Please cite this article in press as: Grimm et al., Mitochondria and brain aging: From cell-specific dysfunction to intercellular cooperation, Neuron (2026), https://doi.org/10.1016/j.neuron.2026.04.048

Neuron

CellPress
OPEN ACCESS

Review

Mitochondria and brain aging: From cell-specific dysfunction to intercellular cooperation

Amandine Grimm,[1,2,*] Undine Lang,[3] and Anne Eckert[4,*]
[1]Cell Biology & Energy Metabolism, University Psychiatric Clinics (UPK), Basel, Switzerland
[2]Research Cluster Molecular and Cognitive Neurosciences, Department of Biomedicine, University of Basel, Basel, Switzerland
[3]University Psychiatric Clinics (UPK), University of Basel, Basel, Switzerland
[4]Neurobiology Lab for Brain Aging and Mental Health, University Psychiatric Clinics (UPK), Basel, Switzerland
*Correspondence: amandine.grimm@unibas.ch (A.G.), anne.eckert@unibas.ch (A.E.)
https://doi.org/10.1016/j.neuron.2026.04.048

SUMMARY

Mitochondria are essential for brain energy metabolism and are increasingly recognized as key contributors to brain aging. Although neurons are exceptionally vulnerable to age-related mitochondrial decline, emerging evidence reveals that glial and vascular cells also exhibit distinct mitochondrial impairments. This review synthesizes recent advances in our understanding of mitochondrial dysfunction across specific brain regions and diverse cell types, highlighting subcellular compartmentalization and metabolic rewiring. We further explore intercellular mitochondrial transfer as a novel form of metabolic cooperation, as well as the therapeutic potential of mitochondrial transplantation. Finally, we highlight recent clinical trials evaluating mitochondria-targeted interventions aimed at preserving brain function in older adults. Together, these findings reposition mitochondria as both integrators and amplifiers of brain aging processes across diverse cell populations. By broadening the focus beyond neurons and emphasizing translational efforts, we offer a comprehensive framework for understanding and therapeutically targeting mitochondrial dysfunction in age-related cognitive decline and neurodegeneration.

INTRODUCTION

More than 40 years ago, Denham Harman (1981) defined aging as the progressive accumulation of damage that increases susceptibility to disease, driven primarily by continuous free-radical reactions.[1] His "free radical theory of aging," later expanded to include mitochondrial production of reactive oxygen species (ROS), established mitochondrial dysfunction as a central mechanism of age-related decline. Complementing this biochemical view, Leonard Hayflick (1998) framed aging through an evolutionary lens, stating that there is no evolutionary pressure to maintain physiological systems indefinitely because the force of natural selection diminishes after reproductive age.[2] Consequently, aging does not appear to be a programmed process but rather an inevitable byproduct of molecular disorder that accumulates as energy-dependent repair mechanisms lose efficiency. Together, these theories established the foundation of modern biogerontology, positioning impaired energy metabolism and oxidative stress as fundamental drivers of aging.

Remarkably, the human brain, despite accounting for only about 2% of total body weight, consumes roughly 20%–25% of the body's energy at rest.[3,4] This high metabolic demand reflects the substantial energy required for neuronal signaling, ion gradient maintenance, and synaptic transmission, all of which depend almost entirely on mitochondrial oxidative phosphorylation (OxPhos) to generate adenosine triphosphate (ATP), the universal energy source.[5] Neurons are especially energy dependent due to their polarized structure, which necessitates efficient ATP delivery to distal axons and synapses.

Brain energy metabolism relies on the coordinated function of the diverse cell types that compose the brain (neurons, astrocytes, oligodendrocytes, microglia, and endothelial cells), whose metabolic interactions sustain neural network activity.[4] Neurons depend almost entirely on mitochondrial OxPhos for ATP generation, making them particularly vulnerable to mitochondrial dysfunction. In contrast, astrocytes rely predominantly on glycolysis and supply lactate to neurons via the astrocyte-neuron lactate shuttle.[3] Oligodendrocytes provide metabolic support to myelinated axons, whereas microglia and endothelial cells dynamically shift their metabolism between glycolysis and OxPhos in response to inflammatory or stress-related conditions.[3,4] This tightly orchestrated metabolic cooperation among brain cells is essential for maintaining neuronal activity and cognitive function. Within this network, mitochondria act as the central metabolic hub, integrating energy production, calcium buffering, and redox signaling to sustain brain homeostasis.

Due to its high energy demands and limited energy reserves, the brain is acutely vulnerable to mitochondrial dysfunction. Aging drives a progressive hypometabolic state in the brain, marked by reduced glucose uptake, lower enzyme activity, and decreased ATP production.[3] This bioenergetic decline disrupts cellular homeostasis and may drive age-related cognitive

This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Please cite this article in press as: Grimm et al., Mitochondria and brain aging: From cell-specific dysfunction to intercellular cooperation, Neuron (2026), https://doi.org/10.1016/j.neuron.2026.04.048

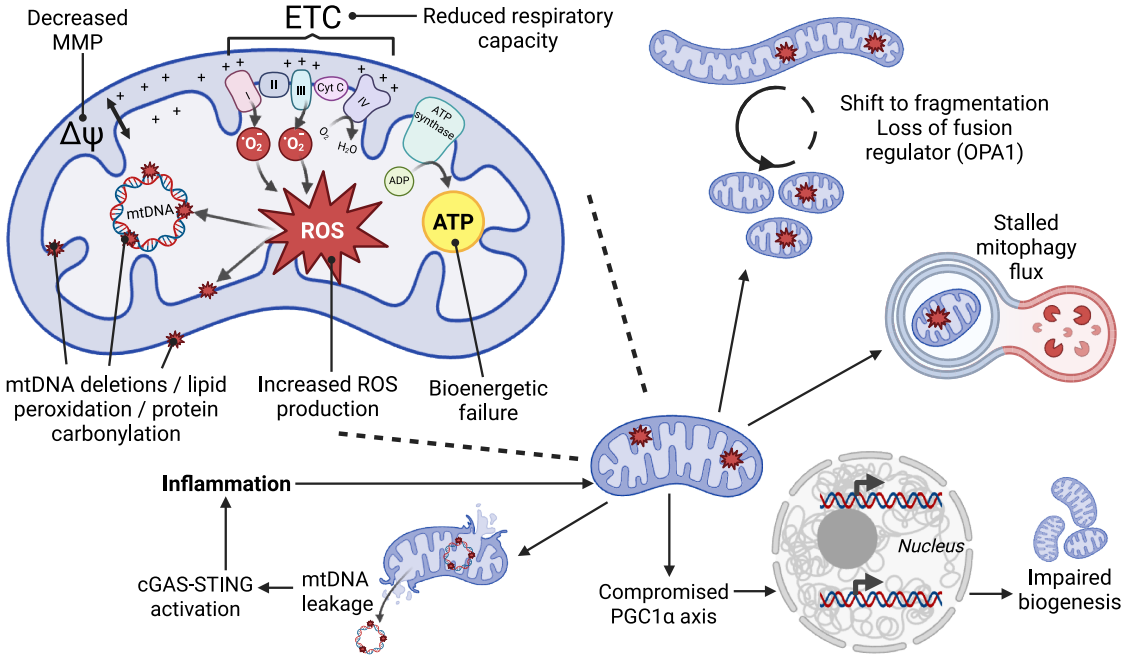


Figure 1. Hallmarks of mitochondrial aging

Schematic summary of the primary mitochondrial alterations detailed in the text. Aging is characterized by a specific decline in ETC complexes I and IV and respiratory capacity, leading to bioenergetic failure. This is paralleled by the accumulation of oxidative damage, including clonal mtDNA deletions and protein carbonylation. Quality control is compromised by a shift toward fragmentation, stalled mitophagy flux, and impaired biogenesis. Ultimately, mtDNA leakage may trigger cGAS-STING-dependent sterile inflammation. The primary literature used to generate this figure is detailed and cited in the section "overview of age-related mitochondrial alterations." I, II, III, IV, mitochondrial complexes I–IV; cGAS-STING, cyclic GMP-AMP synthase-stimulator of interferon genes; cyt C, cytochrome *c*; ETC, electron transport chain; mtDNA, mitochondrial DNA; OPA1, optic atrophy 1; PGC1α, peroxisome proliferator-activated receptor-1α co-activator 1α; ROS, reactive oxygen species. Created with BioRender.com.

impairment, acting as an early, defining feature of neurodegenerative diseases (e.g., Alzheimer's, Parkinson's, and Huntington's), in which mitochondrial failure is both a cause and consequence of pathology.[6,7]

This review presents a current synthesis of mitochondrial aging, outlining the key mechanisms and how they manifest differently across brain regions and cell types, including neurons, glia, and the blood-brain barrier (BBB). We examine intercellular mitochondrial transfer (IMT) and mitochondrial transplantation (MT) as emerging modes of metabolic communication and therapy and conclude with an overview of clinical trials targeting mitochondrial health in older adults.

OVERVIEW OF AGE-RELATED MITOCHONDRIAL ALTERATIONS

Mitochondria undergo profound structural, functional, and molecular remodeling with age, resulting in reduced bioenergetic capacity and increased cellular stress. Figure 1 synthesizes findings from diverse model systems and organs, including skeletal muscle, liver, and brain tissue.

In normal aging, key molecular alterations include a decline in electron transport chain (ETC) complexes I and IV[8,9] and respiratory capacity.[10] This enzymatic deficit is associated with reduced mitochondrial membrane potential (MMP) and ATP output, as well as increased ROS generation, coinciding with the accumulation of oxidized proteins and clonal mitochondrial DNA (mtDNA) deletions.[11–13] Damage accumulation is exacerbated by impairments in quality-control mechanisms. Indeed, aging shifts mitochondrial dynamics toward fragmentation, a phenotype associated with the loss of fusion-fission regulators, such as optic atrophy 1 (OPA1),[14] and increased fission activity.[15] Regarding clearance, although some studies report stalled mitophagy flux contributing to organelle retention,[16] recent *in vivo* reporter analyses suggest that basal mitophagy rates may be preserved or even increased in aged tissues, yet they remain insufficient to counteract the overwhelming accumulation of damage.[17,18] Simultaneously, defects in the AMP-activated protein kinase-peroxisome proliferator-activated receptor gamma coactivator 1α (AMPK-PGC-1α) axis have been shown to compromise biogenesis in aging tissues (e.g., skeletal muscle), limiting the regenerative capacity of the network.[19,20] Ultimately, the leakage of mitochondrial components from these damaged organelles may trigger sterile inflammation via the cyclic guanosine monophosphate (GMP)-AMP synthase-stimulator of interferon genes (cGAS-STING) pathway,[17,21] linking mitochondrial instability to inflammation and degeneration. Of note, although these general mechanisms provide a necessary baseline, the specific manifestation of these defects in the brain is highly compartmentalized and will be discussed in detail in the subsequent section "age-related mitochondrial dysfunction in brain cells: from neurons and beyond."

Beyond energy failure, mitochondrial dysfunction is also recognized as a key driver of biological aging. The recently

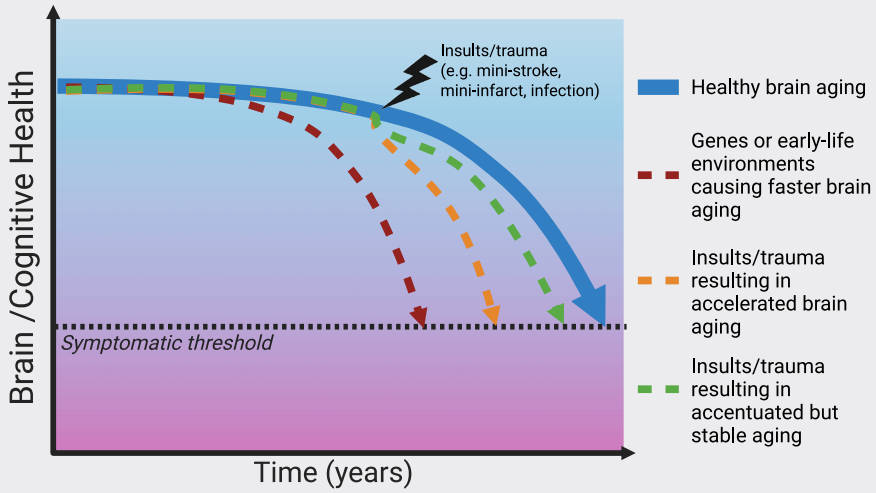
Please cite this article in press as: Grimm et al., Mitochondria and brain aging: From cell-specific dysfunction to intercellular cooperation, Neuron (2026), https://doi.org/10.1016/j.neuron.2026.04.048

CellPress
OPEN ACCESS

Box 1. Healthy vs. pathological aging

López-Otín et al. outline the following twelve hallmarks of aging: genomic instability, telomere attrition, epigenetic changes, loss of proteostasis, impaired macroautophagy, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, chronic inflammation, and dysbiosis.[22] They state that healthy aging reflects a dynamic balance among the molecular hallmarks of aging, thereby maintaining physiological resilience. In contrast, pathological aging occurs when these adaptive mechanisms fail, leading to cumulative molecular damage, chronic inflammation, and tissue dysfunction. Thus, the distinction between healthy and pathological aging appears not to lie in distinct mechanisms but instead in the degree, timing, and systemic integration of hallmark perturbations.

