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The 10 tenets of Brain Health for clinical practice in the era of technology.

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ABSTRACT

Advancements in public health and medicine have increased global life expectancy, but most added years are spent in illness and disability, mainly due to brain health disorders. Brain health disorders are the leading cause of disability: one in four people in the world suffers a brain disease, and one in two people worldwide will be affected by a brain-related disability, either because of illness or because of becoming the primary caregiver of someone affected, or both. There is a lifelong distribution of the risk of different brain disorders. Their shared risk factor profile calls for a different approach to focus on lifestyle interventions, health, and disease prevention rather than treatment of disability or specific diseases—specifically, a focus on the prevention of disease and the promotion of brain health and resilience to enhance each individual brain's ability to cope with and minimize the functional consequences of any brain stressor, insult, injury, or disease is critical. We propose a focus on brain health to address the threat of brain-related disability and promote human healthspan and well-being. The current manuscript outlines 10 key tenets for optimizing brain health while discussing their respective relevance, evidence, methods used to characterize each tenet, and technological developments enabling clinical practice implementation. Leveraging technology can assist with scaling effective personalized care, which is necessary to improve access to essential brain health services. Longitudinal measurements of brain health and monitoring are critical to characterizing individual function, assessing changes, and optimizing brain health interventions throughout the lifespan.

Introduction

Advancements in public health, healthcare, medicine, and education have led to a global increase in life expectancy. However, evidence demonstrates that rather than unlocking additional years of fulfilling life, most individuals spend their added years in illness and disability[1]. Brain diseases are the number one cause of disability, especially in older age. As a result, recent years have been characterized by greater public awareness of neurologic and psychiatric degenerative conditions and increased interest in addressing them.

Each year, neuropsychiatric disorders claim nearly 20 million lives, together accounting for 30% of all deaths. One in 3 people living today will experience the loss of someone to a brain disorder[2]. But the human suffering due to brain disorders goes beyond the lives it takes. At present, approximately 320 million children worldwide have brain developmental disorders, 366 million people struggle with attention deficit disorders, 50 million have epilepsy, 310 million suffer from anxiety disorder, 250 million from depression, and over 100 Million have dementia[3]. This means that overall, one in four people in the world suffers a brain disease and that one in two people worldwide will be affected by a brain-related disability, either because of illness or because of becoming the primary caregiver of someone affected, or both. A disability-adjusted life year (DALY) is an index of a disease's overall burden, representing the number of years of full health loss due to premature mortality and disability combined. In 2021, 406 million DALYs were caused by brain health conditions, which is nearly double the DALYs for cancer (260 million) and more than cardiovascular disease (402 million)[1]. Brain health disorders are rising while the age of onset is decreasing (i.e., disability is reaching individuals earlier and earlier), which means that current global efforts are not moving fast enough to have the desired impact[1]. The World Health Organization (WHO) projects a continued growth in these numbers and that by 2030, brain-related disability will account for half of the worldwide economic impact of disability[4]. While the exact cost of all brain health disorders is difficult to estimate, the economic cost of managing non-communicable neurologic disorders in the US was estimated to be $800 billion annually in 2017[5], depression and anxiety account for >US$3 trillion of lost productivity every year[6], and overall, brain-related disabilities cost >15% of the world's gross domestic product (GDP), more than cancer, diabetes, and respiratory diseases combined[7]. The WHO has warned that brain-related disability represents a major threat to human society.

Further complicating the matter is the continuum of brain health conditions and the overlap in their risk factor profile. For example, the management of cardiovascular disease, diabetes, and obesity can help prevent strokes and dementias. Evidence demonstrates the impact of pursuing healthy lifestyle habits on risk reduction for all major non-communicable neurological disorders[8]. There is a lifelong distribution of the risk of different brain disorders, and their shared risk factor profile calls for a different approach to focus on lifestyle interventions, health, and disease prevention rather than treatment of disability or of specific diseases. In fact, health loss and disability are not sufficiently explained by the presence or even the severity of a disease. Some people are fully functional despite a high pathological burden, while others who have mild cases of brain disorders become severely incapacitated. This is thought to be related to brain resilience and reserve[9,10], refers to the brain capacity that allows some individuals to sustain brain function across the lifespan despite change due to pathology, insults, injuries or lesions. Here again, lifestyle factors can play a critical role. However, the implementation of lifestyle interventions is not a part of standard of care in the treatment of brain health conditions.

A different approach is needed with a focus on the prevention of disease and the promotion of brain health and resilience to enhance each individual brain's ability to cope with and minimize the functional consequences of any brain stressor, insult, injury, or disease. We propose a focus on brain health to address the threat of brain-related disability and promote human healthspan and wellbeing from pre-conception and through childhood, adolescence, middle-age, and into old age. In this challenging endeavor, the use of technology is critical to ensure reach and sustainability.

