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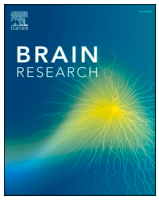

Adipose tissue as a systemic modulator of brain aging: mechanistic links between metabolism, inflammation and neurodegeneration☆

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ABSTRACT

Brain aging involves progressive declines in neuroplasticity, metabolic flexibility, cerebrovascular integrity and immune homeostasis. Although traditionally viewed as brain-intrinsic, growing evidence indicates that peripheral metabolic organs substantially influence neural aging trajectories. Among these, adipose tissue is increasingly recognized as a dynamic endocrine and immune organ capable of modulating central nervous system (CNS) structure and function across the lifespan.

Epidemiological, neuroimaging and experimental studies consistently link adipose tissue dysfunction, particularly the expansion and inflammatory remodeling of visceral fat depots, to accelerated brain aging, cognitive decline and increased susceptibility to neurodegenerative disease. These relationships extend beyond conventional cardiometabolic risk, implicating adipose-derived mechanisms with direct relevance for neural aging. Chronic low-grade inflammation, impaired insulin signaling, dyslipidemia, adipokine imbalance and senescence-associated secretory activity originating in adipose tissue act on the aging brain by promoting microglial dysfunction, cerebrovascular impairment, blood–brain barrier (BBB) disruption and synaptic vulnerability. In parallel, adipose-derived extracellular vesicles and microRNAs have been identified as direct molecular mediators of adipose-brain communication.

Importantly, adipose tissue is structurally and functionally heterogeneous, and its impact on brain aging is strongly depot- and context-dependent. While dysfunctional visceral adipose tissue amplifies neuroinflammatory and neurodegenerative processes, preserved subcutaneous and thermogenic depots may support brain resilience by sustaining metabolic homeostasis and neurotrophic signaling.

By integrating molecular, translational and human evidence, this review frames adipose tissue as a central and modifiable systemic determinant of brain aging. Framing brain aging within a peripheral metabolic context reconciles findings across disciplines and highlights adipose-targeted interventions as promising strategies for preserving cognitive function and reducing neurodegenerative risk.

1. Introduction

Aging of the human brain reflects progressive impairments in neuroplasticity, metabolic resilience, vascular function and immune homeostasis (Mattson and Arumugam, 2018). While these processes have traditionally been attributed to intrinsic neuronal and glial biology, converging evidence demonstrates that extra-cerebral organs critically shape neural aging trajectories (Beck, 2022). Current evidence positions adipose tissue as a major determinant of systemic metabolic and inflammatory states that are central to aging biology; with direct implications for brain structure and function (Kawai, 2021).

Epidemiological and neuroimaging studies consistently associate midlife adiposity, particularly visceral adipose tissue (VAT) expansion, with accelerated cognitive decline, cortical and subcortical atrophy, microstructural white-matter injury and increased susceptibility to neurodegenerative disease (Beck, 2022; Dye, 2017; Boccara, 2023; Anand, 2022). These associations extend beyond classical cardiometabolic risk, suggesting that adipose tissue exerts brain-relevant effects through specific endocrine, immune, metabolic and vascular mechanisms. Experimental models support this view, showing that

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adipose-derived cytokines, adipokines, lipids and extracellular vesicles can modulate blood–brain barrier function, microglial and astrocytic activation states, neuronal metabolism and age-related neuroinflammatory cascades (Lee, 2019; Malaguarnera, 2025; Garcia-Contreras and Thakor, 2021; Huang and Xu, 2021; Jian, 2019; Ormazabal, 2025).

Adipose tissue heterogeneity adds further complexity. Subcutaneous, visceral, perivascular, and brown adipose depots differ profoundly in their metabolic activity and inflammatory tone, such that their contributions to brain aging are not uniform (Sakers, 2022). Aging remodels adipose tissue toward a pro-inflammatory, senescent phenotype that amplifies systemic stress signals capable of influencing the CNS (Tang, 2025). In contrast, metabolically healthy adipose profiles, particularly preserved subcutaneous function and active thermogenic depots, may confer neuroprotection by sustaining insulin sensitivity, reducing systemic inflammation and producing trophic mediators that support neuronal and glial health (Smith and Kahn, 2016).

Despite rapid advances, the mechanistic links connecting adipose biology to neural aging remain conceptually fragmented across metabolic research, neuroimmunology, cerebrovascular biology and geroscience. Integrating these domains is essential to understand how peripheral metabolic organs modulate brain aging and to identify intervention points, given the modifiable nature of adipose tissue across the lifespan.

This review therefore aims to synthesize current knowledge on the mechanistic pathways through which adipose tissue may accelerate or attenuate brain aging, drawing from molecular studies, translational models, human neuroimaging and population-based research. By mapping these interconnected mechanisms, we seek to clarify the role of adipose biology in neural aging and highlight emerging opportunities for targeted intervention.

2. Overview of adipose tissue biology relevant to brain aging

2.1. Structural and functional heterogeneity of adipose tissue

Adipose tissue is no longer perceived as a passive energy depot but as a complex, compositionally diverse organ whose structural and functional heterogeneity exerts profound systemic effects, including on brain aging. Across depots and within each depot, adipose tissue encompasses a mosaic of specialized cell populations, including adipocytes, mesenchymal stem cells, immune cells, endothelial cells, and neural components such as sympathetic nerve fibers and sensory innervation, which collectively orchestrate metabolic, endocrine and immunological outputs. This cellular heterogeneity creates microenvironments capable of dynamically responding to nutritional states, inflammatory signals and aging-related stressors.

Traditionally, adipose tissue has been classified into two principal forms: white adipose tissue (WAT) and brown adipose tissue (BAT). In addition, beige adipocytes represent an inducible thermogenic adipocyte population emerging within WAT depots in response to stimuli such as cold exposure. WAT serves predominantly as an energy-storing and endocrine organ, secreting adipokines such as leptin and adiponectin that govern metabolic homeostasis and insulin sensitivity (Auger and Kajimura, 2023; Dilworth, 2021). In contrast, BAT is specialized for energy dissipation via non-shivering thermogenesis, defined by high mitochondrial density and expression of uncoupling protein 1 (UCP1) and plays a key role in thermoregulation and systemic metabolic control (Dilworth, 2021; Schoettl, 2018; Luong, 2019).

Beyond these canonical depots, bone marrow adipose tissue (BMAT) constitutes a distinct and increasingly appreciated adipose subtype with unique developmental origins and metabolic properties, influencing both skeletal homeostasis and broader systemic metabolism (Hardouin, 2016).

Substantial heterogeneity exists even within WAT. Subcutaneous (SAT) and visceral adipose tissue (VAT) display marked differences in cellular composition, metabolic activity and disease associations, variations that underscore the multifaceted nature of adipose biology (Schoettl, 2018; Luong, 2019; Norreen-Thorsen, 2022). These regional distinctions are highly relevant to disease risk and systemic inflammation. The coordinated interaction between adipocytes and non-adipocyte components, including stromal progenitors, macrophages and endothelial networks, governs adipose remodeling and immune–metabolic crosstalk, processes that become increasingly consequential with aging (Zwick, 2018; Corvera, 2021).

2.2. Changes of adipose tissue with age: inflammation, fibrosis, senescence

Aging profoundly alters adipose tissue structure and function. Progressive immune-cell infiltration, extracellular matrix remodeling and the accumulation of senescent cells collectively disrupt tissue homeostasis and promote systemic metabolic decline.

One hallmark of aging adipose tissue is chronic low-grade inflammation, often termed inflammaging. This state is characterized by increased production of pro-inflammatory mediators, including tumor necrosis factor-alpha (TNF-α), interleukin 6 (IL-6) and monocyte chemoattractant protein-1 (MCP-1), driven in part by expanded macrophage populations and senescent cells exhibiting a senescence-associated secretory phenotype (SASP) (Zhang, 2023; Ou, 2022; Stout, 2017). The sustained release of these factors propagates local and systemic inflammatory signaling.

Multiple mechanisms contribute to the development of adipose tissue inflammation during aging and obesity. Adipocyte hypertrophy promotes local hypoxia due to insufficient vascular expansion, leading to cellular stress responses and increased production of pro-inflammatory mediators. Enlarged adipocytes also exhibit enhanced lipolysis and release excess free fatty acids, particularly saturated fatty acids, which activate toll-like receptor 4 (TLR4)-dependent inflammatory pathways in adipocytes and macrophages. In parallel, mitochondrial dysfunction, oxidative stress and endoplasmic reticulum stress further amplify inflammatory signaling and impair adipocyte metabolic function. These processes promote recruitment and activation of pro-inflammatory immune cells, including M1-like macrophages, and contribute to activation of the NLRP3 inflammasome, thereby sustaining chronic low-grade inflammation within adipose tissue (Shi, 2006; Zatterale, 2020).

