A framework of biomarkers for brain aging: a consensus statement by the Aging Biomarker Consortium

China and the world are facing severe population aging and an increasing burden of age-related diseases. Aging of the brain causes major age-related brain diseases, such as neurodegenerative diseases and stroke. Identifying biomarkers for the effective assessment of brain aging and establishing a brain aging assessment system could facilitate the development of brain aging intervention strategies and the effective prevention and treatment of aging-related brain diseases. Thus, experts from the Aging Biomarker Consortium (ABC) have combined the latest research results and practical experience to recommend brain aging biomarkers and form an expert consensus, aiming to provide a basis for assessing the degree of brain aging and conducting brain-aging-related research with the ultimate goal of improving the brain health of elderly individuals in both China and the world.

Introduction

Brain aging refers to the decline in the structure and function of the brain with age, including a decrease in nerve cells, loss of neural network coupling, cognitive decline, mood swings and behavioral changes [1]. Brain aging causes a decline in mental and physical health and increases the risk of age-related brain diseases, such as neurodegenerative diseases. Finding biomarkers that can reflect the level of brain aging can help assess the functional status of the brain and the risk of neurodegenerative diseases in elderly individuals so that timely individualized anti-aging measures can be taken to prevent and treat age-related brain diseases [2].

On 12 March 2023, the Aging Biomarker Consortium (ABC) convened a seminar of experts in brain-aging-related fields at Tongji University. On the basis of literature reports and peer-reviewed domestic research, an expert consensus was formed by combining medical evidence and expert opinions. Biomarkers reflecting brain aging were recommended, with the aim of addressing clinical issues such as 'How biologically old is the individual now?', 'How fast is the individual aging?', and 'How far is the individual from age-related brain diseases?'

Methods

A literature search was conducted for studies published before March 2023 and indexed in MEDLINE, PubMed, Cochrane Library, and other selected databases related to this consensus. For specific search terms used, readers are referred to the Online Data Supplement, which contains the final evidence tables summarizing the evidence used by the consensus writing group to formulate recommendations. Members of the ABC first identified a list of key issues related to the biomarkers for brain aging through online collaboration based on available publications and the research of the ABC members. The identified biomarkers were further discussed at a face-to-face meeting to reach a consensus. All recommendations were fully reviewed and discussed among the members of the ABC to allow diverse perspectives and considerations for this consensus.

This consensus follows the internationally accepted conventions for expressing the level of evidence and strength of recommendations, which are detailed in Table 2 [3].

Framework of biomarkers for brain aging

Brain aging involves multi-dimensional and multi-scale changes in molecules, cells, tissues, organs, the whole body, and groups of individuals. Brain aging biomarkers refer to markers that can accurately reflect 'real age', brain structure and brain function, which can be used to determine the degree of brain aging and evaluate the effect of anti-aging interventions. Considering the accessibility and convenience of clinical procedures, this consensus screens brain aging biomarkers from the three dimensions including brain function, imaging, and body fluids for reference in clinical work and follow-up studies (Fig. 1).

Functional markers

Brain functions include cognitive function, motor coordination, sensory perception, and emotion. These functions are affected by brain aging, but the changes in different brain functions during brain aging are inconsistent. In recent years, studies have begun to explore brain aging biomarkers that are strongly correlated with age, brain structure, and function.

Table 1. Abbreviations in this consensus

Abbreviation	Full name
ABC	Aging Biomarker Consortium
COR	Class of recommendation
LOE	Level of evidence
MCI	Mild cognitive impairment
AD	Alzheimer's disease
TMT	Trail making test
AVLT	Auditory verbal learning test
fMRI	Functional magnetic resonance imaging
MRI	Magnetic resonance imaging
WMH	White matter hyperintensities
TIWI	T1-weighted image
T2WI	T2-weighted image
FLAIR	Fluid-attenuated inversion recovery
SWI	Susceptibility weighted imaging
DTI	Diffusion tensor imaging
DMN	default-mode network
FDG	18F-fluorodeoxyglucose
OCT	Optical coherence tomography
CSF	Cerebrospinal fluid
p-tau	Hyperphosphorylated tau
t-tau	Total tau
NfL	Neurofilament light chain
TREM2	Triggering receptor expressed on myeloid cells 2
sTREM2	Soluble triggering receptor expressed on myeloid cells 2
GFAP	Glial fibrillary acidic protein
SASP	Senescence-associated secretory phenotype
sPDGFRβ	Soluble platelet-derived growth factor receptor beta
ALCAM	Activated leukocyte cell adhesion molecule
FSH	Follicle-stimulating hormone
IGF-1	Insulin-like growth factor 1
NAD	Nicotinamide adenine dinucleotide
NADH	Nicotinamide adenine dinucleotide reduced
GDF11	Growth differentiation factor 11
GAPDH	Reduced glyceraldehyde-phosphate dehydrogenase

