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The metabolic engine of cognition: microglia–neuron interactions in health, ageing and disease

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Cognitive impairment is associated with perturbations of fine-tuned neuroimmune interactions. At the molecular level, alterations in cellular metabolism can compromise brain function, driving structural damage and cognitive deficits. In this Review, we focus on the bidirectional interactions between microglia, the brain-resident immune cells and neurons to dissect the metabolic determinants of brain resilience and cognition. We first outline these metabolic pathways during development and adult life. Then, we delineate how these processes are perturbed in ageing, as well as in metabolic, neuroinflammatory and neurodegenerative disorders. By doing so, we provide a mechanistic understanding of the metabolic pathways relevant to cognitive function in health and disease, thus paving the way for novel therapeutic targets based on the emerging field of neuroimmunometabolism.

As a clinical manifestation of brain dysfunction, cognitive impairment exists on a continuum from mild deficits to overt dementia[1]. This progression reflects the intricate interplay of multiple biological mechanisms, including metabolic dysregulation, chronic neuroinflammation and neurodegeneration[2]. The convergence of these pathological processes, coupled with the global increase in life expectancy, has led to a concerning rise in the prevalence of cognitive decline (Table 1)[3–6]. With the number of people living with dementia alone projected to increase nearly threefold by 2050, this poses a pressing public health challenge, profoundly affecting individuals and societies worldwide[4,6,7].

The most common neurodegenerative disorders of non-traumatic or non-infectious origin associated with cognitive impairment comprise Alzheimer's disease, Parkinson's disease, Huntington's disease and progressive multiple sclerosis (MS)[8–11]. Rapidly progressive dementias also represent a relatively new distinct entity of high clinical relevance[12]. Rapidly progressive dementias are a heterogeneous group of disorders, including metabolic encephalopathy, immune-mediated or infectious encephalitis, prion diseases and rapidly progressive subtypes of common neurodegenerative diseases. Finally, recent emerging data highlight the high prevalence of neurocognitive sequelae of severe acute respiratory syndrome coronavirus 2 infection (that is, post-coronavirus disease (COVID) cognitive dysfunction or 'brain fog'), which derives from a systemic neuroimmunometabolic disruption involving blood–brain barrier and neuroendocrine dysregulation[12,13].

Beyond these primary causes, the surge of cognitive decline is further accelerated by two powerful epidemiological trends: an ageing global population and the rising prevalence of metabolic diseases. While the progressive deterioration of mental abilities inherent to natural ageing is distinct from overt dementia, ageing remains an independent risk factor for most neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease. Additional risk factors—such as diabetes mellitus, obesity, hypertension and the broader concept of metabolic syndrome—exert significant effects on brain energy metabolism, synaptic integrity and blood–brain barrier permeability, further linking metabolic health to cognitive resilience[14–16].

Regardless of primary driving causes and precipitating comorbidities, a key challenge remains the lack of specific treatments capable of halting the drivers of cognitive impairment. In fact, with the exception of a limited number of reversible cases, the vast majority of individuals with cognitive decline and/or dementia remain untreated as current medical care largely relies on symptomatic treatments (such as

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Table 1 | Actual and expected prevalence of cognitive impairment in common metabolic, neurodegenerative and neuroinflammatory disorders

