction of the dendritic mRNA species activity-regulated cytoskeleton-associated protein (Arc) [178].

Notably, BDNF also facilitates the transport of mitochondria within neurons along axons and dendrites. This transport is crucial for providing energy to distant neuronal compartments and supporting synaptic transmission and plasticity. By regulating mitochondrial motility [179], BDNF ensures adequate energy supply to active synapses and promotes neuronal communication and connectivity. Due to its critical neurotrophic roles in synaptic integrity and function, BDNF can be an essential component of the cellular mechanism supporting memory formation and maintenance by promoting synaptic consolidation, thus enhancing cognitive resilience in aging.

Neurogenesis. Neurogenesis, the process by which new neurons are generated in the brain [180], tends to decline in certain brain regions during biological aging [181, 182]. Our understanding regarding the mechanisms by which neurogenesis facilitates cognitive functions and resilience in healthy adults is still in its nascent stages. More importantly, how and to what extent decreased neurogenesis contributes to cognitive decline in aging appears to be even more elusive. BDNF stimulates neurogenesis [183], particularly in regions that are intimately involved in learning and memory such as the hippocampus [184], offsetting aging-related neuronal loss and supporting cognitive resilience. Subclinical observations suggest that the subventricular zone (SVZ) of the lateral ventricles, and the subgranular zone (SGZ) in the hippocampal (HPC) dentate gyrus are the main cerebral regions for adult neurogenesis. These areas are known to provide neural stem/progenitor cells (NSPCs) that generate neuroblasts undergoing neuronal differentiation. Neurogenesis within the SVZ also supplies fresh interneurons to the olfactory bulb [185, 186]. It appears that age is a co-factor that plays a key role in smaller HPC volumes (an indicator of diminished neurogenesis), reduced levels of serum BDNF, and poor memory performance in older adults [187]. Increased HPC volume, on the other hand, is associated with greater serum levels of BDNF and improved spatial memory in the elderly [188]. BDNF has been also shown to stimulate the proliferation of NSPCs in the brain, precursor cells capable of differentiating into various types of neurons. By increasing the pool of NSPCs, BDNF creates more

opportunities for neurogenesis to occur. Within the revolutionary concept of induced glia-to-neuron conversion [189, 190], originally proposed independently of neurotrophic signaling in the brain, proliferative neuroblasts generated by reprogrammed resident astrocytes have been shown later to develop into mature neurons and functionally integrate into the local neural network when supplied with BDNF [191]. Noteworthy, the significance of neurotrophins in such processes lies in their most characteristic functional aspect, which can be shared with neurogenesis as the fundamental mechanism: both BDNF neurotrophic signaling and neurogenesis represent activity-dependent cellular/molecular dynamics within the brain, highlighting their common vulnerability to activity-dependent changes or exogenous stimulations (e.g., exercise, social support, pharmaceutical intervention, dietary and environmental enrichment) in enhancing neurogenesis and cognitive resilience in older adults ([192, 193], also see [194] for further discussion) (BOX 3).

Neuronal survival and anti-apoptotic mechanisms. The integrity of the BDNF/TrkB pathway and its multifaceted role in enhancing resilience against age-related neuropathogenesis are particularly vital for neuronal viability [195] and anti-apoptotic mechanisms [196, 197] in the aging brain. These mechanisms are typically associated with the activation of downstream signaling cascades such as the phosphoinositide 3-kinase (PI3K)/Akt and mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathways [198, 199]. Upon BDNF binding to the TrkB receptor and the subsequent autophosphorylation of TrkB on specific tyrosine residues within its intracellular domain, PI3K, a critical downstream signaling molecule, is recruited to and activated by the phosphorylated TrkB receptor. The activation of PI3K leads to the production of phosphatidylinositol-3,4,5-trisphosphate (PIP3), a second messenger that recruits Akt (also known as protein kinase B, PKB) to the plasma membrane. Activated Akt plays a central role in promoting neuronal survival by phosphorylating, inactivating, and/or inhibiting several pro-apoptotic factors, such as the pro-apoptotic Bcl-2-associated death promoter (Bad) and glycogen synthase kinase-3 β (GSK-3 β), a kinase implicated in promoting apoptosis [200]. The MAPK/ERK pathways activated by BDNF/TrkB signaling also inhibit apoptotic signaling by, for instance, upregulating anti-apoptotic proteins of the Bcl-2 family [201] and downregulating pro-apoptotic factors such as Bax [202-204]. The MAPK/ERK pathway is initiated when TrkB activates Ras (Fig. 2A), a small GTPase, through the recruitment of the adaptor proteins Shc and Grb2, along with the guanine nucleotide exchange factor SOS. Activated Ras then triggers a kinase cascade involving the sequential activation of Raf, MEK