Using machine learning models applied to magnetic resonance imaging (MRI) data, Cole et al. demonstrated that individuals whose "brain-predicted age" was older than their chronological age had a higher risk of cognitive decline, frailty, and increased mortality.[24] As people age, their risk of cognitive decline and brain disease increases, but the trajectory of brain aging can vary significantly between individuals. Factors such as genetics, early-life environment, or life events such as trauma or infection can lead to faster, slower, or abruptly altered aging paths, as shown in the below image. This model also applies to biological aging in general. The authors emphasize that no single biomarker captures the complexity of aging; instead, integrative approaches combining neuroimaging, epigenetic clocks, and physiological measures are necessary to distinguish between healthy and pathological trajectories of brain aging and to guide early interventions.



Brain aging trajectories. The picture illustrates how people age differently in terms of brain health, with some reaching disease thresholds faster due to genetic or external factors. Adapted from Cole et al.[24] and created with BioRender.com.

revised framework of the twelve hallmarks of aging[22] highlights that mitochondria contribute to every hallmark, directly or indirectly. As discussed by Volkmar Weissig (2025), age-related mitochondrial alterations can influence all the other hallmarks of aging, namely genomic instability, telomere attrition, loss of proteostasis, nutrient-sensing deregulation, cellular senescence, stem cell exhaustion, and chronic inflammation.[23] Indeed, all these processes are energy dependent and depend either directly or indirectly on mitochondrial function and ATP production. In this sense, mitochondria act as the "mother" of all hallmarks of aging, underscoring the central role of mitochondrial health in longevity and cellular homeostasis. It is essential to note that, although aging inevitably alters mitochondrial function, it does not necessarily lead to cell death (Box 1). Understanding how age-related mitochondrial dysfunction occurs within specific brain regions and cell types will be key to disentangling healthy brain aging from pathological neurodegeneration.

REGIONAL VULNERABILITY IN THE AGING BRAIN: A BIOENERGETIC PERSPECTIVE

The brain is a highly heterogeneous tissue, in both its cellular composition and regional organization. Consequently, it is not surprising to observe region-specific vulnerability to aging, in which certain neuronal populations and circuits deteriorate earlier and more severely than others.

Mosharov et al. recently demonstrated that human cortical mitochondria are optimized for high respiratory output.[25] Although this supports complex connectivity, it forces these organelles near their thermodynamic limit, potentially rendering them more susceptible to age-related impairments. Although mitochondrial dysfunction is a hallmark of brain aging, relevant human studies demonstrate that this decline is not uniform. This section focuses on human *in vivo* and postmortem studies demonstrating that the age-related decline in mitochondrial function is not uniform across brain regions. Rather than a global bioenergetic failure, physiological brain aging in humans

Please cite this article in press as: Grimm et al., Mitochondria and brain aging: From cell-specific dysfunction to intercellular cooperation, Neuron (2026), https://doi.org/10.1016/j.neuron.2026.04.048

manifests as a mosaic of selective vulnerabilities, summarized in Table 1.

The substantia nigra pars compacta (SNpc) represents the most acute example of intrinsic mitochondrial vulnerability. Indeed, dopaminergic neurons in the SNpc are intrinsically vulnerable to oxidative stress due to dopamine metabolism, which generates ROS through both auto-oxidation and enzymatic degradation by monoamine oxidase (MAO).[33] These findings suggest an intrinsic redox vulnerability of the nigral region, likely contributing to its selective susceptibility to age-related mitochondrial dysfunction and neurodegeneration. Thus, dopaminergic neurons in the SNpc face a unique basal oxidative burden, creating an oxidative stress gradient where the SNpc exhibits ~2-fold higher damage than the cortex or basal ganglia.[12] These oxidative damages are associated with mtDNA deletions. Indeed, single-neuron PCR analysis has shown that SNpc neurons in aged humans accumulate a massive load of clonal mtDNA deletions (>43% heteroplasmy), which correlates directly with respiratory chain deficiency (cytochrome c oxidase [COX]-negative status).[11] In line with this, age-related declines in mitochondrial complex I activity, glutathione (GSH) depletion, and increased protein oxidation were reported in the substantia nigra.[26] In striking contrast, the caudate nucleus and putamen remain remarkably resilient. These regions accumulate significantly fewer mtDNA deletions (<3%)[11] and show no significant age-dependent decline in mitochondrial complex I activity or antioxidant defenses (superoxide dismutase [SOD], GSH).[26] More recently, proteomic analysis of the aging human SNpc reveals that while cytosolic mitochondrial proteins decrease, they paradoxically accumulate within neuromelanin granules (NMGs).[27] This subcellular distribution suggests that damaged mitochondria are not successfully recycled via mitophagy but are instead sequestered into NMGs, potentially obstructing lysosomal degradation. Together, these findings underscore that nigral vulnerability is characterized by a region-specific failure of organelle quality control, absent in the target fields of the same circuit.

In the cortex, vulnerability appears to correlate with phylogenetic development and metabolic flexibility. Neotenous regions, specifically the frontal and parietal cortices, are defined as brain areas that evolutionarily retain prolonged periods of developmental processes, such as synaptic plasticity and myelination, into adulthood.[28] They are metabolically characterized by high levels of aerobic glycolysis (AG), where glucose is diverted toward the pentose phosphate pathway to generate NADPH (essential for recharging antioxidant defenses). Human positron emission tomography (PET) and magnetic resonance imaging (MRI) reveal that the capacity for AG declines preferentially in the prefrontal cortex and precuneus, while oxidative rates remain relatively stable.[28] Real-time metabolic imaging with hyperpolarized ^{13}C-pyruvate confirmed a significant age-dependent impairment in the conversion of pyruvate to lactate in cortical gray matter, while flux into the Krebs cycle remained stable.[29] Postmortem analysis has also revealed increased oxidative damage, reduced antioxidant defenses, and reduced complex I activity in the frontal cortex with age.[31] In line with this, *in vivo* magnetic resonance spectroscopy (MRS) confirms a significant age-dependent decrease in GSH, specifically in the frontal and parietal cortices, while primary sensory regions such as the occipital cortex maintain a stable GSH level.[30] Interestingly, the cerebellum seems to maintain a stable glucose topography and antioxidant enzyme activities,[28,31] highlighting a posterior-to-anterior vulnerability gradient.

Vulnerability in the hippocampus, a region crucial for learning and memory, might rather be linked to an extrinsic mechanism, namely the failure of the nutrient supply line, because one of the earliest manifestations of spatial vulnerability appears to occur at the neurovascular interface. Indeed, aging is accompanied by progressive BBB breakdown, initially localized to the hippocampus, particularly in the cornu ammonis 1 (CA1) and dentate gyrus, and absent in the frontal cortex or white matter of the same individuals.[32] This leakage correlates with pericyte injury (cells that regulate capillary diameter and metabolic supply), as indicated by elevated cerebrospinal fluid levels of soluble platelet-derived growth factor receptor β (PDGFRβ). The detachment of pericytes may disrupt the precise delivery of glucose and oxygen required by hippocampal neurons. Postmortem analysis confirms that the aging hippocampus exhibits selective downregulation of Cu,Zn-SOD, catalase, and GSH reductase compared with the resilient cerebellum.[31] Thus, hippocampal vulnerability seems to arise from a double hit of compromised vascular supply and eroded enzymatic defense, whereas white matter tracts maintain barrier integrity and lactate flux into old age.[29,32]

Collectively, these data reveal that human brain aging is not a uniform decline but a mosaic of specific metabolic failures (Figure 2). Crucially, this map of physiological fragility mirrors the spatial progression of neurodegenerative diseases.[34] This overlap suggests that the age-dependent erosion of mitochondrial safety margins, whether via clearance failure, metabolic rigidity, or vascular uncoupling, creates the permissive environment necessary for disease pathology to take hold, effectively transforming a metabolically vulnerable region into a pathologically susceptible one.

AGE-RELATED MITOCHONDRIAL DYSFUNCTION IN BRAIN CELLS: FROM NEURONS AND BEYOND

Although mitochondrial dysfunction is a universal hallmark of aging, recent studies reveal that it manifests as a distinct, cell-type-specific mitochondrial alteration. The bioenergetic decline often measured in brain homogenates is, in reality, a composite of specific failures in neurons, astrocytes, oligodendrocytes, microglia, and endothelial cells of the BBB. Table 2 and Figure 3 summarize findings from human and animal data, highlighting cell-specific age-related mitochondrial impairment in the brain. The following sections discuss these findings.

Neurons: Compartment-specific mitochondrial alteration in aging

Neurons are highly structured and complex cells, with the various neuronal compartments (e.g., soma, dendrites, and axons) having distinct mitochondrial needs and responding differently to mitochondrial damage.[54] Consequently, aging does not affect the mitochondrial network uniformly but rather appears to target specific subcellular compartments based on their functional demands.

Please cite this article in press as: Grimm et al., Mitochondria and brain aging: From cell-specific dysfunction to intercellular cooperation, Neuron (2026), https://doi.org/10.1016/j.neuron.2026.04.048

CellPress
OPEN ACCESS

Table 1. Regional vulnerability in the aging human brain: A bioenergetic perspective

Brain region	Reference	Observed vulnerability vs. reference (internal control)	Model system	Age-related mitochondrial/bioenergetic defect
Substantia nigra (SN)	Floor and Wetzel[12]	high in SN vs. prefrontal cortex and basal ganglia	human, postmortem; ages: 33, 35, 46, 70, and 77 years	• 2-fold higher protein carbonyl content (oxidative damage) in SNpc vs. prefrontal cortex and basal ganglia • region-specific oxidative burden
Substantia nigra (SN)	Bender et al.[11]	high in SN vs. hippocampus and putamen	human, postmortem; aged (mean 77 years) vs. young (19–51 years)	• high accumulation of clonal mtDNA deletions (43.3% ± 9.3%) in SNpc • neurons in the hippocampus and putamen accumulate significantly fewer deletions (<3%). • mtDNA mutations correlate with respiratory chain deficiency
Substantia nigra (SN)	Venkateshappa et al.[26]	high in SN vs. caudate nucleus (striatum)	human, postmortem; lifespan study (4–80 years)	• increases in protein oxidation/nitration and significant loss of mitochondrial complex I activity • decrease in total SOD and GSH • no significant age-dependent decline in the caudate nucleus
Substantia nigra (SN)	Eggers et al.[27]	high in SN vs. young SN	human, postmortem; young (27.8 ± 1.3) vs. aged (76 ± 12.2)	• mitochondrial proteins decrease in the cytosol of aging SNpc neurons but accumulate in NMGs • NMGs may sequester mitochondria, potentially hindering their lysosomal clearance
Cortex	Goyal et al.[28]	high in prefrontal cortex vs. cerebellum and primary motor/ sensory cortex	human, *in vivo*; adult lifespan (20–82 years)	• reduction AG in neotenous regions (e.g., prefrontal cortex), possibly causing a loss of the NADPH supply • low baseline AG in primary motor and sensory cortices with minimal age-related metabolic change
Cortex	Uthayakumar et al.[29]	high in frontal cortex vs. deep gray matter and white matter	human, *in vivo*; adult lifespan (21–77 years)	• decrease in the conversion of pyruvate to lactate across all cortical lobes • no significant decline in deep gray matter (putamen, thalamus) and white matter
Cortex	Hu et al.[30]	high frontal cortex vs. occipital cortex	human, *in vivo*; adult lifespan (20–70 years)	• decrease in GSH levels in both the frontal and parietal cortices, correlating with cognitive decline • stable GSH levels in the occipital cortex during aging
Hippocampus and frontal cortex	Venkateshappa et al.[31]	high frontal cortex and hippocampus vs. cerebellum	human, postmortem; lifespan study (0.01–80 years)	• increases in protein oxidation and GFAP expression, associated with a selective decline in antioxidant enzyme activities (SOD, GPx) and mitochondrial complex I activity in the hippocampus and frontal cortex • no significant increase in oxidative damage and stable enzyme levels and complex I activity in the cerebellum
Hippocampus (CA1 and DG)	Montagne et al.[32]	high in CA1 and DG vs. CA3; low/resilient in white matter vs. hippocampus	human, *in vivo*; young (23–47 years) vs. aged (55–90 years)	• BBB breakdown in the CA1 and DG, correlating with markers of pericyte injury (elevated CSF sPDGFRβ), suggesting a disruption of the neurovascular unit • no increase in BBB permeability in white matter tracts, indicating preservation of barrier integrity

AG, aerobic glycolysis; BBB, blood-brain barrier; CSF, cerebrospinal fluid; DG, dentate gyrus; GFAP, glial fibrillary acidic protein; GPx, glutathione peroxidase; GSH, glutathione; mtDNA, mitochondrial DNA; NMGs, neuromelanin granules; SNpc, substantia nigra pars compacta; SOD, superoxide dismutase; sPDGFRβ, soluble platelet-derived growth factor receptor β.

