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The role of brain health and resilience in reshaping trajectories of late-life neuropsychiatric disorders

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Global population aging and increased chronic stress due to numerous mass disasters including those related to pandemics, climate change, war, displacement, and political unrest all challenge our collective resilience, with a growing burden of late-life neuropsychiatric and neurodegenerative disorders placing unprecedented demands on health and social systems worldwide. With these considerations in mind, understanding and promoting brain health is becoming a priority for the prevention of neuropsychiatric disorders across the lifespan. Brain health represents a dynamic balance of neural, cognitive, and emotional processes that determine resilience to neuropsychiatric illness. In later life, this balance becomes particularly critical as neurobiological and psychosocial stressors converge to shape trajectories of neuropsychiatric and neurodegenerative disorders. This review synthesizes current evidence on the determinants of brain health in aging, emphasizing resilience as a modifiable pathway linking neuropsychiatric illness risk and prevention. We integrate insights from neuroscience, lifestyle medicine, geroscience, and social determinants of health to emphasize the value of a whole-person, life-course approach. Particular attention is given to the interplay between stress physiology, interoceptive regulation, emotional resilience, and cognitive and brain reserve across the aging continuum. Emerging frameworks including brain clocks, precision biomarkers, digital phenotyping, and artificial intelligence, are considered as tools for risk stratification, early detection, and personalized intervention. By linking resilience mechanisms to measurable biological indices, we argue for the integration of neurobiological, psychological, behavioral, and sociocultural domains to inform next-generation strategies in neuropsychopharmacology, prevention science, and the promotion of healthy brain aging.

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INTRODUCTION

Most developed countries of the world [1, 2] are observing trends of population aging, lifespan stagnation or even reversals, with the rates of dementia and other neuropsychiatric illness increasing. Besides well-known projections for global aging trends that existed for decades predicting increases in rates of dementia, Alzheimer's disease and late life vascular and neurodegenerative disorders, the COVID-19 pandemic and ongoing mass-disasters around the world have contributed to previously unanticipated rises in stress and mental disorders, with anxiety and major depressive disorders each jumping by about 30%, with mental and neurological disorders accounting for 16% of global disability-adjusted life years [3]. While the known effect of the COVID-19 infection is also likely contributing to increased rates of dementia and neurodegenerative disorders [4], we are yet to understand how rising rates of mental disorders will change prior estimates of dementia in the general population. The staggering cost of brain-related disorders—including mental, neurological, and substance use conditions—are estimated to cost the global economy around $5 trillion per year, and projected to rise to $16 trillion by 2030 [5] (Fig. 1; Table 1).

Against this backdrop, brain health and resilience have emerged as central scientific constructs for understanding and potentially reshaping trajectories of late-life neuropsychiatric and neurodegenerative disorders. A useful metric of healthy longevity refers to the quality-adjusted years of life that can help us track trajectories of brain and biological aging and healthspan [6]. The concept of a "aging healthspan" focuses on maintaining physical, cognitive, and emotional resilience throughout life, and underscores that a life-course approach necessarily underpins efforts to

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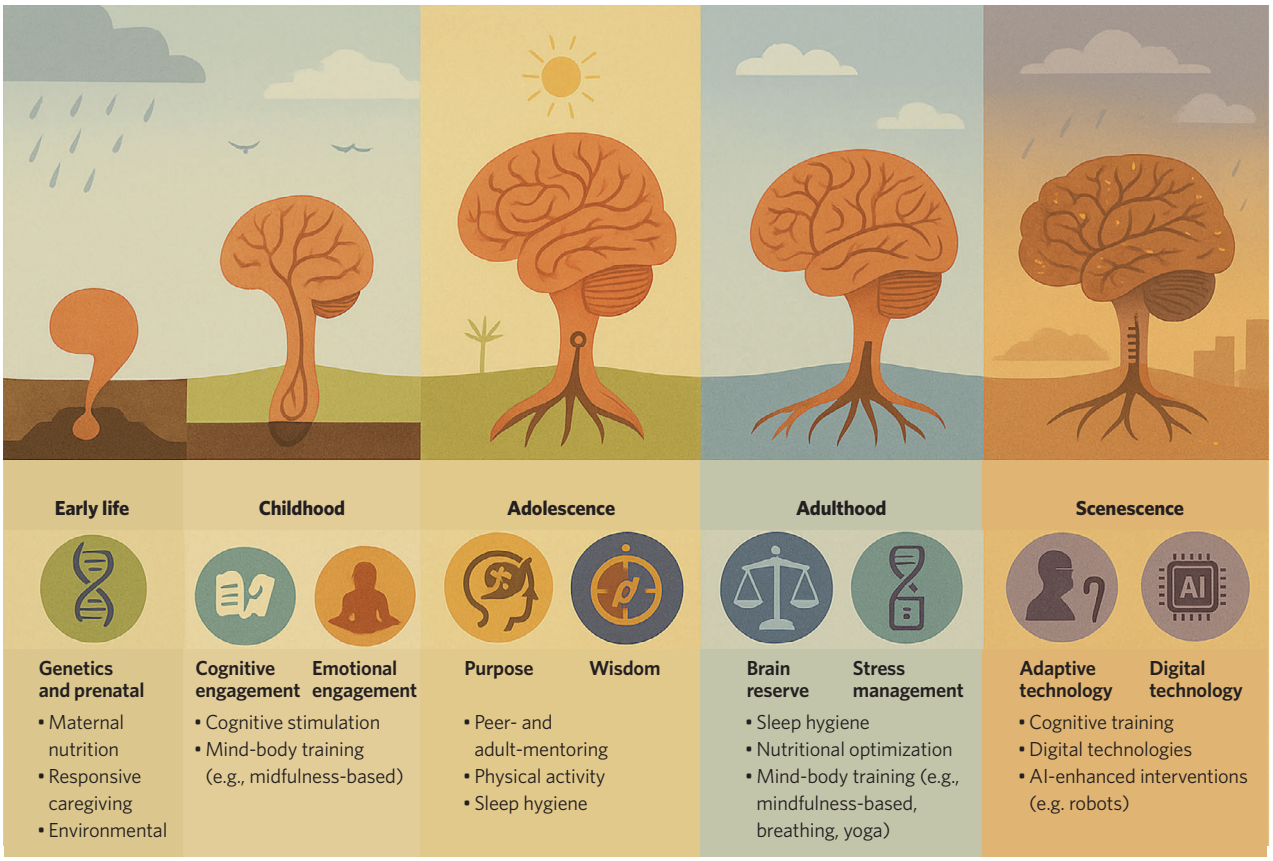


Fig. 1 A lifespan perspective on brain health, resilience, and trajectories of mental health. This conceptual illustration uses a tree metaphor to depict brain health across five life stages—seed (prenatal), seedling (childhood), adolescent (young adulthood), mature (middle age), and senescent (older age)—each integrating key interventions identified in the manuscript. The roots and soil emphasize foundational determinants such as maternal health and prenatal care, while branches and leaves illustrate age-specific strategies, including cognitive exercises, mentorship, mind-body interventions, mindfulness-based stress reduction, and digital technologies. Surrounding environmental elements highlight stressors (rain, wind) and supports (sunshine, watering can), emphasizing the dynamic interplay of biological, psychological, social, technological, and environmental factors. This figure underscores the importance of a multidimensional, lifespan approach to promoting resilience and preventing late-life neuropsychiatric disorders.