(mitogen-activated protein kinase kinase), and ERK (the Ras/Raf/MEK/ERK signaling cascade) [205]. Activated ERK translocates to the nucleus [206], where it phosphorylates and activates transcription factors such as CREB (cAMP response element-binding protein). CREB activation not only leads to the upregulation of anti-apoptotic genes [207, 208] but also promotes the transcription of BDNF genes themselves [209, 210], enhancing neuronal resistance to apoptotic stimuli such as aging and creating a positive feedback loop that sustains neurotrophic support. More importantly, significant crosstalk appears to exist between the PI3K/Akt and MAPK/ERK pathways [211], which enhances the robustness of the survival signals initiated by BDNF/TrkB

signaling. For instance, Akt can phosphorylate and inhibit components of the MAPK pathway to fine-tune the cellular response. Conversely, ERK can modulate the activity of certain Akt targets, creating a coordinated response that optimizes neuronal survival [212]. In the aging brain, the efficacy of these survival pathways is often diminished due to reduced BDNF levels and impaired TrkB receptor signaling, which compromises the ability of neurons to effectively engage these survival pathways. However, maintaining or restoring BDNF/TrkB signaling has been shown to counteract these age-related deficits [[199], see also [213] for further discussion], and preserve neuronal survival and resilience in the aging brain.

BOX 3: Overview: Neurotrophic Hypothesis, BDNF, and Brain Aging

If BDNF can activate neuronal survival mechanisms, it may also possess the potential to enhance neuronal resilience within the aging brain (Fig. 3). Previous hypotheses suggest that deficiencies in neurotrophic support, including impaired BDNF function, could be a significant factor contributing to depression [271-273], leading to pathological deterioration and behavioural decline. Conversely, augmenting neurotrophic support could potentially alleviate these symptoms [273]. When considering neuronal resilience within the aging brain, the neurotrophic hypothesis can be applied through several mechanisms that directly involve BDNF action in the brain: (i) *Promoting neuroplasticity*. Aging brains experience a decline in neuroplasticity, which can contribute to cognitive decline and increased vulnerability to neurodegenerative diseases. Interventions aimed at enhancing neurotrophic factor signaling may help maintain or restore neuroplasticity, thus promoting resilience to aging-related cognitive decline [228, 274, 275]. (ii) *Stimulating neurogenesis*. Neurogenesis declines with age, mainly due to a decrease in the quantity of neural stem/progenitor cells (NSPCs) and transit amplifying progenitor cells (TAPs) [276]. However, neurogenesis persists to some extent in specific brain regions, such as the hippocampus. BDNF has been shown to create a conducive environment for the generation of new neurons and their integration into existing neuronal circuits [234, 277]. Strategies that enhance neurotrophic factor signaling could potentially promote neurogenesis in the aging brain, contributing to neuronal resilience. (iii) *Protecting neurons against degeneration (cellular resilience)*. Neurotrophic factors have neuroprotective effects, shielding neurons from various insults such as oxidative stress, inflammation, and protein aggregation, which are common features of aging and neurodegenerative diseases [278, 279]. Neurotrophic factors may also promote the clearance of toxic protein aggregates (protein degradation), such as beta-amyloid in Alzheimer's disease or alpha-synuclein in Parkinson's disease, further contributing to neuronal protection [56]. Enhancing the availability or activity of neurotrophic factors may help mitigate aging-related neuronal damage and promote neuronal resilience. (iv) *Modulating synaptic function*. Neurotrophic factors such as BDNF and nerve growth factors (NGF) influence synaptic structure and function, including synapse formation, maintenance, and plasticity [156]. Aging-related changes in synaptic connectivity and function contribute to cognitive decline and vulnerability to neurodegenerative diseases. Interventions targeting neurotrophic factor signaling pathways may help preserve synaptic integrity and function, thus fostering neuronal resilience. (v) *Enhancing neuronal repair and recovery*. In response to injury or aging-related changes, BDNF/TrkB signaling can help facilitate brain repair and recovery by promoting synaptic remodeling, and functional reorganization [167, 280, 281]. BDNF may help recover impaired neurons in the aging brain through a close collaboration with M2 microglia [282]. Microglia are the resident immune cells of the central nervous system, and their activation state is generally associated with anti-inflammatory and tissue repair functions. M2 microglia, an alternative microglia phenotype, typically produce anti-inflammatory cytokines (IL-10 and IL-4) and neurotrophic mediators such as BDNF and promote tissue repair [223, 283]. M2 microglia are involved in processes such as synaptic pruning, neurogenesis, and the resolution of inflammation, contributing to repair of neural tissue damage. This ability to support brain plasticity is crucial for maintaining cognitive function and resilience in the face of aging-related challenges. (vi) *Neuronal growth and survival*. BDNF supports the growth and survival of neurons [284], particularly in areas important for learning and memory, such as the hippocampus [285]. In the aging brain, where neuronal connections may weaken or decline, BDNF may help stimulate the growth of new neurons and strengthens existing connections [286]. Given the importance of neurotrophic factors in maintaining neuronal health and function, therapeutic interventions aimed at enhancing neurotrophic factor signaling [284] represent a promising approach for promoting neuronal resilience in the aging brain. These strategies may include pharmacological agents, such as small molecule agonists or gene therapy approaches aimed at increasing endogenous neurotrophic factor production or enhancing receptor signaling, potentially contributing to the preservation of cognitive function and resilience in the aging brain.