Please cite this article in press as: Grimm et al., Mitochondria and brain aging: From cell-specific dysfunction to intercellular cooperation, Neuron (2026), https://doi.org/10.1016/j.neuron.2026.04.048

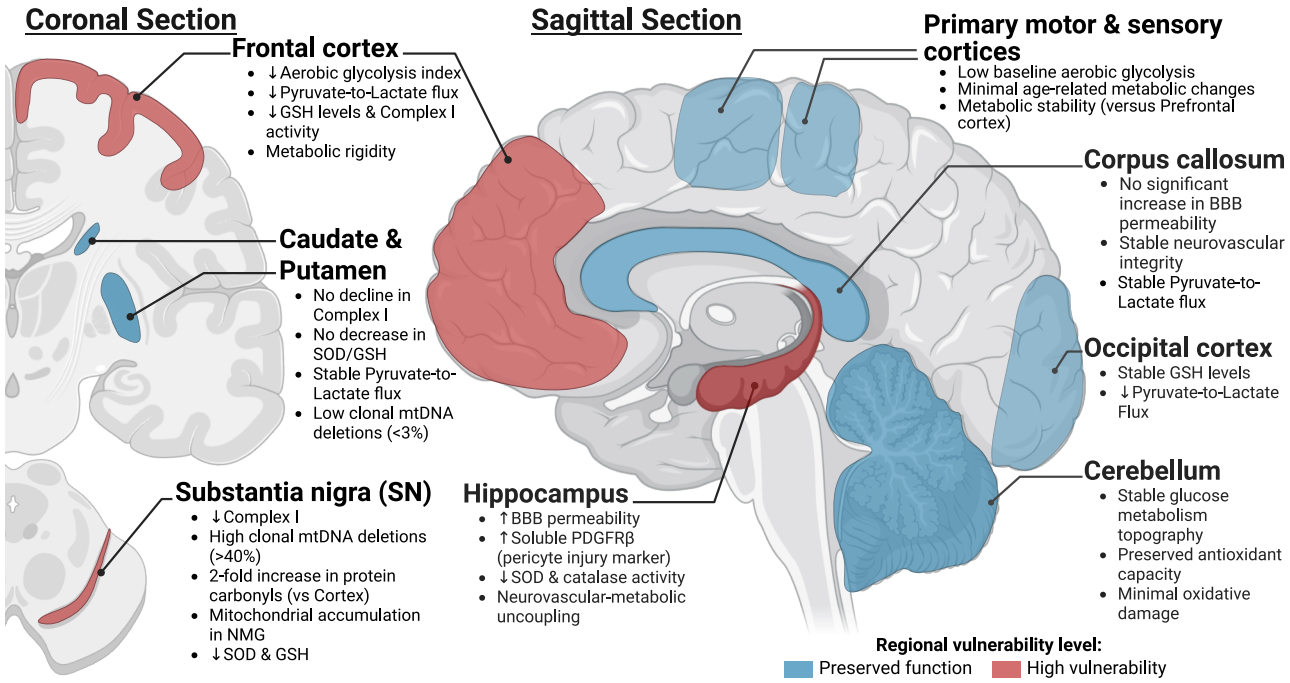


Figure 2. Overview of region-specific bioenergetic failure in the aging human brain

This figure synthesizes findings from selected primary studies on human subjects to provide an overview of regional vulnerability in mitochondrial and bioenergetic function. Due to differences in methodology across studies, direct quantitative comparisons between all regions should be interpreted with caution. The primary literature used to generate this figure is detailed and cited in Table 1. Regions colored red exhibit high susceptibility to age-related dysfunction compared with resilient regions (blue).

BBB, blood-brain barrier; GSH, glutathione; mtDNA, mitochondrial DNA; NMGs, neuromelanin granules; PDGFRβ, platelet-derived growth factor receptor β, SOD, superoxide dismutase; ↑, increase; ↓, decrease.

Created with BioRender.com.

Recent advanced human *in vitro* models provide critical platforms for studying age-related mitochondrial dysfunction. Namely, studies from Jerome Mertens's group revealed that induced pluripotent stem cell (iPSC)-derived neurons undergo rejuvenation by losing the age-dependent transcriptomic signatures of old donors.[35] However, when donor fibroblasts are directly converted into neurons (transdifferentiated or induced neurons [iNs]), they retain transcriptomic and functional aging signatures. Using this human neuronal model, Mertens' group showed that the primary driver of mitochondrial failure appears to be upstream of the organelle itself at the soma. In iNs from aged donors, the loss of the nuclear transport receptor Ras-related nuclear protein (RAN)-binding protein 17 (RanBP17) was paralleled by the deterioration of the nuclear pore complex.[35] This leakiness disrupted the import of nuclear-encoded factors, which are also required for mitochondrial maintenance. This defect is accompanied by transcriptional downregulation of OxPhos genes.[36] Crucially, the metabolic switch to OxPhos, required for neuronal identity, unmasks these latent defects, leading to a collapse of MMP and ATP production that was absent in the precursor fibroblasts. Building on these advances, we recently directly compared human neuronal aging models. First, we demonstrated that cortisol- and rotenone-induced mitochondrial stress in iNs from young donors can mimic the bioenergetic decline observed in aged neurons, providing a scalable tool for probing mitochondrial mechanisms of neuronal aging.[55] In parallel, we showed that iNs from aged donors retain key mitochondrial aging signatures observed in fibroblasts, including reduced ATP, lower MMP, and increased ROS.[13] Aged iNs also exhibited increased mitochondrial network fragmentation, increased mitochondrial mass (possibly reflecting defects in mitophagy), and a compensatory but insufficient shift toward glycolysis. Together, these studies underscore the value of human *in vitro* systems for dissecting mitochondrial aging in human neurons. Importantly, these recent findings suggest that mitochondrial dysfunction is, at least in part, intrinsic to neuronal aging rather than caused by external factors (e.g., nutrient deprivation and stress signals from surrounding cells/tissues), as mitochondrial defects are observed directly in neurons from aged donors.

Age-related alterations appear particularly prominent in synaptic mitochondria, which are highly energy demanding and exhibit earlier functional decline than somatic mitochondria. Indeed, synaptic mitochondria were shown to exhibit intrinsic hypersensitivity to calcium-induced opening of the permeability transition pore (mPTP), driven by elevated cyclophilin D levels.[39] This renders synapses uniquely vulnerable to bioenergetic collapse (ATP/MMP loss and ROS accumulation), oxidative damage (4-hydroxynonenal [4-HNE] accumulation), and mitochondrial swelling compared with the soma.[39,40] Furthermore, aging induces cleavage of transfer RNA-glutamate (tRNA-Glu) in glutamatergic neurons, generating fragments that specifically

Please cite this article in press as: Grimm et al., Mitochondria and brain aging: From cell-specific dysfunction to intercellular cooperation, Neuron (2026), https://doi.org/10.1016/j.neuron.2026.04.048

CellPress
OPEN ACCESS

Table 2. Cell-specific mitochondrial dysfunction in the aging brain

Cell type/ compartment	Reference	Model system	Identified age-related defect	Functional consequence
Neurons	Mertens et al.[35]	human, directly reprogrammed iNs; donors aged 0–89 years	• downregulation of nuclear transport receptor RanBP17 • nuclear pore leakiness	loss of the nuclear-mitochondrial coordination required for organelle maintenance
Neurons	Kim et al.[36]	human, directly reprogrammed iNs; donors aged 0–89 years	• downregulation of OxPhos genes • metabolic switch from glycolysis (fibroblast) to OxPhos (neuron) unmasking latent mitochondrial defects, leading to decreased MMP, reduced ATP, and increased ROS	high metabolic demand of the neuronal identity revealing the underlying age-related mitochondrial dysfunction that was tolerated in the fibroblast state
Neurons	Varghese et al.[13]	human, directly converted iNs; young (24–36 years) vs. aged (60–78 years)	• reduced basal respiration and ATP production • compensatory upregulation of glycolytic genes (PFKFB3)/flux • fragmentation of the mitochondrial network	structural fragmentation possibly serves as a morphological marker of bioenergetic crisis and metabolic rewiring in aged neurons
Neurons (dendrites)	Faitg et al.[37]	mouse hippocampus; young (4 months) vs. aged (18 months)	• adaptive elongation and increased complexity (volume/surface ratio) in dentate gyrus dendrites • mitochondrial atrophy in the soma, suggesting compartment-specific regulation	active remodeling of dendritic mitochondria to support synaptic plasticity in old age
Neurons (synapses)	Li et al.[38]	mouse hippocampus/ cortex and primary neurons; 3, 15, and 22 months	• cleavage of tRNA-Glu (Glu-5′tsRNA-CTC) by angiogenin • tRNA-Glu fragment entry into mitochondria and disruption of the translation of cristae-organizing proteins • loss of cristae integrity	disruption of cristae architecture impairs GLS activity and glutamate production, directly linking mitochondrial structure to neurotransmitter deficits
Neurons (synapses)	Olesen et al.[39]	mouse, hippocampus; 3, 6, 12, and 18 months	• premature loss of MMP • reduced ATP production • increase in ROS levels, driven by cyclophilin D accumulation • dysfunction in the synaptic pool occurring earlier than in the somatic pool	specific failure of synaptic bioenergetics correlates strongly with age-related deficits in spatial and recognition memory
Neurons (synapses)	Torres et al.[40]	mouse hippocampus; young (3 months) vs. aged (18 months)	• compartment-specific accumulation of lipid peroxidation markers in synaptic mitochondria compared with non-synaptic (somatic) ones • increased susceptibility of synaptic mitochondria to swelling • significantly higher oxidative damage in the synaptic compartment	compromised ability of synaptic mitochondria to sustain neurotransmission due to oxidative damages and physical swelling of the inner membrane
Astrocytes	Popov et al.[41]	human, neocortical tissue obtained during glioma resection; adult lifespan (18–71 years)	• significant astrocytic morphological atrophy (shrinkage of leaflets/ branches) • selective loss of mitochondrial cytochrome *c* and *b* types (respiration)	retraction of astrocytic processes and loss of gap junction coupling, possibly driven by the metabolic failure
Astrocytes	Diniz et al.[42]	rat and mouse primary astrocytes; aged culture models (cellular senescence)	• increased maximal respiration in senescent astrocytes • increased mitochondrial mass • decreased MMP and increased ROS • impaired mitophagy flux leading to the retention of damaged organelles, despite maintained biogenesis	mismatch between high biogenesis and blocked clearance leads to the retention of dysfunctional mitochondria, driving a pro-inflammatory state

(*Continued on next page*)

Please cite this article in press as: Grimm et al., Mitochondria and brain aging: From cell-specific dysfunction to intercellular cooperation, Neuron (2026), https://doi.org/10.1016/j.neuron.2026.04.048

Table 2. *Continued*

Cell type/ compartment	Reference	Model system	Identified age-related defect	Functional consequence
Astrocytes	Araujo et al.[43]	mouse primary astrocytes; aged culture models (cellular senescence)	• shift toward excessive fission and mitochondrial network fragmentation • reduced connectivity and calcium-buffering efficiency	fragmented networks are less efficient at ATP production, compromising homeostatic support
Astrocytes	Kim et al.[44]	human PSC-derived astrocytes; senescence model	• increased ROS levels, decreased MMP, and hyperfused mitochondrial network, indicating an imbalance toward fusion	mitochondrial defect paralleled by altered cellular morphology and reduced capacity to provide functional support to adjacent neurons
Astrocytes	Acevedo et al.[45]	mouse brain scRNA-seq; young (1–3 months) vs. aged (18–30 months)	• dysregulation of hub genes associated with mitochondrial respiration and glucose metabolism • increased genes associated with ketone body synthesis	age-dependent rewiring of astrocytic bioenergetics, switching from AG to OxPhos and ketone body utilization, possibly decreasing lactate supply to the neuron
Astrocytes	Zarate et al.[46]	mouse brain slices; young (3–4 months), middle-aged (12–15 months), aged (20–30 months)	• specific downregulation of calreticulin in perisynaptic astrocyte endfeet • impaired local calcium buffering at the synaptic cleft • prolonged mitochondrial calcium signals	destabilization of the synaptic microenvironment leading to aberrant astrocytic calcium signals, and potentially predisposing adjacent neurons to excitotoxicity
OPCs	Bame and Hill[47]	mouse cortex; young (1 month) vs. aged (18–21 months)	• smaller mitochondria (reduced volume) and reduced motility in aged OPCs • failure to execute the mitochondrial network reorganization and transient expansion required for differentiation in mature oligodendrocytes	inability to dynamically expand the mitochondrial network may maintain the OPCs in a progenitor state, preventing remyelination
OPCs	Neumann et al.[48]	rat OPCs; young (2–3 months) vs. aged (20–24 months)	• reduction in ATP levels and OCR, driving an energy-sensing dysregulation reversible by AMPK activation • unresponsiveness to differentiation signals	metabolic inability to exit the progenitor state possibly results in persistent white matter lesions in aging
Microglia	Gulen et al.[21]	mouse microglia; young (3–4 months) vs. aged (24–27 months)	• mitochondrial permeabilization and cytosolic mtDNA release • activation of cGAS-STING pathway	cGAS-STING pathway appears as an important driver of aging-related inflammation (chronic interferon signaling) and cognitive decline
Microglia	Minhas et al.[49]	mouse microglia; young (3–4 months) vs. aged (20–23 months)	• collapse of OCR and ECAR in aged myeloid cells, indicating suppression of both respiration and glycolysis • increased mitochondrial mass but decreased MMP • increased PGE_2-EP_2 signaling, putting cells in an energy-deficient state	energy-deficient state causally prevents energy-demanding functions such as phagocytosis, therefore impairing microglial function
Microglia	Mela et al.[50]	mouse microglia; young (4 months) vs. aged (18 months)	• metabolic shift toward glycolysis driven by the upregulation of PFKFB3 • accumulation of lipid droplets	this PFKFB3-driven glycolytic state supports cellular senescence and inflammation
Microglia	Hayashi et al.[51]	mouse microglia; young (2 months) vs. aged (24 months)	• downregulation of TFAM	TFAM loss possibly leads to mtDNA instability, ROS overproduction, and drives the secretion of pro-inflammatory cytokines
BBB	Sakamuri et al.[52]	mouse isolated microvessels; young (2–4 months) vs. aged (20–22 months)	• reduction in both respiration and glycolytic rates in aged microvessels, leading to a global ATP deficit • glycolytic suppression driven by the downregulation of key proteins, including GLUT1 and PFKFB3	collapse of energy pathways, exacerbated by substrate limitation (GLUT1), compromises the energy-demanding maintenance of the BBB

