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Molecular pathways and biomarkers associated with age-related cognitive decline

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Abstract

Age-related cognitive decline is the gradual decrease in memory, reduced attention, difficulty with multitasking, reduced ability to recall information, and decreased processing speed with age. These changes are considered normal, and the rate and extent of cognitive decline can be significantly impacted by genetics and environmental factors, such as lifestyle behavior, diet, and physical activity. Mild cognitive impairment (MCI) is an intermediate phase between normal aging and Alzheimer's disease (AD). MCI is a risk factor for Alzheimer's disease, but not all individuals with MCI develop AD. There exists a significant challenge in diagnosing MCI and early Alzheimer's disease as they involve very subtle differences in cognitive ability. Thus, several studies are focused on identifying biomarkers that could be utilized for early diagnosis. The decline in cognition with age is influenced by several molecular processes that include protein aggregation, synaptic and mitochondrial dysfunction, epigenetic changes, and oxidative damage. The interplay between these mechanisms can be tracked using genetic, neurophysiological, neuroimaging, biochemical, and neuroinflammatory biomarkers. Despite the existence of several molecular biomarkers, detecting cognitive decline before the clinical symptoms appear remains challenging. There is an unmet need for reliable and non-invasive biomarkers that can precisely monitor the impact of lifestyle on normal aging, which would be able to identify individuals at risk of cognitive decline. In this review, we have summarized the different classes of biomarkers that have been associated with age-related cognitive decline and highlighted the need for integrating different approaches for accurate diagnosis of early cognitive decline.

Keywords: *cognition, aging, biomarkers*

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1. Introduction

The world's population of adults aged 60 and above is expected to reach 2 billion by the year 2050. With this drastic increase in the number of aging individuals across the globe, the prevalence of age-related cognitive decline will also witness a sharp increase. Cognitive decline is among the most feared aspects of growing old. It is also the costliest, in terms of the financial, personal, and societal burdens. Identifying underlying biological processes that contribute to cognitive aging could substantially impact our understanding of the pathophysiological mechanisms that increase the risk of dementia. With the aging global population, there is an urgent need to identify sensitive and specific biomarkers that not only detect early cognitive deterioration but also inform therapeutic efficacy and prognosis. Biomarkers are objectively measurable indicators of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention, and they offer a potential gateway to precision medicine in aging and neurodegeneration. Robust biomarkers in the context of aging-associated cognitive impairment should meet several key criteria: (I) biological relevance to underlying mechanisms of cognitive deterioration; (II) ability to distinguish between normal aging and pathological decline; (III) cross-species translational validity; (IV) responsiveness to therapeutic interventions; (V) must demonstrate reproducibility, accessibility, and cost-effectiveness to support longitudinal population-level screening. However, most existing biomarkers fail to achieve these standards, particularly in transitioning from preclinical to clinical utility [1]. Additionally, a wide array of Alzheimer's and non-Alzheimer's disease-related neuropathologies only account for 20 to 40% of interpersonal variance in cognitive decline among the elderly, and even in the presence of neurofibrillary tangles and amyloid plaques, several individuals do not develop cognitive impairment, offering insights into cognitive resilience [2, 3]. Hence, there is a need to validate current biomarkers, through which the conditions in which they prove reliable and accurately predict relevant outcomes [4].

Several classes of biomarkers have been investigated for their potential to detect cognitive impairment associated with aging, each offering unique insights while posing specific limitations in terms of sensitivity, scalability, and translational relevance (**Figure 1**). Neuroimaging biomarkers, including structural magnetic resonance imaging (MRI) and positron emission tomography (PET), remain among the most widely studied. Structural MRI can detect brain atrophy patterns associated with aging and dementia, while PET imaging enables in vivo visualization of amyloid-beta and tau pathology. Although these

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techniques demonstrate high sensitivity and specificity for Alzheimer's disease (AD) pathology, their application is constrained by high costs, limited accessibility, and invasiveness, especially in the case of PET, which involves exposure to radioactive tracers [5]. Furthermore, structural and molecular brain changes often manifest after significant disease progression, thereby limiting their utility for early or preclinical detection [6] (**Figure 2**).

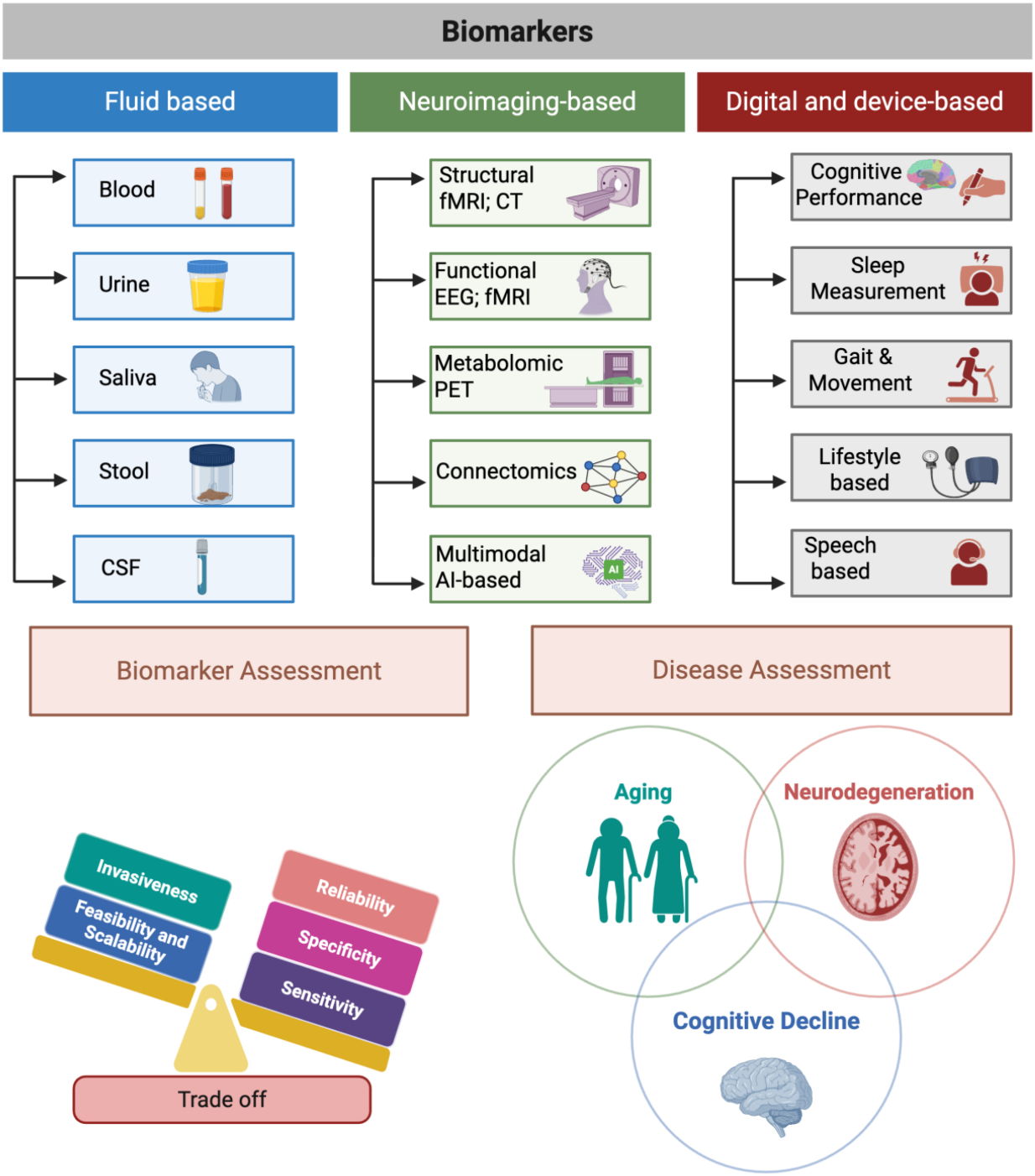

Figure 1 • Classification and evaluation of biomarkers reflecting cognitive decline associated with aging. We broadly classified biomarkers associated with cognitive decline during aging based on their mode of data acquisition. This led to three categories: fluid-based, digital or device-based, and neuroimaging-based biomarkers. This classification framework captured the diversity of biomarkers while covering the essential dimensions linked to age-related cognitive changes. To evaluate the quality of these biomarkers, we applied five key criteria: feasibility/scalability, invasiveness, reliability, specificity, and sensitivity. A notable trade-off was observed between invasiveness and feasibility, which significantly influenced our overall assessment. In parallel, we attempted to decouple biomarkers based on their relevance to aging, neurodegeneration, and cognitive decline, aiming to rank them by their ability to reflect age-related cognitive decline without inherent bias toward any one of these domains. Created in BioRender. Chawla, G. (2025) https://BioRender.com/3iy96uq.

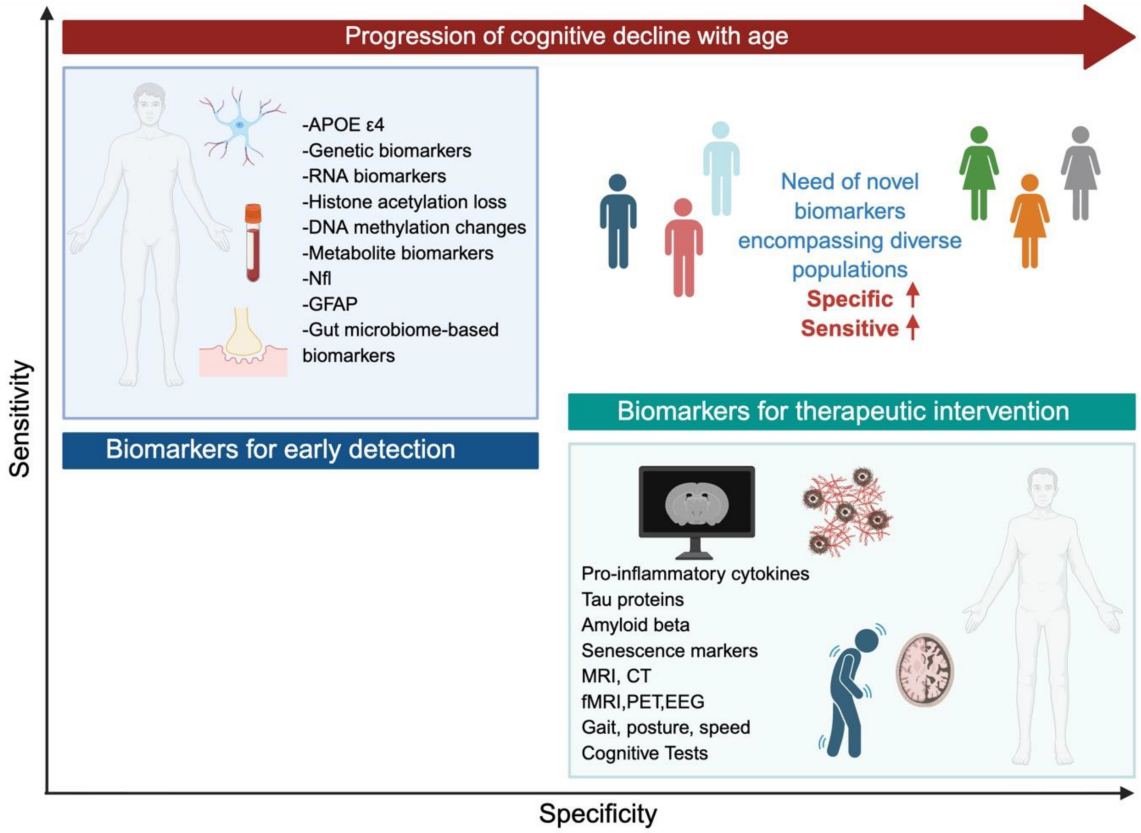

Figure 2 • Classification of biomarkers based on sensitivity and specificity during the progression of cognitive decline. Molecular biomarkers like ncRNAs, altered proteins and metabolite levels, cytokine bursts triggering inflammation, neuronal and astrocyte damage specific markers like Nfl, and adverse changes in the gut microbiome are early indicators of progressive cognitive decline with age. These biomarkers can easily be analyzed from peripheral fluids or tissue samples due to their high sensitivity. Still, they may not be attributed to specific disease conditions early on but rather indicate the development of mild cognitive impairment early during the disease. They can be exploited for the recruitment of new participants into longitudinal cohorts or for screening early therapeutic interventions. Imaging-based, connectomics-based, and cognitive–behavioral test-based biomarkers arise late into the disease course and are highly specific for selective disease conditions. They can be exploited by clinicians to advise potent therapeutic strategies to patients or for follow-up studies. These biomarkers can distinguish between cognitive impairment diseases like AD, PD, and VD, among others. There remains a need for novel biomarkers that will take into account gender and population-based variability, and will also be highly specific and sensitive, allowing disease-specific diagnosis of cognitive impairment in early stages, such that intervention and therapeutics can be employed robustly. Created in BioRender. Chawla, G. (2025) https://BioRender.com/tx5nmmu.