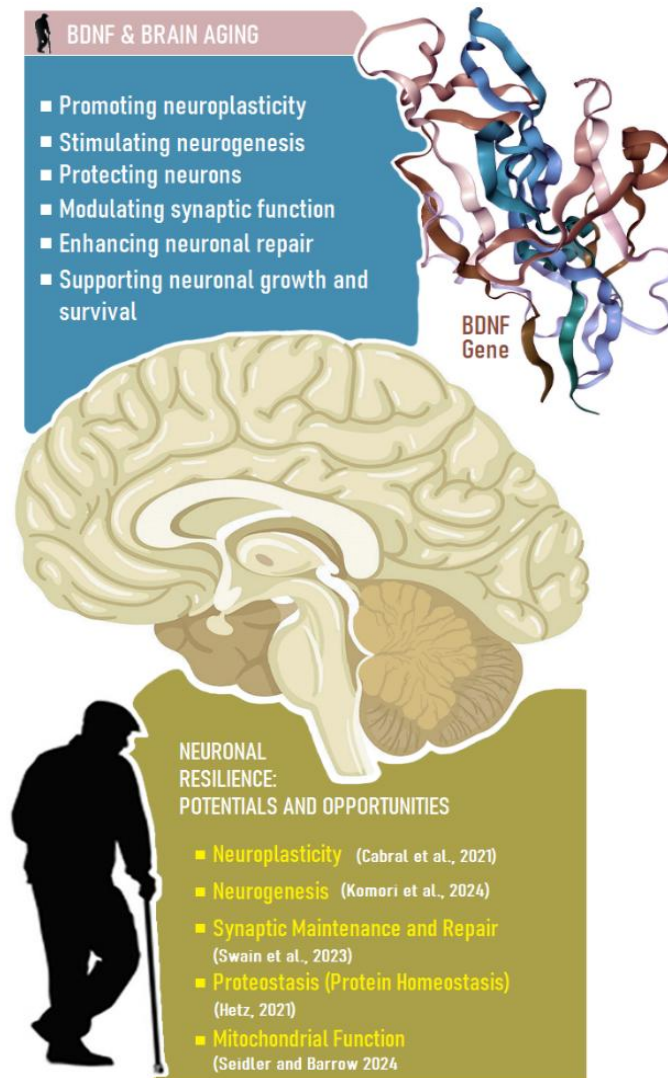


Figure 3. BDNF and neuronal resilience in the elderly. BDNF plays a crucial role in supporting neuronal resilience, especially in the aging brain. Neuronal resilience refers to the brain's ability to resist, adapt to, and recover from various stressors, including aging-related changes. As the brain ages, it undergoes numerous structural and functional modifications. However, certain mechanisms and factors contribute to maintaining neuronal resilience, thus helping preserve cognitive functions and overall brain health.

