

Review

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Reappraisal of the Concept of Accelerated Aging in Neurodegeneration and Beyond

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Review

Reappraisal of the Concept of Accelerated Aging in Neurodegeneration and Beyond

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Abstract: Background: Aging rate is affected by genetic changes, epigenetic modifications, oxidative stress, inflammation, lifestyle and environmental factors. In accelerated aging (AA), biological age exceeds the chronological one. Objective: To undertake a critical reappraisal of the AA concept and to reveal its weaknesses and limitations. Methods: We reviewed over 300 recent articles dealing with physiology of brain aging and pathophysiology of neurodegeneration. Results: (1) Organ systems age at different rates, which interferes with application of the AA concept to individual organs. (2) Aging rate can be decelerated due to individual structure–functional reserves built with cognitive, physical training or pharmacological interventions. (3) The AA concept lacks standardised terminology and methodology. (4) Specific molecular biomarkers (MBM) reflect aging. To consolidate the AA theory, researchers should validate numerous MBM candidates. (5) Aging factors, mechanisms and the exact nature of their biological outcomes are not well understood. Conclusion: Although considered as a perspective theory, the AA concept has serious limitations and it requires an update.

Keywords: aging; accelerated aging; brain aging; neurodegeneration; epigenetics; biological clocks; molecular biomarkers; rejuvenation; structural reserves; functional reserves

1. Introduction

Aging is associated with structural and functional changes that increase risks of diseases and death [1–3]. Multiple factors contribute to aging. Accumulation of damage and dysfunction

may happen due to genetic mutations, epigenetic modifications, oxidative stress and inflammation [4,5]. Physiological or biological age (BA) is defined as the current state of the individual as a biological system. A combination of detectable lifetime-dependent biological parameters characterizes the system state. These parameters include the current profile of genomic DNA methylation, age-associated structural changes in the brain, brain functional reserve, etc.

In normal aging, BA is equal to chronological age. If the process of getting older is accelerated, BA exceeds the chronological age. In decelerated aging, BA becomes lower than the official age [6–8]. Accelerated aging (AA) shares common features with the normal one, but protein aggregation and excitotoxicity are specific to AA [9–11]. Understanding mechanisms of aging opens opportunities for targeted treatment of the diseases that occur late in life [9].

AA is the area of research with unresolved issues such as non-standardized terminology [12] and understudied mechanisms [13]. Researchers have not reached an agreement on whether neurodegeneration (ND) is a type of AA [14,15] or its outcome [14,16–18]. The latter view argues that certain biomarkers (BMs) are ND-specific and they do not detect AA [17].

Different theories were proposed to explain AA pathogenesis [19–21]. The genetic theory assumes that accumulation of DNA mutations and/or gene dysregulation are the major causes of AA [19,22]. The theory considers random DNA changes but ignores chromosomal, multifactorial and monogenic alterations [13,23,24]. The multi-proteinopathies theory describes aggregation of misfolded proteins as a leading cause of cell dysfunction in age-related diseases [20,25]. The free radical theory postulates that the primary accelerator of aging is oxidative damage of DNA and proteins [15,26–28]. But the concept fails to explain difference between normal and abnormal levels of reactive oxygen species [21,29]. In practice, no diagnostic BMs can identify and prognosticate AA reliably [20,30].

2. Biomolecular Aspects of Aging

Neurocentric and neurovascular hypotheses describe aetiology of ND at sub-, cellular, and supra-cellular levels. Initially, research efforts were focused mainly on neurons. Then, investigators recognized the importance of non-neural cells in higher brain functions. Neurovascular (NV) view refers to a neurovascular unit (NVU) which is a dynamic multicellular structure mediating functional interactions between brain tissues per se and blood vessels. The NVU includes astrocytes, microglia, oligodendrocytes, precursor cells, endothelial cells, pericytes, excitatory and inhibitory neurons [31]. The NV hypothesis proposes that neural cells in the NVU and circulating immune cells secrete proinflammatory mediators contributing to age-related neuroinflammation [32], cell degeneration [33,34] and endothelial impairment [34,35]. These changes disrupt molecular networks, induce damage to the blood–brain barrier [36,37] and lead to NVU dysfunction which is a major cause of ND [38]. But the exact role of an NVU in ND remains unclear [39]. A research for ND-associated BMs is difficult due to high complexity and molecular heterogeneity of the NVU network. It requires whole genome studies, e.g., global transcriptome analysis followed by hierarchical data clustering [40] or single-cell/single-nucleus transcriptomics [41,42].