Fluid-based biomarkers, particularly those derived from cerebrospinal fluid (CSF), such as reduced Aβ42 and elevated total tau or phosphorylated tau, are well-established indicators of neurodegeneration [7–9]. Aβ42/Aβ40 ratios often correlate with age but are not directly indicative of cognitive decline in clinical settings [10]. However, lumbar puncture procedures are invasive and not viable for population-wide screening. In recent years, blood-based biomarkers have emerged as a promising alternative, with plasma phosphorylated tau (e.g., p-tau181, p-tau217), neurofilament light chain (NfL), and glial fibrillary acidic protein (GFAP) showing diagnostic accuracy comparable to CSF and PET markers [11, 12]. These blood assays offer a more feasible and less invasive option for longitudinal monitoring, but challenges remain in standardizing assay protocols and controlling for confounding factors such as comorbidities, medication use, and peripheral inflammation that contribute to interpersonal variability [13].

Electrophysiological biomarkers, such as electroencephalography (EEG) and event-related potentials (ERPs), are cost-effective and temporally sensitive measures of neural activity. They hold particular promise for detecting early functional disruptions before structural damage occurs. However, their clinical utility is hindered by low spatial resolution and vulnerability to artifacts and noise, which affect reproducibility [14]. Genetic biomarkers, notably the APOE ε4 allele, provide insight into individual susceptibility to late-onset AD. Nonetheless, genetic risk is neither necessary nor sufficient for disease manifestation; many APOE ε4 carriers remain cognitively intact, while non-carriers may still experience decline, reflecting the complexity of gene–environment interactions [15].

More recently, AI-enabled biomarkers have gained attention. These include machine learning models trained on multimodal data—neuroimaging, speech patterns, digital cognitive assessments, and wearable sensor data—to identify early cognitive changes that might not be detectable by traditional methods [16]. AI models offer the ability to integrate high-dimensional data and account for individual variability, but they also face challenges in generalizability, interpretability, and ethical deployment in clinical contexts. In this review, we have briefly described the different animal models that have been utilized to study cognitive decline and discussed different biomarkers associated with cognitive decline during aging and age-related diseases.

2. Animal models in the study of cognitive decline with aging

Animal models are indispensable tools in neuroscience as they provide controlled conditions for tracking disease progression and dissecting the underlying mechanisms of neuropsychiatric disorders. Due to the complexity and ethical constraints of human studies, these models allow evaluation of potential therapeutic interventions. Rodents, especially mice and rats, are extensively utilized due to their genetic similarity to humans, well-characterized behaviors, and the feasibility of genetic modifications. These models enable researchers to simulate aspects of human aging, facilitating the exploration of pathophysiological processes and the testing of pharmacological treatments. Additionally, non-rodent species such as canines and non-human primates offer valuable insights due to their closer physiological and cognitive parallels to humans, making them particularly useful for translational research.

2.1. Rodent models

Rodent models are widely used in the study of cognitive disorders and aging due to their feasibility of genetic manipulations, well-characterized neuroanatomy, and complex set of traceable behaviors, and they can be utilized to assess the functionality and reliability of various classes of interventions. These models allow researchers to investigate the molecular and cellular mechanisms underlying age-related cognitive deficits, as well as neurodegenerative diseases such as AD. Aged rodents naturally exhibit impairments in learning, memory, and executive function, making them valuable for studying the trajectory of normal cognitive aging. Transgenic models mimic key features of human neuropathology and are thus used to dissect cellular and molecular mechanisms of diseases and biomarker discovery studies. Additionally, the effects of therapeutics, physical or dietary interventions, and progression or retraction of disease under these conditions can be promptly monitored using these models. Standardized behavioral tests, including the Morris water maze and novel object recognition, allow correlation between biomarker fluctuations and specific cognitive outcomes. Additionally, rodent models facilitate the use of invasive techniques such as in vivo imaging, electrophysiology, and longitudinal fluid sampling, which are critical for validating the temporal dynamics and mechanistic relevance of potential biomarkers.

The 5xFAD mouse model is an AD model that (Tg(APPSwFlLon, PSEN1*M146L*L286V)6799Vas/Mmjax) overexpresses amyloid precursor protein (APP) and Presenilin 1 (PSEN1) containing 5 familial AD mutations (APP KM670/671NL (Swedish), APP I716V (Florida), APP V717I (London), PSEN1 M146L, PSEN1 L286V) in the neurons [17]. These mice display the development of robust amyloid pathologies, with plaques appearing in the brain from 2 to 4 months of age, which lead to aggravated robust microgliosis and inflammatory processes along with synaptic and neuronal loss [18].

The JNPL3 mice express the FTDP-17 mutation (P301L) under the control of the mouse prion promoter and report motor defects and development of neurofibrillary tangles at 6.5 months of age in hemizygous condition and 4.5 months in homozygotes [19].

Transgenic pR5 mice bear the human FTD Tau mutation P301L with Parkinsonism linked to chromosome 17, which leads to hyperphosphorylation of Tau and the formation of abnormal Tau filaments [20].

The 3xTg-AD model combines three familial mutations: the Swedish *APP* mutation (KM670/671NL), the *PSEN1* M146V mutation, and the *MAPT* P301L mutation [21]. 3xTg mice have impaired long-term potentiation and display an acute accumulation of fibrillar amyloid beta. It has been shown that 12-to-18-month-old animals exhibit a marked reduction in microglial density and an increase in the population of dystrophic neurites [22].

BAC-LRRK2-R1441G mice display some motor deficits and axonal pathology in the striatum, but lack clear dopaminergic neurodegeneration and the formation of α-synuclein inclusions [23]. Transgenic mice carrying A53T, A30P, and E46K mutations in α-Synuclein encoding gene SNCA are used to study familial PD [24].

2.2. Non-rodent models

Non-rodent models, including non-human primates, canines, and certain invertebrates like *Drosophila melanogaster* and *Caenorhabditis elegans*, have played an increasingly important role in discovering biomarkers linked to aging-related cognitive decline. Mammalian models are particularly suited for studying higher-order cognitive functions and neurodegenerative processes, as well as for validating biomarkers with strong translational relevance, especially those derived from neuroimaging, cerebrospinal fluid, or blood-based assays. They naturally develop cognitive dysfunction syndromes with clinical and neuropathological similarities to human dementia, making them excellent models for identifying behavioral, biochemical, and imaging biomarkers that emerge spontaneously with aging. Invertebrate models like *Drosophila* and *C. elegans*, though offering limited anatomical complexity, offer powerful genetic tools and high-throughput capabilities that facilitate rapid screening of molecular pathways and candidate biomarkers associated with neural aging. These models also support large-scale omics-based approaches to identify conserved aging-related molecular signatures.

Several transgenic *Drosophila* models have been developed to mimic AD-like pathology. These models express human Aβ peptides, such as Aβ42, under the control of tissue-specific promoters like elav-Gal4. Expression of Aβ42 in neurons leads to age-dependent cognitive impairments, including deficits in memory and learning, as well as neurodegeneration. A triple transgenic *Drosophila* model was generated by Greeve et al. and it expresses human APP (hAPP), human β-secretase (hBACE) and *Drosophila* γ-secretase presenilin (dPsn) with point mutations corresponding to familial AD mutations N141I, L235P, and E280A [25]. In a landmark study, Wittmann and colleagues developed the *Drosophila* model expressing mutant forms of human Tau protein, including the R406W mutation, which develops progressive neurodegeneration without the formation of neurofibrillary tangles. The accumulation of hyperphosphorylated tau in neurons leads to axonal degeneration, vacuole formation, and impaired memory, paralleling features observed in human AD [26].

Dogs, particularly aged ones, can develop Canine Cognitive Dysfunction, resembling human AD. They exhibit Aβ accumulation, cortical and hippocampal atrophy, and cognitive symptoms like

confusion and memory loss [27]. Zebrafish can be genetically modified to mimic neurodegenerative disorders associated with age. These models are characterized by Aβ accumulation, synaptic defects, and behavioral changes. In a recent study, zebrafish exposed to 0.04 mM of $AlCl_3$ for 28 days developed senile plaques, and displayed accumulation of phosphorylated tau, and learning and memory defects [28]. Scopolamine, an acetylcholine muscarinic receptor antagonist, and physostigmine, an acetylcholinesterase inhibitor, impairs retention and acquisition of the passive avoidance response in zebrafish [29]. Aged rhesus monkeys exhibit increased astrocyte activity in neuritic plaque-adjacent areas leading to inflammation and hypertrophy [30]. Rhesus monkeys expressing double tau mutation (AAV-P301L/S320F) in the left hemisphere also show accumulation of misfolded tau protein and exacerbated inflammatory response, thus serving as a reliable AD model [31].

3. Genetic biomarkers of age-related cognitive decline

Genetic predispositions also play a critical role, and studies have uncovered genetic biomarkers that aid in predicting age-related cognitive decline [32] (**Table 1**). The APOE ε4 allele remains a robust genetic risk factor for cognitive decline, frequently linked to deficits in memory, executive function, and global cognition, even outside the context of Alzheimer's disease [33]. Adjacent to APOE on chromosome 19, the TOMM40 gene encodes a mitochondrial membrane protein. Specific polymorphisms, such as rs2075650, have been independently associated with diminished cognitive resilience [34]. Another emerging candidate, ADAMTS9, has been linked to late-life cognitive performance [35]. Given its role in insulin signaling and extracellular matrix remodeling, it may provide insights into metabolic contributions to cognitive aging [36].

Table 1 • Potential genetic biomarkers of age-related cognitive decline.

Gene	Function	Effect on aging brain	References
APOE ε4	Lipid transport	↑ Cognitive decline risk	[37]
TOMM40	Mitochondrial function	↓ Resilience to aging	[34]
BDNF	Synaptic plasticity	↓ Memory in Met allele carriers	[38]
COMT	Dopamine metabolism	↓ Executive function (Val allele)	[39, 40]
DNMT3A	Epigenetic regulation	↑ Cognitive decline via CHIP	[41]
ADAMTS9	Insulin pathway	Linked to age-related cognition	[35, 36]
REST	Neural protection	↓ In aging brains with poor outcomes	[32, 42]
Circadian Clock genes	Sleep–wake cycles, hormone release, metabolism, and body temperature	RORA rs13329238, NPAS2 rs17655330, CLOCK rs3749473, and RORB rs10781247 individually and interactively altered cognitive aging for normal aging	[32]
ELOVL2	Epigenetic clocks	Biomarkers of biological aging	[43, 44]

↑, Increased; ↓, Decreased; APOE ε4, Apolipoprotein E ε4 allele; TOMM40, Translocase of Outer Mitochondrial Membrane 40; BDNF, Brain-Derived Neurotrophic Factor; COMT, Catechol-O-methyltransferase; DNMT3A, DNA methyltransferase 3 alpha; ADAMTS9, ADAM metallopeptidase with thrombospondin type 1 motif 9; REST, Repressor Element-1 (RE1)-Silencing Transcription Factor; ELOVL2, Elongation Of Very Long Chain Fatty Acids-Like 2.