2. Inflammatory processes and neuroinflammation.

The hallmarks of aging have been recently updated to include chronic inflammation [8]. A concise biological interpretation of such concepts is that persistent low-grade inflammation, a sophisticated biological condition termed as inflamm-aging, increases with aging [50]. Inflamm-aging, which typically occurs in the absence of overt signs, and immunosenescence collectively underlie the genesis of most diseases and compromised resilience in the elderly [46]. Additionally, inflamm-aging constitutes a hallmark feature of the aging cerebral milieu. Notably, low-grade inflammatory reactions are commonly termed

neuroinflammation when localized in the brain and spinal cord. Such responses in the aging brain primarily involve a cascade of detrimental biochemical reactions that may occur locally in glial populations, particularly in microglia (the brain-resident macrophages). These responses are characterized by the acquisition of an ameboid morphology, the imbalanced production of pro-inflammatory cytokines and chemokines, as well as the overproduction of ROS [214-217]. The overall role of microglia in neuroinflammation is beyond the scope of this discussion. However, it is important to briefly note that the extent to which neuroinflammation impacts

neuronal dynamics (e.g. neurogenesis in AD) in the aging brain depends upon the duration and intensity of microglial activation in response to injury or disease. Chronic neuroinflammatory processes can contribute to neuronal dysfunction and abnormal neural signaling [218], suppressed neurogenesis [219] and neurodegeneration [220] in the aging brain. Accordingly, it is not surprising that neuroinflammation and its subsequent maladaptive functional impacts on brain aging have been implicated in the pathogenesis of many diseases in aged individuals. Nevertheless, findings obtained from diverse interventions, such as caloric restriction, putative neuroprotective interventions by BDNF, and exercise, aimed at reducing aging-related brain pathologies, challenge the prevailing concept of brain aging as a rigid process [6, 221, 222].

BDNF is a prompt synergist of microglial cells [[223], see [224] for more discussion]. Besides its well-known, potent neurotrophic effects, BDNF can modulate inflammatory processes in various tissues and organs, including the brain, even though its anti-inflammatory properties are not as extensively studied as its neurotrophic effects. Preclinical observations indicate that BDNF treatment reduces degrees of microglial activation in the presence of the brain injury along with reduced neuronal injury and death [225-227]. Even though the direct effect of BDNF administration on microglia has rarely been explored, recent findings show that the upregulation of BDNF signaling inhibits aging-related microglial activation via the TrkB-Erk-CREB pathway in aging mice [195]. Interestingly, suppressing BDNF/TrkB signaling during aging was associated with microglial activation, indicating a direct antimicroglial activation effect of BDNF in the aging brain [195].

In the aging brain, microglia have also been shown to play a key role in astrocyte reactivity via the secretion of pro-inflammatory cytokines and components of the complement system [5, 218]. BDNF, on the other hand, has been suggested to inhibit the activation of pro-inflammatory signaling pathways [228]. This includes pathways mediated by cytokines such as tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6), which are implicated in neuroinflammation. Moreover, BDNF can upregulate the expression of anti-inflammatory cytokines such as interleukin-10 (IL-10) [229-231] and promote the activity of anti-inflammatory enzymes such as heme oxygenase-1 (HO-1) [232]. More importantly, BDNF has been shown to modulate the activation state of microglia, thus promoting a phenotype associated with reduced inflammation and enhanced neuroprotection [228, 233, 234]. By regulating microglial activation, BDNF can help maintain a balanced immune response within the aging brain. The concepts of inflamm-aging and neuroinflammation underscore the genesis of numerous

diseases and compromised resilience in the elderly. Indeed, understanding the complex interaction among neuroinflammation, microglial activation, and the modulatory effects of BDNF offers promising avenues for therapeutic interventions aimed at mitigating neurodegenerative processes, cognitive decline, and promoting brain health in older adults.