Table 1. Global impact of brain health.

Domain	Key statistic
Prevalence	Mental disorders affect 12–13% of the global population (970M people in 2019)
Treatment gap	Up to 85% of individuals remain untreated in low- and middle-income countries
Pandemic impact	Anxiety and depression increased by 26–28% in 2020
Youth burden	Suicide rates rose 56% among ages 10–24 (2014–2024); youth shoulder ~45% of disease burden but receive ~2% of research funding
Dementia trajectory	55M cases worldwide in 2021; projected to exceed 150M by 2050
Economic burden	Estimated at $5T annually, rising toward $16T by 2030

maintain or improve mental and brain health outcomes in older adulthood [7]. A consideration of the factors that play a fundamental role in influencing mental health in the aging lifespan is thus crucial. Healthy longevity is best understood through a whole-person approach recognizing the complex interplay of biological, psychological, social and environmental factors that impact health and well-being [8]. The emerging field of geroscience offers a biological framework for understanding aging and identifying preventive strategies that promote health across multiple domains [9, 10]. Within this context, brain health emerges as a foundational determinant of mental well-being, particularly in the later stages of life, where the convergence of psychiatric and neurodegenerative conditions presents complex challenges [11]. Table 1 describes the Global impact of brain health.

The World Health Organization (WHO) position paper defines brain health as "the state of brain functioning across cognitive, sensory, social-emotional, behavioral, and motor domains, allowing a person to realize their full potential over their life course, irrespective of the presence or absence of disorders" [9]. Another similar term, Brain Reserve, refers the structural capacity of the brain to maintain its size, number of neurons, synaptic density, and white matter integrity that can be measured by structural and functional neuroimaging. A brain health approach to prevention of later-life neuropsychiatric disorders extends beyond the traditional illness-centered

Table 2. Allostatic load effects across organ systems.

System	Typical indicators	Functional/Clinical consequences
Neuroendocrine (HPA/SAM axes)	↑ Cortisol, flattened daily diurnal rhythm, ↑ norepinephrine/epinephrine	Dysregulated stress reactivity, impaired feedback inhibition
Cardiovascular	↑ Blood pressure, ↑ resting heart rate, ↓ HRV	Hypertension, vascular stiffness, ↑ risk of stroke/MI
Metabolic	↑ Fasting glucose insulin resistance, ↑ triglycerides, ↑ LDL↓HDL, visceral adiposity	Type 2 diabetes, metabolic syndrome, accelerated atherosclerosis
Immune/Inflammatory	↑ CRP, ↑ IL-6/TNF-alpha, chronic low-grade inflammation	Immunosenescence, increased infection risk, neuroinflammation
Brain function	Hippocampal atrophy, prefrontal cortical thinning	Memory decline, reduced attention, mood and anxiety disorders
Others	Poor sleep quality, chronic fatigue, impaired wound healing, ↓ physical resilience	Cognitive fatigue, impaired recovery, reduced healthspan

CRP C-reactive protein, *HDL* high-density lipoprotein, *HPA* hypothalamic–pituitary–adrenal, *HRV* heart rate variability, *IL-6* Interleukin-6, *SAM* sympathomedullary, *TNF-alpha* tumor necrosis factor-alpha.

framework upon which most current healthcare systems are based. It prioritizes *proactive prevention* of disease and *early intervention* to enhance health and life quality prior to periods of age- or illness-related functional decline. By prioritizing, brain health and resilience, trajectories can be shifted toward preserved cognitive reserve to reduce vulnerability to pathological brain aging and dementia.

Despite growing attention to aging and mental health in the wake of the COVID-19 pandemic, most frameworks continue to address late-life (6th decade or later) psychiatric and neurological disorders in isolation, often overlooking their shared biological and psychosocial mechanisms as well as the cumulative impact of risk exposures across the lifespan. This review advances the field by integrating concepts of allostatic load, stress physiology, cognitive and brain reserve, and emotional resilience into a unified life-course model of mental health in aging (Table 2). We aim to bridge traditionally siloed domains—psychiatry, neurology, public health, and geroscience—into a cohesive framework that positions brain health as a central organizing construct. Within this model, emerging tools such as brain clocks, digital biomarkers, and artificial intelligence offer promising avenues for personalized risk stratification and preventive intervention. Taken together, these perspectives support a mechanistically anchored, transdisciplinary approach to late-life mental health that can inform both clinical practice and public health strategies for healthy brain aging.

BRAIN HEALTH FOR PREVENTION OF LATE-LIFE NEUROPSYCHIATRIC AND COGNITIVE DISORDERS

Brain health provides a unifying construct for preventive strategies aimed at reducing risk for late-life psychiatric and neurological disorders [11]. Promotion of brain health can begin early in life and extend across the lifespan through optimization of lifestyle behaviors and targeted interventions that enhance neuroplasticity, synaptic pruning, and cellular resilience [12]. Minimizing exposure to trauma, both physical and psychological, further supports adaptive plasticity, as neuronal connections expand rapidly in childhood, are refined during adolescence, and decline gradually in adulthood, underscoring the brain's lifelong capacity for change [9]. Evidence shows that brain health can be strengthened throughout the lifetime by reducing certain risk factors (e.g., head trauma [13], particularly in apolipoprotein E4 (APOE-4) allele carriers), and enhancing protective factors (e.g., enriched early education, cognitive stimulation). Many pathological changes underlying dementia begin decades before clinical onset, highlighting the importance of primordial and primary prevention at both population and high-risk levels [9]. Lifestyle and cardiovascular factors collectively constitute about 45% of preventable dementia cases; recent updates also implicate sleep, vision loss and LDL- low-density lipoprotein cholesterol as modifiable contributor (e.g., 2024 Lancet Commission statement on preventable causes of dementia) [14]. Ultimately, prevention requires addressing shared determinants of vulnerability and resilience, including social factors, psychological and cognitive reserve, and brain reserve. These domains represent actionable targets for interventions designed to shift trajectories of brain and cognitive aging across the lifespan. that we address below.

SOCIAL DETERMINANTS OF BRAIN HEALTH

Social factors, such as access to healthcare, social support, quality of education, childhood experiences, and economic stability, can profoundly affect brain health trajectories via increasing negative physical, environmental and psychological trauma exposures [15]. Jeste and Reynolds [12] argue that addressing these factors by identifying and measuring and developing specific interventions can reduce health disparities and generate parity in brain and mental health outcomes. Interventions targeting loneliness and promoting social integration, particularly in underserved populations, could also have significant public health implications. Interventions targeting non-medical determinants of health cannot be based solely on individual factors but would also need to target population-based solutions capable of mitigating the adverse effects of systemic inequalities, as these may significantly impact brain health [16, 17] and, consequently, the capacity for resilience. Social engagement and social activities are the most consistent components of social connections involved in improving cognitive health in older people with or at risk for Alzheimer's disease and other dementias. Socially focused or technology-based interventions could theoretically help improve social engagement and connectedness, but more research is needed to identify their impact on cognitive functioning [18] and determine the optimal balance of benefits/challenges of technology in aging populations. The new technologies can help understand the dynamics and trajectories of the relationships between numerous social factors and brain health, that can be used as targets for brain health-oriented interventions.