Neuroprotective factors also exhibit age-related changes. The RE1-Silencing Transcription Factor (REST) enhances stress resistance and synaptic maintenance as individuals age. A decrease in REST expression, especially in those not carrying the APOE ε4 allele, may heighten susceptibility to neurodegeneration [42]. Likewise, declining levels of brain-derived neurotrophic factor (BDNF)—a crucial component in neuronal survival and plasticity—are often seen with aging. Polymorphisms in BDNF, particularly Val66Met, affect age-related memory performance and interact with the APOE genotype to influence risk [45]. Other loci, such as the COMT-Val1155Met variant, impact prefrontal dopamine metabolism and shape individual aging trajectories [39].

4. Epigenetic biomarkers of age-related cognitive decline

Epigenetics provides a dynamic regulatory framework that shapes how the genome functions over time.

4.1. Histone modifications

Aging brains exhibit profound changes in histone acetylation and methylation, directly impacting genes essential for synaptic function, memory, and neuronal health. Studies have shown that acetylation marks such as H3K27ac and H4K12ac decrease at promoters of synaptic genes in the aging human prefrontal cortex and mouse hippocampus, correlating with reduced gene expression and impaired memory formation [46]. For example, reduced H3K27ac at loci related to synaptic signaling and ion transport is linked to the epigenetic downregulation of these critical processes during neuronal aging (**Table 2**). Experimental interventions in animal models, such as treatment with histone deacetylase (HDAC) inhibitors like Vorinostat (SAHA), can restore these acetylation marks and reverse age-related deficits in synaptic plasticity and memory [46]. Furthermore, increased activity of HDAC3 has been identified as a significant contributor to learning and memory decline, and its deletion in mice reverses age-related impairments in hippocampal long-term potentiation

and cognitive function. On the methylation front, aberrant histone methylation, such as increased H3K27me3 and H3K9me2, has been implicated in neural stem cell quiescence, inflammation, and neurodegeneration, all of which exacerbate cognitive decline. It confirms that age-related hippocampal H3K9me3 gains at BDNF and synaptic plasticity gene promoters contribute to memory decline, while SUV39H1 inhibition reverses these effects [46]. Pharmacological inhibition of SUV39H1 reduced H3K9me3 levels, restored IEG and BDNF expression, improved spine density, and rescued hippocampal-dependent memory in old mice [47]. Additional effects included loss of heterochromatin H3K9me3 in excitatory neurons of aged mice, with increased chromatin accessibility at LINE-1, a soma-specific aging hallmark [46]. Dysregulation of these marks disrupts gene expression, interferes with neuronal cell cycles, and is observed in neurodegenerative diseases like Alzheimer's. Age-related cognitive decline has been linked with deregulation of H4K12acetylation, a cognitive reaction that was reinstated in mice by inducing this mark [48].

Table 2 • Epigenetic determinants of altered functional gene expression in the aging brain.

Changes in the expression of synapse-related functional genes in the aging brain.			
Localization	**Histone modification**	**Function**	**References**
Prefrontal cortex	H3K27ac ↓	GATA3 ↓	[49]
Hippocampus	H4K12ac ↓	-	[49]
	H3K27ac ↓	BDNF ↓	[50]
	H3K9ac ↓, H3K14ac ↓	IEGs ↓	[47]
	H4K8ac ↓	Nr4a2 ↓, c-fos ↓	[47]
	H3K9me3 ↑	BDNF ↓, GluR1 ↓, IEGs ↓	[47]
Changes in the expression of mitochondria-related functional genes in the aging brain.			
Aging neuron	SIRT1 ↓, CREB ↓	-	[51, 52]
Prefrontal cortex	EHMT1 ↑, H3K9me3 ↑	NF-κB ↑, BCL3 ↑	[47]
Changes in stress response and expression of immune-related functional genes in the aging brain.			
Aging neuron	CREB ↓	-	[53]
Brain	H3K27ac (gene body) ↓	NF-κB ↑, BCL3 ↑	[49]
Hippocampus	HDACs ↑	NF-κB ↑, JAK-STAT ↑, TLR/MyD88 ↑	[54]
Prefrontal cortex	H3K4me2 ↑, SETD7 ↑, DPY30 ↑	UBXN4 ↑, TUFT1 ↑, SLC24A4 ↑	[55]
Microglia	H3K27me3 ↑, Jmjd3 ↓	Arginase-1 ↑, CD206 ↑	[56]

↓, Decrease; ↑, Increase; H3K27ac, Histone H3 Lysine 27 Acetylation; H3K9ac, Histone H3 acetylated at Lysine 9; H4K12ac, Histone H4 Acetylated at Lysine 12; H3K14ac, Histone H3 Lysine 14 Acetylation; H4K8ac, Histone H4 lysine 8 acetylation; H3K9me3, Histone H3 lysine 9 trimethylation; SIRT1, Sirtuin 1; CREB, Cyclic AMP Response Element-Binding Protein; EHMT1, euchromatic histone lysine methyltransferase 1; HDACs, Histone Deacetylase; H3K4me2, Histone H3 lysine 4 dimethylation; SETD7, SET domain-containing 7; DPY30, Dpy-30 histone methyltransferase complex regulatory subunit; Jmjd3, Jumonji domain-containing protein D3; GATA3, GATA binding protein 3; BDNF, brain-derived neurotrophic factor; IEGs, Immediate Early Genes; Nr4a2, nuclear receptor subfamily 4 group A member 2; c-fos, cellular Finkel-biskis-Jaret osteosarcoma viral oncogene homolog; GluR1, glutamate receptor subunit 1; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; BCL3, B-cell lymphoma 3; JAK/STAT, Janus kinase-signal transducer and activator of transcription; TLR/MyD88, Toll-like receptor (TLR) and Myeloid differentiation primary response gene 88; UBXN4, UBX domain protein 4; TUFT1, Tuftelin 1; SLC24A4, Solute Carrier Family 24 Member 4; CD206, Mannose Receptor C-Type 1 (MRC1).

4.2. DNA methylation

Aging of the brain is related to genome-wide as well as locus-specific epigenetic shifts in brain tissue and blood, together with histone changes. Longitudinal analyses identify CpG sites and DMRs in blood that correlate with dementia and cognitive decline. These epigenetic marks are indicative of pathophysiology that occurs early in neurodegeneration and often occur in genes that regulate immune functions (e.g., the signaling of cytokines) and metabolism. Beyond specialized methylation clocks, global and site-specific DNA methylation changes in both brain and peripheral blood are increasingly recognized as biomarkers of cognitive decline. Recent large-scale longitudinal cohort studies, such as those from the Framingham Heart Study and Generation Scotland, have identified differentially methylated regions (DMRs) and CpG sites in blood that predict incident dementia and future cognitive impairment, even after adjusting for confounding factors like age, sex, and APOE genotype [57, 58]. These methylation alterations often implicate genes related to immune system function, lipid metabolism, and inflammation, reflecting early

molecular processes in neurodegeneration and dementia [59]. For example, ABCA7, ANK1, and BIN1 exhibit consistent methylation changes in both peripheral blood and postmortem brain tissues of Alzheimer's patients [60]. Moreover, co-methylation network analyses have shown that modules of correlated CpG sites are enriched in glutamatergic signaling, β-amyloid processing, and synaptic plasticity, highlighting their relevance to Alzheimer's pathology [61]. Because blood-derived methylation profiles are relatively stable, accessible, and amenable to high-throughput analysis, these epigenetic markers are emerging as minimally invasive tools for early detection, prognosis, and monitoring of cognitive aging and dementia progression [62, 63].

A reduction in DNA methylation, referred to as DNA hypomethylation, is being explored as a potential biomarker for cognitive decline. DNA methylation patterns differ between individuals with and without cognitive impairment, and thus, DNA methylation profiles could be utilized to identify individuals at risk of cognitive decline or for tracking disease progression [64, 65]. Quantification of genome-wide DNA methylation patterns in the Brains for Dementia Research (BDR) cohort identified neuropathology-associated variation at multiple novel genetic loci and showed that these AD-associated methylomic changes reflected differences in non-neuronal populations [66]. A more recent study examined the interplay between genetic (SNPs) and epigenetic (DNA methylation)-mediated mechanisms in modulating AD risk. This study identified 179 SNP–methylation combination pairs that showed statistically significant interactions associated with the expression of 63 genes enriched in functional pathways associated with immune and post-synaptic assembly pathways [67]. One of the studies that highlighted the use of DNAm profiling as a peripheral marker for cognitive decline and brain health is the Whitehall II imaging sub-study that had forty-eight selected participants, where 24 participants with mild cognitive impairment (MCI) were compared with 24 age and gender matched cognitively normal participants who were free from other comorbidities such as depression. Peripheral blood mononuclear cells [PBMCs] were drawn using the Vacutainer CPT tubes, and genome-wide DNAm profiling was performed using Illumina 450K arrays [68]. This study identified eight different methylated regions associated with cognitive impairment. This study provided support to the hypothesis that blood DNAm changes could be utilized as biomarkers for cognitive dysfunction and brain aging.

4.3. Epigenetic clocks

One of the most promising tools in this field is the DNA methylation clock, which estimates biological age by assessing methylation patterns at specific CpG sites. Advanced models such as DNAm PhenoAge have demonstrated superior predictive power over earlier epigenetic clocks, linking closely to age-related outcomes, including mortality risk and cancer incidence [69]. Even simplified methylation panels, targeting a few critical loci near genes like *ELOVL2*, *FHL2*, and *KLF14*, maintain accuracy across varied populations [43]. Circadian clock genes are emerging as potential genetic biomarkers for age-related cognitive decline. Disruptions in genes like CLOCK, BMAL1, PER1/2, CRY1/2, RORA rs13329238, NPAS2 rs17655330, CLOCK rs3749473, and RORB rs10781247 individually and interactively altered cognitive aging and have been linked to impaired sleep–wake regulation, reduced synaptic plasticity, and neuroinflammation—processes that worsen with aging [32]. Variants or altered expression of these genes may influence the timing and progression of cognitive deterioration, highlighting their role in brain aging and potential as early indicators of neurodegenerative risk.

DNA methylation is regulated in part by enzymes such as DNA methyltransferase 3A (*DNMT3A*), which is essential for de novo methylation. Mutations or polymorphisms in *DNMT3A* have been associated with accelerated cognitive decline [41].

These studies encompassed diverse ethnic backgrounds, incorporating participants from Taiwanese, German, Dutch, non-Hispanic white, and mixed international cohorts. Mean ages across these groups generally fell within the later stages of adulthood, reflecting an aging population. Specifically, Taiwanese participants averaged around 64 years of age, while German cohorts ranged from their mid-60s to early 70s. Non-Hispanic white groups tended to be in their mid-70s to mid-80s, and Dutch participants were also from an older demographic, though exact ages were not specified. The inclusion of these varied populations, all within the age range most susceptible to cognitive decline, provided a broad perspective on how genetic variations influence cognitive aging across different ethnic and cultural contexts.

5. Non-coding ribonucleic acid (RNA)-based biomarkers

The discovery of RNA biomarkers associated with aging-related cognitive decline has significantly increased due to the advances made in transcriptomic technologies. Though noncoding RNAs are classified as epigenetic regulators, we have summarized the role of noncoding RNAs within a separate section in this review. High-throughput RNA sequencing (RNA-seq) and single-cell transcriptomics have revealed age-associated changes in gene expression within specific brain regions and cell types, particularly those involved in synaptic function, neuroinflammation, and mitochondrial regulation. Circulating non-coding RNAs—such as microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs)—have emerged as promising minimally invasive biomarkers, detectable in blood and cerebrospinal fluid, and shown to correlate with cognitive performance and neuropathological burden (**Table 3**). Furthermore, advances in machine learning have enabled the integration of large transcriptomic datasets to identify RNA signatures predictive of early cognitive impairment.