Concomitantly, adipocytes undergo hypertrophy, and extracellular matrix components accumulate, promoting fibrotic remodeling (Ahmed, 2024; Whytock, 2024). Increased tissue stiffness limits adipose plasticity and impairs healthy lipid storage capacity. Senescent progenitor cells and preadipocytes display reduced differentiation potential, resulting in defective adipogenesis and altered lipid handling (Ou, 2022; Tchkonia, 2010). These cellular changes amplify inflammatory signaling and contribute to insulin resistance.

Age-related fibrosis is further associated with altered immune-cell composition and reduced vascularization, particularly within visceral depots (Ahmed, 2024; Varghese, 2021). These structural and immunological shifts compromise metabolic flexibility and promote systemic dysfunction. Importantly, experimental clearance of senescent cells using senolytic approaches, pharmacological strategies designed to selectively eliminate senescent cells, reduces adipose inflammation and improves metabolic performance in aged models (Islam, 2023; Ghosh, 2019), highlighting adipose senescence as a potential therapeutic target with downstream relevance for brain aging.

2.3. Endocrine and immune functions linking adipose tissue to the brain

Beyond its metabolic role, adipose tissue functions as an integrated endocrine–immune organ that actively communicates with the CNS. Through circulating hormones, cytokines and extracellular vesicles, adipose tissue participates in bidirectional signaling pathways that

influence neuronal function, vascular integrity and neuroinflammatory states.

In addition to endocrine and immune signaling, adipose tissue is richly innervated by both sympathetic and sensory nerve fibers, establishing a direct neuro-adipose communication network. While sympathetic innervation regulates lipolysis, thermogenesis and adipokine secretion, sensory afferent fibers transmit metabolic and inflammatory information from adipose depots to the CNS. Experimental studies suggest that adipose sensory innervation contributes to the modulation of hypothalamic activity, energy homeostasis and systemic inflammatory responses, thereby representing an additional pathway through which dysfunctional adipose tissue may influence brain aging and neuronal function (Bartness, 2014; Ryu and Bartness, 2014).

Adipokines such as leptin, adiponectin and resistin represent key mediators of this systemic communication. Leptin and adiponectin receptors are widely expressed in the CNS (Lee, 2019). While leptin readily crosses the BBB through a saturable transport system, adiponectin BBB permeability appears isoform-dependent. Experimental studies indicate that low-molecular-weight adiponectin can access the CNS, whereas high-molecular-weight adiponectin exhibits limited BBB permeability (Spranger, 2006). These findings suggest that adiponectin may influence brain aging through both direct central effects and indirect peripheral metabolic and vascular mechanisms. Within physiological ranges, they modulate synaptic plasticity, neurogenesis, insulin signaling and inflammatory responses, exerting predominantly neuroprotective effects (Lee, 2019; Ormazabal, 2025; He, 2023). However, aging and obesity disrupt adipokine balance, promoting leptin resistance, reduced adiponectin signaling and systemic insulin resistance. These changes contribute to endothelial dysfunction, impaired BBB integrity and heightened vulnerability to neurodegenerative processes (Zhang, 2023; Weijie, 2024).

Adipose tissue also releases extracellular vesicles containing proteins, lipids and microRNAs capable of altering gene expression in distant organs, including the brain (Huang and Xu, 2021). This vesicle-mediated communication provides a mechanistically direct route through which adipose dysfunction may influence synaptic integrity and neuronal metabolism.

With advancing age, adipose-derived inflammatory signaling intensifies. Accumulation of immune cells and activation of pro-inflammatory pathways, including nuclear factor κB (NF-κB) and Janus kinase/signal transducer and activator of transcription (JAK–-STAT) cascades, reinforce systemic cytokine production. Obesity further amplifies this inflammatory state, extending its effects to the CNS and promoting microglial activation, mitochondrial dysfunction and neurodegenerative pathology (Tang, 2025; Weijie, 2024; Zeng, 2025). Experimental models demonstrate that adiponectin deficiency accelerates brain aging through mitochondria-associated neuroinflammatory mechanisms, underscoring the protective potential of balanced adipokine signaling within the adipose–brain axis (He, 2023).

2.4. Why VAT vs SAT matter differently for brain aging?

Visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) differ in their impact on brain aging due to distinct metabolic and inflammatory profiles. VAT is more strongly associated with adverse brain outcomes, including lower total brain volume, cortical thinning, and increased amyloid pathology, likely driven by its pro-inflammatory state and insulin resistance effects (Debette, 2010; Dolatshahi, 2024). In contrast, SAT shows a more complex relationship: higher glucose uptake in SAT correlates with slower brain aging in lean individuals but may accelerate brain aging in overweight or female populations (Lu, 2024). VAT is also linked to microstructural brain damage and neuroinflammation across sexes, whereas SAT's associations weaken after adjusting for confounders like body mass index (BMI) and vascular risk factors (Dolatshahi, 2025; Widya, 2015). These differences suggest VAT contributes more directly to neurodegeneration and cognitive decline, while SAT may have protective roles that diminish with obesity or aging. Thus, the VAT-to-SAT ratio is a critical marker for understanding fat distribution's differential effects on brain health during aging.

3. Mechanisms linking adipose tissue to brain aging

Aging-related adipose tissue remodeling extends beyond local metabolic dysregulation and emerges as a systemic driver of brain aging. The expansion of dysfunctional adipose depots, particularly visceral fat, initiates a cascade of inflammatory, metabolic, vascular and endocrine signals that converge on the CNS. These pathways do not act independently; rather, they form an interdependent network that amplifies neuroinflammation, impairs synaptic homeostasis and accelerates neurodegenerative processes. Below, we integrate the principal mechanistic axes linking adipose tissue dysfunction to brain aging.

3.1. Chronic low-grade inflammation (metaflammation) and microglial aging

Chronic low-grade inflammation, or metaflammation, represents a primary interface between adipose tissue dysfunction and CNS aging. In obesity and aging, hypertrophic adipocytes and infiltrating macrophages activate the NLRP3 inflammasome, leading to sustained IL-1β production. Guo et al. demonstrated that visceral adipose NLRP3 activation increases circulating IL-1β levels, which signal through microglial IL1R1 receptors, promoting microglial activation, synaptic impairment and cognitive decline in obesity models (Guo, 2020).

Adipose-derived IL-1β does not merely activate microglia, it primes them. This primed state renders microglia hypersensitive to subsequent inflammatory stimuli, perpetuating a feed-forward loop of cytokine and chemokine production. Butler et al. showed that high-fat diet exposure enhances hippocampal and amygdalar microglial activation markers alongside elevated IL-1β levels, reinforcing the concept of peripheral-to-central inflammatory propagation (Butler, 2020).

Adipokine imbalance further modulates this process. He et al. linked adiponectin deficiency to accelerated brain aging through enhanced microglial neuroinflammation and mitochondrial dysfunction. Their findings highlight the protective role of adipokines in modulating microglial activity via adenosine monophosphate-activated protein kinase (AMPK)–NF-κB signaling pathways (He, 2023). Jian et al. further confirmed that adiponectin suppresses microglial inflammatory responses to amyloid-β oligomers through AdipoR1–AMPK–NF-κB signaling, and that its deficiency exacerbates neuroinflammation in Alzheimer's disease models (Jian, 2019).

Marschallinger et al. identified lipid-droplet–accumulating microglia (LDAM phenotype) as a hallmark of aging. These cells exhibit elevated reactive oxygen species (ROS) production, impaired phagocytosis and exaggerated cytokine release, representing a senescent-like microglial state that bridges metabolic stress and neurodegeneration (Marschallinger, 2020).

Collectively, metaflammation establishes a self-perpetuating adipose–microglial axis in which peripheral inflammatory mediators drive microglial priming, senescence-like phenotypes and chronic neuroinflammation. Importantly, this feed-forward inflammatory circuit suggests that adipose tissue may function as an upstream regulator of microglial aging rather than merely a contributing factor, reframing obesity and adipose senescence as initiators of central immunosenescence.

3.2. Insulin resistance and impaired brain insulin signalling

Peripheral insulin resistance (IR), largely originating from adipose tissue dysfunction, constitutes a second major axis linking metabolic aging to neurodegeneration. Hypertrophic adipocytes, inflammatory macrophage infiltration and altered adipokine secretion disrupt systemic insulin sensitivity, increasing circulating insulin and

inflammatory mediators such as TNF-α and IL-6 (Bou Matar, 2025; Ahmed, 2021).