An emerging hypothesis is that social determinants of health and related environmental exposomes can induce accelerated aging [15, 19, 20]. Computational aging clocks quantify the discrepancy between brain-predicted and chronological age [19], enabling the assessment of how these age gaps are shaped by environmental and social disparities.

A recent large-scale study [21] of 5306 participants across 15 countries applied deep learning models to estimate brain-age

gaps using functional magnetic resonance imaging ($n = 2953$) and electroencephalography ($n = 2353$). Cohorts included healthy individuals as well as those with mild cognitive impairment (MCI), Alzheimer's disease (AD), and behavioral variant frontotemporal dementia (bvFTD). Participants from the Global South and females exhibited significantly larger brain-age gaps than males in both healthy and AD groups. A progressive increase in brain-age acceleration was observed along the disease continuum, from healthy individuals to MCI, AD, and bvFTD. Structural socioeconomic inequality, environmental pollution, and health disparities significantly contributed to greater acceleration, particularly in under-resourced populations. Another study involving 161,981 individuals across 40 countries introduced a global exposome framework [22]. Using computational tools, the authors developed the biobehavioral age gap (BBAG), a biological marker comparing predicted age to chronological age. BBAGs incorporate health, cognition, education, and risk factors such as cardiovascular disease or sensory impairments. While BBAGs closely approximated chronological age, many individuals exhibited delayed or accelerated trajectories beyond expectations. Analyzes across world regions revealed that Europe displayed the healthiest aging, while African countries showed the most accelerated aging, with Asia and Latin America in intermediate positions. Exposures linked to faster aging included physical factors (e.g., poor air quality), social factors (e.g., economic inequality, gender inequality, migration), and sociopolitical factors (e.g., lack of political representation, restricted voting rights, unfair elections, weak democracies). Importantly, higher BBAGs predicted future declines in cognition and daily functioning, with larger gaps associated with greater subsequent impairment.

Together, these findings illustrate the biological embedding of broad social determinants and exposomes in accelerated brain aging. They may also offer insights into how multimodal resilience (spanning genetic, psychological, social, and environmental levels) [23] can promote brain health and counteract vulnerability to accelerated decline.

CHRONIC STRESS AND BRAIN HEALTH

Chronic psychological stress is a major contributor to accelerated brain aging and vulnerability to late-life neuropsychiatric disorders. According to the Lazarus and Folkman model [24], the appraisal of stressors as threats or challenges, combined with perceived coping resources, determines whether responses become maladaptive (i.e., manifesting as worry, fear, anxiety, or depression), or adaptive (i.e., through problem-focused strategies). These cognitive-emotional processes shape neurobiological outcomes: repeated maladaptive appraisal and rumination amplify hypothalamic–pituitary–adrenal (HPA) axis activity, leading to elevated cortisol, structural and functional impairment of the hippocampus and prefrontal cortex [25], and consequent deficits in emotion regulation and cognition.

Resilience can be fostered through interventions that enhance positive cognitive reappraisal, optimism, and coping flexibility by reframing stressors as opportunities for growth rather than threats. Such strategies reduce HPA reactivity, mitigate stress-induced neurotoxicity, and promote adaptive plasticity. Evidence from clinical and translational research shows that this positive cognitive reappraisal can buffer stress reactivity and preserve neurocognitive function, and it is the source of many positive psychological and psychiatric approaches to resilience building including optimism training, hardiness training and wellbeing therapy [26]. As recently highlighted by Ibáñez and colleagues, resilience represents a dynamic, biopsychosocial construct that integrates psychological regulation, brain reserve, and sociocultural resources to buffer the impact of stress across the lifespan [23]. While psychological appraisal and coping processes shape vulnerability or resilience to stress, these mechanisms are embedded within broader physiological systems whose chronic activation produces cumulative biological costs.

PHYSIOLOGICAL STRESS, ALLOSTATIC LOAD, AND BRAIN HEALTH

Physiological stress arises when environmental challenges disrupt homeostasis, triggering multi-system regulatory responses designed to restore equilibrium [27]. While homeostasis involves reactive correction, repeated stress exposure shifts regulation towards allostasis—anticipatory adjustments that aim to maintain stability through predicted changes [28]. Chronic activation of these systems, particularly the HPA axis and sympathetic-adrenal-medullary system, results in allostatic load: the cumulative "wear and tear" across neuroendocrine, immune, cardiovascular, and metabolic domains [29, 30]. Elevated allostatic load has been linked to hippocampal atrophy, impaired executive function, accelerated cognitive decline, and heightened risk for late-life psychiatric and neurodegenerative disorders [31, 32].

Importantly, the framework of allostasis, the brain's capacity to anticipate and regulate bodily states, offers a mechanistic account of how resilience and vulnerability emerge. When adaptive, allostasis dynamically calibrates stress responses to match environmental demands; when maladaptive, it produces allostatic overload, driving systemic dysregulation and disease risk [23, 33]. Multisystem biomarkers, including cortisol, blood pressure, hemoglobin A1c, and inflammatory markers, now provide quantifiable indices of allostatic load, positioning stress physiology as a measurable and modifiable determinant of brain health.

Allostatic load, whether resulting from chronic or excessive stress, has profound implications for reduced longevity [34] and brain health [35]. It disrupts neural circuits involved in *interoception*, the nervous system's sensing, interpretation and integration of internal bodily states [36], and emotion regulation [37], as well as cognition, and immune function, thereby exacerbating vulnerability to mental and aging-related neurodegenerative disorder across the lifespan. The vital importance of allostasis and interoception in tailoring physiological responses to both environmental and internal demands is increasingly acknowledged [29].

Disruptions in integrated allostatic-interoceptive mechanisms are now implicated in neuro-psychiatric disorders such as anxiety, depression, Alzheimer's disease, and frontotemporal dementia. These disruptions involve complex cascades affecting the entire body, including brain structure and function within an *allostatic-interoceptive* network, and especially impact heart-brain and respiratory-brain interactions, the gut-brain-microbiota axis, inflammatory and immune pathways, and epigenetic regulation [38, 39]. This cumulative burden likely reflects an imbalance between the increased demands of modern, often chronic physiological and psychological stressors and the brain's capacity to adapt to this over time. Unchecked allostatic overload creates a state of systemic breakdown, culminating in what may be considered a global "brain health crisis", evidenced by rising prevalence of physical and mental health disorders and increased mortality. Addressing this crisis requires urgent action to mitigate chronic stress effects on the nervous system and implement preventative strategies that both reduce stress exposures and enhance resilience at individual and societal levels.

RESILIENCE AND BRAIN HEALTH

Resilience is the dynamic capacity to adapt, recover, and thrive in the face of adversity, integrating biological, psychological, social, and cognitive dimensions to maintain optimal functioning and well-being [40]. Resilience is a multifaceted concept spanning biological, psychological, social, and cognitive domains that is critical for preserving population brain health and cognitive

Table 3. Resilience-building psychosocial interventions for different target recipients.