Molecular biomarkers (MBMs) are biomolecules, their components, fragments or modifications with the associated measurable parameters that serve as a tool to diagnose pathologies and monitor biological processes. MBMs can be used to evaluate aging, particularly to estimate the rate of its progression [43]. Aging MBMs include mRNA transcripts, proteins [44], telomere length, serum markers of DNA damage [45], DNA methylation profiles [46,47], histone modifications [48–59], differentially expressed genes [42,60], non-coding RNAs [61–64] and other biomolecules (Figure 1).

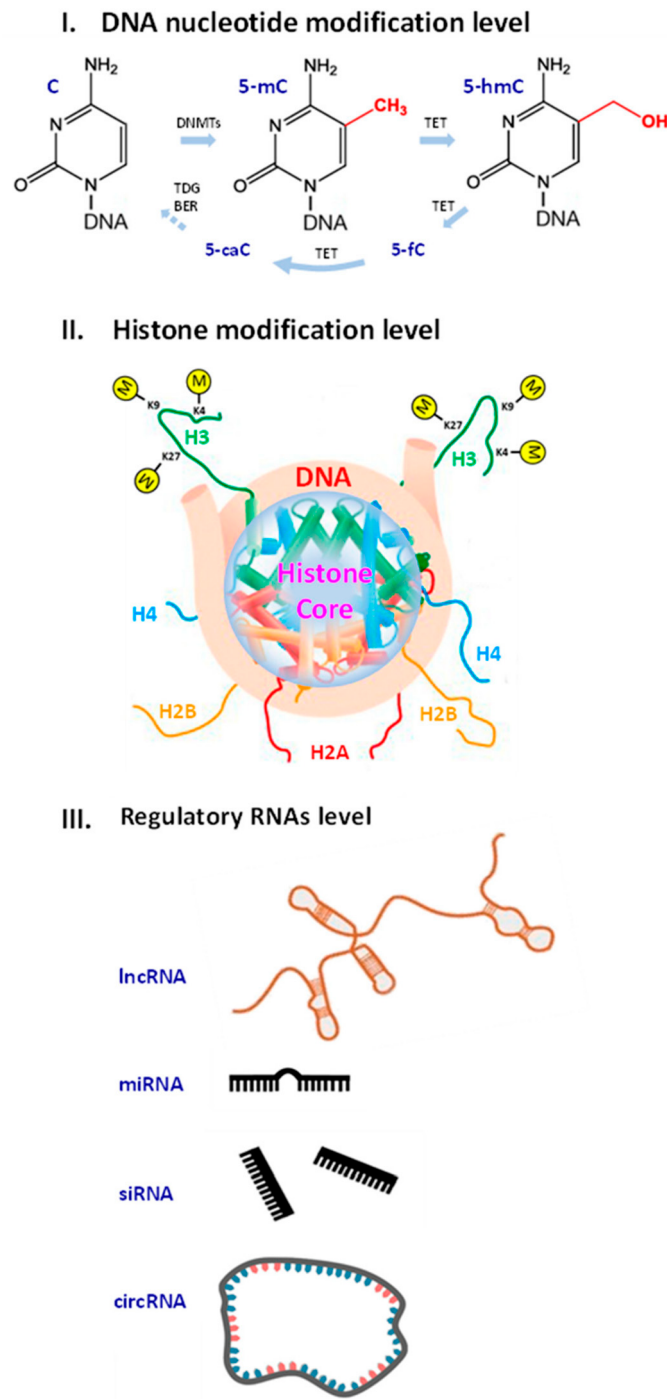


Figure 1. Examples of epigenetic changes and factors affected by accelerated aging at different levels that could serve as potential biomarkers of aging. **(I)** DNA nucleotide modification level: cytosine. (C) can be converted to 5-methylcytosine (5-mC) and oxidised further to 5-hydroxymethylcytosine (5-hmC). **(II)** Histone modification level: Three examples of histone 3 (H3) lysine methylation marks are indicated. Lysine 4 (K4) H3K4me3 mark is associated with active genes, lysine 9 (K9) H3K9me3 is an established mark of transcriptionally repressed heterochromatin and lysine 27 (K27) H3K27me3 mark is linked to both transcriptional activation and repression. **(III)** Regulatory RNAs level: several types of ncRNAs, long non-coding RNA (lncRNA), microRNA (miRNA), small interfering RNA (siRNA), circular RNA (circRNA), shown schematically.

Despite a large number of suggested MBMs of ND, only few of them are validated. In most studies, sample sizes were too small to justify the accuracy and reproducibility of MBM data. For example, a recent study aimed at determining whether age affects different cell types in the NVU.