The first mention of the use of the term "brain health" appeared only in 1989. Still, there has been a large growth in interest in this topic, especially after 2017[11]. The WHO 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 the life course, irrespective of the presence or absence of disorders"[3]. A key aspect of this definition, when compared to preceding approaches, is the shift away from the pathophysiological perspective (i.e., "the absence of disease") in favor of an increased focus on health throughout the lifespan.

The notion that brain health should be promoted throughout life, even in those with neurologic or psychiatric disease, is only now emerging in theoretical and conceptual frameworks and has yet to be operationalized in the standard of care. For example, Chen et al.[11] conducted an international survey to explore the use and context of the term 'brain health' among 180 researchers and practitioners in the field of aging across 40 countries. Half of the respondents reported that the term 'brain health" was not commonly used in their language, culture, or professional contexts. Respondents tended to endorse multiple definitions, revealing a lack of clarity. *We propose 10 tenets of brain health that ought to be translated into specific actions and interventions to address the threat of brain-related disability and transform human brain health. We highlight the role that technologies can help in aiding the adoption of these tenets in clinical practice.*

1. BRAIN HEALTH REQUIRES A BRAIN THAT HAS DEVELOPED APPROPRIATELY

Critical factors influencing life-long brain health start before birth and are related to maternal exposure. For example, studies in primates have demonstrated that maternal exposure to a typical Western diet is considered unhealthy (high in saturated fat, caloric density, and sugar) and is associated with impaired brain development and behavior in the offspring. Compared to control animals, animals whose mothers were exposed to the typical Western diet had double cortisol levels, higher inflammation, impaired serotoninergic and dopaminergic systems development, and cortical-subcortical functional connectivity[12]. In childhood, nurturing care is associated with structural brain development, and its absence can lead to long-term negative consequences[13].

In adolescence, increased autonomy and independence at the participation level are accompanied by the pruning of neural connections and the establishment of neural networks that support overall functioning[14]. This is also a time of the establishment of social-emotional functioning, habits, and health behaviors. Multiple family, cultural, societal, economic, and environmental factors can influence adolescent development, including the sense of belonging and social connectedness at school, social and gender norms, and community cohesion[3]. Given the rise in susceptibility of mental health disorders in adolescents, the monitoring and supporting of social and emotional functioning is critical at this stage.

Adulthood and older age present additional opportunities for intervention as the brain continues to adapt in response to our lives and circumstances. It is helpful to view the brain as engaged in a continuous lifelong path of development that starts in utero and does not end till death[15]. Numerous determinants impact brain health in midlife and later life, including physical activity, diet, tobacco and alcohol use, cognitive activity, and metabolic factors (including weight, blood pressure, cholesterol, and insulin sensitivity).

Determinants of healthy aging that are also relevant to brain health include levels of education, healthy lifestyles, social connections, and their environments[3].

Lifelong attention to brain development is crucial for brain health. The importance of educational, public health and socio-economic policies to address disparities cannot be overemphasized in this context. Technology enables the longitudinal tracking of individuals, establishing personal fingerprints to detect deviations that might herald risk of disease and inform interventions to sustain health.

2. BRAIN HEALTH REQUIRES A BRAIN WITH EFFECTIVE PLASTICITY MECHANISMS

The brain is an experience-dependent organ that undergoes complex and continuous neuroanatomical and neurophysiological modifications throughout an individual's lifetime, resulting from interactions between our experiences, environment, and genetics.

The human central nervous system is made up of highly specialized cells that are highly resistant to change. However, these cells are connected in neural ensembles or networks that represent the functional units of the brain and, in turn, are highly flexible and capable of change. Plasticity refers to the capacity to modify and adapt these networks in response to various stimuli through strengthening, weakening, pruning, or adding synaptic connections and by promoting neurogenesis[16,17]. First introduced by William James in the 1800s (James, 1890): "Plasticity … in the wide sense of the word, means the possession of a structure weak enough to yield to an influence, but strong enough not to yield all at once." It might be conceptualized as the balanced interplay between mechanisms promoting change and those promoting stability (homeostatic plasticity).

Plasticity is the substrate for learning, the acquisition of new skills, and the source of creativity and ingenuity, but it also underlies symptoms of brain disease and disability[18]. Plastic brain changes are neither fundamentally good or bad, the challenge is to guide them for the desirable outcome for a given individual. This demands tools to measure the efficacy of the mechanisms of plasticity, which are affected by disease and vary but need to be optimized at different ages across the lifespan and thus be able to modulate plasticity to improve function in a given individual.