Table 3 • Potential RNA-based biomarkers in age-related cognitive decline.

RNA	Tissue	Target/pathway/function	Effect	Reference
RN7SK LncRNA	Human Blood	Regulates RNA binding proteins, chromatin effectors, senescence, inflammation	Upregulated	[70]
miR-129-5p	Human Brain tissue	Regulates autophagy, neuroinflammation and neuronal cell death by targeting APP, HMGB1, YAP1	Reversely associated with AD	[71]
hsa-miR-92a-3p	Human Blood	-	Downregulated	[72]
hsa-miR-486-5p	Human Blood	-	Downregulated	[72]
hsa-miR-29a	Human Blood	-	Upregulated	[72]
hsa_circRNA_101275, hsa_circRNA_103730, and hsa_circRNA_038416	Human Blood	PI3K–Akt signaling and MAPK signaling pathways	Upregulated in PD patients	[73]
hsa_circRNA_102850	Human Blood	PI3K–Akt signaling and MAPK signaling pathways	Downregulated in PD patients	[73]
piR-hsa-327831, piR-hsa-758566, piR-hsa-1968818, and piR-hsa-3770447	Human Blood	Stability of neurons and synaptic transmission	Upregulated in PD patients	[74]
piR-hsa-1325354 and piR-hsa-2524778	Human Blood	Stability of neurons and synaptic transmission	Downregulated in PD patients	[74]
miR-181a-5p, miR-146a-5p, and miR-148a-3p	Human Blood	ncRNA processing and protein folding, stress, inflammation	Upregulation precedes cognitive impairment	[75]
MicroRNA-206	Human Blood	targets brain-derived neurotrophic factor (BDNF), Histone deacetylase 4 (HDAC4) and JunD	Increases with cognitive decline	[76]

Bioinformatic and expression analysis of the E-MTAB 6094 dataset obtained from PBMCs of 22 AD and 13 normal patients indicated that RN7SK LncRNA and TNF were substantially upregulated in AD samples with p values of 0.006 and 0.023, respectively, while TNFAIP3 expression was significantly decreased [70]. The RN7SK lncRNA regulates several RNA-binding proteins and chromatin modelers, and disruption of RN7SK signaling pathways leads to neurological dysfunction [77]. Analysis of RNA-seq data set from brain tissue of Religious Orders Study/Rush Memory and Aging Project participants (ROS/MAP, 702 individuals), including 102 NCI and 177 AD patients, revealed that miR-129-5p, miR-1260, miR-433, miR-221, and miR-200a were robustly correlated with the pathological features of AD, of which miR129-5p showed the strongest association for all phenotypes. A higher level of miR-129-5p was linked to a decreased risk of AD, better cognition, slower cognitive decline, and lower CERAD and Braak pathologic features of Alzheimer's disease [71]. miR-129-5p targets APP, HMGB1, and YAP1 proteins, thus regulating neuroinflammatory and autophagy pathways. Three microRNAs, hsa-miR-92a-3p, hsa-miR-486-5p, and hsa-miR-29a, have been found to be significantly associated with AD. AD conditions lead to downregulation of hsa-miR-92a-3p and hsa-miR-486-5p, while an increase in levels of hsa-miR-29a is associated with AD, as reported among 46 participants, comprising 8 with preclinical AD, 19 MCI patients, and 19 controls. Individually, either of these miRNAs do not show significant differences among patient groups, but significant potential associations are found by the authors when a multivariate model is used for analysis [72]. In a study conducted with blood samples of 610 aged Japanese patients, EEF2, a member of the GTP-binding translation elongation factor family, had been identified as one of the genes correlated with AD risk by Shigemizu and colleagues [78].

Similarly to AD, PD risk and progression have also been tracked using RNA biomarkers. RNA sequencing from 1570 individuals from the Parkinson's Progression Marker Initiative (PPMI) cohort revealed significant alterations in the expression of >2000 genes. PD patient samples were enriched in neutrophil specific genes, while lymphocyte associated genes were downregulated [79]. hsa_circRNA_101275, hsa_circRNA_103730, and hsa_circRNA_038416 are more highly expressed in patients with PD, with an AUC of 0.938. In contrast, the expression of hsa_circRNA_102850 is downregulated in patients with PD when compared with controls. A circRNA panel consisting of these four

differentially expressed circRNAs could be employed to diagnose and distinguish PD patients. Ten hub genes, *ESR1*, *PTEN*, *SHC1*, *IGF1R*, *SMAD2*, *KRAS*, *MDM2*, *HIF1A*, *BMP4*, and *ACVR2B*, were found to be significantly associated with PD, thus illustrating the regulatory role of a circRNA–miRNA–mRNA network [73]. In another recent study, six piRNAs were found to be significantly differentially expressed in patients with PD in comparison to controls. piR-hsa-327831, piR-hsa-758566, piR-hsa-1968818, and piR-hsa-3770447 were upregulated, while levels of piR-hsa-1325354 and piR-hsa-2524778 were decreased in PD [74].

RNA biomarkers associated with aging and cognitive decline often reflect changes in gene expression linked to synaptic function, mitochondrial activity, and neuroinflammation. These biomarkers can track normal aging processes in the brain as a prelude to neurodegenerative diseases. miR-181a-5p, miR-146a-5p, and miR-148a-3p were identified as forming a three-microRNA signature associated with aging through analysis of blood samples of 132 healthy young adults (aged 25 ± 5), older adults from the DELCODE cohort, and mouse models of cognitive decline. The target genes of these microRNAs are enriched in terms related to cognitive performance in humans. Elevated levels of these three microRNAs precede detectable memory deficits in mice and can potentially function as a biomarker for early detection of aging-associated cognitive decline. Increased miR-146a-5p leads to a decrease in expression of genes associated with ncRNA processing and protein folding. Cellular stress and inflammation pathways were upregulated in response to treatment with miR-148a-3p and especially miR-146a-5p mimics, indicating an increase in these three signature microRNAs lead to development of cognitive impairment as a result of low cognitive reserve [75]. MicroRNA-206 was found to be significantly associated with cognitive decline and memory deficits in two behavioral tests—Free and Cued Selective Reminding Test (FCSRT) and the Mini-Mental State Exam (MSME). Longitudinal follow-up studies of 18 individuals over five years found an increase in microRNA-206 precedes the onset of dementia [76].

Interpersonal variability is a significant determinant of RNA biomarker performance and generalizability. Chronological age and sex both exert pervasive effects on circulating and tissue ncRNA expression and should be adjusted for or explored in sex-stratified analyses. Lifestyle factors, comorbidities, and medication use (e.g., smoking, metabolic disease, anti-inflammatories) substantially alter circulating miRNA/circRNA profiles and are frequent confounders. Many large aging cohorts remain demographically homogeneous (e.g., over-representation of non-Hispanic White participants in the ROS/MAP dataset), limiting applicability across ancestries and regions; therefore, multi-cohort replication and deliberate recruitment of diverse populations are essential.

6. Proteomic and metabolomic biomarkers

Proteomic biomarkers have emerged as promising candidates for identifying pathological processes long before clinical symptoms manifest. Several age-associated diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), frontotemporal dementia (FTD), and Lewy body dementia (LBD) have distinct pathological mechanisms characterized by aberrant protein aggregation, neuroinflammation, and synaptic dysfunction. Protein biomarkers like amyloid-beta (Aβ), tau, alpha-synuclein, and neurofilament light chain (NfL) reflect not only the presence or progression of the disease but also offer insights into underlying cellular processes [80]. These protein biomarkers play a significant diagnostic and prognostic utility in peripheral fluids like cerebrospinal fluid (CSF) and blood, which enables less invasive approaches to early detection and monitoring. In this section, the recent findings related to blood, cerebrospinal fluid (CSF), urine, and exosome-derived proteins and peptides that reflect neurodegenerative progression, neuroinflammation, synaptic dysfunction, and metabolic alterations relevant to cognitive decline are discussed.

6.1. Amyloid-beta

Amyloid beta is a peptide and hallmark of AD and is a product of amyloid precursor protein (APP) metabolism. In recent years, it has emerged as a significant protein biomarker for age-associated cognitive disease, especially AD and mild cognitive impairment (MCI). Since Aβ levels in plasma can predict amyloid positivity and cognitive decline, they are considered a valuable tool for early diagnosis and monitoring disease progression. The deposition of Aβ peptides in the brain is a neuropathological change that can occur up to 30 years before the actual symptoms and diagnosis of AD [81]. The aggregation of Aβ disturbs synaptic function, induces oxidative stress, and is closely linked to cognitive deficits. Measurement of Aβ levels in cerebrospinal fluid (CSF) and blood serves as a diagnostic and prognostic biomarker for AD, with lower CSF Aβ42 indicating plaque deposition in the brain [82]. Because of their significant role in this disease, Aβ peptides, particularly Aβ42 are among the most extensively studied protein biomarkers in age-associated cognitive decline because of their central role in AD [83]. These peptides are generated by the sequential cleavage of the amyloid precursor protein (APP) by β- and γ-secretases and aggregates into oligomers, fibrils, and ultimately the extracellular plaques in the brain, which is the hallmark of AD [84]. Decreased levels of soluble Aβ42 in the cerebrospinal fluid (CSF) is an early and reliable marker of amyloid deposition in the brain and can be detected decades before clinical symptoms like delusion, disorientation, and difficulty thinking and understanding arise [85]. The Aβ42/Aβ40 ratio has been suggested to account for individual variability in Aβ production and improves diagnostic specificity [9]. Association studies between Aβ40-Aβ42 and cognitive performance in an aged population of individuals 100 years old and older has highlighted their potential role in age-associated cognitive decline [86]. Plasma sAPPβ levels are significantly decreased in AD compared to controls and non-amyloid dementias, supporting its potential as a minimally invasive blood-based biomarker for AD diagnosis [87]. Amyloid β protein accelerates neuronal senescence—marked by increased p16 expression—and exacerbates cognitive deficits in 5XFAD mice, linking Aβ-induced neuronal aging to impaired cognition in this Alzheimer's disease model. It accelerates brain cell aging and worsens memory problems in an Alzheimer's disease mouse model [88]. Lim et al. suggested that both continuous and categorical measures of a plasma amyloid-β composite biomarker are significantly associated with the decline in episodic memory and executive function in cognitively normal older adults, supporting its value for early detection of preclinical Alzheimer's disease [89]. Plasma glial fibrillary acidic protein (GFAP) levels rise early in autosomal dominant Alzheimer's disease and are strongly associated with brain β-amyloid pathology, neurodegeneration, and cognitive decline,

supporting GFAP as a sensitive blood biomarker for AD progression [90].

Advancements in ultrasensitive diagnostic techniques like immunoassays and mass spectrometry have enabled scientists and researchers to accurately quantify Aβ in plasma. This has opened the possibility of minimally invasive screening and longitudinal monitoring [91]. What needs to be kept in mind is that Aβ pathology is not exclusive to AD and can appear in cognitively normal elderly individuals when it is interpreted alongside other protein biomarkers like phosphorylated tau, which is discussed in the next section.

6.2. Tau protein

Tau protein is an important protein that plays a crucial role in maintaining the structure of neurons by stabilizing microtubules but when it comes to age-associated cognitive diseases like AD, it undergoes abnormal hyperphosphorylation. This leads to the formation of intracellular neurofibrillary tangles (NFTs), which disrupt neuronal function and correlate more closely with cognitive decline than amyloid-beta plaque burden.