The study resulted in a model discriminating patients with Alzheimer's disease (AD) from healthy controls (HCs). The model revealed 15 genes related to AA (AAG): *IGF1R*, *MXI1*, *RB1*, *PPARA*, *NFE2L2*, *STAT5B*, *FOS*, *PRKCD*, *YWHAZ*, *HTT*, *MAPK9*,

HSPA9, *SDHC*, *PRKDC* and *PDPK1* [42]. Differential expression of *IGF1R*, *MXI1*, *PPARA*, *YWHAZ* and *MAPK9* correlated with ND progression. Therefore, they may function as facilitators or inhibitors of AD. But the research neither demonstrated cell-specific roles of the discovered AAGs nor identified their contribution to AD pathogenesis and interactions in the NVU. Moreover, the study failed to justify the AAGs as MBMs since it had an insufficient sample size of only 11 AD patients and 7 HCs [42]. ND results from multiple structural changes at different genetic loci over a period of time [65,66]. AD accounts for 90% of ND cases. High risk of developing AD is associated with alterations in 15 genes that predispose to ND (NDG): *GBA1*, *APP*, *PSEN1*, *MAPT*, *GRN*, *SETX*, *SPAST*, *CSF1R*, *C9orf72* [67], *TET2* [68], *TBK1* [69], *TOMM40*, *APOC1* [70], *APOE* [70,71] and *TREM2* [72–78]. Surprisingly, the gene sets do not overlap across the studies on AAGs and NDGs. Researchers found that the *APOE* e4 allele and mutation spectrum for *TREM2* gene are risk factors for developing dementia with Lewy bodies, multi-cognitive decline and corticobasal degeneration [78–87]. DNA methylation level reflects rate of aging. Approximately 1.5% of genomic DNA contains 5-methylcytosine (5-mC), and the level decreases during ontogenesis [88]. The level of 5-mC is the highest in embryos, and then it reduces gradually across life [89,90]. In aging, global genomic DNA hypomethylation proceeds along with hypermethylation of CpG islands. These changes in DNA methylation patterns are called “epigenetic drift” [91,92]. In the mammalian genome, 60% of the CpG islands are associated with gene promoters and regulate gene transcription [91].

In normal aging, age-predictive models demonstrate gradual linear changes in the DNA methylation profile, but environmental or genetic risk factors can accelerate the process of getting older [93]. In monozygotic twins, the divergence of the methylome increases at different rates [94]. Change of the DNA methylation profile was proposed as a mechanism of an epigenetic clock [95–97] by analogy with a biological clock [98,99]. Monitoring deviation between biological and chronological age helps to study development and aging across the lifespan [100]. Horvath [101], Hannum [93] and PhenoAge [102] epigenetic clocks serve as markers of ND [102–106], with the first of these showing the strongest correlation between epigenetic and chronological age [107].

Histone modifications can serve as potential MBMs of aging, however, heterogeneity of animal models used to develop the biomarkers limits their applicability. For example, a drop in highly abundant transcription activation mark H3K4me3 [48] correlated with an extended lifespan in *Caenorhabditis elegans* [49]. Contrarily, an increase in the H3K4me3 level was linked with AA in *Drosophila melanogaster* [50]. The level of heterochromatin-associated histone transcription repression mark H3K9me3 gradually decreases during aging in haematopoietic stem cells of humans and mice [51]. In *C. elegans* and other models of senescence, the most significant loss of H3K9me3 occurs in repressive regions [52,53]. H3K27me3 is associated with transcriptional silencing in aging [54]. The role of H3K27me3 is controversial, as studies showed its bidirectional lifelong changes [55–59].

Increased levels of H4K20me3 and H3K4me3 and decreased levels of H3K9me1 and H3K27me3 are common age-associated epigenetic marks [108–110]. Research showed an increase in H3K4me3 promoter methylation in a CK-p25 tauopathy mouse model and hippocampus of AD patients [111,112]. The following histone methylation marks can also be found in an Alzheimer brain: H4K20me2, H3K4me2, H3K27me3, H3K79me1, H3K79me2, H3K36me2, H4K20me3, H3K27me1 and H3K56me1 [113,114]. Besides, histone acetylation marks H3K9ac, H3K14ac and H4K16ac are associated with normal and accelerated aging [110,111,113–115]. Histone phosphorylation marks H4S47p and H3S10p and histone ubiquitination mark H2BK120ub are observed in AD [114,116,117]. Further systematic research should elucidate regulatory mechanisms of histone modifications, their interaction, and interplay between histone marks and other factors.

Non-coding RNAs (ncRNAs) are used as aging MBMs [118–121].