Plasticity can be studied using in-vitro techniques and in-vivo in animal models. Plastic changes at the synaptic level lead to the development and maintenance of neural circuitry. At the synaptic level, this is illustrated, for example, by the balance between long-term potentiation (LTP), which strengthens connections between presynaptic and postsynaptic neurons[19], and long-term depression (LTD), which weakens them[20]. There are also methods that enable the noninvasive investigation of neuroplasticity mechanisms in humans. Transcranial magnetic stimulation (TMS) utilizes electromagnetic fields to induce mild currents that are used to probe intracortical circuits and have been employed throughout the lifespan to study individuals from childhood to older age, healthy as well as those with illnesses[21]. TMS can be used to index cortical excitability to probe the functional integrity of facilitatory or inhibitory intracortical circuits[22]. Repetitive rTMS, for example, using theta-burst stimulation parameters, can induce changes in cortical reactivity, generating a neuroplasticity response that resembles LTD- or LTP-like mechanisms[15,23]. This can be used to probe mechanisms of neuroplasticity in humans across the lifespan and for therapeutic purposes for various symptoms of neurologic and psychiatric disorders[15,23–27].

There is evidence to indicate that the effectiveness of mechanisms of plasticity decreases as we age[21,28]. Plasticity remains, but it takes more input and repetition to secure and implement plastic changes in neural networks. There are identified illnesses that have a core alteration in the mechanisms of plasticity that appears to be a critical component that leads to pathology. Currently, such methods can identify alterations in plasticity as the core problem in illnesses as well. For example, in the very early stages of dementia of Alzheimer's type, there is an alteration of LTP-like plasticity, putting the brain in a hypoplastic state that is associated with delayed acquisition of information, skills, and habits[21,23]. Conversely, in autism spectrum disorders, plasticity mechanisms appear to be hyperactive[23,28]. The brain is too easily modified, and a brain that is too plastic lacks the ability to manage distractions and focus attention because it is influenced in a lasting way by too many things at once, leading to challenges in focused attention concentration.

Noninvasive brain stimulation technologies enable measurement of the mechanisms of plasticity and the development and monitoring of interventions to optimize them for a given individual's age and medical conditions is a critical aspect of promotion of brain health.

3. BRAIN HEALTH REQUIRES AN ADAPTABLE BRAIN, FORTIFIED BY STRONG SCAFFOLDING

Contrary to the previous notion of a peak in brain function and abilities from development to maturity, with an expected decrease in older age, current evidence supports that brain health is a dynamic process that is highly individual. Intrinsic 'scaffolding mechanisms'[29] constitute an adaptive brain response and are recruited for the maintenance of brain behavior and function at a high level in response to increased environmental demands posed by a variety of stimuli, such as physiologic processes, experiences, challenges, and life events, as well as disease-related and pathologic processes that take place throughout the lifespan[30]. Scaffolds comprise age-appropriate structure, connectivity, and oscillation patterns that structure dynamic neural networks. These intrinsic mechanisms are also shaped by individual, genetic, and environmental factors, leading to a marked variability in the individual trajectories of brain health and functioning throughout the lifespan.

New scaffolds can be established, or scaffolds can be rearranged to support shifting demands related to learning, skill acquisition, and dealing with stress or illness. With advancing age, scaffolding processes may be recruited to execute fundamental cognitive functions, given the challenges associated with age-related changes in neural circuits. For example, increased frontal systems recruitment, neurogenesis, distributed processing, and bilaterality has been reported in response to the brain atrophy[31,32], demyelination of white matter tracts[33], imbalances in dopamine and serotonin[34,35], and increase in increased monoamine oxidase, and deposition of amyloid beta (Aβ) that occur with cognitive aging[36]. A stronger scaffolding may be part of the brain mechanism of resilience and is believed to underlie why many people continue to function remarkably well into advanced age despite the presence of a high burden of brain pathology discovered at autopsy[37].

Development of appropriate scaffolding processes, reliance on them and their adaptation to promote resilience and cope with age-related brain changes is a critical mechanism for brain health through the lifespan, and often requires counsel, guidance, and support. Brain imaging neurotechnologies and advanced machine learning and artificial intelligence data analysis approaches offer precise methods to track the neurobiological substrates of scaffolds and guide interventions to adapt them for a given individual's needs.

4. BRAIN HEALTH REQUIRES A BRAIN THAT MAINTAINS A LIFELONG LEARNER'S MINDSET

A healthy brain is not necessarily a young brain. Across life, there are changes in brain structure and function. Part of these are predictable age-related neurobiological changes. Others are unique to each individual, resulting from inherent differences in genetics, life experiences, and cultural, social, and environmental influences. At a functional level, age-related changes often include decreased performance in episodic and semantic memory, executive functioning (especially mental flexibility and response inhibition), slower psychomotor processing speed, focused attention, and multitasking[38]. However, the notion that cognitive decline is a necessary consequence of aging is inconsistent with current evidence. Some cognitive abilities are spared or even continue to improve as we age. Implicit memory and memory storage are relatively resistant to cognitive aging. Lexical richness continues to increase over time[29]. Crystalized abilities, reflecting skills, abilities, and familiar aspects of knowledge, also continue to increase in older age[39]. Wisdom, a multidimensional personality trait involving cognitive, social, and emotional processes, is also reported to increase during older age, leading to greater social maturity, better attention to health, and avoidance of risky situations in older age[40]. In addition, an analysis of 145 countries found that self-reported happiness and life satisfaction, two important brain health-related constructs, are lowest at middle age, around 50 years of age, and peak in later life[41]. A large cross-sectional study of individuals 21-100 years old examining trends in physical, cognitive, and mental health over the lifespan reported that the overall deterioration in physical and cognitive functioning of 1.5-2 standard deviations contrasted with the linear improvement of 1 standard deviation in various attributes of mental health, over the same period, suggesting that some attributes of mental health also continues to improve through older age[42].