Cognitive function

Cognition is the process in which the brain receives, processes, and converts external information into internal mental activities to acquire or apply knowledge, including memory, language, visuospatial processing, executive function, calculation, understanding, and judgment. Behavioral research on aging shows that overall cognitive function declines with increasing age, and the critical time period of decline varies across different cognitive activities [4]. Among these cognitive activities, episodic memory and processing speed decreases are especially effective at revealing the

structure and function change of the brain in the aging process and can be used as functional markers to evaluate brain aging.

Episodic memory is the most age-sensitive indicator of cognitive function and declines with age [5–7]. A cohort study involving 306 subjects showed that episodic memory continued to decline during aging and was significantly correlated with the extent of atrophy in the medial temporal lobe and posterior cingulate gyrus [8]. The decline in episodic memory is also closely related to hippocampal atrophy [9] and reduced white matter integrity in elderly individuals [10]. Another small-sample study confirmed that impairment of episodic memory was associated with altered hippocampal-neocortical structural connectivity and an increased risk of developing Alzheimer's disease (AD) [11]. Functional magnetic resonance imaging (fMRI) studies of episodic memory have shown that the decline in episodic memory encoding performance in elderly individuals is accompanied by increased activation of brain functions in the right prefrontal cortex and orbitofrontal cortex and decreased activation of brain functions in the medial temporal lobe [12, 13]. This suggests that the decline in episodic memory may be related to the decreased connectivity between the prefrontal lobe and the medial temporal lobe [14, 15]. Therefore, episodic memory is closely related to aging and brain structural changes and is a potential biomarker of brain aging. Episodic memory function can be evaluated by cued recall test [16] and an auditory verbal learning test (AVLT) [17]. Coding recognition is a potential tool to evaluate episodic memory and needs to be validated in future studies.

Executive function, a construct that encompasses multiple aspects of cognitive control, exhibits significant age-related differences and may constitute a fundamental feature of human cognitive aging [18]. Attention and processing speed are generally considered to be important components of executive function and are significantly related to aging. Attention refers to the ability to direct and focus mental activities such as perception and thinking toward a specific target. As a multidimensional concept, attention usually includes three functional dimensions: sustained attention, selective attention, and scattered attention. Previous research on attention has shown that while the ability to pay attention to non-task-related information shows a downwards trend with aging [19], the ability to pay attention to task-related information remains unchanged. Therefore, attention cannot be recommended as markers for assessing brain aging.

Processing speed in executive function tasks can be used as a biomarker to predict brain aging. Multiple cross-sectional studies have shown that processing speed decreases linearly with increasing age after 20 years old [20, 21]. A study involving more than 3,000 subjects explored the influence of age on different cognitive domains, and the results suggested that the decline in processing speed with age was the most significant [22]. A meta-analysis that included 91 studies showed a continuous decrease in processing speed with age [23]. Furthermore, the decline in processing speed with age is largely consistent with the

Table 2. Class of recommendation and level of evidence

Class (Strength) of recommendation	Level (Quality) of evidence
Class I (Strong) Benefit >>> Risk **Suggested phrases for writing recommendation** • Is recommended/is indicated • Evidence and/or general agreement that a given treatment or procedure is beneficial, useful and effective	**Level A** • Data derived from multiple randomized clinical trials or meta-analyses
Class IIa (Moderate) Benefit >> Risk **Suggested phrases for writing recommendation** • Should be considered • Weight of evidence/opinion is in favor of usefulness/efficacy	**Level B** • Data derived from a single randomized clinical trial or large non-randomized studies
Class IIb (Weak) Benefit ≥ Risk **Suggested phrases for writing recommendation** • May be considered • Usefulness/efficacy is less well established by evidence/opinion	**Level C** • Consensus of expert opinion, and/or small studies, retrospective studies, registries
Class III (Strong) Risk > Benefit **Suggested phrases for writing recommendation** • Is not recommended • Evidence/general agreement that the given treatment/procedure is not useful/effective and sometimes maybe harmful	**Note:** COR and LOE are determined independently (any COR may be paired with any LOE). COR, class of recommendation; LOE, level of evidence.