Long non-coding RNAs (lncRNAs) are presented with the growth-arrest-specific transcript 5 (*GAS5*) which plays a significant role in cell proliferation and apoptosis [122–124]. Its down-regulation leads to phosphorylation of the tau protein in ND [125,126]. Long intergenic brain cytoplasmic RNA 1 (*BCYRN1*) expressed in the dendritic domains of neurons is down-regulated in aging [127].

MicroRNAs (miRNAs) impact neuronal plasticity, influence tau protein metabolism and mediate brain aging through regulation of gene expression [128–137]. Regulation of miR-145a and miR-375 depends on age in mouse brains [138–140]. The MIR29 family, MIR339-5p, MIR195 and MIR107 modulate expression of beta-secretase 1 involved in cleaving the amyloid precursor protein [141–146]. Interestingly, miR-34 plays a protective role in *Drosophila* [147] and MIR144/MIR451 regulates ADAM metalloproteinase domain 10 in AD [148]. Hypothalamic stem cells secrete over 20 miRNAs into the cerebrospinal fluid. These miRNAs control aging rate in mice [149], which should also be relevant to human brain [150]. Future studies should verify miRNA MBMs in humans [151].

Circular RNAs (circRNAs) are abundant in the brain, and their expression changes with age in skeletal muscles [152,153]. CircRNAs contribute to ND through interaction with miRNAs. For example, ciRS-7 potentially functions as a sponge for MIR7-1 [154] and its level is reduced dramatically in an AD brain [155]. Cerebral circRNAs are linked with neurotransmitter function, synaptic activities and neuronal maturation. They target the expression and availability of specific age-related mRNAs in the brain. At least four circRNAs are involved in postoperative neurocognitive disorders [156]. Another study revealed nearly 1200 cerebral circRNAs in a rat model of aging [157]. Various biomarker candidates including circRNAs await validation in the clinical arena.

3. Aging of Organs and Systems beyond Neurodegeneration

Aging affects organs and systems with different rates of change; therefore, the AA concept needs to be adjusted when applied to individual organs. For example, ovarian aging implies a loss of follicle numbers and decreased oocyte viability. Typically, an accelerated decline in fertility begins around the age of 38 years and continues until the climacteric [158]; however, a non-uniform decrease in follicle numbers results in a large variation in menopause onset. BA of the male reproduction system can also be assessed by fertility, but the arrest of reproductive capacity is reversible in older men, with lifestyle and disease factors prevailing over other determinants of aging [159]. In mice, oxidative stress, inflammation, DNA damage and de novo mutations accelerate testicular aging [160–163], while growth differentiation factor 11 enhances antioxidant enzyme activity and protects the testes [164]. A progressive age-related drop in Leydig and Sertoli cell function [165], testicular size [166] or testosterone level was demonstrated in older men [167]; but no decrease in testicle size or the levels of testosterone was observed in a cohort of older men with healthy lifestyle and affordable healthcare service [168,169].

The cumulative effect of a disease rather than age may account for changes in male fertility throughout life. Chronological age inaccurately reflects reproductive BA. Therefore, the AA concept cannot be adopted to the reproductive system. This illustrates a challenge in assessing BA at the organ and system levels.

Sex hormones that affect fertility are a part of the endocrine system. Susceptibility to aging differ among endocrine glands. In men, hypothalamic–pituitary–testicular axis does not undergo dramatic chronobiological changes: only 35–50% of men over 80 have reduced testosterone levels [170,171]. Diabetes mellitus and obesity predispose to accelerated adipose tissue dysfunction affecting telomere length [172,173]. Adrenal and thyroid functions undergo less prominent age-related transformations than their hypothalamic regulation [174]; therefore, BA assessment from hormonal findings is challenging. With aging, hormone activity decreases and endocrine alterations are established [175]. BA is affected by the level of glycosylated haemoglobin, glucose, triglycerides, low-density lipoproteins and total cholesterol [176–178]. The modulation of these parameters, lifestyle and environmental factors can prevent or contribute to AA [179]. Effectiveness of hormone replacement therapy for aging reversal is questionable though [180].

Environmental and endocrinological factors affect BA of connective tissue. Status of the skeletal system reflects an individual endocrine profile and micronutrient balance [181–183] as well as environmental and occupational attainments [184]. For example, bone resorption in astronauts prevails over its formation due to microgravity; however, bone density normalises after the flight [185,186]. Skin elasticity serves as a marker of aging which rate can be modified due to estrogen deficiency, metabolic alterations and exogenous factors (burns) [187–191]. Fibroblasts constitute a natural cell stock that allows skin rejuvenation, repair and decelerated aging [192]. In connective tissue, a combinatory effect of internal and external factors determines BA more accurately than the chronological one [193,194]. Therefore, an inability to account for the decreased aging rate reveals a weakness of the AA concept.