(*Continued on next page*)

Please cite this article in press as: Grimm et al., Mitochondria and brain aging: From cell-specific dysfunction to intercellular cooperation, Neuron (2026), https://doi.org/10.1016/j.neuron.2026.04.048

CellPress
OPEN ACCESS

Table 2. *Continued*

Cell type/ compartment	Reference	Model system	Identified age-related defect	Functional consequence
BBB	Tyrrell et al.[18]	mouse isolated vessels; young (2–3 months) vs. aged (18–19 months)	• reduction in ATP production, decreased MMP, and complex I/II activity • no change in mtDNA/nDNA ratio, indicating functional decline rather than mass loss • impaired mitophagy flux • mtDNA release and STING activation leading to IL-6 secretion	lack of ATP and inflammation compromises the energy-demanding maintenance of the BBB tight junctions, and increases permeability
BBB	Otu-Boakye et al.[53]	mouse brain endothelium; young (3 months) vs. aged (24 months)	• upregulation of FAO genes (*Cpt1a*) and oxidative stress signatures in lipid-laden endothelial cells • metabolic reprogramming to manage lipid overload	transcriptomic signature is associated with the upregulation of inflammatory markers (*Vcam1*, *Icam1*) and downregulated BBB junction genes

AMPK, AMP-activated protein kinase; BBB, blood-brain barrier; cGAS, cyclic GMP-AMP synthase; CPT1A, carnitine palmitoyltransferase 1A; ECAR, extracellular acidification rate; EP_2, prostaglandin E_2 receptor 2; FAO, fatty acid oxidation; GLS, glutaminase; GLUT1, glucose transporter 1; HK2, hexokinase 2; IL-6, interleukin 6; iNs, induced neurons; MMP, mitochondrial membrane potential; mtDNA, mitochondrial DNA; nDNA, nuclear DNA; OCR, oxygen consumption rate; OPC, oligodendrocyte precursor; OxPhos, oxidative phosphorylation; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase-3; PGE_2, prostaglandin E_2; RanBP17, Ras-related nuclear protein (RAN)-binding protein 17; ROS, reactive oxygen species; scRNA-seq, single-cell RNA sequencing; STING, stimulator of interferon genes; TFAM, mitochondrial transcription factor A; tRNA, transfer RNA.

disrupt mitochondrial translation and cristae architecture, thereby directly impairing glutamate synthesis at the synapse and leading to memory defects.[38]

Interestingly, an ultrastructural 3D reconstruction of hippocampal neurons in the mouse brain showed that age-related mitochondrial morphology is compartment specific.[37] In the dentate gyrus, dendritic mitochondria underwent an adaptive elongation, with mitochondria becoming larger, longer, and more complex (increased volume and surface area), contrasting with somatic atrophy. This age-related elongation was specific to the dentate gyrus and was not seen to the same extent in CA1 dendrites.[37]

Together, these findings suggest that neuronal aging is characterized by a compartmentalized crisis in which somatic transcriptional failure, driven by nuclear pore leakiness, co-occurs with premature synaptic bioenergetic collapse, driven by local translation defects and calcium hypersensitivity (Figure 3).

Astrocytes: Age-related mitochondrial dysfunction and metabolic reprogramming

Astrocytes are central regulators of brain homeostasis, coordinating neuronal metabolism, synaptic signaling, and BBB function. With aging, astrocytes undergo structural, transcriptional, and metabolic alterations that compromise their ability to support neurons and maintain central nervous system (CNS) resilience (reviewed in García-Domínguez[56] and Gildea and Liddelow[57]).

Recent studies have provided critical mechanistic insight into the complex nature of astrocytic aging. For instance, senescent murine astrocyte cultures have been shown to exhibit classic mitochondrial aging signatures, including increased ROS levels, decreased MMP, and increased mitochondrial fragmentation.[42,43] This dysfunction was accompanied by impaired mitophagy flux, resulting in the accumulation of damaged mitochondria. Interestingly, these senescent astrocytes also exhibited increased maximal respiration and mitochondrial biogenesis, interpreted as a compensatory response to the accumulating damage. However, aged astrocytes remained hypersensitive to stress (rotenone).[42] In the aged mouse cortex, although fragmentation and impaired mitophagy were conserved, mitochondrial biogenesis was reduced, a discrepancy likely explained by the heterogeneity of astrocytic subpopulations *in vivo*.[43]

Mitochondrial dysfunction is also evident in human astrocytes. Indeed, older astrocytes display impaired ETC function, characterized by decreased levels of reduced (electron-rich) cytochromes *b* and *c*.[41] These findings suggest faster electron transfer between cytochrome *c* and complex IV, possibly leading to reduced ROS generation (although ROS levels were not directly measured in this study). Unlike the hypertrophy seen in reactive gliosis, these functional defects were paralleled by significant morphological atrophy (reduced branching). Such mitochondrial alterations were not observed in neurons, emphasizing cell-type-specific mitochondrial responses during brain aging. In human pluripotent stem cell (hPSC)-derived astrocytes, senescent astrocytes showed increased ROS levels and decreased MMP, but they also displayed a hyperfused mitochondrial network, suggesting an imbalance in mitochondrial dynamics toward mitochondrial fusion.[44] These features were again paralleled by altered cellular morphology and reduced neuronal support.

Integrative network and transcriptomic analyses of the aging murine brain identified a robust metabolic switch signature in aged astrocytes, characterized by the transcriptional downregulation of glycolytic hub genes and a concomitant upregulation of genes associated with OxPhos.[45] This suggests that astrocytes undergo an age-related metabolic reprogramming. By shifting away from their normal glycolytic phenotype, which is essential

Please cite this article in press as: Grimm et al., Mitochondria and brain aging: From cell-specific dysfunction to intercellular cooperation, Neuron (2026), https://doi.org/10.1016/j.neuron.2026.04.048

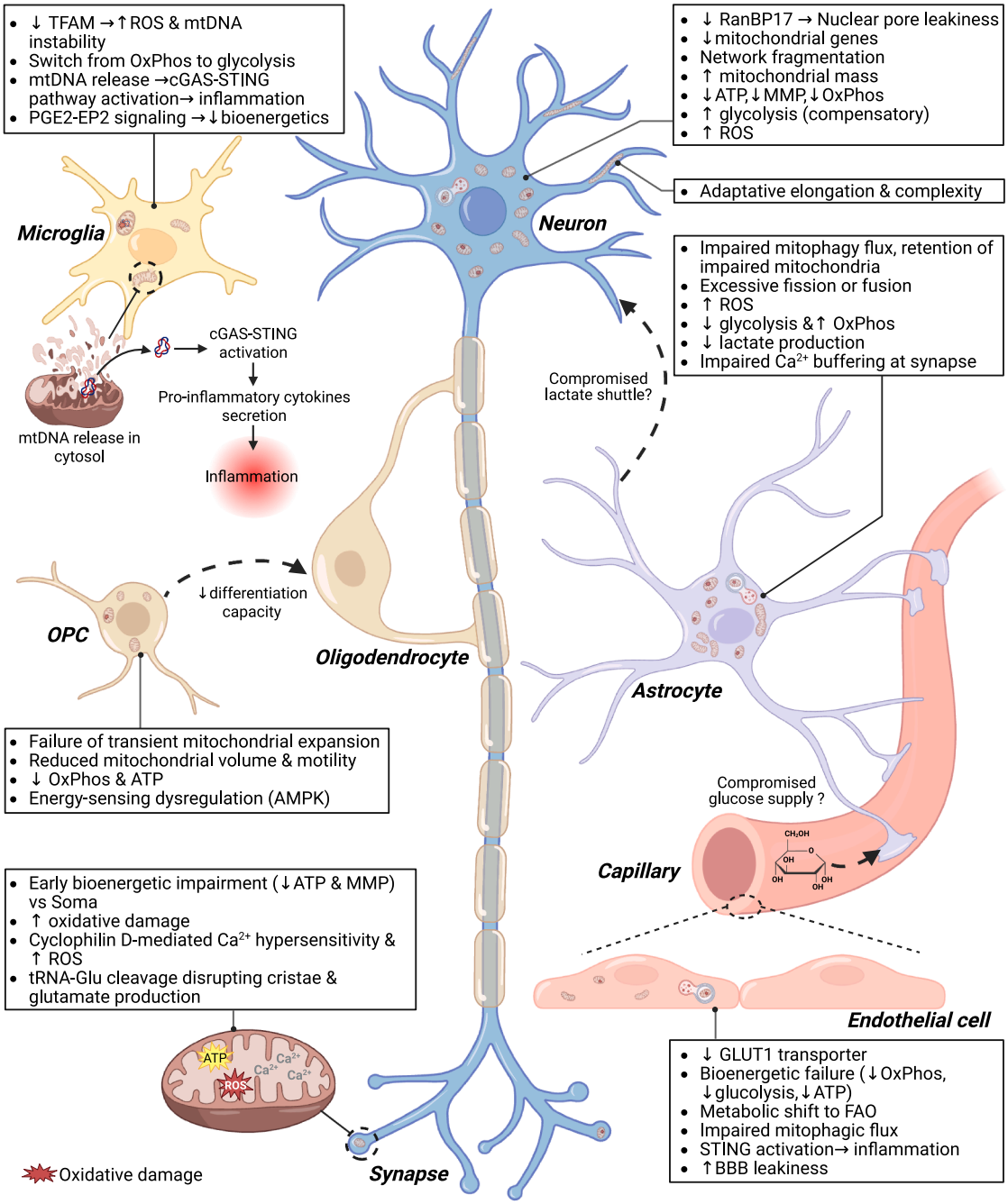


Figure 3. Cell-type-specific mechanisms of mitochondrial aging in the brain

This schematic illustrates the main mitochondrial impairments in the aging brain, highlighting distinct mitochondrial failure modes in neurons (soma, dendrites, and synapse), astrocytes, oligodendrocytes, microglia, and endothelial cells of the blood-brain barrier (BBB). These findings represent a synthesis of data from diverse model systems, including human postmortem tissue, *in vitro* human/rodent models, and *in vivo* rodent models. Therefore, the integration of these mechanisms across species should be interpreted with caution. The specific experimental models and primary literature supporting these findings are detailed in Table 2.

AMPK, AMP-activated protein kinase; cGAS-STING, cyclic GMP-AMP synthase-stimulator of interferon genes; FAO, fatty acid oxidation; MMP, mitochondrial membrane potential; mtDNA, mitochondrial DNA; OxPhos, oxidative phosphorylation; PGE_2-EP_2, prostaglandin E_2-prostaglandin E_2 receptor 2; RanBP17, RAN binding protein 17; TFAM, mitochondrial transcription factor A; tRNA, transfer RNA; ↑, increase; ↓, decrease; →, consequence.

Created with BioRender.com.

Please cite this article in press as: Grimm et al., Mitochondria and brain aging: From cell-specific dysfunction to intercellular cooperation, Neuron (2026), https://doi.org/10.1016/j.neuron.2026.04.048

for generating lactate to fuel neurons via the astrocyte-neuron lactate shuttle, aged astrocytes prioritize their own oxidative metabolism, thereby depriving adjacent neurons of critical energetic support.

Beyond metabolic starvation, astrocytic aging also compromises ionic buffering at the neurovascular unit and tripartite synapse. In the murine striatum, aged astrocytic endfeet suffer a specific downregulation of calreticulin, a key calcium-binding protein.[46] This depletion alters spontaneous calcium signals and shifts reliance onto endoplasmic reticulum calcium stores, ultimately destabilizing the perisynaptic microenvironment and contributing to both BBB impairment and neuronal excitotoxicity.

Overall, astrocytes exhibit significant morphological atrophy, impaired mitophagy flux, and an imbalance in mitochondrial dynamics. This is accompanied by a transcriptomic metabolic switch from glycolysis to OxPhos, which may compromise the astrocyte-neuron lactate shuttle and actively dismantles their neuroprotective and calcium-buffering capacities (Figure 3).