3. Blood-brain barrier (BBB) dysfunction and morphological changes. The cerebral vascular system, which forms the BBB, is a highly specialized network of blood vessels responsible for preserving brain homeostasis and supplying oxygen, nutrients (glucose, amino acids, large neutral amino acids, etc.), and other essential substances to brain tissue while removing waste products [235]. The system and its vulnerability to aging-related changes have been recently discussed extensively by others [138, 236]. Growing evidence indicates that capillary vascular defects including BBB dysfunction contribute to many forms of brain pathologies such as neurodegeneration in aging. As individuals age, there are several changes that occur in all four types of BBBs [236] with a profound impact on their functions as a regulatory and protective network. Though some of these changes in the morphology and functionality of the BBB are adaptive, they can also closely contribute to vasculature deficits, which in turn may compromise cognitive performance, emotional integrity, and resilience in the elderly [235]. Similar to other complexities observed in the aging brain, changes in the aging BBB have not reached a clear consensus due to a simple, but critical observation: even in the absence of overt clinical or pathological manifestations, the human aging brain typically exhibits certain degrees of pathology. Ongoing advances in both clinical (e.g., rigorous physical examinations) and paraclinical (e.g. brain imaging, biomarkers) diagnostics may offer more comprehensive solutions to resolve these complexities in favor of enhancing the brain health and improving resilience in the elderly.

Two major manifestations of capillary vascular defects that may actively involve BDNF/TrkB signaling in the aging brain include permeability of BBB and metabolic changes. *Permeability of BBB.* The debate on whether BBB disruption occurs in the aging brain has persisted for decades. Nevertheless, aging-related changes in BBB have been repeatedly suggested to result in increased permeability (BBB leakage) [237-239], a process through which substances that would normally be restricted by the barrier may be able to pass through more easily. Consequently, harmful molecules such as toxins or pathogens as well as unregulated blood contents may gain access to the brain, potentially contributing to neurodegenerative dynamics or cognitive decline. Substantial evidence suggests that BDNF can support and

maintain the integrity of BBB [240] by enhancing the expression of endothelial tight junction proteins (TJPs) that restrict paracellular permeability [241]. Disruption of the BBB is also associated with increased infiltration of inflammatory mediators and immune cells into the brain, contributing to neuroinflammation [242, 243]. This can create a feedback loop where inflammation further damages the barrier and causes more inflammation and barrier dysfunction. Accordingly, inflammatory processes in the aging brain affect the integrity of BBB, leading to increased permeability and dysfunction. However, BDNF can limit the influx of pro-inflammatory cytokines or circulating T-cells into the brain through maintaining the TJs stability and the regulation of neuroinflammation [240]. *Metabolic changes.* In addition to the BBB hyperpermeability induced by junction structural changes (e.g., TJPs instability), the aging brain experiences metabolic changes such as reduced expression of glucose transporter 1 (GLUT-1) [244] and mitochondrial damage [235]; both defects have been reported to participate in brain pathogenesis and neurodegeneration during aging [154, 245], thus involving BDNF-dependent trophic processes.

GLUT-1 ensures that neurons receive an adequate supply of glucose to meet their energy demands. Hence, subtle deficits in GLUT-1 function in the brain may contribute to neurodegeneration [245]. BDNF has been shown to modulate the expression and activity of GLUT-1 at the BBB. Studies suggest that BDNF can upregulate GLUT-1 expression and enhance glucose transport and metabolism across the BBB [125, 246]. Conversely, reduced BDNF levels or impaired BDNF signaling may lead to decreased GLUT-1 expression and glucose transport, compromising neuronal energy metabolism and increasing susceptibility to age-related cognitive decline and neurodegenerative diseases [247]. More importantly, the functional symbiosis of BDNF and GLUT-1 has been recently shown by Tang and others [248] where GLUT-1 depletion not only triggers a severe neuroinflammatory response in the brain, but also reduces levels of BDNF and causes overt disease. Also, since glucose uptake in microglia is facilitated predominately by GLUT-1, particularly under inflammatory conditions [249], and BDNF-microglia interplay is crucial to reduce neuroinflammation [223], the BDNF/TrkB signaling is the footprint of trophic dynamics in the presence of capillary vascular defects in the aging BBB. It appears that targeting the *BDNF-GLUT-1-Microglia* signaling pathway could be a constructive approach to control neuroinflammation and improve cognitive resilience during aging.