volume reduction of the lateral frontal cortex of the brain [24]. A study on the cognitive function of healthy centenarians found that their cognitive function was at a relatively high level, with no significant impairment of processing speed [25]. These results indicate that processing speed can accurately reflect the degree of brain aging and is a potential marker of brain aging. Processing speed can be assessed using the trailmaking test (TMT) [26, 27].

Motor coordination function
Physical aging is accompanied by a decline in fine motor skills, which can reflect structural and functional changes in the brain. A study involving more than 3,000 subjects showed that fine motor ability decreased significantly during aging and was significantly correlated with a decrease in gray matter volume [28]. Another study assessing changes in hand fine motor ability during aging showed a continuous decline in this domain with increasing age [29]. Thus, the decline in fine motor ability is highly consistent with aging and changes in brain structure and can be used as a marker of motor function to predict brain aging. Fine motor ability can be assessed by the spiral drawing test and a small pegboard test [28, 29].

Sensory perception
Sensory perception includes vision, hearing, smell, taste, and touch. Although the visual and auditory senses decline significantly with age, their dysfunction begins well before the onset of brain aging, due in large part to aging and dysfunction of the peripheral organs themselves, and these senses are, therefore,

not suitable as biomarkers of brain aging. The incidence of olfactory impairment increases progressively with age [30]. A cohort study that included 380 subjects showed that olfactory impairment was associated with cognitive decline and brain neurodegeneration [31]. A large cohort study in China showed that the severity of olfactory impairment was significantly associated with the degree of cognitive impairment, increased plasma tau, and neurofilament light chain (NfL) levels, volume reduction in the hippocampus and internal olfactory cortex, and the severity of white matter hyperintensities [32]. Therefore, olfactory dysfunction is associated with brain aging. But it is not recommended as a functional marker of brain aging because of its closer correlation with diseases.

Emotion
As the body ages, age-related anxiety also increases significantly and is most common in older women [33]. In clinical samples, the prevalence of anxiety disorders is significantly higher in older adults than in younger adults, with a global estimate of 15% [34]. However, anxiety disorders are no more prevalent in community samples of healthy older adults than in middle-aged adults [34]. In the absence of neurological disorders, the increase in anxiety may be the result of physical decline. Similarly, rodent studies have shown that aging is associated with an increase in depressive behaviors. Geriatric depression usually coexists with general medical and neurological diseases. However, the prevalence of major depressive disorder is much lower in older adults than in
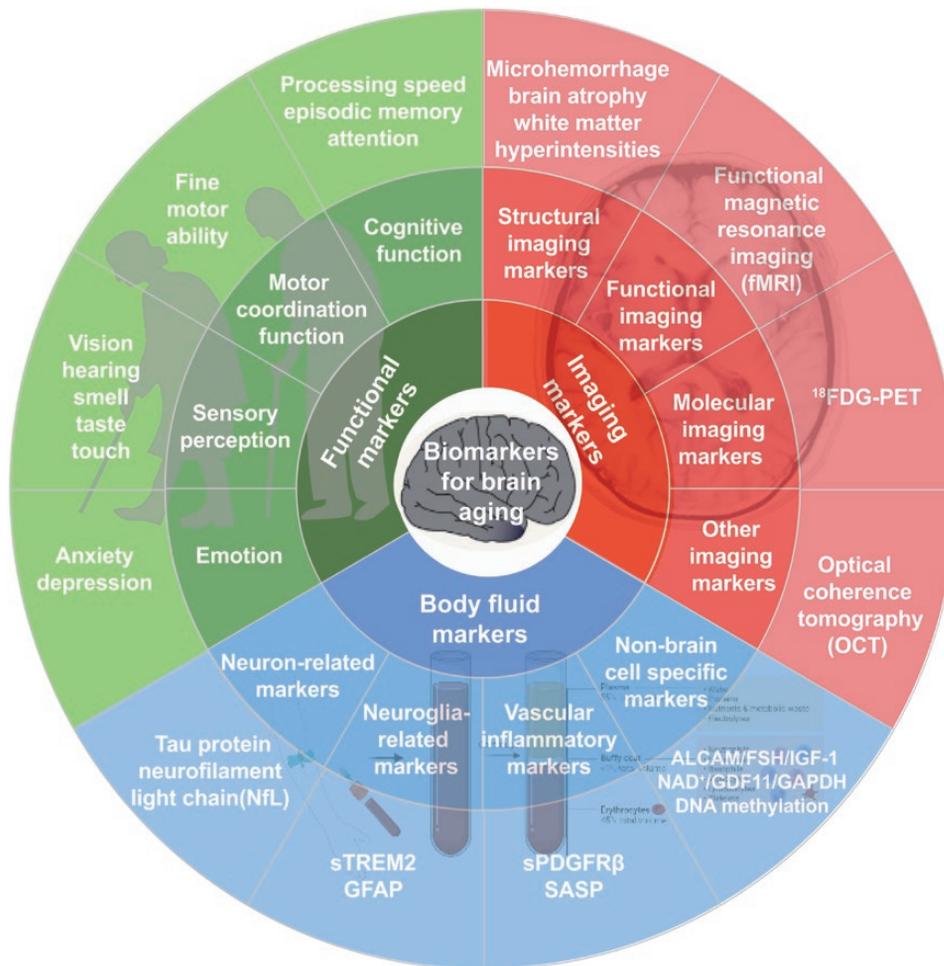
Figure 1. Framework of biomarkers for brain aging.
The proposed framework for brain aging is composed of three categories: functional, imaging, and body fluid biomarkers. The recommended biomarkers cover multi-dimensional and multi-scale changes in the brain during aging and are clinically testable. The value of these markers in assessing biological aging of the brain needs further verification.