Peripheral IR also reduces insulin transport across the blood–brain barrier. As a consequence, insulin receptor activation in neurons and glial cells declines. This central insulin resistance compromises synaptic plasticity and mitochondrial bioenergetics, both essential for cognitive function (Sripetchwandee, 2018; Heni, 2024; Stranahan, 2022).

Experimental evidence supports these mechanistic links. Kacířová et al. showed in a tau pathology mouse model that high-fat diet–induced peripheral IR triggers neuroinflammation and synaptic deficits, with males displaying greater susceptibility (Kacířová, 2021). Their findings underscore the metabolic stress as a disease-modifying factor in neurodegeneration.

Proteostatic disruption provides an additional connection to neurodegenerative pathology. Insulin-degrading enzyme (IDE), which normally clears both insulin and amyloid-β (Aβ), becomes competitively inhibited during hyperinsulinemia. This reduces Aβ clearance and promotes its accumulation, a hallmark of Alzheimer's disease associated with brain insulin resistance (Heni, 2024; Kacířová, 2021). Moreover, adipose tissue can directly influence the brain through extracellular vesicles. Wang et al. demonstrated that adipose-derived vesicles enriched in microRNAs can enter the brain and impair synaptic integrity by altering insulin signaling pathways (Wang, 2022).

Together, these mechanisms link adipose-driven insulin resistance to neuronal bioenergetic failure and cognitive decline.

3.3. Dyslipidemia and lipotoxicity

Dyslipidemia in aging is characterized by the buildup of bioactive lipids, including ceramides, sphingolipids and oxidized lipids, that perturb cellular homeostasis through multiple interconnected mechanisms. Ceramides accumulate in aged brown adipose tissue, where they inhibit brown adipogenesis by disrupting thermogenic signaling pathways, ultimately lowering energy expenditure and accelerating systemic metabolic decline (Gohlke, 2019). Green and colleagues show that ceramides further impair insulin signaling and mitochondrial function by elevating ROS and activating pro-apoptotic cascades, thereby contributing to neurodegeneration and broader metabolic dysfunction (Green, 2021).

Sphingosine-1-phosphate (S1P) exerts context-dependent effects: although it can promote survival and proliferation, its dysregulation intensifies inflammation and tissue injury, underscoring the complexity of sphingolipid signaling in aging (Green, 2021). Microglial lipid droplets, including lipid-droplet-accumulating microglias (LDAMs) and lipid-associated macrophages (LAMs), initially sequester excess lipids to limit lipotoxicity, but chronic accumulation leads to microglial dysfunction, reduced phagocytic capacity and amplified neuroinflammation as noted by Bresgen et al. (Bresgen, 2023).

In dysfunctional adipose tissue, excessive lipolysis further contributes to systemic lipotoxicity by increasing circulating free fatty acids (FFAs), particularly saturated fatty acids such as palmitate. Elevated FFAs promote insulin resistance, activate toll-like receptor 4 (TLR4)-dependent inflammatory pathways and enhance oxidative stress in both peripheral tissues and the CNS (Rogero and Calder, 2018). Saturated fatty acids can also directly induce microglial activation and exacerbate neuroinflammatory responses associated with aging and neurodegeneration. In parallel, altered cholesterol metabolism and accumulation of oxidized cholesterol species disrupt membrane organization, mitochondrial function and synaptic signaling, thereby contributing to amyloidogenic processing and neuronal vulnerability.

Mitochondrial impairment emerges from lipid-induced oxidative stress and defective fatty acid oxidation, which reduce ATP production and elevate ROS, exacerbating aging phenotypes in adipose and neural tissues (Jang and Choi, 2025; Cavaliere, 2023). Oxidized lipids further compromise neuronal membrane integrity by disrupting lipid rafts, altering membrane fluidity and signaling and fostering amyloid-β aggregation and neurotoxicity, hallmarks of Alzheimer's disease pathology highlighted by Cerasuolo et al. (Cerasuolo, 2024).

These findings suggest that dyslipidemia acts as a biochemical bridge between peripheral metabolic aging and central membrane instability, placing membrane lipid composition as a potentially underexplored therapeutic target in metabolic-associated brain aging.

3.4. Blood–brain barrier integrity and cerebrovascular aging

BBB integrity and cerebrovascular aging through multiple interrelated mechanisms, primarily involving endothelial inflammation, oxidative stress and microvascular remodeling. Tarantini et al. demonstrated in nuclear factor erythroid 2-related factor 2 (Nrf2)-deficient mice that obesity-induced oxidative stress exacerbates endothelial dysfunction, leading to impaired neurovascular coupling, the mechanism through which cerebral blood flow is matched to neuronal metabolic demand, and increased BBB permeability, changes that resemble aging-related cerebrovascular decline (Tarantini, 2018). This oxidative stress promotes endothelial senescence and activation of microglia, fostering a pro-inflammatory environment that disrupts tight junction proteins critical for BBB integrity. Adipokines secreted by adipose tissue, such as leptin, resistin, and TNF-α, can cross or modulate the BBB, directly influencing endothelial cells and promoting inflammation and permeability changes, as reviewed by Parimisetty et al. (Parimisetty, 2016). Furthermore, microvascular rarefaction, characterized by the loss of small cerebral vessels, is accelerated by adipose tissue–induced inflammation and oxidative damage, reducing cerebral perfusion and impairing nutrient delivery to neural tissue, which contributes to cognitive decline (Tarantini, 2018; Kiliaan, 2014). Bettinetti-Luque et al. also highlight that adipose tissue–derived factors regulate BBB physiology and may exacerbate Alzheimer's disease pathology by facilitating amyloidogenic processes and vascular dysfunction (Bettinetti-Luque, 2024). These studies reveal a complex crosstalk where adipose tissue–-driven inflammation and oxidative stress compromise cerebrovascular structure and function. BBB disruption may represent the structural gateway through which systemic metabolic signals gain amplified access to the brain, effectively converting peripheral metabolic stress into sustained central pathology.

3.5. Adipokine signaling and neurotrophic modulation

Adipokine signaling mediates a complex, bidirectional interaction between adipose tissue and brain aging by modulating neurotrophic support, inflammatory responses and metabolic pathways. Leptin, an adipocyte-derived hormone, crosses the BBB and binds to receptors in the hippocampus and hypothalamus, where it supports synaptic plasticity and cognitive function. However, aging and obesity promote leptin resistance, which attenuates these neuroprotective effects and is associated with cognitive decline and an increased risk of Alzheimer's disease, as demonstrated in both animal models and human studies (Lee, 2019; Chen and Schneeberger, 2024).

Adiponectin exerts anti-inflammatory and insulin-sensitizing actions that support neurogenesis and enhance brain-derived neurotrophic factor (BDNF) expression, a key determinant of neuronal maintenance during aging. In rodent models fed a Western diet, reduced adiponectin levels in both adipose tissue and the brain correlate with decreased BDNF expression and synaptic dysfunction (Shirafuji, 2025; Mazzoli, 2020). In contrast, resistin is linked to pro-inflammatory signaling pathways that may amplify neuroinflammation and neurodegeneration, although its specific contribution to brain aging remains incompletely characterized (Lee, 2019).

Importantly, adipokine effects on brain aging likely involve both direct central actions and indirect peripheral mechanisms. Leptin and certain low-molecular-weight adiponectin isoforms can cross the BBB and directly influence neuronal and glial signaling pathways involved in synaptic plasticity, energy homeostasis and neuroinflammation

(Kubota, 2007). In parallel, adipokines modulate systemic insulin sensitivity, endothelial function, cerebrovascular regulation and chronic peripheral inflammation, thereby indirectly influencing brain homeostasis through effects on the neurovascular unit and BBB integrity (Parimisetty, 2016; Bettinetti-Luque, 2024; Ponce-Lopez, 2025). Age-related adipose tissue dysfunction further alters adipokine secretion profiles, promoting chronic low-grade inflammation and metabolic dysregulation that exacerbate brain aging processes (Ou, 2022; Mancuso and Bouchard, 2019).

These findings underscore the critical role of adipokine signaling in maintaining neurotrophic support and inflammatory homeostasis during aging. Specifically, the simultaneous emergence of leptin resistance and adiponectin deficiency may create a "dual-hit" state, characterized by impaired neurotrophic signaling and heightened inflammatory vulnerability, that accelerates synaptic aging. By defining this adipose–brain communication as a driver of cognitive decline, these mechanisms identify the adipokine axis as a promising therapeutic target for mitigating neurodegenerative risk.