But there is an important caveat. A learner's mindset throughout the lifespan profoundly affects overall health and well-being. Ageism is defined as discrimination against older people because of negative and inaccurate stereotypes. Individuals who endorsed negative age stereotypes in midlife were more likely to have a cardiovascular event over the next 38 years[43]. Older adults with negative age stereotypes had a three-fold increase in hippocampal atrophy and significantly greater accumulation of amyloid plaques and neurofibrillary tangles than those who did not[44]. Among people with the apolipoprotein (APOE) ε 4 gene, individuals with positive age beliefs were 49.8% less likely to develop dementia than those with negative age beliefs[45]. Researchers found that those with a positive view of aging live 7.5 years longer than those with a negative view of aging[46]. While the exact mechanisms are not fully elucidated, maintaining a positive view about getting older may lead to less stress, a common risk factor for many brain health disorders. Additionally, it may facilitate engagement in healthy behaviors and self-management, such as physical activity and medication compliance.

Accumulating life experiences is not sufficient for healthy aging; the maintenance of a growth perspective and willingness to learn from life experiences is a requisite for developing increased wisdom and sustaining brain health in later life[47]. Education and public health policies that promote multi-generational interactions, suppress ageism, and celebrate getting older are essential. Intelligence technology assistants increase the reach of individual experts, and care management platforms can enable individuals to track their progress.

5. BRAIN HEALTH REQUIRES A BRAIN WITH SUFFICIENT RESILIENCE

Confronted with the same brain stressor, insult, injury, or disease, not all individuals develop the same degree or severity of cognitive, mental, behavioral, or health consequences. In part, this is due to differences in the susceptibility of different individuals to disease. In this context, resilience refers to the family of neural processes that enable an individual to resist the development of symptoms, disability, or distress[9]. In otherwise healthy individuals, resilience conveys the capacity to cope with the impact of life events, traumas, stressors, or insults in order to maintain normal psychological and physical functioning and avoid brain and mental illness. In individuals with established brain diseases, resilience is associated with a greater degree of pathology required to lead to clinical manifestations. Enhancing brain resilience could have a transformative impact on human health, but critical knowledge gaps need to be addressed, including what strategies can be deployed to sustain and enhance resilience and minimize brain-related disability.

Specific resilience constructs have been introduced in recent years. While these have been most discussed in the context of aging, they are also critical to the framework of lifelong brain health initiatives[9,10]. Many institutions and agencies have recognized the importance of such an effort, including most recently, the Collaboratory on Research Definitions for Reserve and Resilience in Cognitive Aging and Dementia, funded by the National Institute on Aging of the National Institutes of Health in the USA[10]. This panel has provided consensus definitions of the constructs of resilience.

Studies have identified neural substrates of resilience behaviors by examining differences in life coping strategies, perceived stress, or differences in individuals exposed to adversity and trauma. Neuroimaging studies have reported structural as well as functional correlates of these resilience behaviors in regions involved in stress processing and emotional regulation, such as the amygdala, hippocampus, insular cortex, and prefrontal cortices, as well as functional differences in the coupling of the mesocorticolimbic system reward areas (ventral striatum, ventral tegmental area) with the hippocampus[48]. The hippocampus is implicated in the hypothalamic-pituitary-adrenal (HPA) stress-axis response and is among the brain areas most sensitive to stress. Chronic stress reduces hippocampal function, which is associated with memory impairments[49,50] and reductions in hippocampal volume are also seen in chronic stress, individuals with low self-esteem, depression, and schizophrenia[51,52], implying shared pathways of susceptibility. Recent studies have revealed that sustaining synaptic connectivity in neural networks and control of changes in glial cell phenotypes and cytokine-associated inflammatory brain cascades are core neurobiological substrates of resilience[53].

The challenge in characterizing a multidimensional construct like resilience lies in the ability to measure all relevant factors, and as such, behavioral, structural, and neuroimaging measures should be combined with biological markers. There is evidence to support the utility of such an approach, wherein a panel of 10 markers representing a model of allostatic load representing cumulative biological burden, including cardiovascular, metabolic, hypothalamic-pituitary-adrenal (HPA)-axis activity, and sympathetic nervous system activity, which reflect cumulative biological burden, was associated with future risk of cognitive, physical decline and mortality amongst older adults[54].