Tau protein is an important biomarker for age-associated cognitive diseases like Alzheimer's disease where abnormal phosphorylation and aggregation of tau lead to neurofibrillary tangles which disrupt the normal functioning of neurons. Elevated levels of tau proteins, especially phosphorylated tau (p-tau), in blood or cerebrospinal fluid (CSF), can indicate neurodegeneration and predict cognitive decline. According to Nam et al., in a study conducted by NIH, serum Tau proteins can be used to monitor AD progression and differentiate between mild cognitive impairment and mild AD [92]. Tau can be a valuable tool for early diagnosis and monitoring such diseases as elevated levels of tau in cerebrospinal fluid and blood are strongly associated with neurodegeneration, disease progression, and cognitive decline [93]. Studies have suggested that tau pathology correlates with cognitive decline in individuals aged 60–80 but the association weakens in those above 80 due to competing pathologies and selective survival [94]. Elevated levels of total tau (t-tau) and phosphorylated tau (p-tau) in cerebrospinal fluid (CSF) and serum have been linked to cognitive impairment, proving their potential as biomarkers for AD progression [95]. In 2024, Ackley et al. suggested that Tau levels correlate with cognitive outcomes in individuals aged 60–80, with higher tau associated with worse cognitive performance. However, in individuals above 80 years of age, the correlation between tau and cognition diminishes due to increased comorbidities [94]. An elevation in the levels of t-tau and p-tau was observed in both serum and CSF in AD patients when compared to controls [95]. Although it does show promise, its diagnostic value is limited, and hence, further research in the field is essential for its improvement. Elevated levels of total tau (t-tau) and phosphorylated tau (p-tau)—particularly p-tau181, p-tau217, and p-tau231—in cerebrospinal fluid (CSF) are considered hallmark biomarkers of tau pathology and neuronal injury in Alzheimer's disease [96].

Development of ultrasensitive assays in recent years, like Simoa and mass spectrometry, has enabled the detection of p-tau species in the blood, which has enhanced non-invasive diagnostics [97]. It can also aid in differential diagnosis. Unlike in AD, tau pathology in other dementias, such as frontotemporal dementia (FTD), exhibits different isoform patterns and distributions, which can aid differential diagnosis. As a dynamic biomarker, tau not only reflects ongoing neurodegeneration but also serves as a promising target for therapeutic monitoring in clinical trials.

6.3. Alpha synuclein

Alpha synuclein (α-syn) is a small 140 amino-acid protein encoded by the SNCA gene and is found mainly in the brain, particularly in presynaptic terminals. It plays an important role in regulating synaptic vessel trafficking and neurotransmitter release. In 2015, Koehler et al. suggested that α-synuclein levels in plasma decline with healthy aging [98]. Although essential for normal brain function, misfolded α-synuclein is linked to neurodegenerative disorders like Parkinson's disease [99]. It serves as a relevant protein biomarker for age-associated cognitive diseases like AD because elevated levels of α-synuclein in the cerebrospinal fluid (CSF) have been observed in early AD and mild cognitive impairment. In neurodegenerative diseases like Dementia with Lewy bodies (DLB) and Multiple System Atrophy (MSA), alpha-synuclein undergoes pathological misfolding and aggregation, leading to the formation of intracellular inclusions known as Lewy bodies [100]. These are accompanied by progressive cognitive decline. Even though the levels of alpha-synuclein in cerebrospinal fluid (CSF) tend to fall in PD and DLB, because of sequestration into insoluble brain deposits, specific conformational and post-translationally modified forms like phosphorylated alpha-synuclein (pS129), have emerged as more disease-specific indicators [101].

The presence of even minute quantities of misfolded Alpha-synuclein in CSF and peripheral tissues can be detected with high sensitivity and specificity by seed amplification assays (SAAs), including real-time quaking-induced conversion (RT-QuIC) [102]. Seed amplification assays refer to a group of techniques that detect misfolded proteins and are used to diagnose synucleinopathies, such as the α-synuclein seed amplification assay (αSyn-SAA), which is used to detect α-synuclein [103].

6.4. Neurofilament light chain

Neurofilament light chain (NfL) is a protein found within neurons, mainly in the axons of myelinated neurons, and serves as an essential structural component. It provides axonal stability, and it is an important biomarker for the detection of neuronal damage in various neurological disorders [104, 105]. When some damage to neurons occurs and they undergo degeneration, NfL is released into the cerebrospinal fluid (CSF) and ultimately into the bloodstream, making it a sensitive biomarker of neuroaxonal injury. In contrast to disease-specific biomarkers like amyloid-beta or tau, NfL reflects the intensity of neuronal damage regardless of the underlying cause, and this makes it particularly useful for disease progression, prognosis, and treatment response.

Higher levels of NfL in blood plasma is directly associated with lower general cognitive ability (GCA) in adults approaching midlife with more pronounced effects in older individuals [105, 106]. Among older adults, serum NfL levels show a strong positive correlation with cognitive impairment mainly affecting attention and information processing abilities [107]. Gao et al. proved their potential as a screening tool for an early prediction of cognitive decline [108]. Meta-analysis indicates significantly higher levels of plasma NfL in AD and MCI patients when compared to healthy controls, with higher levels in AD than MCI [109]. Elevated NfL levels correlate with cognitive decline as measured by AD Assessment Scale cognitive subscale (ADAS-cog) [95]. In 2025, Meng

et al. stated that NfL's strong correlation with cognitive impairment makes it a promising biomarker [107]. However, its diagnostic value is yet to be fully established and exploited. Further research is needed to refine its application in clinical settings and explore its potential in conjunction with other biomarkers.

Advances in ultrasensitive platforms like single molecule array (Simoa) technology have enabled reliable quantification of NfL in both CSF and blood, facilitating longitudinal monitoring and early detection, even in preclinical stages [110]. While its lack of specificity limits its diagnostic power in isolation, when combined with disease-specific markers, NfL offers valuable insight into the neurodegenerative process and cognitive decline associated with aging.

6.5. Pro-inflammatory cytokines

There is increasing evidence to suggest the involvement of pro-inflammatory cytokines in age-related cognitive decline and conditions like AD and Vascular dementia (VaD). Interleukin 17D (IL17D) is notable for its role in enhancing the expression of other pro-inflammatory mediators, and its plasma elevation is negatively correlated with cognitive function [18]. In addition, elevated levels of TNF-α and IL-1β in the brain and periphery have been associated with cognitive impairment and progression of MCI to dementia. These inflammatory cytokines impair synaptic plasticity and memory [111]. Higher systemic levels of IL-6 and C-reactive protein (CRP) have been found to be associated with poorer cognitive performance and increased risk of dementia [112]. In the Northern Manhattan Study (NOMAS), a large community-based cohort of 1224 stroke-free older adults, participants with plasma IL-6 levels above the median demonstrated a significantly faster decline in cognitive performance, measured by the TICS-m test, compared with those with lower levels ($\beta \approx -0.17$ points per year; $p = 0.015$) [113]. Other cytokines and chemokines—including interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), interleukin-17A (IL-17A), and chemokines such as CCL2 (MCP-1) and CXCL10—have been repeatedly implicated in both human and experimental studies as drivers of neuroimmune activity linking peripheral health to brain aging (**Table 4**). IL-1β, a potent microglial activator induced by amyloid-β and other danger signals, has been found at elevated levels in both the brains and cerebrospinal fluid (CSF) of AD patients. Mechanistic studies suggest that IL-1β contributes to tau hyperphosphorylation, synaptic impairment, and neuronal loss, and blocking IL-1 signaling in animal models can rescue synaptic function [114].

Table 4 • Cytokines implicated in cognitive decline with age.

Analyte	Cohort/study	Sample size	Key finding	Reference
IL-6	Northern Manhattan Study (NOMAS)	1224 participants	Higher IL-6 linked to faster cognitive decline (TICS-m).	[113]
CCL2 (MCP-1)	Westin et al., longitudinal AD cohort	56 AD patients vs. 40 controls	Higher CSF CCL2 associated with faster cognitive decline.	[115]
TNF-α	MCI conversion study (CSF tertiles)	129 MCI participants	Intermediate CSF TNF-α tertile associated with higher conversion risk.	[116]
IL-1β	Multiple clinical and post-mortem studies	Varied	Elevated in AD brain and CSF; implicated in tau phosphorylation.	[114]
IL-17A	Animal models and emerging human studies	Varied	IL-17A promotes neuroinflammation and cognitive deficits.	[117]

TNF-α is frequently modestly elevated in both serum and CSF of individuals with mild cognitive impairment (MCI) and AD. In a prospective study of 129 MCI patients, those in the intermediate tertile of CSF TNF-α had a more than two-fold higher risk of progressing to dementia compared with those in the lowest tertile (HR = 2.2; 95% CI 1.15–4.1; $p = 0.016$) [116]. These data indicate that TNF-α can modulate synaptic plasticity, enhance amyloid production, and promote tau pathology. Preclinical studies demonstrate that IL-17A exacerbates microglial activation, increases blood–brain barrier permeability, and reduces amyloid clearance, thereby accelerating cognitive decline. Inhibiting IL-17A in animal models attenuates neuroinflammation and preserves cognitive function, and emerging human studies have reported elevated IL-17 pathway activity in subsets of patients with progressive AD [117]. Chemokines, particularly CCL2 (MCP-1) and CXCL10, also play important roles by facilitating the recruitment of immune cells into the CNS. In a longitudinal study of early AD, higher CSF CCL2 concentrations predicted more rapid cognitive decline, with one example cohort (56 AD patients and 40 controls) showing significantly elevated levels in the patient group ($p \approx 0.02$) [115]. Meta-analyses of CSF chemokines similarly report a 15–20% increase in CCL2 in AD compared with controls. Likewise, elements of the Wnt signaling pathway, such as WNT9A and RSPO1, have shown increased levels in patients with dementia, both correlating inversely with cognitive performance [118]. This underscores the role of aberrant Wnt/β-catenin signaling in synaptic loss and neurodegeneration [119].

Two methodological challenges emerge from the studies discussed in this section. First, heterogeneity in assay platforms, sample handling, and statistical adjustments can contribute to inconsistent findings across studies, with larger and better-controlled longitudinal designs tending to show more robust associations. Second, peripheral and central inflammatory markers often complement each other: CSF cytokines and chemokines more directly capture active neuroinflammatory processes within the CNS, whereas plasma cytokines may reflect

systemic inflammation and risk prediction. Thus, measuring cytokines and chemokines across biofluids offers multiple advantages. These markers can help identify individuals at risk before the onset of overt dementia, serve as pharmacodynamic endpoints in clinical trials of immune-modulating drugs, and point to specific pathways—such as IL-6, IL-1β, TNF-α, and IL-17—that may be amenable to targeted intervention.

6.6. Proteins involved in growth factor signaling

Proteins involved in growth factor signaling and inflammation also present as key biomarkers. IGFBP2, which modulates insulin-like growth factor signaling, increases in AD and is implicated in impaired neurotrophic signaling [118]. OMR1/OMR2, acute-phase proteins found in urine, have been associated with neuroinflammation and cognitive decline [120]. SERPINA3, another urinary biomarker, is elevated in AD and has been linked to tau hyperphosphorylation and plaque deposition, further emphasizing urine's utility as a non-invasive biofluid for early diagnostics [120].

Together, these findings represent a significant shift toward accessible, sensitive, and disease-specific biomarkers for Alzheimer's disease and cognitive decline. The multimodal and multifluid approach—spanning plasma, urine, CSF, and exosomes—provides a comprehensive view of the molecular derangements that underpin neurodegeneration. Importantly, many of these markers are already detectable in cognitively healthy individuals with high dementia risk, emphasizing their potential for early intervention strategies.

6.7. Metabolites as biomarkers for age-related cognitive decline

Metabolomics refers to the comprehensive analysis of small molecules in biological samples. In recent years, it has become a powerful tool in understanding the biochemical alterations underlying age-related cognitive decline (**Figure 1**). There are specific metabolic signatures associated with neurodegeneration and cognitive impairment, offering the potential for early detection and intervention. Whiley et al. published their work correlating altered phosphatidylcholine metabolism in Alzheimer's disease. A significant reduction in phosphatidylcholine (PC) species was observed in patients with AD when compared to controls and this proved that a decline in PCs is linked to cognitive impairment and can serve as predictive biomarker for AD [121]. Alterations in lipid metabolism, such as decreased levels of phosphatidylcholines and sphingomyelins, have been consistently linked to AD and MCI, suggesting a role in disrupted membrane integrity and signaling.