3.6. Adipose-derived extracellular vesicles and miRNAs

Adipose tissue-derived extracellular vesicles (EVs) and their microRNA (miRNA) cargo have been identified as critical mediators of inter-organ communication that influence brain aging. Wang et al. demonstrated that these EVs can cross the blood–brain barrier in a membrane protein-dependent manner and preferentially accumulate in hippocampal neurons, microglia and endothelial cells, where their miRNAs modulate synaptic integrity and cognitive function (Wang, 2022). In models of obesity and diabetes, EVs from adipose tissue carry miRNAs that induce synaptic loss and cognitive impairment, while depletion of these miRNAs significantly alleviates these detrimental effects, highlighting their mechanistic role in neurodegeneration linked to metabolic dysfunction (Wang, 2022). Bettinetti-Luque et al. further showed that adipocyte-derived EVs from Alzheimer's disease patients contain miRNAs predicted to downregulate cycling AMP response element-binding protein (CREB) signaling, a pathway essential for synaptic plasticity and memory, thus providing a molecular link between midlife obesity and increased Alzheimer's risk (Bettinetti-Luque, 2024). Studies by Song et al. also indicate that EVs from young adipose-derived stem cells deliver miRNAs that reduce oxidative stress, inflammation and cellular senescence markers in aged tissues, suggesting a rejuvenating potential through miRNA-mediated pathways (Song, 2020). These findings identify adipose-derived EVs as important mediators of adipose–brain communication in metabolic aging.

3.7. Adipose cellular senescence as a systemic aging amplifier

Adipose tissue cellular senescence, affecting both preadipocytes and mature adipocytes, contributes to systemic aging by sustaining chronic inflammation through the SASP, a pro-inflammatory secretome composed of cytokines, chemokines and matrix-remodeling factors. Senescent adipose cells release pro-inflammatory cytokines, including IL-1β and TNF-α, as well as chemokines that drive inflammaging, disrupt tissue homeostasis and promote secondary senescence in distant tissues (Nerstedt and Smith, 2023; Xu, 2015; Budamagunta, 2023).

Budamagunta et al. demonstrated that senolytic clearance of peripheral senescent cells reduces circulating SASP factors, thereby preserving BBB integrity and preventing age-related synaptic dysfunction in the hippocampus (Budamagunta, 2023). These findings highlight the systemic influence of adipose-derived SASP on brain aging. The SASP further propagates systemic and cerebrovascular inflammatory signaling, thereby contributing to age-related neural dysfunction (Budamagunta, 2023; Ogrodnik, 2021).

At the molecular and signaling level, Xu et al. showed that activation of the JAK signaling pathway in senescent adipose progenitor cells is a major driver of SASP production. Pharmacological inhibition of JAK signaling attenuated adipose and systemic inflammation, identifying a pathway through which adipose senescence may influence brain aging (Xu, 2015). In addition, senescent adipose cells display impaired adipogenic capacity and reduced insulin sensitivity. These metabolic defects can indirectly aggravate neurodegenerative processes by promoting vascular dysfunction and systemic metabolic dysregulation, as reported by Nerstedt and Smith (Nerstedt and Smith, 2023).

Adipose senescence may therefore represent a master upstream driver integrating inflammation, insulin resistance, vascular dysfunction and dyslipidemia, positioning senolytic and senomorphic strategies as potential modulators of brain aging. The interconnected pathways linking adipose tissue dysfunction to brain aging are summarized in Fig. 1.

Emerging from these data is a conceptual framework in which adipose tissue acts as a systemic aging hub, modulating the rate of brain senescence through integrated endocrine, inflammatory, metabolic, and epigenetic mechanisms. While this perspective positions dysfunctional adipose tissue, particularly inflamed visceral depots, as a primary driver of microglial priming, insulin resistance, and cerebrovascular compromise, it represents only one facet of a more complex communication axis. Indeed, the impact of adipose tissue on brain aging is profoundly context-dependent; as a heterogeneous organ, specific depots and functional states can exert protective, rather than deleterious, effects on neural longevity. This duality suggests that adipose tissue should not be conceptualized solely as a source of metabolic stress, but rather as a dynamic regulator capable of either accelerating or buffering brain aging trajectories, positioning adipose health as a critical lever for delaying neurodegenerative decline.

4. Protective pathways: when adipose tissue does *not* accelerate brain aging

While excess and dysfunctional white adipose tissue has been implicated in accelerating brain aging, accumulating evidence indicates that specific adipose tissue depots may exert metabolically and neurobiologically protective effects (Fig. 2). In particular, BAT and inducible beige adipocytes within white adipose depots have attracted increasing attention as modulators of systemic metabolic homeostasis, inflammatory tone and endocrine signaling, factors that directly influence brain aging.

Unlike WAT, which primarily stores energy, BAT and beige AT are specialized for energy dissipation through non-shivering thermogenesis. This process is mediated by uncoupling protein 1 (UCP1) and is under tight neural and endocrine control (Bartelt, 2018; Dinh, 2025). By sustaining metabolic flexibility and reducing ectopic lipid accumulation, thermogenic adipose depots counteract core drivers of neurodegenerative vulnerability, including insulin resistance and chronic inflammation.

This functional divergence between energy-storing and energy-dissipating adipose depots reframes adiposity not as a quantitative trait (fat mass), but as a qualitative metabolic phenotype with distinct implications for brain aging.

4.1. Endocrine functions of BAT: The batokine axis

Beyond thermogenesis, BAT and beige adipocytes within WAT depots function as endocrine regulators through the secretion of bioactive molecules collectively termed batokines. These factors exert autocrine, paracrine and systemic actions that extend beyond metabolic regulation. Key batokines and BAT-associated signaling mediators, including C-X-C motif chemokine ligand-14 (CXCL14), CXCL12 and fibroblast growth factor 21 (FGF21), contribute to the regulation of insulin sensitivity, lipid metabolism and immune cell trafficking. Although FGF21 is predominantly produced by the liver and BAT likely contributes only modestly to circulating systemic levels, BAT-associated FGF21 signaling has been implicated in local thermogenic and metabolic regulation

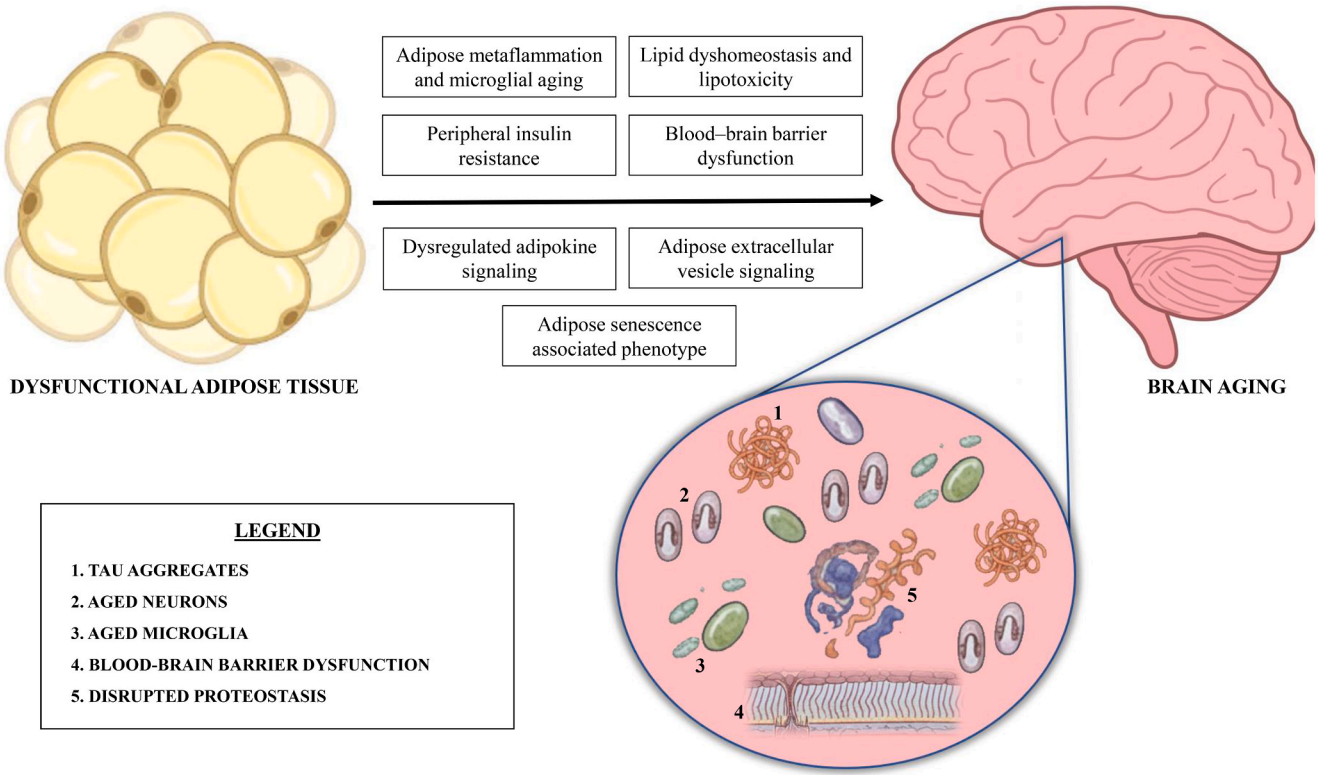

Fig. 1. Mechanistic pathways linking adipose tissue dysfunction to brain aging.