The adoption of a framework that considers themes of resilience is critical for promoting lifelong brain health because resilience is directly tied to the impact of potential risk factors, as well as one's ability to harness available protective factors, which is very useful in the design of individualized brain-healthy initiatives that are more likely to be most effective. Neurophysiologic perturbation-based biomarkers can objectively assess key aspects of an individual's brain resilience and noninvasive brain stimulation methods show promise in promoting cognitive reserve and resilience.

6. BRAIN HEALTH REQUIRES A BRAIN THAT PURSUES PERSONALLY MEANINGFUL GOALS

The WHO's definition of health requires both the measurement of objective and subjective metrics[3]. Subjective metrics are informally collected in routine clinical practice during a patient encounter. Recent evidence indicates the utility of considering this information more systematically for promoting brain health and monitoring and managing brain health disorders. Therefore, to effectively support brain health, it is important to understand details about the patient, including their goals and personal circumstances that could impact treatment options. It is critical to empower individuals to define their brain health goals - often linked to a sense of purpose. Having a defined purpose in life mediates cognitive reserve and high self-perceived cognitive function in adults[55]. Purpose correlates with higher scores on memory and executive function tasks[56]. Similar to cognitive reserve, people with higher purpose have better cognition even with high Alzheimer's Disease pathology[57].

A promising approach to help individuals and understand their priorities, self-perceived health status, and abilities, as well as their goals and desires is the optimization of patient-reported outcome measures to capture, monitor, and track this information. It would be ideal to have an overall metric. Such an index would need to consider what matters most to that individual (purpose, life satisfaction) and their ability (self-efficacy) and support (if needed) to perform this role, activity, or function quantified or expressed in the most descriptive manner possible. The goal in capturing such patient-centered metrics has to guide interventions and inform serial assessments to track patients' progress and identify appropriate timing for further evaluations or treatment modifications[58].

To promote brain health it is critical to aid each individual in defining their brain health goals, develop person-centered outcomes, and deploy personalized interventions. This can be accomplished with mobile technologies and electronic methods.

7. BRAIN HEALTH REQUIRES A BRAIN THAT SUPPORTS SUBJECTIVE MENTAL WELL-BEING

In medicine and science there is the common temptation to focus on the objective and dismiss subjective impressions. However, the subjective vantage point is central to brain health. WHO defines mental health as a state of well-being in which an individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively, and is able to make a contribution to his or her community. Mental health is more than the absence of mental health conditions or disabilities; it is fundamental to our collective and individual ability as humans to think, emote, interact with each other, earn a living, and enjoy life[59].

Many risk and protective factors that impact mental health (e.g. social adversities, air pollution, physical activity) are likely mediated through changes in brain structure and/or function[60–62]. As such, mental health issues are linked to poor brain function and have a direct impact on brain health. Furthermore, illnesses that impact brain function generally lead to mental health consequences and affect subjective mental well-being.

Assessment of subjective well-being is important to identify brain disorders and threats to brain health, while interventions to promote mental well-being have a direct therapeutic and prognostic implication for maintaining brain health, preventing brain-related disability, and minimizing it. Mobile technologies enable individuals to track various aspects of their well-being and share them with their clinicians and caregivers for guidance and input.

8. BRAIN HEALTH REQUIRES A SOCIAL BRAIN COMMITTED TO THE SERVICE OF OTHERS

Nurturing interactions between a child and their caregiver can have a positive impact on neurodevelopment. The absence of a supportive and responsive caregiver in the setting of prolonged exposure to one or more adversities leads to "toxic stress"[63]. Toxic stress can cause changes in the development of brain architecture, including areas of the brain that are responsible for modulating our body's responses to stress (overactivation of the amygdala, hypothalamus-pituitary, and weakening of the prefrontal cortex, and anterior cingulate), with lifelong implications for a person's vulnerability for stress-related mental and physical health conditions[64,65]. In recent years, studies have provided insights into the intergenerational impact of adverse childhood experiences, with lower brain volumes and changes in neural connectivity involving the amygdala seen in infants of mothers who experienced maltreatment or emotional neglect from their caregivers[66,67].

Similar arguments can be made about the impact of social interactions at all ages: the quality of attachments and social connections a person has throughout their life affects their brain health. For example, as an adult, greater numbers of social connections are associated with larger volumes of multiple brain structures in the cerebral cortex, and the quality of social connections is linked with areas of the brain associated with memory[68,69]. The availability of social support in older adults has been linked to networks that involve areas of the brain responsible for executive functioning, emotional regulation, and memory[70]. Social support in the form of supportive listening correlates with higher cognitive resilience in older adults[71].