The metabolic profiling of aging is quite complex. In 2024, Zhang et al. conducted a study in which they analyzed 325 nuclear magnetic resonance (NMR) metabolomic biomarkers in 250,341 UK participants in order to characterize the metabolomic profile of biological aging [122]. It was found that there were 54 representative aging-related biomarkers that were associated with all-cause mortality. Using these biomarkers, the team developed a novel "metabolomic aging score" that outperformed other biological aging metrics, including chronological age, in predicting short-term mortality risk and identifying individuals with accelerated biological aging. GWAS on 95,372 individuals revealed genetic determinants for these biomarkers.

7. Senescence-associated biomarkers

Emerging literature has uncovered the role of cellular senescence, which is defined as a state of irreversible cell cycle arrest of senescent cells either in the G1 or G2 phase of the cell cycle [123]. Cellular senescence is accompanied by a pro-inflammatory secretome (SASP) in driving age-related cognitive deterioration. Recent studies have highlighted senescence as both a cause and a potential therapeutic target in brain aging and Alzheimer's disease (AD). Baier et al. demonstrated that senescence contributes to cognitive imbalances among aged male mice. In the study, impaired mice showed increased senescence in the hippocampus, and treatment with senolytics reduced these markers while balancing cognitive performance by driving neuroinflammatory responses [124]. Similarly, Budamagunta et al. highlighted the impact of peripheral senescence. They used two senolytic drugs, ABT-263 and dasatinib + quercetin (D + Q), and showed that clearing senescent cells improved cognition, preserved blood–brain barrier (BBB) integrity, and attenuated neuroinflammation in aged rats [125]. The pathophysiology of senescence involves multiple factors such as DNA damage and mitochondrial dysfunction in both neural and immune cells [126]. Tau oligomers (TauO), implicated in AD, were shown to directly induce senescence and SASP, further worsening neuroinflammation and neuronal dysfunction [127]. Chronic unpredictable stress (CUMS) was found to accelerate hippocampal senescence and cognitive deficits in mice, which could be reversed by the use of senolytics [128]. These studies are consistent with the view that aging and pathological tau mutually promote a senescent microenvironment in the brain, characterized by SASP-mediated synaptic loss. Saunders et al. added another dimension by linking plasma biomarkers, such as phosphorylated tau (p-tau181), neurofilament light (NfL), and GFAP, to age-related cognitive decline in a longitudinal human cohort [129]. Highlighting the therapeutic potential of senotherapeutics (dasatinib, quercetin, navitoclax), show promise in improving senescence-driven neurodegeneration. Studies reviewed demonstrated that restoration of synaptic gene expression, reduction in neuroinflammation and oxidative stress, improved cognitive performance following senescent cell clearance by senolytics [124, 125, 128]. However, challenges remain there as senescence markers lack specificity, and clearance of senescent cells may disrupt essential roles (e.g., in tissue repair).

Research into biomarkers associated with age-related cognitive decline reveals significant distinctions among various demographic groups, including race and sex. For instance, research indicates that Black Americans experience a greater prevalence of dementia compared to non-Hispanic Whites, while exhibiting unique biomarker profiles for Alzheimer's disease (AD). The existing AT (N) cut-off points for amyloid, tau, and neurodegeneration—primarily established from studies involving White cohorts—may not effectively categorize pathology within Black populations, highlighting the necessity for contextually relevant thresholds [130, 131]. Furthermore, longitudinal aging studies indicate that variations in phosphorylated tau-181 (p-tau181) over time are predictive of cognitive decline in females, whereas this is not the case for males [129]. Regarding the therapeutic potential, senotherapeutics, particularly senolytics (dasatinib, quercetin, navitoclax) and senomorphics, show promise in improving senescence-driven neurodegeneration.

Studies reviewed demonstrated that restoration of synaptic gene expression, reduction in neuroinflammation and oxidative stress, and improved cognitive performance followed senescent cell clearance [124, 125, 128]. Thus, consideration of the above-mentioned factors can enhance diagnostic precision, accurate assessment of biomarker information, and aid in the design of fair interventions for addressing age-related cognitive decline.

8. Gut microbiome-based biomarkers in age-related cognitive decline

While we have discussed significant biomarkers associated with cells in our body, a symbiotic "microecology" of the gut microbiota has gained significant attention in recent years and is now recognized as a major hallmark of aging [132]. Advances in detection, quantification, and sequencing technologies (e.g., metagenomic shotgun sequencing, single-cell RNA-seq, and AI-driven bioinformatics pipelines) have provided new mechanistic insights into this complex microbial ecosystem [18]. The gut microbiota's role in pathophysiology is not new. For decades, specific microbes have been identified as biomarkers for diseases like gastric lymphoma (*Helicobacter pylori*), colorectal cancer (*Fusobacterium nucleatum*), and breast cancer (*Firmicutes* and *Bacteroides*) [133–135]. Large-scale studies analyzing microbial signatures in centenarians have identified microbiome patterns linked to healthy aging. For example, centenarian populations show enrichment of *Desulfovibrio piger* and *Gordonibacter pamelaeae* compared to younger populations [136]. Hence, the identification of gut–brain axis (GBA) biomarkers that are specifically associated with age-related cognitive decline, it is very important to first decouple and understand the biomarkers associated with aging, cognitive decline, and near degeneration individually, as a great amount of evidence shows the presence of mild cognitive impairment well before the biomarkers such as amyloid-beta (Aβ) and Tau appear.

The use of gut microbial signatures as biomarkers for cognitive decline primarily derives from high-resolution RNA sequencing-based profiling of clinical stool samples. In one study analyzing RNA-seq data from stool samples of 268 individuals with varying degrees of cognitive impairment, reduced cognitive function was associated with a lower abundance of *Bifidobacteria*, as well as decreased levels of γ-aminobutyric acid (GABA), a metabolite linked to depression-like symptoms [137]. Complementing these findings, data from the Coronary Artery Risk Development in Young Adults (CARDIA) study comprising 3358 participants aged 48 to 60 years revealed that beta diversity (inter-individual variation in microbiome composition) was significantly associated with cognitive performance, whereas alpha diversity (intra-individual microbial richness and evenness) showed no such relationship [138]. Additionally, a cross-sectional analysis reported that patients with mild cognitive impairment (MCI) exhibited a significantly higher relative abundance of Bacteroides. This microbial shift correlated with neuroimaging markers of cerebral atrophy, including white matter hyperintensities and elevated voxel-based specific regional analysis system for Alzheimer's disease (VSRAD) scores. Multivariable logistic regression confirmed that increased Bacteroides abundance was independently associated with MCI in individuals without a diagnosis of dementia [139].

The gut microbiota also contributes to plasma and blood metabolomic-based biomarkers. Direct evidence linking gut microbiota to age-related cognitive decline (e.g., Alzheimer's and Parkinson's) comes from observed differences in metabolically critical bacteria like *Firmicutes* in individuals with these conditions [140]. Mounting evidence highlights gut bacterial genera that produce metabolites such as short-chain fatty acids (SCFAs), anti-inflammatory molecules, and neurotrophic factor precursors. Butyrate, for instance, serves as both a biomarker and a proxy for gut–brain axis health. Reduced fecal butyrate levels correlate with frailty, sarcopenia, cognitive decline, and diminished SCFA-producing bacteria like *Faecalibacterium prausnitzii* [141].

Another approach uses microbial diversity as a gut health biomarker. Studies consistently report increased *Akkermansia* abundance with aging, alongside declines in *Faecalibacterium*, *Bacteroidaceae*, and *Lachnospiraceae* (linked to nutrient processing and microbiome aging) [142]. Translational aging interventions like dietary restriction (caloric restriction, intermittent fasting) could leverage alpha/beta diversity metrics to qualitatively assess efficacy. Key metabolic markers of the gut–brain axis include neurotransmitters and neuromodulators like SCFAs, butyrate, GABA, acetylcholine, dopamine, glutamine, and serotonin [143].

Alzheimer's disease is characterized by pro-inflammatory signals regulated by microbial dysbiosis. Shifts in pro- vs. anti-inflammatory microbe ratios drive systemic inflammation (e.g., elevated NLRP3, CXCL2, IL-6, IL-1β), a hallmark of aging and cognitive decline [144]. Neurotoxins like β-N-methylamino-L-alanine (BMAA), produced by cyanobacteria, further exacerbate Alzheimer's progression [145]. A similar pattern is observed in PD, with enrichment of *Lactobacillus*, *Akkermansia*, and *Bifidobacterium* genera and depletion of SCFA-producing *Lachnospiraceae* and *Faecalibacterium* [146]. *E. coli*-mediated respiratory byproducts create oxidative conditions that catalyze dopamine-derived quinones and α-synuclein aggregation [147].

Invertebrate neurodegenerative models like *C. elegans* have yielded important information regarding gut–brain axis mechanisms. Gnotobiotic *C. elegans* models, for instance, reveal microbes essential for neurodevelopment and therapeutic potential [148]. *Drosophila* models (e.g., elav-Gal4; UAS-BACE/UAS-APP for Alzheimer's, PINK1 mutants for Parkinson's) offer genetic tractability and simpler gut microbiomes to probe gut–brain interactions. Probiotic strains in flies have alleviated Alzheimer's symptoms, highlighting translational potential [149].

Mouse models demonstrate that microbiota depletion increases amyloid-β pathology in Alzheimer's models while impairing memory [150]. Fecal transplants from young donors reduce neuroinflammation in older recipients and the synaptic plasticity modulators such as PSD-95 and FNDC5/Irisin were upregulated, and *E. coli*-derived Curli proteins were shown to cross-seed cerebral amyloid aggregation [151, 152]. Probiotics like Lactobacillus murinus rescue microglial dysfunction [153].

Biomarker discovery for age-related cognitive decline increasingly incorporates gut ecosystem dynamics, where dysbiosis patterns (*Akkermansia* enrichment and *Faecalibacterium* depletion) and metabolite shifts (reduced butyrate, neurotoxic β-Methylamino-L-alanine {BMAA}) correlate with neuroinflammation and amyloid pathology. Microbial diversity indices and fecal butyrate serve as non-invasive biomarkers, while pathogens (*Fusobacterium*, and *E. coli)* exacerbate neurodegeneration through innate

immune pathway activation and protein cross-seeding. Cross-species validation from *C. elegans* neurodevelopment to murine probiotic interventions further confirms the therapeutic potential for microbiome-targeted approaches.

9. Neuroimaging-based biomarkers

Neuroimaging has revolutionized the identification and observation of cognitive deterioration, especially in neurodegenerative disorders such as Alzheimer's disease (AD). Improvements in structural, molecular, and functional imaging now facilitate accurate monitoring of pathological alterations, providing essential understanding of disease development and treatment targets (**Figure 1**).

9.1. Structural biomarkers (MRI, CT-scan)

Structural Magnetic Resonance Imaging (MRI) is a technique utilized for identifying early and ongoing alterations in brain structure that are linked to cognitive deterioration. Reduced thickness and volume in the hippocampus, entorhinal cortex, and amygdala are closely linked to poorer cognitive performance and a more rapid decline in individuals with mild cognitive impairment (MCI) and Alzheimer's disease (AD) [154–156]. The thickness of the left entorhinal and temporal regions, along with the right isthmus cingulate, was especially indicative of overall cognitive and memory deterioration [156]. T1-weighted imaging is essential for clinical assessment and computational analysis in diagnosing dementia. A three-dimensional T1-weighted scan, like Magnetization-Prepared Rapid Gradient Echo (MPRAGE) or Spoiled Gradient Recalled Acquisition (SPGR), is frequently employed for volumetric assessments, allowing accurate evaluations of regional brain volumes and minor structural alterations that suggest cognitive decline [157]. Voxel-based morphometry and advanced volumetric assessments further validate that different brain regional alterations are strong indicators of disease advancement [158]. Computed tomography (CT) scans are not as sensitive as MRI for identifying early neurodegenerative alterations linked to cognitive decline; however, they are still helpful in clinical settings for ruling out other causes of cognitive symptoms [157]. CT offers quantitative data pertinent to brain atrophy, but its effectiveness in diagnosing early Alzheimer's disease and mild cognitive impairment is lower than that of MRI. Nevertheless, CT-derived volumetric measurements are a valuable initial assessment tool for diagnosing neurodegenerative diseases upon additional validation. CT-based volumetric assessments can differentiate between individuals with neurodegenerative diseases and healthy subjects, as well as between those with prodromal dementia and controls [159].