Alterations in mitochondrial function and dynamics also impair BBB integrity in the aging brain [250, 251]. BDNF has been shown to enhance mitochondrial function

by increasing peroxisome proliferator-activated receptor- γ coactivator-1 α (PGC-1 α)-dependent mitochondrial biogenesis [139], improving ATP production, and reducing oxidative stress [155, 156]. This interaction is essential for maintaining cellular energy homeostasis and protecting neurons from aging-related damage. BDNF signaling pathways intersect with mitochondrial dynamics [252], including fission (mitochondrial division), fusion (mitochondrial interconnection), and mitophagy (recycling dysfunctional mitochondria) within the cerebral vasculature. An impaired balance between mitochondrial fission and fusion is one of the most characteristic mitochondrial defects in AD [253]. Additionally, all three mitochondrial dynamics - fusion, fission, and mitophagy - diminish with age, leading to a decline in mitochondrial quality in the aging BBB. However, BDNF promotes mitochondrial fusion and inhibits fission, leading to the formation of elongated and interconnected mitochondria, which are associated with enhanced bioenergetic capacity and resistance to stress [250, 254, 255]. Additionally, BDNF-mediated activation of mitophagy helps remove damaged mitochondria, thereby preserving overall mitochondrial function [139]. Furthermore, the BDNF-dependent trophic process to improve mitochondrial function can be facilitated through its well-known central anti-inflammatory effects. Since cerebrovascular inflammation disrupts BBB function in the aging brain [256] and vascular aging may impair neuronal health by reducing BBB integrity [250], BDNF is expected to play a critical role in mitigating these effects, potentially through its wide-spectrum effects on cellular energetics and metabolic homeostasis [252].

It is noteworthy that while substantial evidence supports a link between BDNF and specific aging outcomes, the field is also marked by several inconsistencies. Evidence positively linking BDNF to aging may include its role in enhancing cognitive performance by maintaining neuronal integrity, improving physical health, and protecting against emotional decline in the elderly. Inconsistencies in the evidence, however, are due to varying methodologies and differing study populations [257, 258]. For instance, although BDNF can be measured in serum, plasma, whole blood or cerebrospinal fluid (CSF), these methods often yield different results [259, 260]. This may lead to confusion about which biomarker is most reliable. Even within the same clinical population with different profiles of AD, serum BDNF could not predict disease group membership despite adequate power [261]. It is also notable that differences in study design, sample size, or population heterogeneity may further confound the reliability of results linking BDNF to aging outcomes. Importantly, lifestyle factors (e.g., exercise, diet) and genetics (e.g., BDNF Val66Met polymorphism) which

can modulate the relationship between BDNF and aging may lead to variability in BDNF levels and complicate the interpretation of findings in older individuals. Furthermore, longitudinal studies tend to present an alternative picture of the associations between BDNF and aging outcomes compared to cross-sectional studies. Thus, the temporal dynamics of BDNF may also be crucial for understanding its role in aging [262-264]. It appears that these inconsistencies in the BDNF contribution in aging outcomes and resilience can be adequately addressed through standardized measurement techniques, larger and more diverse cohorts, as well as a better understanding of how BDNF interacts with other biological factors, particularly other neurotrophins and environmental contributors in the aging process.