Studies in other systems have also reported reversibility of age-related changes in them. For example, physical training can rejuvenate the respiratory system by expanding the alveolar space. However, studies on these issues did not comprehensively evaluate BA of the lung since the impact of muscle atrophy on results in the spirometry test was not considered [195–197]. Lifestyle changes (e.g., calorie restriction and physical activity) could also reverse aging in patients with early stages of chronic kidney disease [198]. Another example is shown by the discovered potential to rejuvenate kidneys with up-regulation of the *Klotho* gene [199]. These evidences speak for a limited generalisation of the AA concept. AA affects various systems and cross-organ communication. The interaction between systems can impede the atrophy of an organ through compensatory mechanisms in other organs. Several studies have demonstrated the role of the central nervous system in reversing the aging of other systems and organs [200–202]. Endocrine and cardiovascular diseases promote renal aging [203]. Conversely, kidney transplantation can revive other parts of the body [204,205]. The characterisation of organ- and system-specific aging processes is challenging and it will require combinatory approaches that are largely missing in the AA concept.

4. Limitations of the AA Concept

The AA concept should be considered within the context of individual capacities and personalised structure–functional reserve mechanisms (Figure 2). A generalized term “structure–functional reserves” is introduced to denote an observed variability in multiple structural and functional parameters at different levels in a population: expression of genetically and epigenetically regulated genes, number, viability and functionality of cells, amount of synapses and intercellular contacts, secretion of cytokines, potency of physiological responses, etc. The term definition could be further developed and linked to statistical distributions of measurable biological parameters in the population and to a norm of reaction.

Physiological reserves reflect the remaining capacity of an organ to perform its function. Aging and diseases lead to atrophy due to a reduction in the number of cells and supracellular structures [206,207]. In the context of brain aging, physiological cognitive reserve reflects the level of education, occupational and environmental attainments and performance in cognitive tests [206]. Reversible forms of mild cognitive impairment (MCI) and dementia represent clinical examples of restoring individual reserve potential. The examples are not aligned with AA theory [208,209]. Neural compensation in the elderly leads to formation of secondary brain networks [210], which decelerate the aging of the brain [206,211]. In elderly patients, reversion of MCI results from specific lifestyle activities and cognitive stimulation throughout life [212,213].