The feeling of loneliness, or the sense of being socially isolated, is a significant factor affecting people's health and is linked to higher mortality rates. A recent survey found that 24% of the global population is currently experiencing loneliness[72]. Individuals dealing with chronic loneliness often exhibit disruptive emotional behaviors, such as being more alert to negative emotions like anger and sadness, as well as other signs of social rejection or threat[73]. Loneliness is also associated with changes in the volume of gray matter or the integrity of white matter in certain brain areas, such as the prefrontal cortex, insula, amygdala, hippocampus, and posterior superior temporal cortex. Furthermore, it leads to different brain activation patterns in attentional networks, visual networks, and default mode networks[74]. Loneliness can contribute to increased feelings of depression and anxiety, as well as having systemic effects, including a higher inflammatory burden and increased stress, which may be responsible for the elevated risk of cardiovascular disease[75], cognitive decline[76] and dementia[77] and Parkinson's Disease[78].

It's important to have a purpose that extends beyond oneself and allows for opportunities for interpersonal connections. The positive effects of volunteering on health have been extensively researched. Studies have shown that engaging in volunteer work is associated with improved mental and physical health[79], greater life satisfaction[80], increased happiness[81], and lower depressive symptoms[82], functional impairment and mortality[83]. Especially volunteering that directly helps other people is reported to reduce depressive symptoms and increase life satisfaction[84]. Volunteering has also been shown to delay or even reverse decline in brain function among older adults, and was accompanied by increased brain and cognitive function[82].

Social connectivity and the quality of social connections are crucial for brain health. Volunteering should be promoted by public health, and clinical initiatives as a key aspect of a brain-healthy lifestyle. Assessing the risk of loneliness and social isolation is also crucial. Technology-supported social networks offer a valuable tool for scalability and universal reach.

9. BRAIN HEALTH REQUIRES A BRAIN THAT EXISTS IN A HEALTHY BODY

Comorbidities undoubtedly increase the risk of developing brain disorders, and as such, the pursuit of healthy lifestyles is a key part of both their prevention and management. The benefits of maintaining a healthy lifestyle are undisputed; a recent meta-analysis found that physical exercise as an intervention improved the quality of life for people with various chronic brain disorders, including Alzheimer's disease, Parkinson's disease, Huntington's disease, multiple sclerosis, depression, and schizophrenia[85]. Compelling evidence from longitudinal trials demonstrates that a healthier lifestyle can not only decrease dementia risk by as much as 40%[86–88] but also, even in the presence of cognitive decline, a healthier lifestyle can reduce the severity of the associated disability. It has been estimated that up to 60% of strokes might be prevented by implementing preventative strategies[89]. Physical inactivity alone is responsible for nearly 8% of DALYs due to stroke globally[1], so the impact of multicomponent brain health programs is significant and far-reaching.

One pertinent example is the groundbreaking study that demonstrated a causal effect between participation in a lifestyle program and significant dementia risk reduction and cognitive improvement in older premorbid adults[90]. It is important to note that this multi-faceted approach was crucial, as previous studies have shown that individual interventions such as exercise, nutrition, or cognitive training alone did not yield the same benefits for brain health. Furthermore, the intervention delivery involved collaboration among healthcare providers: physicians managed vascular /metabolic risks, physical therapists supervised exercise sessions, nutritionists conducted nutritional visits, and psychologists oversaw the cognitive training. The program's success also emphasized addressing multiple aspects such as physical activity, sleep, nutrition, cognitive challenges, and social relationships to achieve the greatest impact on brain health and functioning. Another key element for the success of this study that directly influences real-world implementation is that the intervention was individually tailored to the specific needs of each participant.

The importance of lifestyle management is widely recognized by both the general public and their clinicians. There is abundant access to information about healthy lifestyles, such as the American Heart Association Essential 8 guidelines[91]. These guidelines were initially developed to promote heart health but have also been found to reduce the risk of neurological diseases like stroke and dementia while improving brain health. The main challenge lies in the fact that access to knowledge is not enough to change behavior. Although people trust their healthcare providers, they often fail to modify their behavior based solely on advice. Behavior changes occur when individuals are empowered to make decisions about their brain health journey and have access to ongoing support. While the clinical workforce possesses knowledge of lifestyle management guidelines such as exercise, nutrition, and sleep hygiene, time constraints, competing clinical priorities, and other factors can cause health promotion to become a "bonus" or "add-on" during routine clinical visits for physicians, nurse practitioners, physical therapists, and other professionals. Committing to a lifelong brain health program requires empowering individuals with the knowledge to pursue self-selected goals, which in turn necessitates dedication, motivation, coaching, and support. A broader real-world translation of this evidence on lifestyle management and behavior change to the public is critically needed. Most people are motivated to improve their brain health. According to a Global Brain Health Survey[92]. 70% of respondents indicated that memory problems would be a key motivator for improving their lifestyle, provided that the advice came from their care team and was indeed beneficial.

Lifestyle interventions that address multiple aspects of brain health, are personalized to each individual, and are anchored in reliable longitudinal metrics to enable continuous optimization is a key element of brain health. Technology platforms that enable chronic disease management and virtually delivered interventions empower individuals to benefit from expert guidance in overcoming access barriers.