younger adults, while approximately 15%–20% of older adults nonetheless present with subclinical depression [35]. Although emotional changes occur during aging, these emotions are mostly secondary to physical frailty and psychological events that are not experienced by all older adults and are therefore not recommended as markers for assessing brain aging.

Other functional markers
Language is an important and complex lifelong ability underpinned by dynamic interactions within and between specific networks of the brain. While normal aging compromises specific aspects of language production, most core language processes are robust to brain aging [36]. Frailty syndrome is defined as a state of physiological vulnerability associated with the aging process, resulting in a reduction in homeostatic reserve and difficulty in responding adequately to stressful events [37]. Frailty is a manifestation of various diseases and, in turn, is a risk factor for age-related diseases. Studies have shown that frailty is associated with lower and sharply reduced levels of cognitive function and is most closely related to executive function [38]. As it is influenced by

multiple factors, whether frailty can be used as a marker of brain aging needs to be investigated by further studies.

Recommendations

(i)   The decrease in processing speed can reflect the degree of brain aging. Clinically, the TMT can be used for evaluation (Level A, Class IIa).

(ii) The decline of episodic memory indicates the possibility of brain aging and an increased risk of developing AD. Episodic memory function can be evaluated by cued recall test and AVLT. (Level B, Class IIa).

(iii) Fine motor ability can be used as a biomarker to reflect brain aging. It can be clinically assessed by the spiral drawing test and a small pegboard test (Level B, Class IIa).

Imaging markers

Imaging has been widely used to show age-related structural changes in the brain due to its intuitive, accurate, and

easy-to-manipulate properties. Increasing evidence shows that structural, functional, and molecular imaging markers can reflect the level of brain aging and predict the risk of age-related brain diseases to varying degrees.

Structural imaging markers

Brain atrophy

Brain atrophy, defined as morphological changes caused by a decrease in the volume of the brain parenchyma, is one of the most common changes in the elderly brain [39]. A longitudinal follow-up cohort study that included 92 subjects aged 59–85 years found progressive atrophy of brain gray matter with age in healthy elderly people, with frontal and parietal lobe atrophy being the most prominent [40]. A cranial magnetic resonance imaging (MRI) study pooling 10,216 subjects aged 20–90 years from 11 cohorts showed that the frontal lobe, parietal lobe, superior temporal cortex, and insula had the most pronounced atrophy with age in a normal aging population and that this atrophy was significantly associated with executive function decline. For patients with mild cognitive impairment (MCI) or early AD, brain atrophy is mainly manifested as atrophy of the hippocampus, amygdala, entorhinal cortex, and inferior temporal cortex [41, 42]. These results suggest that the pattern of physiological brain atrophy differs from that of pathological brain atrophy, with differences in the brain regions where the atrophy begins.