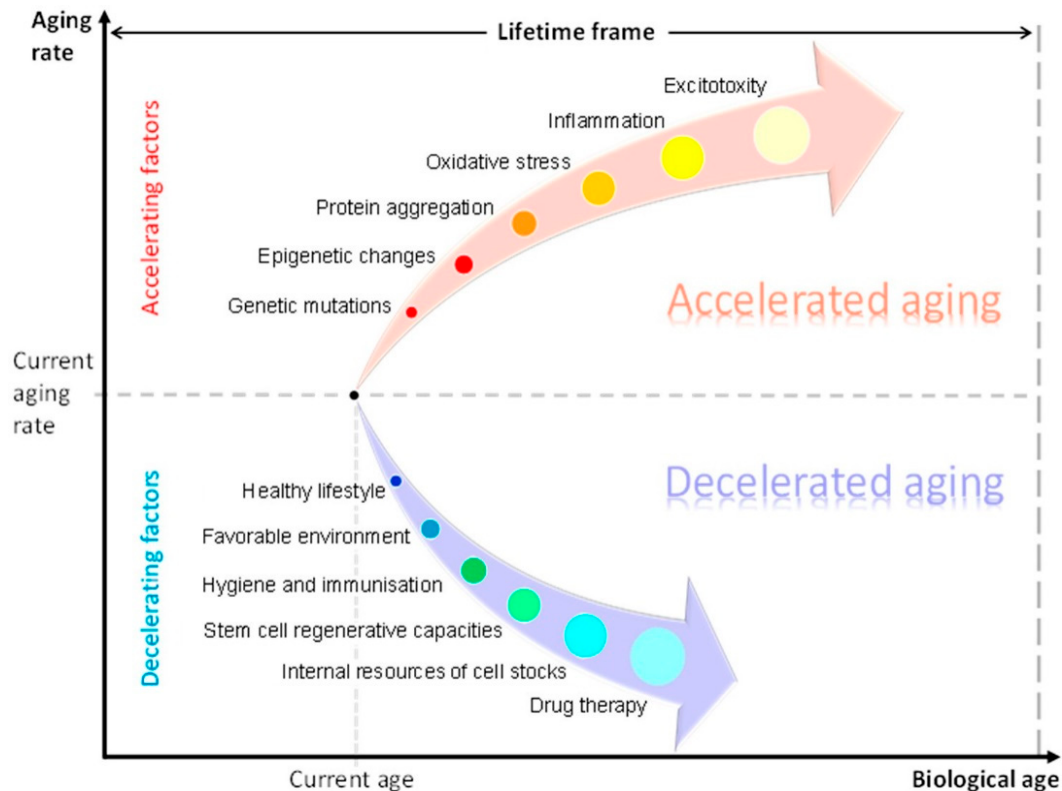


Figure 2. Factors influencing the rate of aging. Factors accelerating aging include: genetic mutations, epigenetic changes, protein aggregation, oxidative stress, inflammation and excitotoxicity. Factors decelerating aging include: a healthy lifestyle, favourable environment, hygiene and immunisation, stem cell regenerative capacities, internal resources of cell stocks and drug therapy.

Age assessment requires an accurate estimation of individual reserves that account for biological and chronological age differences. In neuroscience, machine learning models predicted total years lived in good health from brain-imaging data with error of 2.1–4.9 years [214,215]. Individual brain age can also be calculated as a difference between chronological age and the predicted BA [216]. In obstetrics, the evaluation of gynecological status takes into account both reproductive health and potential fertility. Overall BA depends on reserve capacities of individual systems and organs [217,218].

Variance in reserve capacities complicates precise BA assessment. Criteria of AA of the brain are unclear since indicators of normal aging are still missing [219]. Methods for BA assessment are not standardized, they do not take into account individual reserve potential, and reference curves for brain changes have not yet been created. Methodological discrepancies lead to contradictory findings in different studies. For example, AD adds 1.5 years to brain age, MCI adds 1 year, multiple sclerosis—0.41 years, Parkinson's disease (PD)—3 years and schizophrenia—5.5 years. The last two pathologies impact cognition in a milder and slower way than AD [220–222]. Another research on AD revealed the added brain age between 6 and 9 years [223].

Several methodologic limitations demonstrate the need for caution when assessing research findings. For example, studies on age-related brain atrophy commonly have a cross-sectional design that is less accurate compared to the longitudinal one [224]. Many studies are based on small non-representative cohorts [225–227]; therefore, applicability of the designed mathematical models is low. Certain studies of brain aging focus on the middle-aged and elderly population and they fail to report individual prenatal pathologies and childhood trauma affecting brain health and BA of study participants [228]. Application of the concept of AA to localised degeneration presents a challenge since different brain parts become older unevenly [229]. For example, in localised ND, BA assessment reflects the level of damage to the most vulnerable brain parts (e.g., substantia nigra and ruber nuclei

in PD) [230–232]; however, one should also consider the brain resources that can minimise the atrophy effects [233]. In systemic ND, the brain ages faster than in localised ND [234,235], and the difference in the speed of atrophic changes is apparent [236].

ND has polyetiological nature, and contemporary neuroscience lacks a clear explanation of cooperation between different causal factors. It is still unclear whether chronic diseases lead to or result from ND [237,238] since the genetic, environmental and lifestyle factors interact in an undefined way [18,239,240]. Several articles have revealed a misalignment between dementia risk, cognitive performance and MBM levels [241,242]. Another disadvantage of AA studies is an inability to report an impact of medications on study results [243]. Last but not least, AA represents a diagnostic but not pathognomonic signature in ND and in psychiatric diseases such as schizophrenia, bipolar disorder and major depressive disorder [222,244,245]. The entire range of symptoms observed in these patients cannot be explained by brain aging only [222,246,247].

Drug therapy could extend reserves. For instance, antidepressants can help to reverse MCI [248]. Certain cognitive disorders demonstrated a reversible pattern in cognitive performance upon treatment [248,249]. Sex hormone replacement in ND reduces risk of cognitive impairment, delays symptom onset and slows the progression [250]. Antioxidant-based therapy also alleviates severity of the disease [251,252]. Recent ND studies described a number of novel therapeutic options targeting mitophagy, protein aggregation and cellular senescence. These options include specific antibodies, inducers of cell proliferation and NAD⁺ supplementations [9,18,253]. The observed treatment effects contradict the idea of irreversibility of changes claimed by the AA concept.