10. BRAIN HEALTH REQUIRES A BRAIN IN A HEALTHY ENVIRONMENT

Arguably body health could be viewed as the 'internal environment' of our brain, the "milieu intérieur" coined by Claude Bernard in the 1850's. But there is also an 'external environment', a "milieu extérieur" that affects the organism and its brain.

Exposure to certain external environmental factors causes alterations in the pathways associated with Alzheimer's Disease and other disorders (ADOD) and may account for 30% of ADOD risk factors[86,93]. Exposure to heavy metals, such as lead and mercury, during neurodevelopment or during childhood can cause neurodevelopmental disorders[3]. These are also neurotoxic to adults who may be exposed due to occupational or household contexts. Organophosphates present in many pesticides are harmful to brain health and associated with neurodevelopmental and cognitive, motor, and behavioral deficits[94]. Commonly used industrial solvents can also have neurotoxic effects. For example, trichloroethylene (TCE), which is used as a refrigerant, degreasing solvent, and cleaning agent, is known to have harmful impacts on neurodevelopment and also changes in cognition, vision, psychomotor and other nervous system functions[95]. TCE is also linked with an increased risk of Parkinson's disease[3].

Air pollution is increasingly recognized as a major global threat to brain health. WHO estimates that 99% of all people worldwide breathe polluted air in their ambient environment, which threatens brain development and health throughout their lives[3]. Exposure to air pollution during pregnancy and early childhood has been associated with neurodevelopmental delays. New research also indicates a potential connection between air pollution and autism spectrum and attention deficit hyperactivity disorders[96–99]. Air pollution is believed to influence brain function and structure via multiple mechanisms, including direct neurotoxicity, neuroinflammation, oxidative stress, impaired energy metabolism, and injury to brain vessels[100,101]. Studies found associations between higher pregnancy and childhood air pollution exposures with smaller corpus callosum, smaller hippocampus, larger amygdala, smaller nucleus accumbens, and larger cerebellum pre-adolescence[102]. Similarly, one-year-olds exposed to air pollution related to traffic demonstrated reduced volume of brain gray matter and cortical thickness by early adolescence[103].

Drugs are behavioral risk factors that can have widespread deleterious effects on neuronal networks due to impaired neuronal function and neurotransmitter activity[104]. Excessive alcohol consumption is also prejudicial to brain health and function, as it is known to trigger seizures and induce epilepsy[105].

It is also important to consider climate as well. As people age, their ability to maintain a stable internal body temperature diminishes due to impaired thermoregulation, fluid regulation, and cardiovascular function[106]. Conditions such as type 2 diabetes reduce the density of sweat glands and limit thermoregulation via perspiration. Additionally, older adults often experience changes in their autonomic nervous system due to underlying health conditions or the effects of medications, further increasing their susceptibility to heat. Understanding the behavioral patterns of older adults during heatwaves is important, as heatwaves can have negative effects on mental health and long-term health outcomes[107]. Alternatives to air conditioning, such as heat-resilient housing designs and urban cooling strategies, should be considered. Additionally, public health messaging and education should be tailored to reach older adults in different communities, considering language and cultural barriers to communication.

Exposure to natural environments such as forests, parks, street trees, and rivers is associated with a decreased risk of cardiovascular disease and cognitive disorders such as dementia[108] and Parkinson's Disease[109]. There are many factors believed to underlie this association; trees and plants mitigate air pollution, which is a risk factor for many neurologic disorders, but also natural spaces decrease feelings of depression and facilitate engagement in other healthy behaviors, such as exercise.

Importantly, social determinants, which include the availability of daily resources, access to educational and health services, transportation, safety, exposure to segregation, violence or crime, social support, and opportunities for recreational and leisure-time activities, also constitute part of one's environment and must be considered in the evaluation of brain health.

The environment has profound effects on brain health, which has implications for clinical care and policymaking. Exposure to natural spaces needs to be considered more seriously as a potential community-based approach for improving brain health. Urban planners need to consider the public health importance of incorporating designated and protected natural environments. Technologies for environmental monitoring and control enable tracking and optimization of settings for each individual.

Brain Health Index: How can we best measure and track a healthy brain?

Multiple factors can influence brain structure and function, from development to continuous reshaping throughout life. We have presented a framework containing 10 important tenets of brain health that are critical for optimizing brain health across the continuum. The promotion of the factors described herein would lead to the ultimate goal, characterized by a state of well-being, wherein an individual would be adaptable and able to cope with life situations and critical life events, able to establish and nurture social circles that serve to support them, autonomous and independent, according to their current level of function.