Target group	Intervention method	Key components	Intended outcomes
Individuals	Cognitive-Behavioral Skills Training	Thought reframing, stress management, problem-solving	Better emotional regulation, reduced anxiety
Individuals	Mindfulness & Relaxation Programs	Breathing exercises, meditation, body scanning	Lower stress, improved focus, increased self-awareness
Individuals	Physical Wellness Programs	Exercise routines, sleep hygiene, nutrition education	Improved health, higher energy, better stress tolerance
Stressed individuals	Stress Inoculation Training	Controlled exposure to challenges, coping rehearsal	Increased adaptability, lower stress reactivity
Trauma survivors	Psychological First Aid & Narrative Therapy	Safety creation, emotional validation, storytelling	Faster recovery, reduced PTSD symptoms
Schools (Students)	Resilience Curriculum	Emotion recognition, coping skills, positive self-talk	Higher self-esteem, better coping with challenges
Workplace teams	Peer Support & Mentoring	Buddy systems, regular check-ins, mutual feedback	Stronger social bonds, reduced burnout
Communities	Social Connection & Community Engagement	Volunteering, group activities, neighborhood projects	Increased trust, social support, shared resources
All groups	Goal-Setting & Adaptive Planning	SMART goals, action steps, contingency planning	Greater sense of control, future-oriented thinking

reserve. Resilience is modifiable, either with a number of psychological interventions [41] (e.g., "stress inoculation" cognitive behavioral therapy; "Acceptance and Commitment Therapy", Problem Solving Therapy) [42, 43] or with lifestyle mind-body (i.e., meditation-based programs such as mindfulness-based stress reduction, yoga, biofeedback) and physical activity interventions showing promise in enhancing emotional stability and cognitive function, among others [44]. Recent NIH-supported resilience-oriented research provides a better understanding of the role of utilizing complementary and integrative health [45] approaches in promoting resilience through a whole person perspective and incorporating one or more of the three primary therapeutic targets—nutritional, psychological, or physical [46, 47]. Neuroimaging studies reveal that resilience correlates with regional gray matter volumes, particularly in areas associated with mood regulation [48]. These findings align with work targeting stress pathways to mitigate late-life psychopathology and to improve brain health [49, 50]. Beyond the individual, resilience extends to systemic and societal levels. The WHO and the United Nations Sustainable Development Goals highlight system-level resilience —the ability of societies to absorb, adapt, and transform in response to crises such as economic downturns, pandemics, and environmental challenges [51].

PSYCHOLOGICAL AND EMOTIONAL RESILIENCE

Psychological and emotional resilience have been broadly defined as "the capacity to maintain, or regain, psychological well-being in the face of challenge" [52]. Resilience serves as a critical buffer against stress. Individuals with higher psychological resilience demonstrate reduced susceptibility to brain health disorders and better outcomes in the face of adversity [53]. Conversely, those with lower resilience are more vulnerable to the detrimental impacts of allostatic load. Based on different theoretical perspectives and risk factors in question, resilient outcomes may be operationalized as either the presence of a positive outcome (e.g., life satisfaction, emotional well-being), or the absence of a negative one (e.g., lack of depression, anxiety, dementia) [54].

In the context of psychiatric disorders (e.g., depression), psychological or emotional resilience refers to the cumulative effect of a variety of psychosocial and biological factors that decrease risk of the onset or relapse, decrease symptom severity, or increase probability of recovery. Other facets of resilience include cognitive function (e.g., cognitive reserve, brain health), physical, motivational, and motor capacity (i.e., the ceiling of what is possible), all of which would be affected by chronic stress. Psychobiological factors of stress resilience include a host of endocrine, genetic, inflammatory, metabolic, neural, and cardiovascular processes that bidirectionally interact to affect risk for the onset and trajectory of late-life depression [55].

COGNITIVE RESILIENCE AND COGNITIVE RESERVE

Cognitive reserve refers to the functional adaptability of the brain in the ability to use networks efficiently and flexibly to compensate for damage, where neural efficiency, flexibility and alternative network use can be detected on the performance on cognitive task despite brain pathology [56]. With the expected increase in AD and related dementias in the coming decades due to the aging population and at best modestly effective disease-modifying treatments, there is a need for resilience-building interventions to reduce the likelihood of developing dementia. A variety of resilience-building strategies have been studied including leveraging genetics, socioeconomic status, lifestyle modifications, behavioral changes, and management of comorbid disease. These strategies can be broadly classified as distinguishing between modifiable and non-modifiable risk factors, some of which can be quantified so that their clinical intervention can be effectively accomplished. Research focus has shifted from identifying dementia risk to addressing disease resistance and resilience with new potential therapeutic targets. These targets include identifying genetic variants that may help identify novel pathways (e.g., lipid metabolism, cellular trafficking, synaptic function, inflammation, senescence) for therapeutic interventions and biomarkers allowing for a precision medicine approach. In addition, innovative structural and molecular neuroimaging analyzes may assist in detecting and quantifying pathological changes well before the onset of clinical symptoms setting up the possibility of primary and secondary prevention trials [57]. (Table 3).

Similarly, cognitive resilience is a property of the brain that allows for cognitive performance that is better than expected given the degree of life-course-related brain changes or disease with better than expected cognitive performance measured longitudinally [58]. These properties include multiple potential mechanisms including molecular, cellular and network levels.

Theoretically, these mechanisms, if boosted, can help compensate for brain changes and the consequences of brain injury or disease, in biological or cognitive experiments. These efforts will compliment and may synergize with ongoing efforts to pursue biological treatments that may reduce the impact of neuropathological processes such as Alzheimer's disease.

In the next two sections, we review two approaches that can help anchor resilience and promote post-traumatic growth, eudaimonia and wisdom. While eudaimonia fuels motivation and meaning, giving you the "why" to endure challenges. *Wisdom* guides how you respond, making your coping strategies more skillful and less self-destructive. Together, they do not just restore baseline functioning after stress—they make post-traumatic growth and how that might affect brain health.

EUDAIMONIA AND BRAIN HEALTH

Eudaimonia, rooted in Aristotelian philosophy, encapsulates the idea of flourishing through meaningful engagement, self-realization, and the pursuit of excellence. In contemporary psychological research, it is operationalized through dimensions such as autonomy, purpose in life, self-acceptance, environmental mastery, and personal growth. Studies suggest that this multidimensional construct has profound implications for physical and mental health outcomes, particularly in aging populations [59]. Eudaimonia promotes restorative health behaviors, such as regular physical activity, balanced nutrition, and improved sleep patterns [60–62] which are critical in mitigating chronic disease risk. For instance, longitudinal studies demonstrate that individuals with higher levels of purpose and mastery are more likely to adhere to healthier lifestyle practices, even in later life [63]. Furthermore, these behaviors act as buffers against deteriorative health practices, including smoking and sedentary lifestyles.

A 15-year Norwegian study of 4944 adults aged 40 to 95 years showed that in young-old adults, increasing subjective well-being was associated with adaptive behaviors and coping resources, while downturns in subjective well-being were associated with limits to psychological adjustment due to increased health-related and social threats and constraints [64].

A study of 1042 individuals in California across the adult lifespan reported that both presence of and search for meaning (purpose) in life are important for health and well-being, though the relationships differs in adults younger versus older than 60 years [65]. Presence of meaning showed an inverted U-shaped relationship whereas search for meaning had a U-shaped relationship with age, with presence being at its highest point and search being at its lowest around age 60. Mental well-being correlated positively with age and presence of meaning but negatively with search, whereas cognitive function correlated inversely with age and search. Thus, search for purpose in life, which is the critical component of eudaimonic well-being, can help enhance well-being when purpose and cognition begin to decline in old age.