Oligodendrocytes: Mitochondria and age-related loss of progenitor differentiation capacity

Oligodendrocytes are highly specialized glial cells responsible for myelin production and axonal metabolic support, making them among the most energy-demanding cell types in the brain.[58] With age, oligodendrocytes show white matter atrophy, accumulation of abnormal myelin sheaths, and increased vulnerability to oxidative stress and mtDNA damage.[59] Because maintaining the extensive myelin network is metabolically costly, age-related mitochondrial impairments particularly affect the oligodendrocyte lineage, which relies heavily on ATP production for myelin synthesis.[58]

Studies in adult oligodendrocyte progenitor cells (OPCs) isolated from young and old rat brains showed that aged OPCs exhibit decreased differentiation capacity, paralleled by lower basal mitochondrial respiration and ATP production.[48] Interestingly, young OPCs treated with rotenone also showed impaired differentiation, whereas aged OPCs treated with metformin, an activator of the AMPK pathway, showed increased mitochondrial respiration, ATP content, and differentiation capacity. Importantly, metformin treatment enhanced remyelination in aged rats, suggesting that targeting mitochondrial metabolism can reverse age-associated deficits in myelination.

In vivo imaging in mice and ultrastructural analysis in the human cortex were recently performed to investigate mitochondrial dynamics across the oligodendrocyte lineage.[47] Oligodendrocyte differentiation is characterized by a transient expansion of mitochondrial networks, followed by a sharp reduction of mitochondrial content in the cells' processes during myelin compaction. Strikingly, aged OPCs presented smaller, less motile, and less abundant mitochondria, consistent with diminished capacity for differentiation and myelin formation. These findings highlight how mitochondrial reorganization is not only essential for developmental myelination but is also impaired in aging.

Together, these studies highlight that OPC aging involves a differentiation blockade resulting from impaired mitochondrial expansion and is paralleled by bioenergetic defects, thereby preventing the generation of new myelinating cells.

Microglia: Age-related immunometabolic switch

Microglia, the resident immune cells of the CNS, play critical roles in maintaining homeostasis, clearing debris, and modulating synaptic function. However, with aging, microglia undergo profound functional changes that compromise their ability to support brain health. A recent report describes how aged microglia exhibit dystrophic morphology, reduced surveillance, and a heightened pro-inflammatory "primed" state.[60] These cells adopt senescence-like features, including upregulation of cell cycle inhibitors and secretion of pro-inflammatory cytokines, alongside impairments in proteostasis and clearance. Together, these features render aged microglia less effective at maintaining homeostasis and more likely to contribute to chronic neuroinflammation.

At the metabolic level, aging seems to shift microglial energy homeostasis. Indeed, aged microglia have been shown to lose OxPhos capacity and rely more heavily on glycolysis via upregulation of 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase-3 (PFKFB3), a metabolic reprogramming that promotes a pro-inflammatory phenotype.[50]

Several experimental studies provide mechanistic evidence for these metabolic alterations. For instance, overexpression of mitochondrial transcription factor A (TFAM) in the mouse brain was shown to reduce age-related oxidative mtDNA damage in microglia, thereby preventing behavioral and cognitive impairments.[51] This finding directly linked age-related microglial mitochondrial dysfunction to cognitive decline. In line with this, hippocampal microglia from old mice exhibit more disrupted mitochondria and higher cytosolic mtDNA levels than those from young mice.[21] This cytosolic mtDNA leakage in aged microglia activates the cGAS-STING pathway, driving an inflammatory response that contributes to age-related neuronal dysfunction and cognitive impairments. Interestingly, STING inhibition reduced microglial activation and preserved neuronal survival, underscoring mitochondrial damage as a causal trigger of inflammaging. Another mechanism linking microglia and age-related mitochondrial impairments was also recently identified. Indeed, prostaglandin E_2 receptor 2 (EP_2) signaling was shown to drive bioenergetic alterations in aged microglia, leading to glycogen accumulation, impaired glycolysis, and reduced OxPhos.[49] Inhibition of EP_2 restored glucose metabolism, improved the ultrastructural integrity of hippocampal microglia, and rescued cognition in aged mice.

Collectively, these findings emphasize mitochondria as both sources and regulators of inflammation in the aging brain (Figure 3). Microglial aging appears closely linked to mitochondrial decline, causing microglia to become chronic drivers of neuroinflammation and neuronal vulnerability and establishing a mitochondrial-immune checkpoint in brain aging.

BBB: Age-related metabolic shift in endothelial cells

The BBB is essential for maintaining CNS homeostasis, but it is highly susceptible to age-related decline. As previously mentioned, the BBB becomes more permeable with age, especially in the hippocampus.[32] Aging is associated with reduced expression of tight junction proteins (claudin-5 and occludin), diminished pericyte coverage, alterations in astrocytic endfoot morphology, and impaired endothelial transport (reviewed in

Please cite this article in press as: Grimm et al., Mitochondria and brain aging: From cell-specific dysfunction to intercellular cooperation, Neuron (2026), https://doi.org/10.1016/j.neuron.2026.04.048

Knox et al.[61]). These changes compromise barrier integrity, leading to increased permeability, impaired nutrient transport, and enhanced vulnerability to neurodegeneration.

Emerging evidence links these structural and functional BBB alterations directly to mitochondrial dysfunction in brain endothelial cells. Isolated cerebral vessels from aged mice exhibit impaired mitochondrial respiration, loss of MMP, and stalled mitophagy flux compared with those of young mice.[18] Importantly, this dysfunction was accompanied by the activation of the STING-interleukin 6 (IL-6) signaling pathway and compromised tight junctions, which collectively contributed to BBB leakiness. Blocking IL-6 signaling restored mitochondrial function and improved barrier integrity, underscoring the interplay between inflammation and mitochondrial health in vascular aging. Interestingly, aged brain microvessels exhibit a collapsed bioenergetic profile with reduced rates of both glycolysis and respiration, possibly due to downregulation of glucose transporter 1 (GLUT1) and PFKFB.[52] To compensate for this energy crisis, aged vessels increase their reliance on glutamine utilization. Recent transcriptomic and proteomic evidence revealed that brain endothelial cells in aged mice accumulate lipid droplets and undergo metabolic reprogramming.[53] Lipid-laden endothelial cells displayed reduced glycolysis, downregulated mitochondrial complex I- and IV-related genes, and increased reliance on fatty acid oxidation (FAO). Of note, because FAO generates more ROS than glycolysis, it is usually not primarily used for energy production in the brain.[62] The metabolic shift from glycolysis to FAO was associated with increased endothelial senescence markers and inflammation, and with downregulation of BBB integrity genes, such as claudin-5 and occludin.[53] These findings suggest that mitochondrial dysfunction and altered metabolism are central drivers of BBB breakdown in the aging brain.

In summary, BBB aging is characterized not only by structural deterioration but also by mitochondrial alterations in endothelial cells, involving impaired mitophagy, metabolic reprogramming, and chronic inflammation, paralleled by lipid droplet accumulation, which compromises the integrity and transport capacity of the BBB (Figure 3).

Taken together, these findings suggest distinct checkpoints of mitochondrial failure across various brain cell types (Figure 3). In post-mitotic, highly compartmentalized neurons, aging seems to manifest as transcriptional erosion, driven by transcriptional silencing due to nuclear pore leakiness in the soma and by local translation failure resulting from tRNA cleavage at the synapse. By contrast, in proliferating glia, aging appears to induce a maladaptive metabolic switch, in which astrocytes abandon lactate production and endothelial cells shift to FAO, dismantling the metabolic support networks required for neuronal survival. To fully understand this cellular mosaic, future studies must evaluate mitochondrial dysfunction across diverse brain cell types in parallel to determine the exact temporal sequence of these events and identify which cell type fails first.

EMERGING EVIDENCE OF AGING EFFECTS ON IMT AND POTENTIAL OF MT

The brain's extraordinary energy demands are sustained not only by cell-autonomous mitochondrial function but also through continuous metabolic cooperation.[63] Recent discoveries highlight intercellular mitochondrial transfer (IMT) as a critical layer of this cooperation, in which mitochondria are shuttled between brain cells via tunneling nanotubes (TNTs), extracellular vesicles (EVs), or gap junctions (reviewed in Fairley et al.[64]). In the healthy brain, this bidirectional process allows glial cells, particularly astrocytes, to donate functional mitochondria to stressed neurons, thereby restoring ATP production and buffering oxidative stress.[65] Conversely, neurons have been shown to transfer damaged mitochondria to adjacent astrocytes, where they are degraded via a process termed "transmitophagy."[66] Although emerging evidence indicates changes in IMT across several brain disorders,[64] the literature on brain aging still remains scarce.

Nevertheless, a recent study showed that mitochondria released by astrocytes from aged mice (22 months) exhibit significantly lower MMP and oxygen consumption rates than those from young mice.[67] This implies that in the aged brain, astrocytes may transfer dysfunctional, bioenergetically compromised organelles rather than healthy ones, potentially propagating metabolic failure to neurons. Interestingly, the dynamics of IMT also appear to change with age. A recent study reported that astrocytic mitochondrial transfer to endothelial cells at the BBB increased with aging.[68] The authors used an inducible mouse model expressing the green fluorescent protein mito-dendra2 (mtD2) in astrocytic mitochondria and examined mitochondrial transfer to endothelial cells in purified brain capillaries from 3- and 7-month-old animals. They observed a higher percentage of mtD2-positive capillaries in older mice and demonstrated that this transfer occurs via EVs. It is crucial to note that the aged cohort was only 7 months old (early middle age). Therefore, the increased transfer likely represents an early compensatory attempt to rescue the failing bioenergetics of the BBB. In contrast, a significant reduction in mitochondrial transfer efficiency was observed in truly geriatric mice (20 months old), more specifically, a decreased transfer from Dmp1-expressing astrocytes to endothelial cells.[69] Using confocal microscopy and flow cytometry to track labeled organelles, they quantified a significant reduction in the number of endothelial cells containing astrocyte-derived mitochondria in the aged brain. They further found that this decline was driven by age-dependent downregulation of astrocytic mitofusin 2 (Mfn2), which directly contributes to BBB leakage.

Taken together, these studies suggest that astrocytic secretion of mitochondria is an adaptive attempt to counterbalance mitochondrial dysfunction across brain cell types at early stages of aging but might be detrimental later, when astrocyte mitochondria are themselves energetically compromised (Figure 4). This fascinating field certainly deserves more attention, and further experiments are needed to uncover the underlying mechanisms of IMT in aging.

Importantly, the discovery of natural mitochondrial transfer between cells has inspired a novel therapeutic strategy: mitochondrial transplantation (MT). This approach aims to artificially replicate the rescue effect by delivering viable, exogenous mitochondria into damaged cells. Preclinical studies across various disease models consistently demonstrate that MT enhances neuronal survival, restores respiratory chain function, and reduces oxidative stress (reviewed in Riou et al.[70]). These findings

Please cite this article in press as: Grimm et al., Mitochondria and brain aging: From cell-specific dysfunction to intercellular cooperation, Neuron (2026), https://doi.org/10.1016/j.neuron.2026.04.048

CellPress
OPEN ACCESS

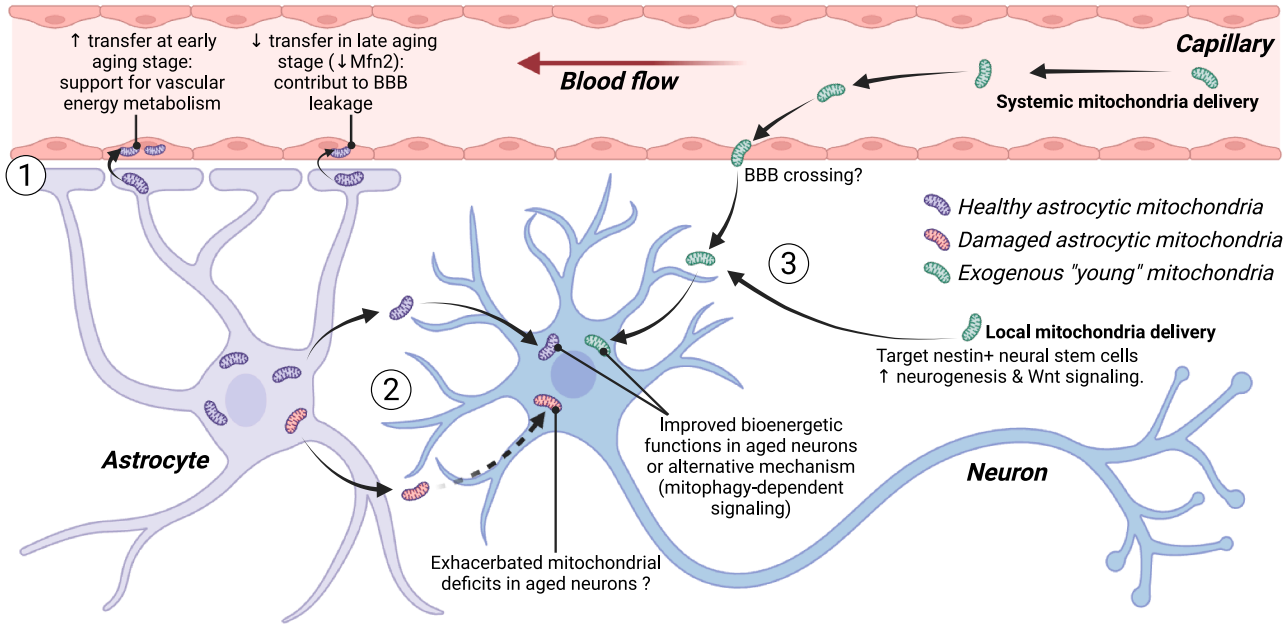


Figure 4. Intercellular mitochondrial transfer and transplantation in the aging brain

This schematic illustrates intercellular mitochondrial transfer (IMT) and the therapeutic potential of mitochondrial transplantation (MT) in the context of brain aging, based on published evidence. (1) In early aging stages, astrocytes may donate functional mitochondria to endothelial cells via extracellular vesicles, supporting vascular energy metabolism and blood-brain barrier (BBB) function. However, in late aging, this transfer decreases due to the downregulation of astrocytic Mfn2, contributing to BBB leakage. (2) Astrocytes can also transfer mitochondria to neurons. This is likely a process that is initially neuroprotective but may become detrimental when astrocytic mitochondria are damaged with age. (3) Local delivery of exogenous mitochondria targets neural stem cells and restores neurogenesis via Wnt signaling. Systemic delivery of exogenous mitochondria has been shown to reach the brain, where they improve mitochondrial bioenergetics and promote functional recovery of neurons. Transplanted mitochondria may also function as signaling organelles, triggering repair pathways via mitophagy. How they cross the BBB remains to be determined. The primary literature used to generate this figure is detailed and cited in the section "emerging evidence of aging effects on IMT and potential of MT." ↑, increase; ↓, decrease. Created with BioRender.com.

have established MT as a promising strategy to restore brain energy metabolism in pathological conditions.