There is an important challenge in introducing a framework that includes many factors or indices, many of which are multidimensional (resilience, plasticity, stress, lifestyle fitness). It is important to emphasize that this framework does not imply that this is a task carried out by any member of the healthcare workforce alone. It is quite the opposite. While separately, many professional organizations have specifically addressed brain health as one of their priorities (including physicians of many specialties, nursing, physical therapy, and occupational therapy), an important risk is that when everyone is engaged in a task, no individual is focused on any task. Perhaps borrowing from the frameworks of centers of excellence for cancer treatments, there could be more specific frameworks that can enable transdisciplinary work and shared responsibilities for brain care. With the growth of the aging population, the demand for these professionals is expected to increase exponentially over the next decades.

Importantly, it is insufficient to rely on a single measure to assess the overall health of the brain, and a one-size-fits-all measure is likely inadequate for many reasons. Instead, it would be best to consider a person-centered approach, where the clinician considers all relevant factors when evaluating the patient's brain health. This could be used to create an individual brain health index (BHI) that incorporates as many insights from the 10 tenets we presented but is ultimately guided by the individual goals and desires of the person (i.e., what would they most value continuing doing or pursue, to maintain their sense of self and/or become their best version of themselves?). Clinicians should use their best judgment in identifying the best assessments that would comprise the brain health index for each individual. While these "personalized brain health assessments" will vary greatly based on both the individual (presence of specific goals, levels of function, interests, and possible impairments) and their clinician (access, knowledge, expertise), the most relevant aspect is the continued, longitudinal tracking of these individuals, which can uncover the earliest signs of deficits, which can then be promptly attended to.

The brain health field must evolve to accommodate this paradigm shift and support individuals in achieving a lifelong commitment to brain health. Enhancing training and resources for neurology professionals, physicians in other specialties, and other healthcare professionals, such as physical therapists, occupational therapists, nurses, health coaches, social workers, and others, as relying on specialists alone will not be sufficient to meet the demands of an aging population. Critically, as the world population continues to age and the demand for brain health management grows, there is a pressing need for innovative and scalable solutions. Technological advancements have the potential to play a pivotal role in extending the reach of the clinical workforce to effectively address the increasing demand for brain health management.[110] By leveraging technology, healthcare professionals can reach a larger audience, provide personalized care, and deliver interventions in a more efficient and timely manner. This can ultimately enhance access to essential brain health services, especially as the demand for these services continues to increase due to the aging population and the higher prevalence of neurological conditions. Table 1 provides illustrative examples of the use of technology to capture each brain health tenet.

Table 1. Tenets of brain health, along with examples of relevant technology solutions.

Brain Health Tenet	Illustrative examples of relevant technology solutions
1. Brain Health requires a brain that has developed appropriately	Longitudinal trajectories of digital biomarkers of cognition
2. Brain Health requires a brain with effective plasticity mechanisms	TMS/EEG to evaluate mechanisms of brain plasticity
3. Brain Health requires an adaptable brain, fortified by strong scaffolding	Connectome analysis of brain imaging data
4. Brain Health requires a brain that maintains a lifelong learner's mindset	Intelligent Technology Therapy Assistant for lifestyle monitoring and coaching
5. Brain Health requires a brain with sufficient resilience	Neurophysiologic perturbation-based biomarkers as "toy models" of brain resilience
6. Brain Health requires a brain that pursues personally meaningful goals	Electronic capturing of patient-reported outcomes
7. Brain Health requires a brain that supports subjective mental well-being	Electronic apps that enable mental health tracking and facilitate behavioral interventions
8. Brain Health requires a social brain committed to the service of others	Technology-supported social networks
9. Brain Health requires a brain that exists in a healthy body	Platforms that enable chronic disease management and virtually delivered interventions
10. Brain Health requires a brain in a healthy environment	Technology-supported environmental monitoring

Ultimately, a multidimensional and longitudinal (lifelong) assessment of large numbers of individuals (i.e., many "N of 1 big-data experiments"), will enable scaling from individual to clusters or canonical profiles that apply to sub-cohorts of larger populations. The suggestion of such an approach has been introduced before in brain stimulation,[28] and resilience.[9] and the value of such a "vital sign" has been clearly illustrated in other medical specialties. Now that brain diseases are the first cause of disability, exceeding cardiovascular disease and cancer, we need a similar "index" to measure people's resilience and characterize their risk of developing, as well as their capacity to resist, brain pathologies and related disability.

Conclusion

The number of people with or at risk for brain-related disability continues to rise rapidly. There is an urgent need for novel approaches focused on brain health and resilience. Emphasizing brain health, disease prevention, and lifestyle interventions can help enhance resilience and minimize the impact of brain disorders. The current manuscript outlines 10 key tenets for optimizing brain health while discussing their respective relevance, evidence, methods used to characterize each tenet, and technological developments enabling clinical practice implementation. Leveraging technology can assist with scaling effective personalized care, which is necessary to improve access to essential brain health services. Longitudinal measurements of brain health and monitoring are critical to characterizing individual function, assessing changes, and optimizing brain health interventions throughout the lifespan.

Conflict of Interest:

None.

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