White matter hyperintensities

White matter hyperintensities (WMH) are regions of abnormally high T2-weighted images (T2WI) or T2-fluid attenuated inversion recovery (FLAIR) signal strength in the white matter that is believed to be associated with vascular changes and ischemia in the aging brain. White matter hyperintensities are a common imaging manifestation of brain aging, with a prevalence of more than 85% in people over 60 years of age and a dramatic increase in overall load with age. A craniocerebral imaging study of 10,216 subjects aged 20–90 years found that in a normal aging population, cerebral white matter hyperintensities gradually appeared after the age of 50 years, and their severity was significantly associated with cognitive dysfunction, executive function decline, and amyloid levels in the brain [43]. A large sample study confirmed that cerebral white matter hyperintensities showed a significant correlation with age-related brain atrophy in a healthy aging population [43]. A cohort study that included 491 subjects confirmed that the severity of white matter hyperintensities was negatively correlated with visual executive function and could reflect age-related neurovascular health [44].

Cerebral microhemorrhage

With increasing age, the incidence of cerebral microhaemorrhage also increases gradually. The Rotterdam Community Population Study, which included 4,759 subjects followed for an average of 4.9 years, showed an increased risk of stroke with microbleeds at baseline [45]. A small-sample cohort study showed that a cerebral microbleed counts greater than 4 represented diffuse vascular and neurodegenerative injuries, which increased the risk of cognitive decline and dementia in individuals [46]. Therefore, cerebral microhemorrhage is closely related to disease.

Functional imaging markers

fMRI reflects neural network activity in the brain. Studies have identified changes associated with normal aging and age-related cognitive impairment. When a person closes their eyes and stops interacting with their surroundings, activity in neural networks, including the precuneus, posterior cingulate cortex, medial prefrontal cortex, and angular gyrus, increases. This 'default-mode network' (DMN) is thought to play an important role in recalling the past, thinking about the future and 'mind wandering'. Reduced functional connectivity of the DMN occurs in the normal aging process and is significantly aggravated in cognitively impaired elderly individuals [47, 48]. fMRI analysis found that the fronto-parietal network and its attached neural networks were active in young people and inactive in elderly people in the resting state, and these changes in elderly people were associated with reduced grey matter volume and white matter integrity [49]. In elderly individuals, functional connectivity between the DMN and hippocampus is related to memory ability as measured by performance on memory tasks [50]. Functional connections identified by fMRI analysis have been applied to construct a criterion for 'brain age' (see below).

Molecular imaging markers

^{18}FDG-PET: Reduced brain glucose metabolism is a manifestation of brain aging, and ^{18}F-fluorodeoxyglucose (FDG) PET imaging is the primary imaging basis for measuring brain glucose metabolism. A cohort study that included 120 healthy volunteers showed that ^{18}F-FDG uptake in the frontal lobes was significantly reduced during normal aging [51]. Another cohort study with a sample size of 123 healthy frontal and inferior parietal cortices with age, which is consistent with structural imaging findings showing significant frontal and parietal atrophy during normal aging [52]. A Japanese study that included 139 healthy volunteers found that ^{18}F-FDG metabolism in the brain regions around the medial frontal lobe and lateral sulcus was significantly reduced with age, and this difference was no longer significant after correction by brain atrophy, suggesting that the decrease in ^{18}FDG uptake with age as detected by ^{18}F-FDG PET is mainly due to age-related brain volume loss [53]. In addition, it has been demonstrated that patients with cognitive decline have reduced metabolism in the posterior cingulate cortex and temporoparietal lobe compared to normal elderly people, and this difference may predict cognitive progression and the risk of conversion to AD during aging [54].

Other imaging markers

Optical coherence tomography (OCT) is a new three-dimensional laminar imaging technique that was first used in the field of ophthalmology. In recent years, as the technology has matured, OCT has been gradually applied to the coronary artery and intracranial fields. Animal studies have shown that OCT can reflect the structure and function of cerebral vessels related to aging [55]. Whether OCT can be used as a marker of brain aging needs to

be explored and verified by conducting a large number of clinical studies.