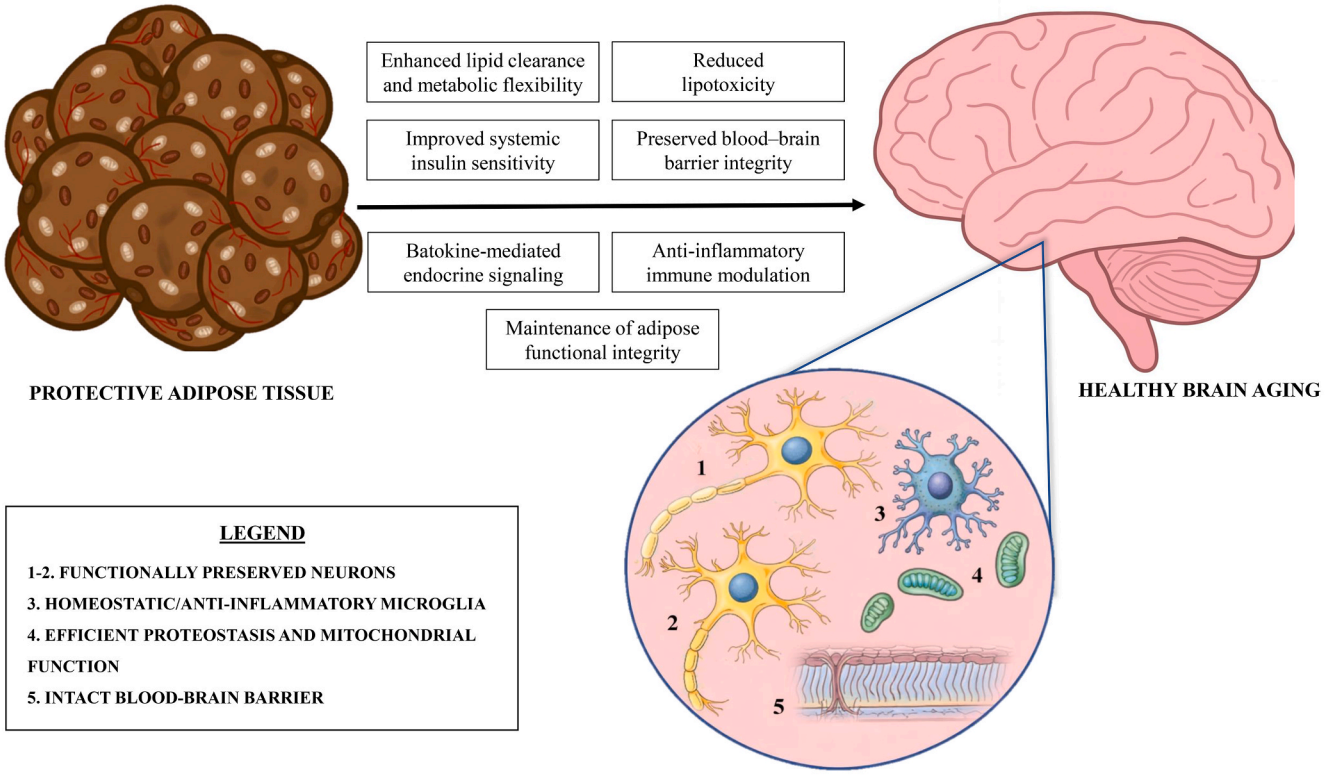

Fig. 2. Protective mechanistic pathways linking adipose tissue to resilience in brain aging.

(Cereijo, 2018; Agueda-Oyarzabal, 2025; Jurado-Fasoli, 2024).

Through these mechanisms, the BAT secretome may indirectly influence brain aging by reducing peripheral inflammation and improving vascular and metabolic health.

4.2. Thermogenesis, immunomodulation and inflammation control

BAT activation, whether by cold exposure or pharmacological means, increases glucose and fatty acid uptake, enhances energy expenditure and reduces circulating triglycerides and glucose levels (Bartelt, 2018; Dinh, 2025; Jurado-Fasoli, 2024; Herz, 2021).

BAT also recruits alternatively activated (M2) macrophages via secreted chemokines, fostering an anti-inflammatory microenvironment (Cereijo, 2018; Agueda-Oyarzabal, 2025). This shift contrasts sharply with the pro-inflammatory macrophage infiltration observed in dysfunctional VAT.

Given the established role of chronic low-grade inflammation in microglial priming and neurodegeneration, BAT-mediated immunomodulation may indirectly attenuate central immune aging.

4.3. Age-related decline of BAT and implications for brain health

BAT mass and thermogenic activity decline with age. This reduction parallels increases in visceral adiposity, systemic inflammation and metabolic impairment, all of which are associated with accelerated brain aging (Félix-Soriano, 2021). Conversely, experimental strategies that preserve BAT function in aging models, including sirtuin 1 (SIRT1) overexpression, inhibition of senescent immune cell infiltration and modulation of pathways such as olfactomedin 4 (OLFM4), ubiquitin specific peptidase 2 (USP2) and Nrf1, maintain thermogenic capacity and improve metabolic profiles. Notably, these interventions have been associated with reduced inflammatory burden and improved cognitive performance in preclinical studies (Bartelt, 2018; Dinh, 2025; Agueda-Oyarzabal, 2025; Xu, 2025; Li, 2021).

Importantly, much of the evidence supporting the neuroprotective and metabolic effects of BAT derives from rodent and experimental models, in which BAT mass and thermogenic capacity are substantially greater than in adult humans. In humans, BAT depots are relatively small, decline with aging and obesity and likely contribute only modestly to whole-body energy expenditure under physiological conditions. Consequently, the translational relevance of BAT activation as a therapeutic strategy for obesity-related brain aging remains uncertain. While human studies suggest that BAT activity associates with improved metabolic profiles (Cypess, 2009); whether pharmacological or environmental BAT activation can meaningfully influence cognitive aging or neurodegenerative risk in humans has yet to be established.

These results raise the possibility that BAT decline is not merely a correlate of aging but a contributory factor to systemic and neural aging trajectories. Preservation of thermogenic competence may therefore constitute a previously underappreciated determinant of cognitive resilience.

4.4. Adipose tissue distribution and the concept of metabolic protection

The concept of metabolically healthy obesity highlights that adipose distribution and functional quality are more relevant than total fat mass. Individuals with this phenotype typically display higher BAT volume and activity, greater SAT and lower VAT. This distribution associates with preserved insulin sensitivity and reduced cardiometabolic risk (Jurado-Fasoli, 2024; Herz, 2021).

Importantly, the differential effects of VAT and SAT on brain aging extend beyond inflammation alone and involve major differences in lipid handling, lipolytic activity and systemic insulin sensitivity. SAT is generally considered metabolically protective because it serves as a relatively efficient lipid-buffering depot capable of safely storing excess fatty acids and limiting ectopic lipid accumulation in non-adipose organs. In contrast, VAT exhibits higher basal lipolytic activity and releases larger amounts of free fatty acids directly into the portal circulation, thereby promoting hepatic lipid accumulation, insulin resistance and dysregulated glucose metabolism. Through this portal drainage system, visceral adiposity is closely linked to hepatic steatosis and altered hepatokine secretion, which further amplify systemic metabolic dysfunction and may indirectly contribute to brain aging processes.

Compared with SAT, VAT exhibits reduced adipogenic expandability, impaired lipid storage and greater susceptibility to hypertrophy and inflammatory remodeling, thereby promoting ectopic lipid deposition and metabolic stress (Kahn, 2022; Witczak-Sawczuk, 2024; Suárez-Cuenca, 2021).

From a brain aging perspective, depot distribution may therefore determine whether adipose tissue functions predominantly as a source of neuroinflammatory and metabolic stress signaling (VAT-dominant phenotype) or as a metabolic buffer capable of maintaining lipid homeostasis and systemic insulin sensitivity (SAT/BAT-dominant phenotype).

4.5. The late-life BMI paradox and BAT-associated resilience

Epidemiological observations describing a “late-life BMI paradox”, whereby higher BMI in older adults associates with reduced mortality, may partially reflect preserved adipose tissue function rather than excess adiposity per se. Reverse causation, driven by frailty-related weight loss, likely contributes. However, maintenance of SAT and BAT mass and function may also provide metabolic and inflammatory buffering in late life (Jurado-Fasoli, 2024; Herz, 2021; Dojo, 2025).