At the biological level, promoting eudaimonia appears to influence stress response systems, reducing inflammatory markers and modulating allostatic load [66], defined as the cumulative wear and tear on the brain and body resulting from repeated cycles of physiological stress responses. Evidence highlights the reduced activation of pro-inflammatory genes and enhanced antiviral gene expression in individuals with higher eudaimonic well-being, i.e., the subjective experiences associated with eudaimonia or living a life of virtue in pursuit of human excellence and flourishing [67]. These findings underscoring eudaimonia's potential for protective effects against stress-induced physiological deterioration, although longitudinal controlled studies are needed.

Eudaimonia is also inversely correlated with depression, with higher levels of reported wellbeing linked to reduced risk and severity of depressive symptoms [68]. This relationship extends beyond simple associations, as interventions designed to enhance eudaimonic well-being, such as cognitive-behavioral therapy, mindfulness, and acceptance-based approaches, have shown some efficacy in alleviating depression, albeit with small effect sizes [69, 70]. These findings are compatible with emerging research emphasizing the role of eudaimonia in fostering emotional resilience, which mitigates the impact of adverse experiences and promotes recovery. In the context of healthy aging, eudaimonia seemingly contributes to slower functional decline and greater physiological resilience [71]. Key components of eudaimonia such as environmental mastery and self-acceptance, tend to stabilize or even increase in later adulthood, offering a foundation for improved quality of life. In the context of these findings, it seems reasonable to hypothesize that interventions aimed at cultivating these components will empower older adults to navigate age-related challenges while maintaining psychological and physical vitality.

Concurrent with the increased interest in healthy aging, the NIH Institutes, Centers, and Offices have prioritized research that advances understanding of health-promoting processes [72, 73]. Building off momentum from a 2018 meeting on emotional well-being (EWB; Emotional Well-Being: Emerging Insights and Questions for Future Research [74]), the National Center for Complementary and Integrative Health [45], National Institute on Aging (NIA), and *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), together with the NIH Office of Disease Prevention and Office of Behavioral and Social Sciences Research, established six research networks to advance the study of Emotional Well Being [74]. Investigators from these networks are examining the neurobiological, physiological, and behavioral processes that may underlie the positive associations between resilience, EWB, and health. A recent framework of how CIH approaches, such as mind and body interventions (for example, yoga, mindfulness-based or music-based interventions) and natural products (nutritional and/or dietary supplement interventions; precision probiotics), might mitigate the effects of chronic stress by engaging, and possibly enhancing, health restoration (salutogenic) processes has been proposed [75].

WISDOM AND BRAIN HEALTH

Another brain health-protective and aging-relevant construct is "Wisdom" that can be characterized by traits such as adaptive emotional regulation, prosocial behavior, self-reflection, acceptance of diverse perspectives, and spirituality [76]. It has emerged as a protective factor for mental health across the late lifespan. For example, studies demonstrate that wisdom enhances subjective well-being and mitigates loneliness, a major risk factor for late-life mental illness [77, 78]. Several cross-sectional studies have reported that older adults score higher than younger adults on several components of wisdom, including empathy, compassion, self-reflection, emotional regulation, positivity, decisiveness, and spirituality [79–81]. Cumulative knowledge and continuous processes of adaptation and self-efficacy in response to adverse as well as positive experiences likely contribute to higher levels of those attributes in older persons, although these traits may also be found in young adults. There is a potential neurobiological basis for an increase in wisdom with aging, particularly in people who stay active physically and psychosocially [82]. Considerable neuroscience research has demonstrated that neuroplasticity continues into old age (although to a lesser degree than in youth), allowing for new learning and adaptation. Neuroplasticity can be trained in old age as well, with domain-focused cognitive remediation training [83]. For example, underlying mechanisms may include neural compensation for age-related decline through recruitment of additional brain circuits, dendritic arborization, synapse proliferation, increased vascularity, and a limited subcortical neurogenesis (e.g., in the hippocampal dentate gyrus)

[80, 81]. Wisdom-based interventions can also appear to benefit brain health and wellbeing in aging. A meta-analysis of interventions that targeted specific components of wisdom identified 57 randomized controlled trials (RCTs): 29 focused on empathy and compassion, 13 on emotional regulation, and 15 on spirituality defined as beliefs in something bigger then oneself [84]. In that meta-analyzes, 47% of the trials had positive impact on emotion regulation with medium to large effect sizes. For example, a high-intensity 8-session group-based self-compassion intervention and another self-help intervention with self-compassion lessons and e-mail guidance demonstrated improved self-compassion and well-being compared to the control group. Five spirituality interventions also demonstrated significant improvements in spirituality.

RESILIENCE-BUILDING LIFESTYLE INTERVENTIONS FOR BRAIN HEALTH

One way to improve the trajectories of late-life neuro-psychiatric disorders is to build resilience and brain health across the lifespan. According to the 2020 *Lancet* Commission on dementia prevention, the twelve modifiable risk factors include hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, low social contact, low education, alcohol consumption, traumatic brain injury, and air pollution [11, 14]. Regular physical activity, and a healthy diet, sleep, weight, as well as healthy levels of blood lipids, glucose, and pressure, are key ingredients of cardiovascular health [85–88] that also support cognitive engagement, reduce the risk of cognitive decline, and enhance overall brain health [11, 87–89]. Accordingly, the integration of a whole-person health and lifestyle medicine approach into routine care, if effective at modulating these risk factors, should conceivably substantially mitigate late-life psychopathology [90].

The limited progress to date in successful treatment or reversal of dementia may require a shift towards a primary and primordial prevention approaches that starts decades before the onset of symptoms. The rationale for this approach is that earlier interventions may reduce the cumulative effects of psychological and physical trauma, lifestyle, and environmental exposures that precipitate or exaggerate neuropathological changes in the brain that trigger or promote progression of dementia. We have estimated that modification of these twelve risk factors has the potential to delay—or perhaps even prevent—up to 40% of dementias [11]. In addition, primordial prevention of late-life neurodegenerative and cerebrovascular brain disorders could start in early childhood by addressing risk factors and non-medical determinants of health such as low education and air pollution, and targeted prevention of cardio- and cerebrovascular risk factors (e.g., obesity, diabetes) [91].

Resilience-building intervention modalities have shown inherent promise for prevention and treatment of late-life neuropsychiatric disorders, including cognitive/psychological (e.g., positive psychology), or mind-body (bio- and neurofeedback, meditation), movement-based (aerobic exercise; yoga; tai chi), and biological approaches (pharmacotherapy, non-invasive brain stimulation [92] and electroconvulsive therapy [55]. Resilience-promoting interventions are shown to improve neuroplasticity, enhance emotional regulation, and stabilize physiological systems. Integrating insights from genomics, multi-omics, and exposomics [7] can help to understand resilience as not solely genetically predetermined but shaped by biopsychosocial-environmental interactions.

Besides the interventions targeting individual, resilience can be built with thin the groups and communities through peer support programs including mentoring and group discussions and buddy systems, communication skill building and strengthening the community ties; skill building and problem-solving training. Enhancing resilience requires a holistic, equity-focused approach integrating biological, environmental, and cultural insights to develop sustainable, tailored strategies for lifelong brain health and well-being.