Direct experimental evidence in the context of brain aging also supports these beneficial effects. In aged mice, the systemic injection of mitochondria isolated from young livers or secreted by young astrocytes has been shown to reverse key aging phenotypes. For instance, injecting young astrocyte-derived mitochondria reduced hippocampal levels of the aging factor C-C motif chemokine 11 (CCL11) and improved cognitive function in 22-month-old mice.[67] In line with this, intravenous administration of mitochondria isolated from the liver of young mice (1 month old) increased levels of succinate dehydrogenase subunit B of complex II (SDHB) selectively in the hippocampus of 12-month-old animals.[71] Similarly, systemic injection of liver mitochondria from young mice (2-month-old) reduced mtDNA deletions in several organs, including the brains of 18-month-old mice.[72] In parallel, increased activity of pyruvate dehydrogenase (PDH), alpha-ketoglutarate dehydrogenase (α-KGDH), and NADH dehydrogenase was observed, along with higher ATP levels and lower ROS, in the brains of mitochondria-treated aged animals compared with untreated ones. Importantly, these bioenergetic improvements were accompanied by better cognitive performance in the Morris water maze and enhanced motor endurance.

Direct intra-hippocampal injection of mitochondria isolated from young (2 months) rats into aged (20 months) rats was also shown to normalize the age-related decrease in hippocampal ATP levels and mitochondrial complexes I–IV activity.[73] Strikingly, the transplanted mitochondria were preferentially internalized by Nestin-positive neural stem cells in the dentate gyrus rather than by mature neurons. This targeted uptake improved spatial learning and memory in the Morris water maze, an effect mechanistically linked to the restoration of hippocampal neurogenesis (increased doublecortin-positive cells) and activation of the Wnt signaling pathway.

Although these results are promising, critical questions remain regarding the mechanism and delivery of MT: can systemically delivered mitochondria cross the BBB, and if so, do they exhibit regional or cell-type specificity? Current advances focus on engineering transplants with peptide coatings or nanocarriers to enhance CNS delivery[74,75]; however, the precise fate of systemically injected mitochondria remains to be fully elucidated. Although local injection studies demonstrate targeted uptake by Nestin-positive neural stem cells,[73] it is unclear whether intravenous delivery achieves similar specificity or whether therapeutic effects are mediated indirectly through systemic metabolic improvements. Furthermore, recent work challenges the assumption that transplanted mitochondria function solely as bioenergetic rescue. A consensus statement by Brestoff et al. highlights that transplanted mitochondria may exert effects beyond metabolic support, serving as signaling organelles.[76] Supporting this, a recent report showed that even dysfunctional

Please cite this article in press as: Grimm et al., Mitochondria and brain aging: From cell-specific dysfunction to intercellular cooperation, Neuron (2026), https://doi.org/10.1016/j.neuron.2026.04.048

or mtDNA-depleted mitochondria could enhance endothelial cell engraftment in ischemic tissues.[77] The therapeutic benefit was not driven by ATP production but by the activation of mitophagy-dependent signaling pathways in the recipient cells. Although these findings are outside the brain's immediate context, they suggest that MT may operate through alternative mechanisms, such as triggering quality-control pathways or structural signaling, thereby broadening the potential therapeutic landscape for age-related neurodegeneration.

Although significant challenges remain regarding long-term safety and immune recognition, MT represents a promising frontier that leverages the brain's natural capacity for mitochondrial exchange to reverse age-related metabolic decline (Figure 4).

TARGETING MITOCHONDRIA IN BRAIN AGING: OVERVIEW OF CLINICAL PERSPECTIVES

Translating preclinical insights into human therapies is the ultimate goal for mitigating age-related cognitive decline. Promising anti-aging therapies have already reached the clinical stage and target different aspects of age-related mitochondrial impairments in humans.

For instance, the ongoing Mito-Frail Trial (expected completion in 2027) evaluates whether reducing mitochondrial oxidative stress with MitoQ directly improves cerebrovascular and cognitive function in older adults (NCT06027554). Elamipretide, a mitochondria-targeted peptide, is currently being investigated for its ability to improve cognitive outcomes and circulating neuroplasticity markers (such as brain-derived neurotrophic factor [BDNF]) in healthy aging (NCT07275424), with an expected trial completion of April 2026. In another approach, oral NMN (nicotinamide mononucleotide) was shown to successfully elevate blood NAD^+ levels, translating into tangible functional benefits, including reduced fatigue and improved sleep quality in older adults.[78] A novel related precursor, dihydronicotinamide mononucleotide (NMNH), is also being tested to evaluate its systemic impact in healthy adults (NCT06889740).

We previously discussed that mitochondrial quality control is important for maintaining a homogeneous mitochondrial population and preventing the accumulation of damaged organelles. Urolithin A, a postbiotic known to potently induce mitophagy, has been shown to improve muscle strength and exercise performance in middle-aged adults.[79] Its effects on cognitive function are currently being evaluated (NCT07060898). Similarly, pyrroloquinoline quinone (PQQ), which induces mitochondrial biogenesis, has been tested in older subjects with mild cognitive impairment.[80] PQQ supplementation increased serum BDNF levels, cerebral oxygenation saturation levels, and Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) scores for orientation compared with placebo.

Alongside targeted pharmaceuticals, dietary and lifestyle interventions that fundamentally rewire brain metabolism are gaining clinical traction. For instance, the ketogenic diet and ketone supplements have been shown to provide alternative mitochondrial substrates (e.g., β-hydroxybutyrate) that improve cognition and stabilize the brain network.[81,82] Similarly, the Mediterranean diet, which is based on whole plant foods, olive oil, and lean proteins and avoids processed foods, appeared to protect against cerebral glucose decline.[83] Finally, aerobic exercise was shown to elevate circulating lactate to compensate for glucose hypometabolism and to increase BDNF levels.[84] Currently, these metabolic strategies primarily aim to prevent or mitigate pathologies such as Alzheimer's disease. Moving forward, their efficacy in actively preserving mitochondrial health during healthy aging warrants rigorous clinical investigation.

Collectively, the functional outcomes from these pioneering clinical trials underscore the critical importance of mitochondria as therapeutic targets. They demonstrate that actively mitigating organelle dysfunction can successfully translate into tangible cognitive and physical resilience in older adults.

CONCLUSIONS

Brain aging is not solely a neuronal phenomenon but a complex, multicellular process driven by cell-type-specific mitochondrial dysfunction. From impaired energy metabolism in neurons and astrocytes to compromised BBB integrity and chronic inflammation in endothelial and microglial cells, mitochondrial health emerges as a unifying factor in age-related brain vulnerability. Notably, certain brain regions, such as the hippocampus, frontal cortex, and substantia nigra, exhibit heightened susceptibility to mitochondrial decline, reflecting region-specific metabolic demands and redox sensitivities. Framed within the foundational theories of Harman and Hayflick, healthy brain aging may be viewed as the preservation of a dynamic metabolic equilibrium between the brain's diverse cellular players. In contrast, pathological aging likely arises when this intercellular energy balance collapses, leading to inflammation, synaptic failure, and neurodegeneration. Novel strategies such as IMT and MT offer promising therapeutic avenues but remain in the early stages of development in the context of brain aging. As we refine our understanding of mitochondrial roles in the aging brain, key questions arise. Do all brain cell types age at the same pace, or do some act as early sentinels of mitochondrial dysfunction? Specifically, which cell type first shows mitochondrial impairments, and how might this lead to vulnerability in specific brain regions? Addressing these questions will be critical for designing targeted, cell-specific strategies to preserve brain function across the lifespan.

ACKNOWLEDGMENTS

This work was supported by grants from the OPO Foundation, Dementia Research, Synapsis Foundation Switzerland (2022-PI05), and the Bürgenstock Foundation.

DECLARATION OF INTERESTS

The authors declare no competing interests.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this manuscript, the authors used Google's large language model (Gemini Advanced version) to refine the language and grammar of the text and to assist with literature searches to identify relevant publications. The authors have reviewed and edited the output and take full responsibility for the content of this publication.

Please cite this article in press as: Grimm et al., Mitochondria and brain aging: From cell-specific dysfunction to intercellular cooperation, Neuron (2026), https://doi.org/10.1016/j.neuron.2026.04.048

CellPress
OPEN ACCESS

REFERENCES

1. Harman, D. (1981). The aging process. Proc. Natl. Acad. Sci. USA *78*, 7124–7128. https://doi.org/10.1073/pnas.78.11.7124.

2. Hayflick, L. (1998). How and why we age. Exp. Gerontol. *33*, 639–653. https://doi.org/10.1016/s0531-5565(98)00023-0.

3. Camandola, S., and Mattson, M.P. (2017). Brain metabolism in health, aging, and neurodegeneration. EMBO J. *36*, 1474–1492. https://doi.org/10.15252/embj.201695810.

4. Cunnane, S.C., Trushina, E., Morland, C., Prigione, A., Casadesus, G., Andrews, Z.B., Beal, M.F., Bergersen, L.H., Brinton, R.D., de la Monte, S., et al. (2020). Brain energy rescue: an emerging therapeutic concept for neurodegenerative disorders of ageing. Nat. Rev. Drug Discov. *19*, 609–633. https://doi.org/10.1038/s41573-020-0072-x.

5. Bordone, M.P., Salman, M.M., Titus, H.E., Amini, E., Andersen, J.V., Chakraborti, B., Diuba, A.V., Dubouskaya, T.G., Ehrke, E., Espindola de Freitas, A., et al. (2019). The energetic brain – A review from students to students. J. Neurochem. *151*, 139–165. https://doi.org/10.1111/jnc.14829.

6. Demetrius, L.A., Eckert, A., and Grimm, A. (2021). Sex differences in Alzheimer's disease: metabolic reprogramming and therapeutic intervention. Trends Endocrinol. Metab. *32*, 963–979. https://doi.org/10.1016/j.tem.2021.09.004.

7. Grimm, A., and Eckert, A. (2017). Brain aging and neurodegeneration: from a mitochondrial point of view. J. Neurochem. *143*, 418–431. https://doi.org/10.1111/jnc.14037.

8. Navarro, A., and Boveris, A. (2004). Rat brain and liver mitochondria develop oxidative stress and lose enzymatic activities on aging. Am. J. Physiol. Regul. Integr. Comp. Physiol. *287*, R1244–R1249. https://doi.org/10.1152/ajpregu.00226.2004.

9. Ojaimi, J., Masters, C.L., Opeskin, K., McKelvie, P., and Byrne, E. (1999). Mitochondrial respiratory chain activity in the human brain as a function of age. Mech. Ageing Dev. *111*, 39–47. https://doi.org/10.1016/s0047-6374(99)00071-8.

10. Pandya, J.D., Grondin, R., Yonutas, H.M., Haghnazar, H., Gash, D.M., Zhang, Z., and Sullivan, P.G. (2015). Decreased mitochondrial bioenergetics and calcium buffering capacity in the basal ganglia correlates with motor deficits in a nonhuman primate model of aging. Neurobiol. Aging *36*, 1903–1913. https://doi.org/10.1016/j.neurobiolaging.2015.01.018.

11. Bender, A., Krishnan, K.J., Morris, C.M., Taylor, G.A., Reeve, A.K., Perry, R.H., Jaros, E., Hersheson, J.S., Betts, J., Klopstock, T., et al. (2006). High levels of mitochondrial DNA deletions in substantia nigra neurons in aging and Parkinson disease. Nat. Genet. *38*, 515–517. https://doi.org/10.1038/ng1769.

12. Floor, E., and Wetzel, M.G. (1998). Increased Protein Oxidation in Human Substantia Nigra Pars Compacta in Comparison with Basal Ganglia and Prefrontal Cortex Measured with an Improved Dinitrophenylhydrazine Assay. J. Neurochem. *70*, 268–275. https://doi.org/10.1046/j.1471-4159.1998.70010268.x.