Concluding remarks

BDNF is the gardener of brain dynamics; it represents a critical component in the complex landscape of resilience and offers profound insights into the mechanisms underlying our capacity to withstand and overcome adversity. As a neurotrophin, BDNF exerts wide-ranging effects on brain architecture by impacting neuroplasticity, stress regulation, and emotional well-being. Why does BDNF emerge as a pivotal factor in fostering resilience in the aging trajectory? BDNF supports neuronal function and dynamics (survival of neurons, neuroplasticity, and neuroprotection) which are essential for maintaining cognitive function and resilience against aging-related cognitive and motor decline. Numerous findings also indicate that BDNF is involved in the regulation of the stress response system, including the HPA axis. BDNF helps to modulate stress hormone levels and attenuate the destructive effects of chronic stress, promoting resilience to stress-related disorders in aging. Moreover, aging involves a potent neuroinflammation dynamic in the brain which is directly accompanied by a heightened risk of neurodegenerative diseases. By reducing inflammation in the brain, BDNF contributes to resilience against cognitive decline and neurodegeneration associated with aging. Also, vascular pathology is a common feature of a range of neurodegenerative diseases that contribute to reduced resilience in aging. BDNF has been shown to promote vascular health by enhancing endothelial function and promoting angiogenesis. By improving blood flow and nutrient delivery to the brain, BDNF can support brain health and resilience against aging-related vasculature and metabolic challenges. Finally, BDNF plays a role in regulating mood and emotional resilience. Low levels of BDNF have been associated with mood disorders such as depression, while increased BDNF levels have been linked to improved mood and resilience

to stress and negative emotions in aging adults [63, 65, 84, 166, 223].

The role of BDNF in brain aging is crucial, as it can significantly contribute to the development of enhanced therapeutic strategies and interventions. By understanding the mechanisms through which BDNF influences aging such as neuroprotection, mood regulation, neurogenesis, and cognitive function researchers can devise more effective approaches to maintain brain health, improve cognitive and emotional resilience, and potentially extend the healthy lifespan. If lower levels of BDNF are associated with smaller hippocampi and poor memory function in older adults [187], targeted interventions and therapies aimed at increasing BDNF levels can potentially counteract these age-related changes. However, though provocative, therapeutic approaches using BDNF-induced improvements for neurodegenerative diseases in late adulthood have encountered many challenges in recent years. For example, supplementing with exogenous BDNF presents several complications due to its molecular structure, which affects its ability to cross the blood-brain barrier [[265], see also [266] for a counterargument], as well as the pharmacokinetics and volume fluctuations of BDNF once it reaches the brain. These issues can lead to imbalanced BDNF/TrkB signaling and potential upregulation or downregulation of BDNF/TrkB-related pathways. Nevertheless, the use of low-dose BDNF sequentially kinetic activated (SKA), as an alternative delivery method, has recently been shown to counteract some mechanisms underlying the degeneration and aging of nervous tissue [6]. Also, given the regional variation in BDNF molecule concentration in the brain [188], which can contribute to region-dependent volume decline, it is unlikely that a common intervention for BDNF delivery would resolve age-related neuronal challenges in all regions. Hence, future investigations need to prioritize elucidating the complex mechanisms underlying BDNF function in the aging brain, particularly its role in enhancing resilience to aging-related cognitive decline and neurodegenerative disorders. Furthermore, researchers should delve into exploring novel therapeutic interventions that target BDNF pathways to promote resilience in older adults. Such interventions may include pharmacological agents and the development of small molecule compounds or biologics that specifically target BDNF receptors or signaling pathways to enhance BDNF levels or activity in the aging brain. For instance, pharmacological interventions targeting the MAPK/ERK pathways activated by BDNF/TrkB signaling could present new opportunities for developing therapeutic strategies aimed at enhancing neuronal resilience in the elderly. This can be achieved by upregulating anti-apoptotic proteins within the Bcl-2 family and downregulating pro-apoptotic factors such as Bax. Also,

the activation of Ras, which triggers the sequential activation of the Ras/Raf/MEK/ERK signaling cascade, may further contribute to the inhibition of apoptotic signaling by suppressing pro-apoptotic proteins within the Bcl-2 family. Accordingly, the modulation of Bax/Bcl-2 signaling, which plays a central role in regulating neuronal apoptotic dynamics [267, 268] by BDNF/TrkB signaling and the MAPK/ERK pathways can potentially enhance neuronal survival and resilience. This

modulation may help to fine-tune the balance between pro-apoptotic and anti-apoptotic factors, thus mitigating neurodegenerative processes and promoting cellular longevity. It was previously suggested that the neuroprotective action of BDNF could be a potential mechanism for counterregulating Bax/Bcl-2 proteins within the ischemic penumbra following focal ischemia [204].