9.2. Functional biomarkers (fMRI, EEG)

A functional biomarker in cognitive decline signifies a quantifiable measure of brain activity or neural network performance, typically evaluated using methods like functional MRI (fMRI) or EEG (Electroencephalogram). These biomarkers reveal variations in the communication and responses of various brain areas during rest or cognitive activities, indicating underlying changes in neural circuits linked to conditions such as Alzheimer's and mild cognitive impairment. Functional biomarkers can indicate disturbances in brain networks, like the default mode network, prior to the onset of clinical symptoms, and are useful for forecasting the advancement and intensity of cognitive decline. Functional MRI (fMRI) studies show that cognitive decline is associated with disruptions in the default mode network (DMN), executive control, and sensorimotor networks [160]. Reduced functional connectivity and dynamic efficiency, as measured by resting-state fMRI, are observed in individuals with subjective cognitive decline (SCD) and MCI, indicating early network dysfunction before overt symptoms [160]. While the search results focus more on MRI and PET, recent original research also supports the use of EEG for detecting early changes in neural oscillatory patterns, especially when combined with fMRI for network-level analysis [161].

9.3. Metabolomic biomarkers (PET scan)

PET (Positron Emission Tomography) imaging offers molecular indicators for cognitive deterioration, especially via amyloid beta (Aβ) PET, tau PET, and FDG-PET. Recent extensive studies indicate that Aβ PET is a strong predictor of cognitive performance in advanced AD. At the same time, tau PET and FDG-PET (which assesses glucose hypometabolism) are more closely linked to cognitive deterioration and brain shrinkage in early and late phases. These biomarkers based on PET, particularly when used alongside MRI, enhance the prediction and tracking of disease advancement. Recent integrative and multimodal research underscores that the combination of PET-based biomarkers (tau, amyloid, FDG) with MRI or metabolomic panels improves early prediction and tracking of disease progression [162, 163].

9.4. Connectomics

Connectomics involves the detailed mapping and examination of both structural and functional brain networks, frequently employing sophisticated neuroimaging methods such as MRI and fMRI, to describe the interconnections among various brain regions. It serves as a biomarker for cognitive decline by pinpointing disruptions in brain networks, including diminished network integration, unusual connectivity patterns, or changes in network topology linked to neurodegenerative conditions such as Alzheimer's disease and mild cognitive impairment. Recent studies utilizing graph theory and sophisticated connectivity analyses reveal that cognitive decline is characterized by diminished network integration and impaired connectivity, especially in the Default Mode Network (DMN) and among temporal and frontal areas [8, 164]. Diffusion tensor imaging (DTI) and tractography have revealed that the left uncinate fasciculus and various white matter tracts are significantly associated with cognitive function and deterioration [164]. For instance, changes in the uncinate fasciculus and diminished integrity in the fronto-temporal and parietal connections are strongly associated with cognitive function and the advancement from MCI to AD [164]. Connectomics studies indicate that alterations at the network level occur prior to clinical symptoms and are strong indicators of future deterioration.

10. Artificial intelligence (AI)- and machine learning (ML)-based biomarkers

Recent developments in AI/ML within biological science have significantly advanced our ability to uncover inherent biological

complexity. These algorithms aid in lead discovery, novel biomarker identification, and geroprotector development, offering plausible solutions to address aging [165, 166]. Integrating biomarkers across hierarchical levels could yield universal biomarkers capable of quantifying organ-specific aging rates, such as brain aging in cognitive decline. In this section, we have discussed the role of AI/ML primarily based on its increased aid in digital-based biomarkers, neuroimaging-based biomarkers, and fluid-based markers (which are primarily based on blood cell ratios and methylation patterns).

10.1. AI/ML in digital biomarkers

Photographic biomarkers (e.g., eye corner imaging) and wearable devices capturing health data enable accessible age prediction via neural networks [167]. Amini et al. applied Natural Language Processing techniques along with ML to develop a novel method for predicting AD progression within 6 years using the speech of people with MCI. The random forest method was utilized to distinguish the cognitive states of the individual solely based on the speech of old-age individuals. It was able to predict the cognitive impairment severity [168]. Deep phenotyping (cognition, PET/CSF pathology markers, structural MRI neurodegeneration) and experimental modalities (fMRI, MEG/EEG, gait metrics, ophthalmological/smartphone-based assessments, and fluid biomarkers) are being integrated through initiatives like Dementias Platform UK, generating rich datasets for AD research [169]. It is also reported that the Computerized Cognitive test proved to be a better performing and more reliable assessment tool than the traditional methods for predicting cognitive decline in cases of MCI [170].

10.2. AI/ML in neuroimaging

Regression-based ML processing of imaging data underpins "brain age gap estimation" (estimated brain age minus chronological age). Yin et al. designed a 3D CNN from MRI data yielding reliable biomarkers that quantify brain aging pace for cognitive decline risk assessment. EEG-based biomarkers also contribute to brain age estimation and the linked cognitive decline [171]. Structural covariance networks (SCNs) combined with ML predict brain age from network perspectives, with key SCNs involving the caudate nucleus, hippocampus, putamen, amygdala, and cerebellar regions [172]. Recent fMRI analyses use CNNs on T1-weighted MRI data to decipher age-related brain network changes which can be correlated with the cognitive status of the individual [173].

10.3. AI/ML in fluid-based biomarker development

First-generation (Horvath's Clock, Hannum's Clock) [43, 44] and second-generation (PhenoAge and GrimAge) [69, 174] generation methylation clocks successfully distinguish biological from chronological age. However, DNA methylation-based epigenetic clocks often fail to establish causal relationships between methylation patterns and aging, though exceptions like AdaptAge incorporate causality [175]. Advances in single-cell sequencing and spatial transcriptomics now accelerate the development of causal, age-responsive biomarkers. AI/ML not only identifies such biomarkers but also demonstrates clinical relevance in disease diagnosis, prognosis, and outcome prediction [176]. These methylation clock-based biomarkers can also be used to quantify the brain age. A key limitation remains the variability and stochasticity of the aging brain, where organs and different regions age at distinct rates governed by the genotype and phenotype of the individuals.

To address cognitive decline, we must decouple brain aging and cognitive decline from normal aging phenotype and precisely quantify its rate. Large-scale studies with a follow-up cognitive assessment in addition to the blood and imaging test can singlehandedly boost the development of AI/ML algorithms that predict biomarkers for age-related cognitive decline. Current plasma proteomic and whole-blood-based clocks face limitations in predicting brain age-related cognitive decline due to the blood–brain barrier. Despite this, they remain cost-effective and accessible. Non-invasive methods like sMRI and fMRI reliably predict age and associated cognitive decline. As algorithms evolve, we must prioritize integrated aging clocks and biomarkers unified by a common framework for cognitive decline or develop multimodal biomarkers that synthesize data across biological scales (**Table 5**). Equally critical is curating robust datasets for AI/ML training. Major repositories include the following:

- Genomic: Alzheimer's Disease Sequencing Project (ADSP), UK Biobank (polygenic risk scores).
- Proteomic: AMP-AD Knowledge Portal (CSF/blood biomarkers like GFAP, NfL).
- Neuroimaging: ADNi (Alzheimer's disease Neuroimaging Initiative), OASIS, HCP-Aging (longitudinal MRI/PET).
- Fluid biomarkers: EMIF-AD (tau/Aβ kinetics).
- Digital biomarkers: DigiCog.

Table 5 • Tools that can be used to assess cognitive decline.

Tool	Type	Modality	Application	Reference
BrainAge	Neuroimaging-based Age Prediction	MRI	Estimates brain-predicted age to detect accelerated aging	[177]
DeepSurv	Deep Learning Survival Model	Clinical and Genomic Data	Predicts survival and aging-related risk factors	[178]
DNAmAge/Horvath's Clock	Epigenetic Clock	DNA Methylation	Biological age prediction from blood or tissue	[44]
PhenoAge	Epigenetic Clock	DNA Methylation	Biological aging prediction linked to disease phenotypes	[69]
GrimAge	Epigenetic Clock	DNA Methylation + Protein Markers	Mortality prediction, cognitive decline association	[174]
XGBoost-based Classifiers	Machine Learning Classifier	Multi-omics (transcriptomic, proteomic)	Feature selection and prediction of Alzheimer's risk	[179]
DeepGeni	Deep Learning Model	Gut Microbiome Data	Predicts mental health or cognitive status using microbiota	[180]
iMethyl	Machine Learning Framework	DNA Methylation	Age- and disease-associated methylation site prediction	[181]
BrainSpan	Spatiotemporal Gene Expression Atlas	Transcriptomic (Human Brain)	Analyzing brain development and age-related decline	[182]
MethylNet	Deep Learning for Methylation	DNA Methylation	Predicts age and disease from epigenetic features	[183]

11. Association of cognitive decline with comorbidities

Early cognitive decline often overlaps with several comorbidities in older adults, which levy considerable financial burden and exacerbate one another over time, and can accelerate the development and progression of cognitive failure. Type 2 diabetes (T2DM) and hypertension are two prevalent diseases among the older population; however, little is known about their additive effect on cognitive function. Hassing and colleagues found that in participants drawn from the "Origins of variance in the Old-Old" longitudinal study, an exaggerated cognitive decline was observed in patients with comorbid diabetes. Still, a similar trend was not found in correlation to patients with hypertension. The most significant cognitive decline was observed in patients having comorbid diabetes and hypertension [184]. Another study from 2021 reported that the highest contributors to comorbidity burden in older adults were osteoarthritis (67.4%), hypertension (65.7%), and hyperlipidemia (36.6%) [185]. A study of the Chinese population indicated depressive symptoms are an independent risk factor associated with a decrease in cognitive function, with the strongest association observed in the rapid cognitive decline group [186]. Anxiety symptoms are reported to be associated with decline in verbal memory in adults aged 65 or older with heterogeneity observed across sexes, and results in poorer cognitive performance in women [187]. Depression leads to greater decline in episodic memory and executive function, while the presence of both anxiety and depression symptoms led to a decline in attention in subjective cognitive decline patients [188]. Furthermore, the prevalence rates of anxiety and depression increase with a decline in cognitive performance, but decline in the later stages of cognitive impairment, possibly due to the lack of insight caused by AD [189]. Older people are often afflicted by chronic pain, which is significantly associated with higher cognitive decline, particularly in processing speed [190, 191].

Recent work indicates that alterations in the circadian rhythm and sleep may be a contributing factor towards progression of cognitive decline associated with aging [192]. Pineal melatonin in the first half of sleep is synchronized with a rise in cortisol in the second half of sleep that peaks in the cortisol awakening response [193]. The loss of pineal melatonin will alter the consequences of cortisol actions via GR-α activation in the second half of sleep. Pineal melatonin also decreases gut permeability and gut dysbiosis [194], indicating that the loss of pineal melatonin over the course of aging will be intimately linked to the alterations in the gut, including levels of butyrate production. Butyrate also suppresses the GR-α nuclear translocation, indicating its relevance to stress as well as circadian cortisol activation of the GR-α [195]. Butyrate may also upregulate the local melatonergic pathway, as shown in intestinal epithelial cells [196], which leads to relief from oxidative and inflammatory stress. Butyrate's capacity to optimize mitochondrial function [197], which may be attenuated over the course of aging, may also contribute to cognitive decline. As butyrate is a histone deacetylase inhibitor, many of its effects on aging and dementia are mediated by epigenetic regulation. The suppression of pineal melatonin and alterations in the regulation of local melatonergic pathway induction across systemic cells may therefore be an important regulator of many of the alterations in physiological processes associated with cognitive decline with aging.