LIFESTYLE STRATEGIES TO BOOST RESILIENCE INCLUDE

- *Physical activity*: Aerobic and resistance exercises [93, 94], as well as mind-body practices improve mood regulation and cognitive resilience, and physical health. Emerging evidence even supports the cognitive benefits of the "weekend warrior" approach to physical activity, with a recent study demonstrating that engaging in just one to two sessions of exercise per week were associated with a reduced risk of mild dementia by 25% [95]. These findings highlight the potential of low-frequency but structured physical activity to protect cognitive health, particularly in populations facing time or socioeconomic constraints [89].
- *Dietary optimization*: Balanced, nutrient-rich, anti-inflammatory diets enhance neural integrity, and the rapidly growing field of nutritional cognitive neuroscience is increasing our understanding of the beneficial effects of nutrition on the aging brain [89, 96]. By using precise methods to assess nutrient patterns, the interactive effects of nutrients in various diets, such as the Mediterranean diet [97], the Dietary Approach to Stop Hypertension (DASH) [98], the Mediterranean-DASH Intervention for Neurodegenerative Delay [99], with Nutrient Biomarker Patterns [100] biomarkers that can be captured and tracked as a result of dietary interventions. Likewise, changes in brain structure and function associated with the beneficial effects of nutrition on the aging brain may be measured using high-resolution neuroimaging methods [101, 102]. Integrating nutritional epidemiology (nutrient biomarkers) methods and cognitive neuroscience (high-resolution MRI measures structure/function) data offer some promising avenues of research [103]. Other evidence of nutritional supplements comes from the epidemiological and scientific studies linking consumption of omega-3 fatty [104, 105] acids, vitamins B and D to brain function, cognition and mood states. Cohort studies linking diets [106] rich in antioxidants, flavonoids, and polyphenols with lower Alzheimer's risk. Functional MRI (fMRI) and PET scans reveal how these compounds protect against amyloid buildup and preserve functional connectivity.
- *Cognitive engagement*- Cognitive exercises and mental engagement, higher educational attainment, and learning new skills promote resilience by enhancing cognitive capacity and cognitive reserve. For instance, engaging in cognitively stimulating activities throughout adulthood has been consistently associated with reduced dementia risk and slower cognitive decline in later life [14, 58].
- *Stress reduction*- Mindfulness, meditation, breathing practices and yoga promote autonomic balance and stress recovery. Practicing yoga and Tai Chi physical postures may increase balance and strength, thereby reducing risk of falls and increasing strength of muscle mass that declines with age, and leads to improvement in chronic pain [107]. Cognitive benefits of yoga and Tai Chi include learning new postures, adopting philosophy and mindfulness that may improve cognitive flexibility, and memory, thus potentially improving brain health on cellular, structural and functional levels [107, 108].
- *Reduction in loneliness and increase in social support- in person or virtual; intergenerational communities and activities*- Chronic isolation and loneliness can also increase the risk of dementia in older adults by 50%. Interventions that foster strong social support networks and intergenerational activities significantly enhance adaptive capacity and improve mental and cognitive health [18, 91].

- *Spirituality-based interventions*- For aging adults, spirituality is an important facet of daily life that can serve as one of the key factors of resilience [109]. Spirituality is highly correlated with wisdom and resilience, and serves as a resilience-promoting tool through five key domains: reliance on relationships, spiritual transformation, spiritual coping, power of belief and wisdom, and commitment to spiritual values and practices, suggesting that focusing on spirituality in older adults who face chronic mental and physical illnesses is important [76, 109]. A recently published meta-analysis by Lee et al. [110] included fifty-seven studies ($N = 7096$ participants) and reported that widely ranging interventions to enhance spirituality, emotional regulation, and prosocial behaviors were effective in people with mental or physical illnesses.
- *Sleep*: Quality sleep for 7–9 h per day is essential for restoring neural circuits, mitigating allostatic load, and facilitating brain clearance via the glymphatic system, which efficiently removes metabolic waste and toxic proteins implicated in brain disorders including Alzheimer's disease [89, 111, 112]. Aging reduces sleep quality and quantity, thus interventions to emphasize the importance of adequate sleep and steps to improve quality and quantity of sleep may pay significant dividends in mitigating the effects of brain aging.

BUILDING RESILIENCE THROUGH PUBLIC POLICY AND INCLUSIVE WELL-BEING

Resilience is not solely an individual attribute but is deeply intertwined with social, economic, and policy structures that influence well-being at the population level [23]. During global crises, such as the COVID-19 pandemic, the socioeconomic vulnerabilities of certain groups have underscored the need for a multidimensional approach to resilience. Financial insecurity, housing affordability, and disparities in access to healthcare and education have all been shown to exacerbate stress and its impact on mental and brain health. According to OECD findings, the unequal distribution of resources and opportunities significantly hinders the ability of economically and politically marginalized communities to recover from adversity [113]. While addressing these challenges is not a current systematic priority of governments around the world, several of us have argued for the prioritization of policies that reduce structural inequities that inhibit or reduce inclusive well-being [114]. We have advocated that adopting measures such as ensuring equitable access to healthcare, integrating resilience-building programs into educational curricula, and investing in mental health services can provide foundational support for cognitive and emotional resilience at the population level [115]. One way to ensure this approach is sustainable and successful is by embedding brain health into broader policy agendas, including environmental and social reforms [116, 117].

World governments need to move beyond anecdotal inclusion of resilience into public health frameworks and pursue deep structural alignment with local realities. This means positioning resilience not as a reactive concept, but as a measurable, upstream determinant of brain health—embedded within health systems, educational strategies, and economic reform [23, 117]. Health policy should incorporate indicators of adaptive stress regulation, ecological exposure, and social buffering capacity into routine surveillance. Aligning these metrics with system-level interventions, such as community-based mental health services and culturally grounded care models, can shift resilience from theory to sustained impact [118].

The World Economic Forum Brain Economy Action Forum [119, 120]: Recently launched with the McKinsey Health Institute to advance the brain-positive economic transition which is an economic model that prioritizes investment in brain capital across the lifespan. Brain capital is a new form of capital that integrates brain health and brain skills to maximize societal growth, resilience and human wellbeing. This Action Forum convenes a dynamic group of stakeholders globally to put the brain economy at the center of global dialogues and drive action toward sustainable economic growth and societal well-being. A WEF Brain Economy Insights Report will be published at the next Annual Meeting in Davos, Switzerland, January 2026.

WHOLE PERSON HEALTH

Recent interest in whole person health [12] shifts from a narrow focus on a single organ system function to a holistic approach to well-being across multiple domains—biological, behavioral, social, and environmental—through research on multicomponent nutritional, psychological, cognitive, and physical approaches to care. This approach offers new avenues for developing prevention strategies for neuropsychiatric disorders of aging that will take a lifespan approach with early detection and prevention of risk factors and the population-based approaches to brain health, and reduction in chronic stress and allostatic load. In addition, a whole person research is not simply studying all the components of the whole person, but also examining the how the connections between these components (such as the "balance" and "adaptability") influence complex system behaviors [45, 121] This is particularly important given that the life-long path toward cognitive decline may start as early as environmental exposures in childhood (i.e., toxic and infectious exposures, head and psychological traumas), the fact that onset of pathological brain dysfunction occurs decades before symptom onset, and the subsequent limited pharmacological interventions that exist to reduce such dysfunction. In the context of the new evidence that modifiable lifestyle factors constitute about 40% of the risk for AD, Whole Person and Brain Health approaches may delay the onset of cognitive decline and in some cases prevention of dementia via improvement in modifiable risk factors for AD and other dementias [122, 123].