BOX 4: BDNF and its Synergy with other Biological Modulators in Aging

The brain is a complex system in which the synergy between its components is fundamental to its systemic function. BDNF synergizes with various molecules and compounds to promote brain health. These interactions can be leveraged to develop strategies for protecting neural integrity, preserving cognitive function and enhancing resilience in the elderly. Notable synergistic processes that may contribute to BDNF's neuroprotective effects during aging include its cooperation with insulin, serotonin and oxytocin, antioxidants, and exercise-induced molecules. For instance, BDNF interacts with insulin signaling pathways to enhance glucose metabolism and protect neurons [287]. Because, insulin resistance, a common concern in aging, (e.g., brain-specific insulin signaling deficiencies in the early stages of AD pathogenesis, [288]) is linked to cognitive decline, BDNF interaction with insulin is crucial for maintaining energy metabolism and cognitive function. Also, BDNF and serotonin are involved in a complex biological communication; serotonergic signaling pathways modulate BDNF expression, and BDNF, in turn, regulates the development and function of serotonergic neurons [[289], see also [65] for more discussion]. Serotonin can also enhance the expression of BDNF in specific brain regions, such as the hippocampus [290]. Changes in BDNF levels during aging can also be hypothesized to impact synaptic function and compromise oxytocin-mediated synaptic plasticity [291], a condition that may lead to alterations in social behaviour and cognitive function. The interaction between BDNF and serotonin and oxytocin, therefore, supports neurogenesis and helps mitigate social disintegration and emotional disturbances experienced by older individuals and age-related cognitive decline. Furthermore, antioxidants, such as flavonoids and polyphenol, can protect neurons from oxidative stress and ROS while also increasing BDNF levels through both the ERK/CREB/BDNF and PI3K/Akt pathways [292]. Antioxidants such flavonoids [293] and polyphenols [294] support BDNF's role in promoting neuronal survival, thus enhancing its overall efficacy in preserving brain function during aging. An alternative way to increase BDNF levels in the aging brain is physical exercise [295-297], which is accompanied by elevated levels of irisin, an exercise-induced myokine that are primarily released by muscles in response to physical exercise [295, 298]. This synergistic relationship between BDNF and irisin highlights the importance of physical activity in maintaining brain health during aging. The synergistic interactions of BDNF with various biological modulators play a crucial role in maintaining neural integrity and cognitive function during aging. More importantly, these interactions offer significant potential for developing promising strategies to enhance brain resilience in the elderly.

Lifestyle modifications such as regular exercise (BOX 4), dietary changes, cognitive training or other lifestyle enrichments may also impact BDNF expression and function, thus promoting resilience against aging-related complications. Additionally, future investigations may need to evaluate the efficacy of nutraceuticals (dietary supplements and natural compounds) with known neurotrophic properties, such as polyphenols, omega-3 fatty acids, or flavonoids, in promoting BDNF expression and neuroplasticity in the aging brain. Genetic and epigenetic approaches to BDNF signaling and resilience can explore the feasibility of gene-based interventions, including viral vector delivery or CRISPR/Cas9 gene editing, to enhance BDNF expression or signaling in the brain as potential therapeutic strategies for improving resilience in aging. Furthermore, the potential of stem

cell-based approaches, such as neural stem cell transplantation or induced pluripotent stem cell-derived neuronal grafts, has recently been suggested to promote BDNF production and neuroregeneration in the aging brain [269], thus enhancing resilience against aging-related neurodegeneration. However, it is important to note that while exerting influence on neural networks across various brain regions, BDNF may elicit distinct effects in specific brain areas. Therefore, interventions targeting a global elevation of BDNF in the brain may result in diminished efficacy compared to more localized interventions. In addition to these interventions, longitudinal studies examining the effects of BDNF modulation on cognitive resilience across different stages of aging are warranted to develop personalized interventions for optimizing brain health and resilience in

the elderly population. Strategies for lowering age-dependent brain complications and improving resilience may emerge as high priorities for incorporation into social engineering interventions and aging health policies.

Declaration of competing interest

The authors declare no potential conflict of interest.

Author contributions

JF and GASM designed the study. JF wrote the paper. GASM acquired the funding and provided resources and edited the paper.

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