5. Recommendations for Further Development and Improvement of AA Concept

5.1. Statistical Models

Building highly accurate machine learning models is the most common solution for distinguishing AA from normal aging. Recent articles suggested ways to improve the models. These are identification of potential gaps or inconsistencies in study methodology, search for additional data sources, rigorous statistical analysis. Following the suggestions, scientists will reveal the trends or correlations that have been overlooked. Below, we list a set of model parameters that should be controlled:

- *Sample size.* The number of individuals in the study can affect the statistical power of the analysis, and larger sample sizes generally provide more robust results.
- *Biomarker types.* The choice of biomarkers can impact the diagnostic model used, as different types of biomarkers may require different statistical analyses.
- *Age range.* The age range of the study population can influence the types of biomarkers identified, as some biomarkers may be more prevalent in certain age groups.
- *Data normalization.* Normalization of the data is critical to ensure that data collection or processing differences do not affect the analysis.
- *Statistical methods.* The choice of statistical methods can impact accuracy of analysis, and different methods may be more appropriate for different data types.

Careful consideration of these parameters will advance diagnostic models based on specific MBMs of AA. Recommendations also include functional characterisation of all types of molecular clocks: organ-tissue-specific, single-cell-specific and disease-specific. Studies can benefit from integration of epigenetics, exploration of additional epigenomic markers of aging, and generation of data in robust non-human aging models.

5.2. Molecular Clocks

Molecular clocks could help to study aging in specific organs and tissues. Organ- and tissue-specific clocks will unravel the complexity of aging in multicellular biological system. Animal

studies reported a number of useful techniques that use the mutation rate of biomolecules to deduce the time [254]. These include organ-specific clocks for liver [255–257], lungs [255,256], blood [256,258], heart and cortex [255], adipose, kidney, muscle tissues [256], and multiple tissue [259].

5.3. Single-Cell Epigenomics

Analysis of gene expression at a single cell level provides a deep insight into aging [260,261]. For instance, lifetime-dependent cell-to-cell variability in methylation, or so called “epigenomic noise”, occurs in human immune cells in blood and in mouse muscle stem cells [262,263]. Epigenomic noise results in increased transcriptional heterogeneity, especially in stem cell niche genes [262]. A recent trend is construction of epigenetic clocks at a single-cell level by applying novel methods [264,265] and deep-learning computer algorithms [266–268].

5.4. New Epigenetic Biomarkers

Search for new epigenetic marks of aging represents another challenge and opens exciting opportunities. Connections between aging and DNA modifications other than methylation are puzzling. Evidently, such connections exist. In the mouse, senescence of hippocampus cells deregulated histone H4 acetylation (H4K12) [269] and accumulated histone variant H2A.Z [270]. In the brain of AD patients, researchers found acetylated histones H3 (H3K9ac) and H4 (H4K16ac) [113,271]. Longevity in mammals is linked to histone acetylation by SIRT6 HDAC, and this discovery unlocks potential for development of pharmacological agents targeting AA [272–274].

5.5. Consideration of Ageotypes

Recently, longitudinal, deep multiomic profiling enabled identification of distinct aging phenotypes, termed ‘ageotypes’. These personalised physiological subsets of aging reflect impact of various individual factors on aging rate which depends on genetics, epigenetic changes, lifestyle habits and environmental exposure. Models reflecting age will improve diagnostic accuracy as new information is added [44]. Potential biomarkers of aging and health metrics can be incorporated into the model with ageotypes, and this approach will allow us to monitor the intervention effectiveness in each subset [44,275,276].

5.6. Genetic Predisposition to AA

Human mutations in prototypical progeroid syndromes deepen our knowledge on mechanisms underlying aging. Some autosomal recessive mutations are associated with in- effective genome maintenance systems, deficient DNA helicase activity or aberrant nuclear architecture. Genome instability disorders caused by these mutations are classified into groups three of which include sunlight hypersensitivity disorders: (i) *Xeroderma pigmentosum*, Cockayne syndrome and trichothiodystrophy; (ii) ionizing radiation hypersensitivity disorders such as Ataxia telangiectasia, Nijmegen breakage syndrome; (iii) progeroid disorders such as Werner syndrome, Hutchinson–Gilford progeria syndrome, Bloom syndrome, Rothmund–Thompson syndrome and Fanconi anemia [277–279]. Studies on the aforelisted disorders can also lead to the discovery of anti-aging treatment.

5.7. Application of Animal Models

Future studies will benefit from emergence of new animal models exhibiting age- related features – accelerated senescence, damage of nuclear envelope, increased accumulation of genomic lesions [280]. Interventions and modulators are commonly tested with well-developed mouse aging models [254]. Mouse models demonstrated epigenetic clock acceleration by a high-fat diet, effects of rapamycin and caloric restriction [255,257]. Killifish (*Nothobranchius furzeri*) is a vertebrate with the shortest captive lifespan, which makes the species suitable for modeling senescence [281–287]. The following animals can also mimic aspects of human aging in longevity

models: naked mole rats (*Heterocephalus glaber*, *Fukomys mechowii*) [288–290], Brandt's bat (*Myotis brandtii*) [291–293], olm (*Proteus anguinus*) [294–296], bivalve (*Arctica islandica*) [297,298], Hydra (*Hydra vulgaris*/*Hydra mag-nipapillata*) [299–302] and Planaria (*Schmidtea mediterranea*) [303–305]. These animal models can provide robust data on aging.