Recommendations

(i) Brain atrophy can be used as an imaging marker to assess brain aging, with frontal and parietal atrophy predicting the level of brain aging, while temporal lobe and hippocampal atrophy suggest a potential risk of developing AD. Clinical assessment can be performed by cranial MRI (Level B, Class I).

(ii) The severity of white matter hyperintensities correlates with age and brain function decline and can be used as an imaging marker to assess brain aging. It can be evaluated using FLAIR sequences and diffusion tensor imaging sequences of MRI (Level B, Class I).

(iii) ^{18}FDG-PET can be used as an imaging marker to assess brain aging. Decreased ^{18}F-FDG uptake in the frontal lobe suggests brain aging and predicts an elevated risk of cognitive impairment; decreased metabolism in the posterior cingulate gyrus and temporoparietal lobe suggests an elevated risk of cognitive decline and development of AD (Level B, Class I).

Body fluid markers

Components of body fluids such as plasma, urine, and cerebrospinal fluid (CSF) are indispensable biomarkers for the assessment of brain aging due to their noninvasive or minimally invasive collection, high sensitivity, and ease of accurate measurement [56]. This consensus aims to recommend brain aging-related markers; therefore, the search strategy for body fluid markers is to screen body fluids for brain-cell-specific markers or biomarkers that are likely to be highly correlated with brain aging levels. Since these markers also change in various acute and chronic brain diseases, interference from brain diseases should be excluded when the markers are used as brain aging markers.

Neuron-related markers

Tau protein

Tau protein is a highly soluble microtubule-associated protein that is mainly distributed in the axons of neurons. Under pathological conditions, the normal tau protein in neurons is hyperphosphorylated (p-tau) and aggregated to form neurofibrillary tangles. Elevated p-tau levels in CSF and blood are indirect markers of tau pathology in neurodegenerative diseases, which increase with disease progression and are associated with an increase in neurofibrillary tangles. Studies have found that plasma levels of p-tau and total tau (t-tau) both increase with age, and their increase is associated with reduced cognitive levels and an accelerated rate of cognitive decline [57]. Another small-sample study confirmed that elevated plasma t-tau levels were associated with widespread reductions in cortical glucose uptake, temporal lobe thinning, and memory decline [58]. A longitudinal follow-up cohort study of 276 cognitively normal older adults showed that elevated plasma t-tau levels were positively associated with atrophy of the

basal forebrain cholinergic system and could predict the risk of developing AD [59]. Therefore, plasma t-tau and p-tau levels can be used as biological markers to predict brain aging, but care must be taken to differentiate aging from tauopathies.

Neurofilament light chain

NfL is a structural protein of neuronal cells that can be detected in body fluids and is a potential biomarker of brain aging and longevity. A large cohort study suggested that plasma NfL increases nonlinearly with age and predicts cognitive decline [60]. Another study found that high levels of plasma NfL were associated with reduced hippocampal volume and the severity of leukoencephalopathy [61]. A cross-sectional study of 335 subjects showed that increased plasma NfL was associated with decreased brain volume in elderly patients [62]. Therefore, plasma NfL levels can be used as a body fluid biomarker to assess brain aging.

Microglia-related markers

Triggering receptor expressed on myeloid cells 2 (TREM2) is a transmembrane receptor that plays an important role in regulating microglial phagocytosis and the response to inflammatory stimuli. The extracellular structural domain of TREM2 can be cleaved to produce soluble TREM2 (sTREM2) and released into the CSF and subsequently the blood, serving as an indicator of microglial activity. A cross-sectional study involving 150 subjects showed that CSF and plasma sTREM2 levels were positively correlated with age and significantly correlated with t-tau and p-tau levels in CSF [63]. Another clinical study showed that plasma sTREM2 was correlated with the severity of white matter hyperintensities [64]. Studies have also confirmed that sTREM2 levels in plasma and CSF can predict the risk that MCI will progress to AD [65, 66]. Therefore, plasma and CSF sTREM2 may be considered for use as body fluid markers of brain aging.

Astrocyte-related markers

Glial fibrillary acidic protein (GFAP) is a signature intermediate filament in astrocytes that contributes to synaptic formation and axon metabolic homeostasis in the central nervous system. Currently, plasma GFAP is mainly used for the assessment and identification of traumatic brain injury, CNS demyelinating diseases and neurodegenerative diseases [67–69]. Animal studies have shown that plasma GFAP levels increase with age [70, 71]. A meta-analysis based on brain tissue transcriptome datasets showed that the decline in synaptic transmission function and the increase in plasma GFAP were most significant with age [72]. A cross-sectional study of 114 healthy subjects and AD patients confirmed that plasma GFAP levels were significantly associated with the degree of cognitive impairment and white matter lesions [73]. In conclusion, plasma GFAP levels may be considered for use as a body fluid biomarker for the assessment of brain aging, but aging must be distinguished from related diseases.