13. Varghese, N., Szabo, L., Cader, M.Z., Lejri, I., Grimm, A., and Eckert, A. (2025). Tracing mitochondrial marks of neuronal aging in iPSCs-derived neurons and directly converted neurons. Commun. Biol. *8*, 723. https://doi.org/10.1038/s42003-025-08152-2.

14. Tezze, C., Romanello, V., Desbats, M.A., Fadini, G.P., Albiero, M., Favaro, G., Ciciliot, S., Soriano, M.E., Morbidoni, V., Cerqua, C., et al. (2017). Age-Associated Loss of OPA1 in Muscle Impacts Muscle Mass, Metabolic Homeostasis, Systemic Inflammation, and Epithelial Senescence. Cell Metab. *25*, 1374–1389.e6. https://doi.org/10.1016/j.cmet.2017.04.021.

15. Goulding, R.P., Charlton, B.T., Breedveld, E.A., van der Laan, M., Strating, A.R., Noort, W., Kolodyazhna, A., Appelman, B., van Vugt, M., Grootemaat, A.E., et al. (2024). Skeletal muscle mitochondrial fragmentation predicts age-associated decline in physical capacity. Aging Cell *24*, e14386. https://doi.org/10.1111/acel.14386.

16. Sun, N., Yun, J., Liu, J., Malide, D., Liu, C., Rovira, I.I., Holmström, K.M., Fergusson, M.M., Yoo, Y.H., Combs, C.A., et al. (2015). Measuring In Vivo Mitophagy. Mol. Cell *60*, 685–696. https://doi.org/10.1016/j.molcel.2015.10.009.

17. Jiménez-Loygorri, J.I., Villarejo-Zori, B., Viedma-Poyatos, Á., Zapata-Muñoz, J., Benítez-Fernández, R., Frutos-Lisón, M.D., Tomás-Barberán, F.A., Espín, J.C., Area-Gómez, E., Gomez-Duran, A., et al. (2024). Mitophagy curtails cytosolic mtDNA-dependent activation of cGAS/STING inflammation during aging. Nat. Commun. *15*, 830. https://doi.org/10.1038/s41467-024-45044-1.

18. Tyrrell, D.J., Blin, M.G., Song, J., Wood, S.C., and Goldstein, D.R. (2020). Aging Impairs Mitochondrial Function and Mitophagy and Elevates Interleukin 6 Within the Cerebral Vasculature. J. Am. Heart Assoc. *9*, e017820. https://doi.org/10.1161/jaha.120.017820.

19. Reznick, R.M., Zong, H., Li, J., Morino, K., Moore, I.K., Yu, H.J., Liu, Z.-X., Dong, J., Mustard, K.J., Hawley, S.A., et al. (2007). Aging-Associated Reductions in AMP-Activated Protein Kinase Activity and Mitochondrial Biogenesis. Cell Metab. *5*, 151–156. https://doi.org/10.1016/j.cmet.2007.01.008.

20. Short, K.R., Bigelow, M.L., Kahl, J., Singh, R., Coenen-Schimke, J., Raghavakaimal, S., and Nair, K.S. (2005). Decline in skeletal muscle mitochondrial function with aging in humans. Proc. Natl. Acad. Sci. USA *102*, 5618–5623. https://doi.org/10.1073/pnas.0501559102.

21. Gulen, M.F., Samson, N., Keller, A., Schwabenland, M., Liu, C., Glück, S., Thacker, V.V., Favre, L., Mangeat, B., Kroese, L.J., et al. (2023). cGAS–STING drives ageing-related inflammation and neurodegeneration. Nature *620*, 374–380. https://doi.org/10.1038/s41586-023-06373-1.

22. López-Otín, C., Blasco, M.A., Partridge, L., Serrano, M., and Kroemer, G. (2023). Hallmarks of aging: An expanding universe. Cell *186*, 243–278. https://doi.org/10.1016/j.cell.2022.11.001.

23. Weissig, V. (2025). Mitochondrial dysfunction as the "mother" of all hallmarks of aging. J. Mitochondria Plastids Endosymbiosis *3*, 2560191. https://doi.org/10.1080/28347056.2025.2560191.

24. Cole, J.H., Marioni, R.E., Harris, S.E., and Deary, I.J. (2018). Brain age and other bodily 'ages': implications for neuropsychiatry. Mol. Psychiatry *24*, 266–281. https://doi.org/10.1038/s41380-018-0098-1.

25. Mosharov, E.V., Rosenberg, A.M., Monzel, A.S., Osto, C.A., Stiles, L., Rosoklija, G.B., Dwork, A.J., Bindra, S., Junker, A., Zhang, Y., et al. (2025). A human brain map of mitochondrial respiratory capacity and diversity. Nature *641*, 749–758. https://doi.org/10.1038/s41586-025-08740-6.

26. Venkateshappa, C., Harish, G., Mythri, R.B., Mahadevan, A., Bharath, M.M.S., and Shankar, S.K. (2011). Increased Oxidative Damage and Decreased Antioxidant Function in Aging Human Substantia Nigra Compared to Striatum: Implications for Parkinson's Disease. Neurochem. Res. *37*, 358–369. https://doi.org/10.1007/s11064-011-0619-7.

27. Eggers, B., Hausherr, M., Lim, M., Schork, K., Karacora, B., Grugel, R., Eisenacher, M., Aldea, I.G., Riederer, P., Gerlach, M., et al. (2025). A Spatially Resolved View on the Aging Substantia nigra: An Exploratory Proteomic Study. Adv. Biol. (Weinh) *9*, e00358. https://doi.org/10.1002/adbi.202500358.

28. Goyal, M.S., Vlassenko, A.G., Blazey, T.M., Su, Y., Couture, L.E., Durbin, T.J., Bateman, R.J., Benzinger, T.L.S., Morris, J.C., and Raichle, M.E. (2017). Loss of Brain Aerobic Glycolysis in Normal Human Aging. Cell Metab. *26*, 353–360.e3. https://doi.org/10.1016/j.cmet.2017.07.010.

29. Uthayakumar, B., Soliman, H., Bragagnolo, N.D., Cappelletto, N.I.C., Lee, C.Y., Geraghty, B., Chen, A.P., Perks, W.J., Ma, N., Heyn, C., et al. (2023). Age-associated change in pyruvate metabolism investigated with hyperpolarized ^{13}C-MRI of the human brain. Hum. Brain Mapp. *44*, 4052–4063. https://doi.org/10.1002/hbm.26329.

30. Hu, X., Pan, K., Zhao, M., Lv, J., Wang, J., Zhang, X., Liu, Y., Song, Y., Gudmundson, A.T., Edden, R.A.E., et al. (2024). Brain extended and closed forms glutathione levels decrease with age and extended glutathione is associated with visuospatial memory. NeuroImage *293*, 120632. https://doi.org/10.1016/j.neuroimage.2024.120632.

31. Venkateshappa, C., Harish, G., Mahadevan, A., Srinivas Bharath, M.M., and Shankar, S.K. (2012). Elevated Oxidative Stress and Decreased Antioxidant Function in the Human Hippocampus and Frontal Cortex with Increasing Age: Implications for Neurodegeneration in Alzheimer's Disease. Neurochem. Res. *37*, 1601–1614. https://doi.org/10.1007/s11064-012-0755-8.

Please cite this article in press as: Grimm et al., Mitochondria and brain aging: From cell-specific dysfunction to intercellular cooperation, Neuron (2026), https://doi.org/10.1016/j.neuron.2026.04.048

32. Montagne, A., Barnes, S.R., Sweeney, M.D., Halliday, M.R., Sagare, A.P., Zhao, Z., Toga, A.W., Jacobs, R.E., Liu, C.Y., Amezcua, L., et al. (2015). Blood-Brain Barrier Breakdown in the Aging Human Hippocampus. Neuron *85*, 296–302. https://doi.org/10.1016/j.neuron.2014.12.032.

33. Burbulla, L.F., Song, P., Mazzulli, J.R., Zampese, E., Wong, Y.C., Jeon, S., Santos, D.P., Blanz, J., Obermaier, C.D., Strojny, C., et al. (2017). Dopamine oxidation mediates mitochondrial and lysosomal dysfunction in Parkinson's disease. Science *357*, 1255–1261. https://doi.org/10.1126/science.aam9080.

34. Fu, H., Hardy, J., and Duff, K.E. (2018). Selective vulnerability in neurodegenerative diseases. Nat. Neurosci. *21*, 1350–1358. https://doi.org/10.1038/s41593-018-0221-2.

35. Mertens, J., Paquola, A.C.M., Ku, M., Hatch, E., Böhnke, L., Ladjevardi, S., McGrath, S., Campbell, B., Lee, H., Herdy, J.R., et al. (2015). Directly Reprogrammed Human Neurons Retain Aging-Associated Transcriptomic Signatures and Reveal Age-Related Nucleocytoplasmic Defects. Cell Stem Cell *17*, 705–718. https://doi.org/10.1016/j.stem.2015.09.001.

36. Kim, Y., Zheng, X., Ansari, Z., Bunnell, M.C., Herdy, J.R., Traxler, L., Lee, H., Paquola, A.C.M., Blithikioti, C., Ku, M., et al. (2018). Mitochondrial Aging Defects Emerge in Directly Reprogrammed Human Neurons due to Their Metabolic Profile. Cell Rep. *23*, 2550–2558. https://doi.org/10.1016/j.celrep.2018.04.105.

37. Faitg, J., Lacefield, C., Davey, T., White, K., Laws, R., Kosmidis, S., Reeve, A.K., Kandel, E.R., Vincent, A.E., and Picard, M. (2021). 3D neuronal mitochondrial morphology in axons, dendrites, and somata of the aging mouse hippocampus. Cell Rep. *36*, 109509. https://doi.org/10.1016/j.celrep.2021.109509.

38. Li, D., Gao, X., Ma, X., Wang, M., Cheng, C., Xue, T., Gao, F., Shen, Y., Zhang, J., and Liu, Q. (2024). Aging-induced tRNAGlu-derived fragment impairs glutamate biosynthesis by targeting mitochondrial translation-dependent cristae organization. Cell Metab. *36*, 1059–1075.e9. https://doi.org/10.1016/j.cmet.2024.02.011.

39. Olesen, M.A., Torres, A.K., Jara, C., Murphy, M.P., and Tapia-Rojas, C. (2020). Premature synaptic mitochondrial dysfunction in the hippocampus during aging contributes to memory loss. Redox Biol. *34*, 101558. https://doi.org/10.1016/j.redox.2020.101558.

40. Torres, A.K., Jara, C., Olesen, M.A., and Tapia-Rojas, C. (2021). Pathologically phosphorylated tau at S396/404 (PHF-1) is accumulated inside of hippocampal synaptic mitochondria of aged Wild-type mice. Sci. Rep. *11*, 4448. https://doi.org/10.1038/s41598-021-83910-w.

41. Popov, A., Brazhe, N., Morozova, K., Yashin, K., Bychkov, M., Nosova, O., Sutyagina, O., Brazhe, A., Parshina, E., Li, L., et al. (2023). Mitochondrial malfunction and atrophy of astrocytes in the aged human cerebral cortex. Nat. Commun. *14*, 8380. https://doi.org/10.1038/s41467-023-44192-0.

42. Diniz, L.P., Araujo, A.P.B., Carvalho, C.F., Matias, I., de Sá Hayashide, L., Marques, M., Pessoa, B., Andrade, C.B.V., Vargas, G., Queiroz, D.D., et al. (2024). Accumulation of damaged mitochondria in aging astrocytes due to mitophagy dysfunction: Implications for susceptibility to mitochondrial stress. Biochim. Biophys. Acta Mol. Basis Dis. *1870*, 167470. https://doi.org/10.1016/j.bbadis.2024.167470.

43. Araujo, A.P.B., Vargas, G., Hayashide, L.S., Matias, I., Andrade, C.B.V., de Carvalho, J.J., Gomes, F.C.A., and Diniz, L.P. (2024). Aging promotes an increase in mitochondrial fragmentation in astrocytes. Front. Cell. Neurosci. *18*, 1496163. https://doi.org/10.3389/fncel.2024.1496163.

44. Kim, D., Yoo, S.H., Yeon, G.B., Oh, S.S., Shin, W.H., Kang, H.C., Lee, C.K., Kim, H.W., and Kim, D.S. (2024). Senescent Astrocytes Derived from Human Pluripotent Stem Cells Reveal Age-Related Changes and Implications for Neurodegeneration. Aging Dis. *16*, 1709–1731. https://doi.org/10.14336/AD.2024.0089.

45. Acevedo, A., Torres, F., Kiwi, M., Baeza-Lehnert, F., Barros, L.F., Lee-Liu, D., and González-Billault, C. (2023). Metabolic switch in the aging astrocyte supported via integrative approach comprising network and transcriptome analyses. Aging *15*, 9896–9912. https://doi.org/10.18632/aging.204663.

46. Zarate, S.M., Huntington, T.E., Bagher, P., and Srinivasan, R. (2023). Aging reduces calreticulin expression and alters spontaneous calcium signals in astrocytic endfeet of the mouse dorsolateral striatum. NPJ Aging *9*, 5. https://doi.org/10.1038/s41514-023-00102-8.