T2DM is associated with increased circulating lipopolysaccharide (LPS) derived from a leaky gut, which activates toll-like receptor (TLR)4 on pineal microglia to increase tumor necrosis factor (TNF)α to suppress pineal melatonin [198]. T2DM may therefore contribute to a coordinated decrease in pineal melatonin and gut butyrate coupled to an increased circulating LPS. Many of the detrimental effects of T2DM are mediated by hyperglycemia induced methylglyoxal, which binds tryptophan via protein–protein interactions to inhibit the initiation of the tryptophan/serotonin/N-acetylserotonin/melatonin pathway, to suppress systemic melatonergic pathway activation [199]. This is proposed to be of particular relevance in astrocytes, which regulate neuronal function and survival across diverse neuropsychiatric and neurodegenerative conditions [200].

12. Variation in cell types in the brain and blood as biomarkers in AD biology

Alzheimer's disease (AD) is not exclusively a neuron-centric condition. It involves myriad complex interactions between different brain cell types, ranging from neurons, microglia, oligodendrocytes, astrocytes, and endothelial cells among others. By studying their contribution, researchers are better able to advance their understanding of the disease and hence open up new avenues for treatment. An ideal AD biomarker should have the ability to diagnose AD with high specificity and sensitivity, should be able to recognize the initial stage of the disease and monitor the progress, and should be able to monitor the therapeutic effectiveness of administered drugs [201].

The primary cells affected are the neurons or nerve cells, the fundamental unit of the nervous system. In AD the neurons get injured and stop working correctly, their connections break down, and brain regions begin to shrink—a condition known as brain atrophy. This loss of synaptic connections and neuronal death is central to cognitive decline in AD [202, 203]. When observed through the microscope, amyloid plaques and neurofibrillary tangles are not the only hallmarks of AD, but also the glial cells clustered around the plaques. These cells, particularly microglia and astrocytes mediate neuroinflammation in AD and play an important role in disease pathogenesis by serving as novel therapeutic targets. Microglia, the brain's immune cells, are initially responsible for clearing away the amyloid-beta plaques in early stages. However, with time, as the disease progresses, microglia become overactive and contribute to chronic neuroinflammation. In 2013, a landmark study by Guerreiro et al. linked TREM2 variants like R47H to increased risk of AD by impairing microglial clearance of plaques and promoting neuroinflammation [204]. Astrocytes are another type of glial cells which are responsible for maintaining metabolic balance in the brain and supporting neuronal function. They are signaled to help clear the buildup of plaques and other cellular debris. In 2017, Liddelow et al. discovered that reactive A1 astrocytes induced by microglial cytokines become neurotoxic and directly contribute to neuronal death in neurodegenerative diseases, thus highlighting astrocyte regulation as a therapeutic target in Alzheimer's disease [205]. Oligodendrocytes form a myelin sheath around the axons enabling efficient neuronal signaling. Their dysfunction and the loss of myelin which lead to cognitive decline are early features in Alzheimer's. According to Habes et al. (2016), white matter hyperintensities, which are indicative of oligodendrocyte dysfunction, are early markers of AD [206]. Protecting them preserves brain function and slows down disease progression. Oligodendrocyte progenitor cells (OPCs) contribute to remyelination and they can respond to myelin loss but their function may be impaired in disease [207]. Endothelial cells and pericytes form the blood–brain barrier (BBB) and maintain the brain's microenvironment. In 2020, a study conducted by Montagne et al. supported this evidence by suggesting that the loss of BBB integrity influenced by factors like APOE4 accelerates Alzheimer's progression by increasing neurovascular damage, highlighting endothelial and BBB preservation as a therapeutic strategy [208].

Besides brain cells, there are also blood cell-related biomarkers in AD. They involve proteins and molecules measurable in the blood rather than the blood cells themselves. By measuring these blood-based biomarkers, AD pathology can be tracked. Cerebrospinal fluid (CSF) is an important source of biomarkers for AD because it comes into direct contact with the extracellular space of the brain and reflects the molecular changes in the brain. Among the most important ones are the amyloid beta (Aβ) peptides Aβ42 and Aβ40. A decreased ratio of Aβ42/Aβ40 in CSF is a strong biomarker for AD, reflecting reduced clearance of Aβ42 and increased amyloid plaque accumulation in the brain. Soluble Aβ42 oligomers are considered more neurotoxic than plaque-deposited Aβ, disrupting neurotransmission and synaptic plasticity. These CSF biomarker changes correlate with pathological Aβ processing derived from sequential cleavage of amyloid precursor protein (APP) by β- and γ-secretases, generating toxic Aβ species, while α-secretase cleavage leads to non-amyloidogenic fragments [209]. In 2016, Olsson et al. identified core CSF biomarkers T-tau, P-tau, and Aβ42, together with CSF NFL and plasma T-tau, as strong differentiators of Alzheimer's disease from controls, supporting their clinical and research use in AD diagnosis [210]. In 2009, Avagyan et al. exhibited that patients with AD have impaired innate immune function, because of reduced amyloid-β (Aβ) phagocytosis by peripheral blood mononuclear cells (PBMCs), and that leads to cognitive decline [211]. Aloma et al. showed that p-tau181, p-tau217, and p-tau231 are strong blood biomarkers of tau pathology in AD. Out of these, plasma p-tau 217 shows superior diagnostic accuracy, which is comparable to CSF tests and strongly correlates to AD pathology [212]. Neurofilament light chain (NfL) is a protein fragment that is released into body fluids like blood and CSF when neurons get damaged. It can also serve as a biomarker because their elevated levels can strongly indicate neuronal injury [213]. Glial fibrillary acidic protein (GFAP) is a protein found in astrocytes and their elevated levels in the blood can also be an indicator of AD as they are associated with neuroinflammation. It correlates with early stages of AD and tracks disease progression [214].

A factor to be considered, however, is that the level of brain-specific proteins in the blood is much lower than those detected in CSF and hence requires ultrasensitive analytical approaches such as neuron-derived extracellular vesicles and single-molecule array [215].

13. Additional peripheral biomarkers

Although blood and CSF biomarkers are the most used biomarkers for AD diagnosis, there are several other peripheral biomarkers that appear promising for Alzheimer's disease (AD) diagnosis and progression. These other sources of biomarkers have been

contemplated, given the invasiveness, cost, and limited availability of neuroimaging and CSF biomarker analysis [215]. Body fluids, including serum, plasma, and urine, are easy to collect from the comfort of the patient's home and are relatively non-invasive [216]. An Aβ-PET scan is a type of Positron Emission Tomography (PET) scan used for detecting the presence and extent of amyloid plaques in the brain. This technique allows researchers to visualize plaques during the lifetime of the affected individual, which was earlier only possible through autopsy [217]. FDG-PET (Fluorodeoxyglucose-PET) measures the brain's energy utilization to infer synaptic number. Impaired connectivity between brain regions is indicated by diffusion tensor imaging and MRI spectroscopy provides metabolic markers of diminished cell number [218]. The human body has several endogenous antioxidants like peroxidase, superoxide dismutase, and glutathione (GSH), which scavenge excessive ROS produced and nullify their ill effects. Alterations in these antioxidant levels are indicative of cognitive impairment. Elevated levels of markers of LPO, including hydroxynoneal (HNE) and malondialdehyde (MDA), were reported in AD [219].

Researchers have also been keen on exploring saliva as a potential biomarker for AD, including protein and RNA markers [215]. Saliva biomarkers include elevated levels of Aβ42, altered p-tau/t-tau ratios, and reduced lactoferrin [220]. Urine has been an actively researched as a potential source of biomarkers. They encompass differentially expressed proteins (SPP1, GSN, IGFBP7), amyloid beta peptides (Aβ42), neuronal thread proteins (AD7c-NTP), metabolic phenotypes including formic acid, and oxidative stress markers [221]. Retinal imaging has also revealed important non-invasive biomarkers for AD diagnosis, including thinning of the retinal nerve fiber layer (RNFL), alterations in retinal vascular density, and changes in neuronal and capillary networks detected by optical coherence tomography (OCT) and OCT angiography. These reflect the cerebral neurodegenerative and vascular pathology associated with AD [222]. Impaired sense of smell is an early symptom of AD, and olfactory testing is a non-invasive way of assessing AD [223]. Epigenetic changes in gene expression patterns can also be detected in peripheral blood and can serve as a valuable biomarker. DNA methylation changes in CpG sites in genes like NXN, TREML2, ABCA7, HOXA3, and APOE show strong potential as blood-based biomarkers [224]. Then, histone modifications and non-coding RNAs like miRNA and lncRNA serve as complementary diagnostic and therapeutic indicators. Increased levels of cytokines like IL-1β, TNF-α, chemokines, and proteins like YKL-40, soluble TREM2 (sTREM2), and glial fibrillary acidic protein (GFAP) can serve as some other peripheral biomarkers in AD [225].

Age-related decline in sensory functions—such as vision, hearing, olfaction, and somatosensation—has emerged as a potential early indicator of mild cognitive impairment (MCI). Multiple clinical studies suggest that sensory deficits often precede measurable cognitive decline, indicating a shared neuropathological basis. For example, hearing loss in older adults has been associated with accelerated brain atrophy and increased MCI risk, possibly through mechanisms involving reduced auditory input, increased cognitive load, and social isolation [226]. Similarly, olfactory dysfunction is frequently observed years before the onset of MCI or Alzheimer's disease, reflecting early involvement of limbic and olfactory-related brain structures [227]. Visual impairments, including reduced contrast sensitivity and visual field loss, have also been linked to poorer cognitive performance and structural brain changes [228]. These findings indicate that sensory organ disability may serve as a non-invasive biomarker for the early detection of cognitive decline, enabling timely intervention strategies.

14. Conclusions

Detection of cognitive decline before the emergence of clinical symptoms remains a challenge. Despite advances, a major hurdle lies in translating these diverse biomarkers into clinically validated diagnostic tools (**Figure 1**). Many biomarkers demonstrate strong associations with cognitive outcomes in research settings, but their predictive validity in heterogeneous, real-world populations is less robust. The interpersonal variability, shaped by genetics, lifestyle, education, and comorbid conditions, undermines generalizability. For broader clinical application, biomarker deployment should be stage specific. Highly sensitive markers—including early amyloid changes, a rise in Nfl levels, and selective ncRNA alterations—often emerge decades before symptom onset and are most useful for screening at-risk individuals for recruitment into prevention trials or longitudinal cohorts. These can enrich study populations and improve statistical power. Highly specific markers, such as p-tau217, typically rise closer to symptomatic conversion and are more suitable for tracking disease progression and evaluating therapeutic efficacy in intervention studies (**Figure 2**). In follow-up studies, combining sensitive and specific biomarkers facilitates continuous risk monitoring and adaptive trial designs—switching from early detection to intervention testing as individuals progress. Clinically, this approach supports a tiered workflow: broad screening with minimally invasive, sensitive assays, followed by confirmatory testing with more specific, possibly invasive measures when the severity of symptoms increases. For selection of appropriate participants for cognitive deficit intervention studies, a combination of plasma biomarkers, imaging techniques and cognitive assessments could be utilized. Plasma biomarkers could help identify individuals at risk or with early signs of neurodegeneration. Imaging techniques such as MRI and PET scans would provide information regarding disease progression, and cognitive assessments would aid in tracking cognitive changes over time. To move toward precision diagnostics, future efforts must prioritize large-scale validation across diverse cohorts, harmonization of biomarker protocols, and integration of multimodal data within user-friendly, clinically actionable platforms. Multimodal biomarker panels, supported by artificial intelligence, may offer the most comprehensive approach to early diagnosis, prognosis, and treatment response monitoring. Ultimately, transforming these biomarkers into routine clinical tools will require not only technical refinement but also interdisciplinary collaboration, regulatory standardization, and equitable access.

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