4.6. Genetic and sex-specific modifiers

BAT abundance, activity and secretory profiles are influenced by genetic and sex-dependent factors. Variants in genes such as OLFM4, USP2 and Nrf1 modulate thermogenic capacity and immune-adipose interactions. Female sex is consistently associated with higher BAT prevalence and a more favorable lipid mediator profile (Bartelt, 2018; Félix-Soriano, 2021; Xu, 2025; Lai, 2025).

Sex-specific patterns of adipose tissue distribution also substantially influence metabolic and brain aging trajectories. Premenopausal women preferentially accumulate subcutaneous adipose tissue, particularly in gluteofemoral depots, whereas men exhibit greater visceral fat accumulation. Estrogens contribute to this protective adipose distribution by promoting subcutaneous lipid storage, enhancing insulin sensitivity and suppressing adipose tissue inflammation. In addition, estrogens exert direct vascular and neuroprotective effects, including improved endothelial function, mitochondrial regulation and attenuation of neuroinflammatory signaling. Following menopause, declining estrogen levels are associated with visceral fat redistribution, worsening metabolic dysfunction and increased susceptibility to cognitive decline and neurodegenerative disease. These observations indicate that sex hormones represent important modulators of the adipose–brain axis across the lifespan.

Together, these findings suggest that adipose tissue distribution and functional quality, rather than adiposity alone, critically influence brain aging trajectories.

5. Evidence from human studies

Human epidemiological, neuroimaging and biomarker studies provide growing evidence that adipose tissue distribution and function influence trajectories of cognitive decline and brain aging. In particular, increased visceral adiposity is consistently associated with adverse structural, metabolic and inflammatory brain changes independent of traditional vascular risk factors (Boccara, 2023; Anand, 2022).

5.1. Neuroimaging correlates of regional adiposity

Neuroimaging studies using structural MRI, diffusion tensor imaging (DTI) and positron emission tomography (PET) scans further demonstrate that higher VAT volume correlates with adverse brain structural

changes, including reduced gray matter volume and altered white matter integrity. These associations are further modulated by demographic factors, being most evident among males and at earlier stages of midlife (Moran, 2024). In contrast, PET-based metabolic imaging indicates that increased glucose uptake in VAT may paradoxically associate with slower brain aging, highlighting complex and depot-specific metabolic influences of adipose tissue on brain health (Lu, 2024). Thus, human imaging data reinforce the concept that adipose tissue quality and metabolic activity, rather than absolute mass, determine its impact on the brain.

5.2. Molecular mediators: Extracellular vesicles and adipose-derived signaling

At the molecular level, cerebrospinal fluid (CSF) and blood biomarker analyses indicate that adipose tissue-derived factors actively contribute to brain aging processes. Wang et al. show that extracellular vesicles released from adipose tissue, enriched in specific microRNAs, can cross the BBB and induce synaptic loss and cognitive deficits under insulin-resistant conditions (Wang, 2022). These findings provide mechanistic support for a circulating adipose-to-brain inflammatory signal capable of modulating synaptic integrity.

Complementing this pro-inflammatory pathway, Shirafuji et al. identify a neurotrophic adipose–brain signaling pathway in which white adipose tissue regulates hippocampal brain-derived neurotrophic factor (BDNF) via the chemokine CX3CL1 (Shirafuji, 2025). Aging and obesity disrupt this pathway, whereas exercise restores it, highlighting the role of adipose tissue in synaptic plasticity and cognitive maintenance.

Similarly, Mazzoli et al. report that a Western diet induces parallel inflammatory responses in adipose tissue and brain. These changes include increased TNF-α, reduced adiponectin, impaired insulin signaling and decreased synaptic proteins such as BDNF, linking adipose inflammation to neurodegenerative mechanisms (Mazzoli, 2020).

5.3. Interventional evidence: modifiability of the adipose–brain axis

Crucially, human intervention studies support the modifiability of adipose-related brain risk. Weight loss, physical exercise and bariatric surgery improve adipose tissue function and cognitive outcomes. These benefits may arise from restored adipose-derived neurotrophic signaling, normalization of BDNF regulation and reduced systemic and central inflammation (Shirafuji, 2025; Mazzoli, 2020). Exercise, in particular, appears to restore disrupted adipose–brain chemokine signaling pathways and improve metabolic flexibility, highlighting lifestyle modulation as a powerful regulator of systemic–central crosstalk.

Collectively, human epidemiological, imaging and molecular data converge to support a clinically meaningful adipose–brain axis. Visceral adiposity consistently associates with structural brain changes, microstructural white matter alterations, pro-inflammatory circulating signals and increased dementia risk. At the same time, the reversibility of adipose-related neural alterations provides strong evidence that visceral adiposity represents a modifiable risk factor rather than a fixed determinant of neurodegenerative decline.

The critical next step is to translate these mechanistic and observational insights into therapeutic strategies capable of altering systemic inflammatory tone and metabolic signaling in ways that promote cognitive resilience.

6. Adipose-derived biomarkers of brain aging

The growing recognition of AT as a regulator of brain aging raises an important translational question: how can the adipose–brain axis be quantified in vivo? Beyond mechanistic insights, identifying reliable peripheral biomarkers is essential for risk stratification, longitudinal monitoring and therapeutic targeting (Table 1).

6.1. Circulating inflammatory and adipokine signatures

Systemic inflammatory markers, including IL-6, TNF-α and C-reactive protein (CRP), are consistently elevated in individuals with increased visceral adiposity and associate with cognitive decline. While individually non-specific, these markers may acquire greater predictive value when interpreted in the context of adipose distribution and metabolic status.

Adipokines provide a more tissue-informed signature. Reduced adiponectin levels, elevated resistin and leptin resistance patterns reflect dysfunctional visceral adipose tissue and correlate with neuroinflammatory and metabolic disturbances. Rather than isolated concentrations, composite adipokine profiles, such as the adiponectin–resistin or leptin–adiponectin ratios, may better capture adipose functional quality and its neurobiological impact.

Importantly, longitudinal changes in these markers may precede overt cognitive symptoms, positioning adipokine dynamics as early indicators of systemic vulnerability.

6.2. Senescence-associated and extracellular vesicle biomarkers

Adipose tissue is a major reservoir of senescent cells, suggesting that circulating markers of cellular senescence may reflect adipose-driven

Table 1
Candidate biomarkers capturing structural, inflammatory and functional dimensions of the adipose–brain axis.

Biomarker Category	Representative Markers	Reflects Adipose Function	Association with Brain Aging	Clinical Readiness
Circulating inflammatory markers	IL-6, TNF-α, IL-1β, CRP	Visceral adipose inflammation; systemic inflammatory tone	Associated with cognitive decline, white matter changes and neuroinflammation	Widely available; limited specificity; useful in composite panels
Adipokine profile	Adiponectin, resistin, leptin; leptin/adiponectin ratio	Adipose endocrine balance; insulin sensitivity; metabolic resilience	Linked to synaptic plasticity, BBB integrity and AD pathology in experimental and human studies	Clinically measurable; promising for risk stratification
Senescence-associated markers	SASP components; circulating p16ˆINK4a expression	Adipose senescent cell burden; pro-inflammatory secretome	Associated with systemic aging; emerging links to neurodegeneration	Experimental; requires validation in longitudinal human cohorts
Extracellular vesicles (EVs)	Adipose-derived EVs carrying pro-inflammatory microRNAs	Inter-organ signaling from dysfunctional adipose tissue	Mechanistic link to synaptic dysfunction and insulin resistance in the brain	Preclinical/early translational stage
Imaging-based depot quantification	VAT/SAT ratio (MRI/CT)	Regional adipose distribution	VAT burden correlates with gray matter loss and white matter disruption	Clinically accessible; strong epidemiological support
Functional adipose imaging	FDG-PET glucose uptake in VAT; BAT volume/activity	Metabolic activity of adipose depots; thermogenic capacity	VAT metabolic activity associated with brain age metrics; BAT linked to metabolic resilience	Limited availability; promising research tool
Composite adipose-brain indices (proposed)	Integrated panel combining VAT volume, adipokine ratios, inflammatory markers and brain age delta	Multidimensional adipose quality and systemic impact	Potential to improve prediction of cognitive decline trajectories	Conceptual framework; requires prospective validation

aging processes. Components of the SASP, including pro-inflammatory cytokines and matrix-remodeling factors, as well as p16ˆINK4a expression in circulating immune cells, represent potential systemic indicators of adipose senescence burden.