47. Bame, X., and Hill, R.A. (2024). Mitochondrial network reorganization and transient expansion during oligodendrocyte generation. Nat. Commun. *15*, 6979. https://doi.org/10.1038/s41467-024-51016-2.

48. Neumann, B., Baror, R., Zhao, C., Segel, M., Dietmann, S., Rawji, K.S., Foerster, S., McClain, C.R., Chalut, K., van Wijngaarden, P., et al. (2019). Metformin Restores CNS Remyelination Capacity by Rejuvenating Aged Stem Cells. Cell Stem Cell *25*, 473–485.e8. https://doi.org/10.1016/j.stem.2019.08.015.

49. Minhas, P.S., Latif-Hernandez, A., McReynolds, M.R., Durairaj, A.S., Wang, Q., Rubin, A., Joshi, A.U., He, J.Q., Gauba, E., Liu, L., et al. (2021). Restoring metabolism of myeloid cells reverses cognitive decline in ageing. Nature *590*, 122–128. https://doi.org/10.1038/s41586-020-03160-0.

50. Mela, V., Mota, B.C., Milner, M., McGinley, A., Mills, K.H.G., Kelly, Á.M., and Lynch, M.A. (2020). Exercise-induced re-programming of age-related metabolic changes in microglia is accompanied by a reduction in senescent cells. Brain Behav. Immun. *87*, 413–428. https://doi.org/10.1016/j.bbi.2020.01.012.

51. Hayashi, Y., Yoshida, M., Yamato, M., Ide, T., Wu, Z., Ochi-Shindou, M., Kanki, T., Kang, D., Sunagawa, K., Tsutsui, H., et al. (2008). Reverse of Age-Dependent Memory Impairment and Mitochondrial DNA Damage in Microglia by an Overexpression of Human Mitochondrial Transcription Factor A in Mice. J. Neurosci. *28*, 8624–8634. https://doi.org/10.1523/jneurosci.1957-08.2008.

52. Sakamuri, S.S.V.P., Sure, V.N., Kolli, L., Evans, W.R., Sperling, J.A., Bix, G.J., Wang, X., Atochin, D.N., Murfee, W.L., Mostany, R., et al. (2022). Aging related impairment of brain microvascular bioenergetics involves oxidative phosphorylation and glycolytic pathways. J. Cereb. Blood Flow Metab. *42*, 1410–1424. https://doi.org/10.1177/0271678x211069266.

53. Otu-Boakye, S., Natarajan, D., Plakkot, B., Raghavendiran, I., Hoppa, P., Kiss, T., Subramanian, M., and Balasubramanian, P. (2026). Lipid-laden endothelial cells exhibit a transcriptomic signature linked to blood–brain barrier dysfunction, metabolic reprogramming, and increased inflammation in the aging brain. GeroScience *48*, 1735–1750. https://doi.org/10.1007/s11357-025-01986-y.

54. Grimm, A., Cummins, N., and Götz, J. (2018). Local Oxidative Damage in the Soma and Dendrites Quarantines Neuronal Mitochondria at the Site of Insult. iScience *6*, 114–127. https://doi.org/10.1016/j.isci.2018.07.015.

55. Varghese, N., Grimm, A., Cader, M.Z., and Eckert, A. (2024). From Young to Old: Mimicking Neuronal Aging in Directly Converted Neurons from Young Donors. Cells *13*, 1260. https://doi.org/10.3390/cells13151260.

56. García-Domínguez, M. (2025). Interplay Between Aging and Glial Cell Dysfunction: Implications for CNS Health. Life (Basel) *15*, 1498. https://doi.org/10.3390/life15101498.

57. Gildea, H.K., and Liddelow, S.A. (2025). Mechanisms of astrocyte aging in reactivity and disease. Mol. Neurodegener. *20*, 21. https://doi.org/10.1186/s13024-025-00810-7.

58. Harris, J.J., and Attwell, D. (2012). The Energetics of CNS White Matter. J. Neurosci. *32*, 356–371. https://doi.org/10.1523/jneurosci.3430-11.2012.

59. Sams, E.C. (2021). Oligodendrocytes in the aging brain. Neuronal Signal. *5*, NS20210008. https://doi.org/10.1042/ns20210008.

60. Carr, L., Mustafa, S., and Collins-Praino, L.E. (2025). The Hallmarks of Ageing in Microglia. Cell. Mol. Neurobiol. *45*, 45. https://doi.org/10.1007/s10571-025-01564-y.

61. Knox, E.G., Aburto, M.R., Clarke, G., Cryan, J.F., and O'Driscoll, C.M. (2022). The blood-brain barrier in aging and neurodegeneration. Mol. Psychiatry *27*, 2659–2673. https://doi.org/10.1038/s41380-022-01511-z.

62. Lushchak, V.I., Duszenko, M., Gospodaryov, D.V., and Garaschuk, O. (2021). Oxidative Stress and Energy Metabolism in the Brain: Midlife as a Turning Point. Antioxidants (Basel) *10*, 1715. https://doi.org/10.3390/antiox10111715.

Please cite this article in press as: Grimm et al., Mitochondria and brain aging: From cell-specific dysfunction to intercellular cooperation, Neuron (2026), https://doi.org/10.1016/j.neuron.2026.04.048

63. Mayorga-Weber, G., Rivera, F.J., and Castro, M.A. (2022). Neuron-glia (mis)interactions in brain energy metabolism during aging. J. Neurosci. Res. *100*, 835–854. https://doi.org/10.1002/jnr.25015.

64. Fairley, L.H., Grimm, A., and Eckert, A. (2022). Mitochondria Transfer in Brain Injury and Disease. Cells *11*, 3603. https://doi.org/10.3390/cells11223603.

65. Hayakawa, K., Esposito, E., Wang, X., Terasaki, Y., Liu, Y., Xing, C., Ji, X., and Lo, E.H. (2016). Transfer of mitochondria from astrocytes to neurons after stroke. Nature *535*, 551–555. https://doi.org/10.1038/nature18928.

66. Davis, C.H., Kim, K.-Y., Bushong, E.A., Mills, E.A., Boassa, D., Shih, T., Kinebuchi, M., Phan, S., Zhou, Y., Bihlmeyer, N.A., et al. (2014). Transcellular degradation of axonal mitochondria. Proc. Natl. Acad. Sci. USA *111*, 9633–9638. https://doi.org/10.1073/pnas.1404651111.

67. Tashiro, R., Ozaki, D., Bautista-Garrido, J., Sun, G., Obertas, L., Mobley, A.S., Kim, G.S., Aronowski, J., and Jung, J.E. (2023). Young Astrocytic Mitochondria Attenuate the Elevated Level of CCL11 in the Aged Mice, Contributing to Cognitive Function Improvement. Int. J. Mol. Sci. *24*, 5187. https://doi.org/10.3390/ijms24065187.

68. Velmurugan, G.V., Vekaria, H.J., Patel, S.P., Sullivan, P.G., and Hubbard, W.B. (2024). Astrocytic mitochondrial transfer to brain endothelial cells and pericytes in vivo increases with aging. J. Cereb. Blood Flow Metab. *46*, 418–429. https://doi.org/10.1177/0271678x241306054.

69. Liu, D., Liao, P., Li, H., Tong, S., Wang, B., Lu, Y., Gao, Y., Huang, Y., Zhou, H., Shi, L., et al. (2024). Regulation of blood-brain barrier integrity by Dmp1-expressing astrocytes through mitochondrial transfer. Sci. Adv. *10*, eadk2913. https://doi.org/10.1126/sciadv.adk2913.

70. Riou, A., Broeglin, A., and Grimm, A. (2025). Mitochondrial transplantation in brain disorders: Achievements, methods, and challenges. Neurosci. Biobehav. Rev. *169*, 105971. https://doi.org/10.1016/j.neubiorev.2024.105971.

71. Adlimoghaddam, A., Benson, T., and Albensi, B.C. (2022). Mitochondrial Transfusion Improves Mitochondrial Function Through Up-regulation of Mitochondrial Complex II Protein Subunit SDHB in the Hippocampus of Aged Mice. Mol. Neurobiol. *59*, 6009–6017. https://doi.org/10.1007/s12035-022-02937-w.

72. Zhao, Z., Yu, Z., Hou, Y., Zhang, L., and Fu, A. (2020). Improvement of cognitive and motor performance with mitotherapy in aged mice. Int. J. Biol. Sci. *16*, 849–858. https://doi.org/10.7150/ijbs.40886.

73. Zhang, Z., Wei, D., Li, Z., Guo, H., Wu, Y., and Feng, J. (2022). Hippocampal Mitochondrial Transplantation Alleviates Age-Associated Cognitive Decline via Enhancing Wnt Signaling and Neurogenesis. Comput. Intell. Neurosci. *2022*, 9325302. https://doi.org/10.1155/2022/9325302.

74. Kubat, G.B., Picone, P., Tuncay, E., Aryan, L., Girgenti, A., Palumbo, L., Turkel, I., Akat, F., Singh, K.K., and Nuzzo, D. (2025). Biotechnological approaches and therapeutic potential of mitochondria transfer and transplantation. Nat. Commun. *16*, 5709. https://doi.org/10.1038/s41467-025-61239-6.

75. Zhao, R., Dong, C., Liang, Q., Gao, J., Sun, C., Gu, Z., and Zhu, Y. (2024). Engineered Mitochondrial Transplantation as An Anti-Aging Therapy. Aging Dis. *16*, 1918–1945. https://doi.org/10.14336/AD.2024.0231.

76. Brestoff, J.R., Singh, K.K., Aquilano, K., Becker, L.B., Berridge, M.V., Boilard, E., Caicedo, A., Crewe, C., Enríquez, J.A., Gao, J., et al. (2025). Recommendations for mitochondria transfer and transplantation nomenclature and characterization. Nat. Metab. *7*, 53–67. https://doi.org/10.1038/s42255-024-01200-x.

77. Lin, R.-Z., Im, G.-B., Luo, A.C., Zhu, Y., Hong, X., Neumeyer, J., Tang, H.-W., Perrimon, N., and Melero-Martin, J.M. (2024). Mitochondrial transfer mediates endothelial cell engraftment through mitophagy. Nature *629*, 660–668. https://doi.org/10.1038/s41586-024-07340-0.

78. Morifuji, M., Higashi, S., Ebihara, S., and Nagata, M. (2024). Ingestion of β-nicotinamide mononucleotide increased blood NAD levels, maintained walking speed, and improved sleep quality in older adults in a double-blind randomized, placebo-controlled study. GeroScience *46*, 4671–4688. https://doi.org/10.1007/s11357-024-01204-1.

79. Singh, A., D'Amico, D., Andreux, P.A., Fouassier, A.M., Blanco-Bose, W., Evans, M., Aebischer, P., Auwerx, J., and Rinsch, C. (2022). Urolithin A improves muscle strength, exercise performance, and biomarkers of mitochondrial health in a randomized trial in middle-aged adults. Cell Rep. Med. *3*, 100633. https://doi.org/10.1016/j.xcrm.2022.100633.

80. Baltic, S., Nedeljkovic, D., Todorovic, N., Ranisavljev, M., Korovljev, D., Cvejic, J., Ostojic, J., LeBaron, T.W., Timmcke, J., Stajer, V., et al. (2024). The impact of six-week dihydrogen-pyrroloquinoline quinone supplementation on mitochondrial biomarkers, brain metabolism, and cognition in elderly individuals with mild cognitive impairment: a randomized controlled trial. J. Nutr. Health Aging *28*, 100287. https://doi.org/10.1016/j.jnha.2024.100287.

81. Fortier, M., Castellano, C.A., Croteau, E., Langlois, F., Bocti, C., St-Pierre, V., Vandenberghe, C., Bernier, M., Roy, M., Descoteaux, M., et al. (2019). A ketogenic drink improves brain energy and some measures of cognition in mild cognitive impairment. Alzheimers Dement. *15*, 625–634. https://doi.org/10.1016/j.jalz.2018.12.017.

82. Mujica-Parodi, L.R., Amgalan, A., Sultan, S.F., Antal, B., Sun, X., Skiena, S., Lithen, A., Adra, N., Ratai, E.-M., Weistuch, C., et al. (2020). Diet modulates brain network stability, a biomarker for brain aging, in young adults. Proc. Natl. Acad. Sci. USA *117*, 6170–6177. https://doi.org/10.1073/pnas.1913042117.

83. Berti, V., Walters, M., Sterling, J., Quinn, C.G., Logue, M., Andrews, R., Matthews, D.C., Osorio, R.S., Pupi, A., Vallabhajosula, S., et al. (2018). Mediterranean diet and 3-year Alzheimer brain biomarker changes in middle-aged adults. Neurology *90*, e1789–e1798. https://doi.org/10.1212/wnl.0000000000005527.

84. Green, Z.D., John, C.S., Kueck, P.J., Blankenship, A.E., Kemna, R.E., Johnson, C.N., Yoksh, L.E., Best, S.R., Donald, J.S., Mahnken, J.D., et al. (2024). Acute exercise alters brain glucose metabolism in aging and Alzheimer's disease. J. Physiol. *604*, 2473–2490. https://doi.org/10.1113/jp286923.