Senescence-associated secretory phenotype molecules

The senescence-associated secretory phenotype (SASP) refers to the proinflammatory factors secreted by cellular senescence, including YKL-40, TNF-α, and IL-1β, which can cause chronic

low-grade inflammatory responses and may have an impact on brain aging. Previous studies have shown that the SASP is associated with neuronal apoptosis, decreased synaptic function, and cognitive impairment [74]. However, because these inflammatory markers are nonspecific and are highly influenced by inflammatory diseases and multiple brain diseases, they are not suitable to use alone as brain aging markers.

Cerebrovascular markers

CSF levels of soluble platelet-derived growth factor receptor beta (sPDGFRβ), a marker of pericyte damage, increase from 20 years of age onward and are associated with blood-brain barrier dysfunction, dysfunction of neurovascular coupling, and cognitive decline. This molecule can be used as a cerebrovascular aging marker to provide direction for the study of brain aging mechanisms [75].

Non-brain-cell-specific markers

Activated leukocyte cell adhesion molecule (ALCAM) is a transmembrane immunoglobulin that is involved in cellular immunity and neuroinflammatory processes. A peer-reviewed domestic cohort study of aging has shown that plasma ALCAM levels are significantly correlated with brain aging, and this needs to be further verified in future cohort studies. Multiple studies have confirmed that plasma follicle-stimulating hormone (FSH), insulin-like growth factor 1 (IGF-1), nicotinamide adenine dinucleotide (NAD$^+$) or NAD$^+$/ nicotinamide adenine dinucleotide reduced (NADH), GDF11 and GAPDH mRNA, and DNA methylation levels are significantly correlated with overall aging [76–80]. However, there is a lack of relevant clinical evidence indicating whether they can be used as specific markers to assess the level of brain aging. These markers may be considered for use as brain aging biomarkers to be validated in follow-up cohort studies.

Recommendations

(i) Plasma t-tau and p-tau levels may be useful body fluid biomarkers to predict brain aging, and their elevation suggests the possibility of brain aging and an increased risk of neurodegenerative diseases (Level B, Class IIa).

(ii) Plasma NfL levels may be a useful body fluid biomarker to predict brain aging, and increased NfL levels suggest the possibility of brain aging and the risk of cognitive decline (Level B, Class IIa).

(iii) Plasma and CSF sTREM2 may be considered for use as body fluid biomarkers to assess brain aging (Level B, Class IIa).

(iv) Plasma and CSF GFAP may be considered for use as body fluid biomarkers for the assessment of brain aging (Level B, Class IIa).

(v) Plasma ALCAM, FSH, IGF-1, NAD$^+$ or NAD$^+$/NADH, GDF11 and GAPDH mRNA, and DNA methylation levels may be considered for use as candidate biomarkers of brain aging, but should be validated in follow-up cohort studies (Level C, Class IIb).

Brain age model

Brain aging involves changes in all aspects of the brain, from molecular to functional levels. Therefore, multi-dimensional and multi-scale information needs to be integrated to accurately evaluate the state of brain aging. In recent years, remarkable progress has been made in exploring the biological age of the brain.

Brain age assessment model

Biological age is the age deduced according to the developmental state of normal human physiology and anatomy, so as to accurately reflect the actual state of human organization structure and physiological function. Biological age can provide a more accurate quantitative index than chronological age for evaluating the senescence of the human body and answering the scientific question of age in physiological terms. The abovementioned brain aging biomarkers provide options for the construction of biological age of the brain (hereinafter referred to as 'brain age'), and conversely, brain age can provide a reference standard for the study of brain aging markers. In addition, brain age can provide a basis for research on the mechanisms of brain aging, a method for early identification of pathological aging, and a basis for early intervention and efficacy evaluation. The rise of machine learning has promoted research on 'brain age assessment models'. Currently, the construction of brain age is mostly based on structural imaging and electroencephalography [81–83]. With the development of functional imaging, functional connectivity (FC) and multi-modal imaging (sMRI+FC) have been gradually applied to the construction of brain age [84, 85]. These brain age models are currently evaluated based on the difference between predicted and actual brain age, that is, the brain-age gap (BAG), which is usually between 1 and 10 years. However, the current brain-age models lack external validation in different cohorts or centers.