6. Conclusions

- i. The review revealed certain weaknesses and limitations of AA concept. In particular, no unified methodology and terminology has been established in the field. The studies that justify the AA concept have too low sample sizes. Under certain conditions, some changes reverse with age.
- ii. Age-related diseases and exhaustion of individual reserves can indicate accelerated senescence. Specific molecular biomarkers reflect aging in individual organs, especially in the brain. Still, validation of a biomarker candidate remains a challenge. Scientists struggle to provide clinical interpretation and apply biomarkers to disease subtyping. Mechanisms of getting older and their exact nature are not well understood.
- iii. Activation of regenerative mechanisms is a potential way to decelerate brain aging. Another opportunity for rejuvenation is to restore metabolic homeostasis and energy reserves at a molecular level with novel therapeutic options. For example, neurodegeneration can be delayed with sex hormone replacement, antioxidants, targeted therapy, lifestyle improvement and safe environment. Future longitudinal studies could provide clinics and society with novel therapeutic options on preventing accelerated aging and slowing aging rate.

7. Afterword: Aging Science History and Theories

Several theories have been postulated to explain a possible biological meaning or evolutionary role of aging: evolutionary advantage of species (1890s, Weisman), accumulated mutations (1952, Medawar), antagonistic pleiotropy (1957, Williams), replicative senescence (1965, Hayflick), and the disposable soma theory (1972, Kirkwood) [306]. Theories about what causes aging commonly fall into either of two categories: genetic or stochastic. The genetic, or programmed, group refers to endocrine, immunological and programmed longevity theories. They suggest that aging is predetermined through genetics and that organisms have a built-in clock which dictates life expectancy. Stochastic, or damage, theories propose that random errors and damage accumulate over time and limit longevity. This group includes wear-and-tear, rate of living, cross-linking, free radical and somatic DNA damage hypotheses [307].

Theories of aging can also be classified by biological level. Gene regulation, codon restriction, error catastrophe, somatic mutation and dysdifferentiation theories describe molecular-level processes. Cellular senescence–telomere, free radical, wear-and-tear and apoptosis theories focus on the cellular level. Neuroendocrine, immunologic and rate of living theories conceptualise changes at the system level [308].

In 1920s, Laboratories of the Rockefeller Institute for Medical Research conducted experiments on AA and published findings. The author applied the terms “normal aging” and “aging rate” to effects of light on *Drosophila* inbred in the dark [309,310]. Since then, the numbers of references on “aging”, “aging rate” and “AA” has reached 614,132; 56,088 and 21,401, respectively [311].

In 1928, a Professor of Neurology of the Columbia University, Frederick Tilney, published the work “The aging of the human brain”, where an AD patient brain was compared to the normally aged one in the diagnostic context of the number of plaques. In this work, he also claimed an abundance of senile plaques in all human brains after the age of 90 years, influence of

unfavourable factors and diseases on the brain. Recorded a century ago, his words are worth repeating today: “It is amazing how little general or particular interest man has shown in the most important organ of his body and life. Up to the present time he has devoted relatively little attention and much less capital to the understanding of that part of his machinery which is the secret of his success and the only hope for his future progress, if not his actual salvation. . . The ridiculous stupidity of annually consecrating appalling sums of money to the savage purposes of destruction should in time shock human intelligence out of patronizing such futilities and into wiser realizations. Certainly, one liberally supported and effective brain institute would prove an incomparably more profitable investment for civilization than the most powerful battle fleet that ever sailed the seas.” (Tilney, 1928 [312]).

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Abbreviations

The following abbreviations are used in this manuscript:

5-mC	5-methylcytosine
AA	accelerated aging
AAG	gene related to accelerated aging
AD	Alzheimer’s disease
BA	biological age
BM	biomarker
circRNA	circular RNA
HC	healthy control
lncRNA	long non-coding RNA
MBM	molecular biomarkers
MCI	mild cognitive impairment
miRNA	microRNA
ncRNA	non-coding RNA
ND	neurodegeneration
NDG	gene that predispose to neurodegeneration
NV	neurovascular
NVU	neurovascular unit
PD	Parkinson’s disease

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