PRECISION BRAIN HEALTH SCIENCES

Advancing precision brain health involves the leveraging of biomarkers, neuroimaging, and computational modeling to personalize interventions [124–126]. Precision approaches enable targeted prevention and treatment strategies that account for individual variability in etiopathogenesis and treatment response. A key element of this approach requires careful attention to the role of dynamic timescales [21] for the allostatic expression and therapeutic modulation of psychopathology, across contextually sensitive biopsychosocial spheres [39, 127]. One pragmatic approach as previously mentioned is the development of "brain clocks" which allow estimations of discrepancies between chronological age and brain age [21]. Structural factors, particularly in differences in structural determinants of health, may also play a role in population variation in brain health [128], suggesting the need for structural solutions. Precision brain health strategies, integrating individual variability, environmental exposures, and cultural contexts, offer promising pathways to enhance resilience and guide targeted interventions and policy reforms. Future frameworks should incorporate biological, ecological, and cultural dimensions while emphasizing the dynamic interplay between micro- and macro-level systems [118].

DIGITAL TECHNOLOGIES IN ENHANCING RESILIENCE AND HEALTH

The rapid development of digital technologies presents significant opportunities to support resilience and improve mental and brain health. Emerging tools, such as wearable devices and AI-driven applications, are redefining approaches to the assessment of chronic stress and its management and mental health care [129]. Wearable devices can monitor physiological markers of stress,

such as heart rate variability and sleep patterns, providing real-time feedback to users and enabling early detection of stress-related health risks. AI-powered platforms offer personalized mental health interventions, including cognitive behavioral therapy modules, mindfulness training, and tailored cognitive and physical exercise programs, thereby enhancing emotional stability and cognitive resilience.

Telemedicine has also revolutionized access to mental health services, particularly for medically underserved populations and individuals facing geographic or mobility constraints [130]. During the COVID-19 pandemic, telehealth consultations played a pivotal role in maintaining continuity of care and addressing the surge in mental health needs, demonstrating its efficacy as a resilience-promoting tool [131]. By integrating telemedicine into broader healthcare strategies, governments and organizations can ensure equitable access to mental health resources and resilience-building interventions.

ARTIFICIAL INTELLIGENCE AND BRAIN HEALTH

Artificial intelligence (AI) is increasingly positioned as a transformative tool for advancing brain health and healthy aging by enabling the analysis of high-dimensional, multimodal data. Systematic reviews demonstrate that AI models can be used to detect complex patterns in neuroimaging, behavioral, and digital phenotyping data, predict risk trajectories, and personalize interventions in aging and dementia research [132–135]. For neuropsychopharmacology, perhaps the most compelling applications involve mechanistic risk stratification (e.g., identifying subgroups with accelerated brain aging), circuit-level insights from neuroimaging, and AI-driven biomarkers that can guide preventive or therapeutic interventions [136]. These emerging applications can be grouped into three domains:

- Prediction and risk stratification: AI-driven models integrating genetic, cardiovascular, neurological, and lifestyle data to forecast dementia and late-life psychiatric risk. Brain clocks estimating "brain age gaps" have revealed contributions of socioeconomic disparities, environmental exposures, and cardiometabolic factors [21].
- Intervention and rehabilitation: AI-powered neurofeedback, virtual reality rehabilitation, and adaptive cognitive training tools show early promise in enhancing cognitive resilience, recovery after stroke, and neuropsychiatric symptom management [137]. While still early, predictive analytics applied to digital biomarkers may allow early identification of depressive or manic episodes, PTSD flashbacks, or psychotic onset.
- Neurotechnologies and precision therapeutics: AI-driven closed-loop neuromodulation (e.g., adaptive deep brain stimulation in Parkinson's, epilepsy, and depression) [138], brain–computer interfaces for motor restoration, and digital twins simulating individual brain trajectories exemplify the move toward personalized, mechanistically grounded interventions. Digital therapeutics, including smartphone-based apps delivering CBT, mindfulness, or biofeedback, will also extend intervention accessibility.

Artificial Wisdom (AW) has been proposed as a next step beyond AI, incorporating emotional intelligence, ethical reasoning, and social context into decision-support systems [139, 140]. In healthcare, AW could augment clinical judgment by embedding patient values, long-term outcomes, and societal impacts into treatment planning. For brain health, AW is particularly relevant where predictive technologies intersect with stress and resilience: for example, ensuring that risk models for allostatic load or digital twins of brain aging integrate not only biological and behavioral signals but also cultural, ethical, and psychosocial context. Pilot efforts, such as socially assistive robots for older adults in Japan, demonstrate potential for reducing loneliness and enhancing wellbeing [141, 142], but future AW applications may extend further to ethical governance of neuromodulation, value-sensitive personalization of digital therapeutics, and culturally adaptive resilience training. By aligning predictive precision with humanistic wisdom, AW could bridge the mechanistic divide between brain health models and their real-world adoption.

Ultimately, AI and neurotechnologies hold the potential to deliver interventions tailored to an individual's brain activity and biology. Large language models (LLMs), hold promise for expanding access to care. These systems can deliver preliminary psychotherapeutic interventions with encouraging early results [143]. Yet such progress primarily augments machine intelligence, which is insufficient to enhance mental health. A conceptual shift is warranted: from optimizing intelligence to cultivating wisdom. Unlike intelligence, which does not reliably predict well-being, wisdom is typically associated with improved mental well-being. The current epidemic of loneliness illustrates a need for focusing on this distinction. Intelligence shows no consistent relationship with loneliness, whereas wisdom is inversely associated with loneliness and positively linked to well-being in diverse populations [53]. A recent trial in Hong Kong demonstrated that a telephone-based wisdom-enhancement intervention by trained lay therapists more effectively reduced loneliness than simple supportive calls [144]. These data support the development of artificial wisdom (AW), defined as the computational implementation of specific wisdom-related functions, without implying machine consciousness or subjective experience.

Clinical trials of AI-assisted psychotherapies report early favorable outcomes, though methodological limitations highlight the need for larger, more rigorous studies with longer-term follow-ups [145]. AW systems could function as continuously available counselors; however, ethical frameworks specific to AW are imperative. A recent review of digital mental health technologies, including LLMs, concluded that human connection remains essential for clinical effectiveness and emphasized the importance of co-design, personalization, and patient responsiveness. With scientific rigor, ethical transparency, and innovative design, AW offers the potential to integrate technology with human wisdom to address global mental health needs. The critical next steps are rigorous validation, mechanistic interpretability, and equitable implementation to ensure these tools truly reshape trajectories of brain health rather than simply add technological complexity.

SOCIAL CONNECTIVITY AND ADDRESSING LONELINESS

Loneliness is a complex state of cognitive, emotional, and physical experiences and expressions that can cause mental disturbances. Loneliness contributes broadly to physical ailments such as cardiovascular disease, weakened immune systems, and increased mortality risk. Chronic loneliness can raise the risk of premature death risk of premature death by 26% [146] according to research published in the National Library of Health. In 2023 U.S. Surgeon General, Dr. Vivek Murthy launched an advisory, that highlighted loneliness as a serious public health issue, comparing its impact to smoking 15 cigarettes a day [147]. Technology and AI can server as important tools in combatting loneliness via improving social connectivity.