Brain aging and age-related brain disease prediction model

The BAG reflects whether the aging of the brain is accelerated or delayed, laying a foundation for the prediction of age-related brain diseases. It can accurately predict how fast an individual is aging and how far an individual is from age-related brain diseases. To date, BAG has been used to predict a variety of brain diseases, including AD, MCI, epilepsy, and psychiatric diseases. Studies have found that positive BAG or increased levels of BAG are associated with the risk of cognitive impairment, traumatic brain injury, and schizophrenia [82]. It should be noted that the prediction of brain age cannot be used as an independent predictor of disease due to its lack of specificity; therefore, disease-specific markers should be combined. Current predictive models of brain age are based on cross-sectional studies; therefore, there is a lack of effective comparison and verification with longitudinal follow-up data for prognostic assessment.

The aging process involves multi-scale and multi-dimensional changes in molecules, cells, organs, and the whole body, and indicators on different scales convey different information. The establishment of brain age models and age-related brain disease prediction models based on multi-scale,

Table 3. Recommended biomarkers of brain aging

Dimension	Biomarker	Test method	COR	LOE
Functional markers	Processing speed	Trail making test (TMT)	IIa	A
	Episodic memory	Cued recall test and auditory verbal learning test (AVLT)	IIa	B
	Fine motor ability	Spiral drawing test and small pegboard test	IIa	B
Imaging markers	Brain atrophy	MRI	I	B
	White matter hyperintensities	MRI using FLAIR and DTI sequences	I	B
	18FDG uptake	18FDG-PET	I	B
Body fluid markers	t-tau/p-tau	Plasma/ELISA	IIa	B
	NfL	Plasma/ELISA	IIa	B
	sTREM2	Plasma/ELISA	IIa	B
	GFAP	Plasma/ELISA	IIa	B
	ALCAM*	Plasma/ELISA	IIb	C
	IGF-1*	Plasma/ELISA	IIb	C
	FSH*	Plasma/ELISA	IIb	C
	NAD+*	Plasma/mass spectrometry	IIb	C
	GDF11/GAPDH*	Plasma/qRTPCR	IIb	C
	DNA methylation*	Plasma/methylation PCR array	IIb	C

*These indicators lack clinical evidence related to brain aging and need to be validated in future cohort studies.

multi-dimensional, and multi-modal markers may be more accurate, stable, and universal, and research is moving in this direction.

Conclusion and future perspectives

According to the experts' discussion, the brain aging markers are recommended in the three dimensions of behavioral function, imaging, and body fluids; these markers will be further validated in different age groups in the future (Table 3).

The working road map of brain aging biomarker research in China includes the following goals: (i) To establish a national multicentre aging cohort of approximately 1000 subjects to discover and validate brain aging biomarkers, establish detection techniques and methods, determine the reference values of brain aging biomarkers in the Chinese population, predict the 'turning point' of brain aging and determine the time window for intervention. (ii) To establish a brain aging assessment model and age-related brain disease prediction model by using artificial intelligence calculations. (iii) To establish a research and development paradigm combining industry, academia, research, and government to promote the translation and application of research achievements. Establishment of the framework of biomarkers for brain aging will also facilitate the research for neurodegenerative diseases for which aging is a major risk factor. The ultimate goal is to improve the level of brain health of the elderly and achieve healthy aging worldwide.

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Due to space constraints and our knowledge limitation, certain important

Author contributions

Gang Pei, Yan-Jiang Wang, Yi Eve Sun, and Guang-Hui Liu conceived of this consensus. All authors participated in the Consensus Statement Working Group and contributed to the manuscript during the drafting or revision process. Yu-Juan Jia, Jun Wang and Jun-Rong Ren drafted the manuscript. All authors read and approved the final version of the manuscript.

Conflict of interest

All of the authors declare no competing interests. Guang-Hui Liu holds the position of Editor-in-Chief, Moshi Song and Yan-Jiang Wang hold the position of Editorial Board Member for *Life Medicine*. They are blinded from peer review and decision-making for the manuscript.

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