Emerging evidence further implicates adipose-derived EVs carrying specific microRNAs in modulating synaptic function and neuroinflammation. Quantification of EV cargo signatures may therefore provide mechanistically informative biomarkers directly linking peripheral metabolic dysfunction to neuronal vulnerability.

6.3. Imaging-based adipose biomarkers

Advances in imaging enable depot-specific and functional assessment of adipose tissue. Visceral-to-subcutaneous fat ratios derived from magnetic resonance imaging (MRI) or computed tomography (CT), BAT volume and thermogenic activity, and FDG-PET–based measures of adipose glucose uptake offer complementary information beyond total fat mass.

Notably, functional characteristics of adipose depots may outperform volumetric measures in predicting brain aging trajectories. Associations between visceral fat metabolic activity and machine-learning–derived brain age metrics suggest that adipose function, rather than adiposity per se, may better reflect systemic influences on neurobiological aging. In this context, "brain age delta" refers to the difference between predicted brain age derived from neuroimaging models and chronological age, with higher values indicating accelerated brain aging.

6.4. Toward an integrated adipose–brain risk framework

Collectively, these observations support a multi-dimensional biomarker approach. A composite adipose–brain risk index integrating (i) visceral fat burden, (ii) adipokine balance, (iii) inflammatory or senescence markers and (iv) brain-specific outcomes such as cognitive performance or brain age delta could enhance precision stratification.

Such an approach moves beyond single-marker associations and acknowledges the systemic, network-based nature of brain aging. Future longitudinal studies will be essential to validate adipose-derived biomarker panels as predictors of cognitive decline and as responsive readouts in intervention trials.

7. Translational and therapeutic perspectives

Accumulating evidence positions AT as a modifiable therapeutic target capable of influencing trajectories of brain aging. Beyond its mechanistic role, AT, particularly VAT and thermogenic fat, offers multiple points of clinical intervention through anti-inflammatory, senotherapeutic, metabolic and lifestyle-based strategies. Importantly, interventions that improve adipose quality, rather than simply reducing fat mass, may recalibrate systemic inflammatory tone, adipokine signaling, and metabolic homeostasis. Through these effects, adipose-targeted therapies have the potential to indirectly mitigate neurodegenerative risk. Below, key adipose-centered therapeutic avenues with translational relevance to brain aging are outlined (Table 2).

7.1. Targeting adipose inflammation

Chronic low-grade inflammation originating from dysfunctional VAT represents a primary therapeutic entry point. In humans and rodents, reducing VAT mass, surgically or metabolically, lowers circulating pro-inflammatory cytokines (IL–1β, IL–6, TNF–α) and improves BBB integrity and white matter markers in aged animals (Kelly, 2016; Shin, 2015).

Clinically relevant interventions include metabolic drugs such as glucagon-like peptide-1 (GLP-1) receptor agonists, metformin, thiazolidinediones and sodium glucose cotransporter 2 (SGLT2)/dipeptidyl peptidase-4 (DPP-4) inhibitors. These agents consistently reduce inflammatory markers while shifting adipokine profiles toward higher adiponectin and lower resistin (Ormazabal, 2025).

Among these approaches, thiazolidinediones are particularly relevant because, beyond their anti-inflammatory effects, they promote adipose tissue expandability and lipid buffering capacity through peroxisome proliferator-activated receptor-γ (PPARγ) activation. By enhancing adipocyte differentiation and facilitating safer lipid storage within subcutaneous adipose depots, TZDs reduce ectopic lipid accumulation, circulating free fatty acids and lipotoxic stress in peripheral tissues. Similarly, GLP-1 receptor agonists and other insulin-sensitizing therapies may improve adipose tissue function by reducing visceral adiposity, improving lipid handling and attenuating systemic metabolic stress (Ormazabal, 2025). Collectively, these effects improve systemic insulin sensitivity and may indirectly mitigate neuroinflammatory and neurodegenerative processes linked to metabolic dysfunction.

Nutritional strategies reviewed by Wang, Xu and Li, ranging from caloric restriction to resveratrol supplementation, similarly dampen

Table 2
Adipose-centered therapeutic strategies with translational relevance for brain aging.

Therapeutic target	Representative interventions	Primary effects on adipose tissue	Downstream effects on brain aging	Translational status
Adipose inflammation (primarily VAT)	GLP-1 receptor agonists, metformin, thiazolidinediones, SGLT2/DPP-4 inhibitors; caloric restriction; resveratrol; structured exercise	↓ IL-1β, IL-6, TNF-α; ↑ adiponectin; ↓ resistin; improved insulin sensitivity; reduced ectopic lipid deposition	Improved BBB integrity; reduced neuroinflammation; improved white matter integrity; potential cognitive stabilization	Established metabolic therapies; limited trials with cognitive endpoints
Cellular senescence in adipose tissue	Dasatinib + quercetin (D + Q); senomorphic approaches	Clearance of senescent adipocytes; ↓ SASP signaling; improved adipose insulin sensitivity	Reduced peripheral inflammatory burden; improved hippocampal function; reduced amyloid burden (preclinical models)	Preclinical evidence; early translational exploration
BAT activation and thermogenic remodeling	β3-adrenergic agonists (e.g., mirabegron); CL316,243 (preclinical); exercise; S100A8 inhibition (paquinimod)	↑ UCP1 expression; enhanced thermogenesis; improved glucose homeostasis; favorable adipokine profile; beiging of WAT	Reduced systemic inflammation; improved metabolic buffering; potential resilience to neurodegeneration	Human metabolic data available; cognitive effects largely untested
Adipokine modulation (adiponectin–resistin axis)	AdipoRon; lifestyle interventions; metabolic drugs	↑ adiponectin signaling; ↓ resistin; improved mitochondrial function; reduced cytokine dysregulation	Reduced neuroinflammation; improved synaptic plasticity; improved cognition in AD models; improved BBB function	Strong preclinical evidence; biomarker potential in humans
Depot-specific reduction of VAT	Bariatric surgery; targeted weight loss; partial VAT removal (preclinical)	↓ visceral fat mass; reduced macrophage infiltration; improved metabolic profile	Improved hippocampal connectivity; improved vasoreactivity; reduced inflammatory tone	Strong human metabolic data; limited direct cognitive trials
Lifestyle and dietary patterns	Exercise; Mediterranean diet; MIND diet	Reduced VAT; improved adipose quality; enhanced fatty acid oxidation; anti-inflammatory remodeling	Improved cognitive outcomes; reduced dementia risk; preserved neurotrophic signaling	Strong epidemiological and interventional support

adipose inflammation and associate with reduced cognitive risk (Wang, 2022). Exercise emerges as a robust anti-inflammatory intervention. Tang et al. demonstrate that physical activity remodels aged AT, limits ectopic lipid accumulation and mitigates immunosenescence, with downstream benefits for brain inflammatory status (Tang, 2025). Despite these converging data, trials explicitly linking adipose anti-inflammatory therapies to cognitive or neuroimaging outcomes remain limited.

7.2. Senolytics and senotherapeutics

Adipose tissue has been identified as a major reservoir of senescent cells, making it an attractive target for senotherapeutic intervention. Palmer and Kirkland propose adipose senescence as a central driver of age-related metabolic dysfunction (Palmer and Kirkland, 2016). Supporting this concept, Islam et al. provide *in vivo* evidence that intermittent treatment with dasatinib plus quercetin (D + Q) selectively clears senescent cells from in perigonadal WAT, improves insulin sensitivity and suppresses SASP-related gene expression (Islam, 2023).

Importantly, senolytic strategies also show promise in neurodegenerative contexts. Fang et al. demonstrate that D + Q treatment in $APP^{NL-F/NL-F}$ AD mice reduces visceral fat mass and lowers senescence markers in both adipose tissue and hippocampus. These changes are accompanied by reduced amyloid burden and improved spatial memory, with notable sex-specific effects (Fang, et al., 2024). Together, these findings support the translational concept that adipose-directed senolysis may indirectly modify brain aging by reducing a major peripheral source of pro-inflammatory and pro-degenerative signals. However, safety, depot specificity, and long-term efficacy in humans remain open questions.

7.3. BAT activation and thermogenic remodeling

Age-related loss of BAT and beige adipocyte function represents another therapeutically relevant target. Zoico et al. summarize evidence that aging is associated with reduced BAT mass, impaired UCP1 expression and diminished thermogenic responsiveness (Zoico, 2019). Feng et al. further show that senescent immune cells infiltrate BAT in aged rodents, disrupting sympathetic innervation. Pharmacologic inhibition of S100A8 with paquinimod rejuvenates BAT innervation and function, suggesting that targeting senescent immune cells may restore thermogenic capacity in late life (Feng, 2023).