In addition to health monitoring, digital technologies hold potential in fostering social connections, particularly for populations vulnerable to isolation, such as older adults [148]. Virtual platforms and social networking tools can facilitate meaningful interactions, counteracting loneliness—a critical determinant of mental health and resilience. For instance, online support groups and virtual communities enable individuals to share experiences, seek guidance, and form supportive networks [149]. However, the dual role of these technologies must be acknowledged. While they bridge physical distances and foster connections, they may also perpetuate superficial interactions or digital fatigue, which can undermine well-being if not managed effectively. To maximize

their benefits, digital platforms must prioritize user-friendly interfaces, promote authentic engagement, and include features tailored to the unique needs of vulnerable groups. Policymakers and technology developers should also address accessibility barriers, such as costs, technological literacy, sensory impairments, and national security threats.

LARGE-SCALE BRAIN HEALTH PLANS

At a nationwide level, the Swiss Brain Health Plan (SBHP) [150] exemplifies how large-scale strategies can facilitate the implementation of brain health initiatives at the population level. The SBHP was conceptualized within the context of global efforts to promote brain health, both neurological and psychiatric across the entire lifespan, aligning with initiatives like the World Health Organization's (WHO) global action plan on epilepsy and other neurological disorders and the WHO comprehensive mental health action plan. The SBHP articulates five strategic objectives: (1) to raise awareness of brain health and its determinants [151]; (2) to strengthen cross-disciplinary and interprofessional training for healthcare professionals [152]; (3) to foster research on biological, psychological, and non-medical determinants of brain health, with an emphasis on individualized prevention and treatment of brain disorders; (4) to prioritize a holistic, integrated, person-centered public health that bridges clinical neuroscience and population health through collaborations with scientific, healthcare, commercial, societal, and governmental stakeholders; and (5) to support, empower, and engage patients, caregivers, and advocacy groups, while reducing stigma and discrimination associated with brain disorders. The first steps in the implementation of the SHBP taken in 2024, established (1) establishing a governance structure with defined targets and evaluation metrics; (2) organizing interdisciplinary events on key topics such as dementia (Geneva), stroke (Basel), neurohumanities (Bellinzona), sleep (Lugano), brain research (Lausanne), and psychiatry (Zurich), thereby fostering dialogue between clinical neuroscience and public health sectors; (3) launching a national study on the global burden of brain disorders in Switzerland to inform data-driven policies; (4) developing an international Certificate of Advanced Studies on Brain Health at the University of Bern to train future leaders in this field. With respect to the field of neuropsychopharmacology, the SBHP highlights the need to integrate advances in precision medicine (e.g., humoral, neurophysiological and digital biomarkers) with public health strategies to facilitate early detection and personalized treatment of mental and neurological disorders. The plan's emphasis on collaborative research also creates opportunities for translating discoveries in molecular and synaptic mechanisms into scalable interventions that bridge pharmacological and non-pharmacological strategies. These comprehensive approaches position national brain health plans like the SBHP as transformative models that unite basic and clinical neuroscience with implementation science to promote healthy brain aging and resilience across populations.

The "National, Regional and International Plans for Brain and Mental Health: Bridging the Gaps (June 12–13, 2025) symposium" was organized by the SBHP and the Swiss Brain Health Foundation [117]: The gathering featured 22 brain health initiatives from organizations worldwide. Despite local differences, a clear consensus emerged via a virtual survey of participants identified the top three priorities among 20 brain health topics: definition of brain health, identification of measures of brain health, and development of population-wide strategies to promote brain health.

The Davos Alzheimer's Collaborative [153] Africa Task Force on Brain Health [115] recently published the 6×5 Plan, a 5-year roadmap designed to address brain health challenges in Africa. It identifies six priority actions: building advocacy and health literacy to combat stigma, recognizing brain health as a socio-economic driver, breaking down silos of people and data, repurposing existing health resources and networks, harnessing AI and digital innovations, and strengthening research funding. This plan aims to safeguard brain health while promoting economic resilience, emphasizing community engagement and culturally sensitive tools.

LIMITATIONS OF OUR REVIEW

Our review serves as a call to action to mobilize all parties interested in the concept of brain health concept that currently lacks clear definitions and funding [117] to provide reliable evidence of its usefulness. Brain health is a complex transdisciplinary construct with critical exposures across the lifespan that have a cumulative effect in later life, making it difficult and expensive to study. It can only be fully studied with the application of a biopsychosocial model that integrates neurological and psychiatric dimensions linked to environmental health. Developing clear definitions and measurements and linking those to desired outcomes, like wellbeing, successful aging. longevity, healthspan, and human flourishing can facilitate an easier adoption of the concept that will need to be tested across populations and cross-cultural groups. Although new technologies, data science, and artificial intelligence can offer clear benefits, ethical risks and digital overexposure that must be carefully studied. Developing new policies can encourage and fund brain health promotion across the lifespan and allow investigations of these policies on the prevention of late-life neuropsychiatric and cognitive disorders. Because the concept is new and disruptive for the healthcare system and governmental policies around the world as it is using a lifespan and un-siloed approach, it will require an all-hands-on-deck movement with all stakeholders agreeing on the next steps.

CONCLUSION

A central conceptual contribution of this review is the integration of allostatic-interoceptive overload as a transdiagnostic mechanism linking chronic stress to late-life psychiatric and neurodegenerative disorders. While allostasis and interoception have been studied independently, their dynamic interaction, particularly under conditions of sustained environmental, psychological, and physiological demand, offers a powerful explanatory model for stress-related vulnerability in aging. This framework posits that disruptions in the brain's ability to predict, interpret, and regulate internal states under cumulative stress (i.e., interoceptive prediction errors) can lead to maladaptive homeostatic recalibrations. These maladaptive changes contribute to dysregulation across neural circuits implicated in emotion, cognition, and systemic inflammation. Crucially, this integrated overload model explains how early-life adversity, environmental exposures, and social determinants can become biologically embedded, precipitating both affective psychopathology and neurodegenerative processes. It thus provides a unifying mechanistic lens for identifying novel intervention targets across domains—ranging from neuromodulation and anti-inflammatory agents to behavioral and lifestyle approaches.

Addressing trajectories of brain-based disorders in later life requires a multidimensional approach that integrates cognitive and brain reserve, stress resilience, wisdom, lifestyle medicine, social determinants, and precision health strategies, all of which will serve to mitigate and possibly prevent these conditions. Understanding the interplay between stress, resilience, and brain health highlights the urgency of proactive, personalized interventions that reduce allostatic load and foster resilience across the lifespan. A comprehensive shift toward whole-person, brain health-centered care demands collaboration among psychiatry, neurology, primary care, and public health, alongside early intervention to reduce risk factors. Given the growing shortage of geriatric specialists, all healthcare providers should be equipped to incorporate brain health strategies, including stress reduction, cognitive therapies, sleep health, resilience training, social connection, and purposeful engagement, into routine practice [11].

Future research should prioritize multicomponent interventions that combine lifestyle and integrative therapies, bridging disciplines to promote meaningful, person-centered outcomes. By empowering patients and providers alike, such efforts can add life to years, not just years to life.

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AUTHOR CONTRIBUTIONS

HL, HE, and SK created paper concept, outline and invited co-authors, wrote the first draft and co-wrote and edited the entire paper. HAO co-wrote and co-edited the manuscript. AI, JC, EE, PN, CLAB, IB, ASW, and DVJ provided text sections relevant to their expertise, and contributing to the editing and writing the final draft.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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