At the interventional level, Natarajan et al. demonstrate that chronic β3-adrenergic stimulation with CL316,243 in aged mice enhances BAT thermogenesis, improves glucose homeostasis and reshapes adipokine profiles (Natarajan, 2024). Mechanistically, CL316,243 enhances UCP1-dependent thermogenesis in BAT while activating a futile lipid cycling program in WAT, accompanied by a more favorable adipokine profile, indicating that thermogenic stimulation can reshape adipose phenotype and systemic metabolism in preclinical models of aging. Complementarily, long-term exercise training, as demonstrated by Félix-Soriano and co-authors in aged obese female mice, induces browning, mitochondrial biogenesis and anti-inflammatory remodeling in inguinal WAT and maintains BAT thermogenic markers, changes that parallel improved insulin sensitivity (Félix-Soriano, 2023).

Collectively, these findings support the concept that thermogenic remodeling may beneficially influence systemic metabolism and inflammatory tone in aging, at least in preclinical models. However, translation to humans requires caution, as most mechanistic and interventional evidence derives from rodent studies with substantially higher BAT abundance and thermogenic capacity than typically observed in older adults with obesity. Although selective β3-agonists such as mirabegron demonstrate metabolic effects in humans (Dwaib and Michel, 2023), whether BAT activation can meaningfully influence cognitive aging or neurodegenerative trajectories in clinical settings remains to be determined. In addition, chronic pharmacological or environmental stimulation of thermogenic adipose tissue may carry potential risks, including excessive sympathetic activation, cardiovascular effects, altered thermoregulation and incompletely understood consequences of prolonged batokine signaling. These considerations highlight the need for cautious evaluation of BAT-targeted therapies in humans, particularly in older individuals with obesity and cardiometabolic disease.

7.4. Adipokine modulation

Therapeutic modulation of adipokines represents a central link between adipose-targeted interventions and brain outcomes. Using human and experimental data, He and colleagues show that declining adiponectin levels in aged individuals associate with dysregulated cytokines, while adiponectin-knockout mice exhibit accelerated brain aging, with anxiety-like behavior, cognitive impairment, neuroinflammation and mitochondrial dysfunction; pharmacological activation of adiponectin signaling (AdipoRon) or inhibition of histone deacetylase 1 (HDAC1) reverses mitochondrial deficits and age-related inflammation (He, 2023). In AD models, demonstrate that high-fat diet accelerates cognitive decline and Aβ production in APP/PS1 mice; exogenous adiponectin restores glucose metabolism, improves cognition by roughly 50%, and reduces the Aβ42/40 ratio by ~ 65%, whereas resistin worsens Aβ pathology, oxidative stress and metabolic impairment (Cisternas, 2023). These data provide causal evidence that the adiponectin–resistin axis modulates AD progression.

At the vascular and barrier level, Bettinetti-Luque et al. review how adipokines such as leptin, adiponectin and resistin influence BBB integrity and cerebrovascular dysfunction in AD (Bettinetti-Luque, 2024). Zhai and co-authors further integrate adipokine dynamics into the broader picture of obesity-induced adipose inflammation as a gateway to AD, highlighting leptin resistance, low adiponectin and pro-inflammatory adipokines as central nodes linking VAT dysfunction to neurodegeneration (Weijie, 2024). Together, these findings support the use of adipokine-targeting drugs and adipokine panels as both therapeutic tools and peripheral biomarkers in metabolic–cognitive intervention trials.

7.5. Lifestyle and depot-specific interventions

Lifestyle interventions remain among the most immediately translatable strategies for targeting VAT. Exercise and dietary patterns such as the Mediterranean and MIND diets consistently reduce VAT mass, improve adipose quality and attenuate systemic inflammation. Félix-Soriano and colleagues show that long-term treadmill training in aged obese mice preferentially remodels subcutaneous WAT, enhancing fatty acid oxidation genes, reducing macrophage infiltration and promoting beiging, while also maintaining BAT thermogenic gene expression and improving glucose tolerance (Félix-Soriano, 2023). In parallel, Tang et al. highlight that exercise counters adipose aging by suppressing inflammation, limiting ectopic lipid accumulation and mitigating immunosenescence in metabolic organs including the brain (Tang, 2025).

Direct evidence for a causal role of VAT in brain dysfunction comes from Seidel et al., who show that partial removal of epididymal VAT in obese mice improves hippocampal vasoreactivity and cortico-hippocampal functional connectivity, without major effects on liver disease or atherosclerosis, establishing a causal contribution of VAT to obesity-associated brain impairments (Seidel, 2025). At the same time, Shirafuji and co-authors present a complementary view in which WAT, via CX3CL1 signaling, supports hippocampal BDNF levels, with aging and obesity disrupting this adipose–brain trophic axis and exercise restoring it (Shirafuji, 2025). Lu and colleagues extend the translational horizon by linking FDG-PET–derived glucose uptake in abdominal fat to a machine-learning–derived "brain age" metric: higher VAT glucose uptake associates with a "younger" brain across subgroups, whereas SAT glucose uptake shows a more complex pattern, suggesting that functional characteristics of regional depots, not simply their volume, may

influence brain aging trajectories (Lu, 2024).

7.6. How targeting AT may alter trajectories of brain aging

Collectively, translational evidence supports adipose tissue as a peripheral yet powerful therapeutic hub for influencing brain aging. Interventions targeting adipose inflammation, cellular senescence, thermogenic capacity, adipokine balance and visceral fat burden, through pharmacological, lifestyle or combinatorial approaches, demonstrate convergent benefits across metabolic and neurodegenerative models.

Conceptually, targeting AT may shift systemic physiology from a pro-neurodegenerative to a pro-resilience state, thereby modifying the pace of brain aging rather than merely treating its late consequences.

From a clinical trial perspective, integrating detailed adipose phenotyping with brain-specific outcomes, including cognition, neuroimaging markers, fluid biomarkers and machine-learning–derived brain age metrics, may enable precision-based, adipose-centered therapeutic strategies.

Such an approach moves beyond symptom management toward upstream modulation of the metabolic–inflammatory networks that shape neurodegenerative vulnerability across the lifespan.

8. Limitations

Despite encouraging preclinical and early clinical findings, several challenges remain. Human trials rarely integrate comprehensive adipose phenotyping with longitudinal neuroimaging and cognitive endpoints. Depot-specific effects, sex differences, and genetic modifiers are often underpowered or not systematically assessed. Furthermore, long-term safety of senolytic and thermogenic pharmacotherapies requires careful evaluation in older populations.

Future studies must move toward stratified trial designs incorporating VAT/SAT ratios, adipokine panels, BAT activity markers and brain-based biomarkers to determine which individuals are most likely to benefit from adipose-centered interventions.

9. Conclusions

Accumulating evidence positions adipose tissue not as a passive metabolic reservoir, but as a central regulator of brain aging. Evidence from experimental models, neuroimaging and population-based cohorts converges on the conclusion that: dysfunctional adipose tissue, particularly visceral depots, promotes neurobiological vulnerability.

Visceral adipose tissue acts as a source of chronic low-grade inflammation, metabolic stress, adipokine imbalance and senescence-associated signaling. These peripheral disturbances reach the brain and alter its aging trajectory. They influence microglial activation, impair insulin signaling, disrupt lipid homeostasis and compromise blood–brain barrier integrity. Over time, these changes accelerate cerebrovascular dysfunction and increase susceptibility to cognitive decline and neurodegeneration.

Importantly, the impact of adiposity on the brain is depot-specific and context-dependent. Visceral fat consistently associates with adverse outcomes. In contrast, preserved subcutaneous and thermogenic adipose depots may exert protective effects. These depots enhance metabolic buffering, reduce systemic inflammation and support neurotrophic signaling pathways. This heterogeneity helps reconcile epidemiological paradoxes, including the late-life BMI paradox. It also underscores that adipose quality and distribution matter more than total fat mass.

Collectively, the evidence supports a bidirectional model. Adipose tissue can either accelerate or buffer brain aging, depending on its inflammatory, endocrine and metabolic state.

From a translational perspective, adipose tissue represents a modifiable therapeutic hub. Targeting adipose inflammation, cellular senescence, adipokine signaling and thermogenic capacity offers new opportunities to influence brain aging indirectly. Lifestyle interventions, metabolic drugs and emerging senotherapeutics may reduce systemic inflammatory burden and restore metabolic balance. By acting upstream of neuronal damage, such strategies could slow the pace of cognitive decline.

Future research should integrate detailed adipose phenotyping with longitudinal neuroimaging, fluid biomarkers and cognitive outcomes. This approach will enable precision-based, adipose-centered interventions aimed at promoting healthy brain aging and reducing dementia risk across the lifespan.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability statement

This study is a literature review and did not generate any new experimental data. All data referenced and analyzed in this review are publicly available in the cited publications.

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