Neurodegenerative/ neuroinflammatory/ metabolic disorders	Epidemiological data for cognitive impairment	Major cognitive symptoms
The number of people with dementia is expected to increase from 57.4 million cases globally in 2019 to 152.8 million cases in 2050. GBD 2019 Dementia Forecasting Collaborators, Lancet Public Health (2022)[6]		
AD[2,4,6,8]	Global prevalence of AD dementia: 32 million cases Expected global prevalence of late-stage AD in 2050: 47.48 million cases	• Declarative (both semantic and episodic) and working memory deficits • Problem solving, speech production and visuospatial deficits
PDD[10,6]	Global prevalence of PDD dementia: 11.77 million cases Expected global prevalence of PDD in 2050: 25.2 million cases	• Attention and working memory/long-term memory deficits • Executive functioning (cognitive flexibility, planning, problem solving) and visuospatial deficits
HD[9]	Global prevalence of HD: 4.88 cases per 100,000 persons, with cognitive symptoms (after motor onset) reported in 67.6% of patients	• Earlier deficits: lower speed of cognitive processing, difficulties with the estimation of time, recognition of other people's emotions, and attention deficits • Later deficits: memory deficits (especially implicit rather than explicit learning and memory) and executive dysfunction
MS[11,185]	Global prevalence of MS: 23.9 cases per 100,000 persons (total 1.89 million cases), with cognitive deficits in >50% of people with MS (clinically isolated syndrome: ~34%, relapsing–remitting MS: ~50%, progressive MS: ~80–90%)	• Decreased information processing speed (mainly in relapsing–remitting MS) • Visual and verbal memory impairment, deficits in executive functions and visuospatial processing (mainly in progressive forms of MS)
RPDs[12]	NA	• Various cognitive symptoms with rapid onset and progression of cognitive decline
PCCD[13]	7.2% to 59.2% of individuals after COVID-19 infection, with variability across studies due to different time of PCCD onset after COVID-19 diagnosis and heterogeneous study populations	• Often described as 'brain fog' or 'fuzziness' • Episodic memory, attention and concentration deficits • Lack of motivation, executive functioning and processing speed deficits
Metabolic syndrome[14–16]	Older individuals classified as overweight or obese are affected by concomitant MCI or dementia in 32.54% or 9.47% of the cases, respectively	• Various cognitive symptoms including visuospatial memory and processing, executive functions, processing speed and psychomotor abilities

AD, Alzheimer's disease; HD, Huntington's disease; NA, not applicable; PCCD, post-COVID cognitive dysfunction; PDD, Parkinson's disease dementia; RPDs, rapidly progressive dementias.

cholinesterase inhibitors and medications to alleviate neuropsychiatric symptoms)[1]. Crucially, effective disease-modifying treatment options are absent from the therapeutic armamentarium, suggesting an urgent need to intensify research efforts towards the development of novel therapeutic approaches. In light of this critical necessity, the emerging field of neuroimmunometabolism has the potential to open new avenues within the realm of translational cognitive neuroscience and revolutionize our approach to treat cognitive decline.

The emerging field of neuroimmunometabolism

Key principles of neuroimmunometabolism

Neuroimmunometabolism is a rapidly evolving interdisciplinary field that focuses on the intersection between immunologic and metabolic cascades within the central nervous system (CNS). It lies at the nexus of neuroscience, immunology and metabolism, seeking to unravel the intricate relationship between neuronal and glial cell bioenergetics and how they influence brain physiology and pathology[17,18].

The dynamic interplay between immune, neuronal and metabolic cascades is complicated by differential metabolic profiles of glial cells and neurons, which exhibit unique bioenergetic signatures reflecting their specialized functions[19]. For example, resident brain innate immune cells, such as microglia, undergo significant metabolic shifts in response to damage-associated molecular patterns, infectious agents or traumatic injury[20,21]. Under acute conditions, these transient metabolic adaptations are mostly protective, favouring pathogen/debris clearance. However, in chronic neuroinflammatory states, persistent metabolic dysregulation can contribute to a self-sustaining cycle of tissue damage[17,18].

Neurons exhibit instead constantly high energy demands, which are necessary to convey nerve impulses especially in long-range projecting neurons (such as pyramidal cells), and to maintain resting membrane potential and neurotransmitter release. However, this rather inflexible energetic profile renders neurons particularly susceptible to even subtle metabolic perturbations[18,22].

Recently, it has emerged that these unique bioenergetic signatures are driven by diverse cellular 'neuroimmunometabolic sensors'. These sensors form a complex network of receptors and transporters on neural and immune cells that detect and respond to metabolic molecules in their immediate environment[18]. They function as a neuroimmune interface, enabling neural cells to 'read' the metabolic state of immune cells and their microenvironment, and vice versa. This includes the local availability of energy substrates such as glucose, lactate, glutamate, arginine, fatty acids, lipoproteins, cholesterol and sphingolipids[18].

Ultimately, it is expected that decoding these complex cellular energy dynamics will be key to reveal the foundations of brain function in health and disease.

Focus on microglia

Microglial activation states. Glial cells in the CNS, including astrocytes, oligodendrocytes and microglia, are highly adaptable and undergo phenotypic and functional changes contingent on shifts in their metabolic state. While the metabolic diversity of astrocytes and oligodendrocytes in relation to cognitive impairment is an emerging field of investigation, in this Review we focus on microglia, given their fundamental immunological roles guiding neuroimmune interactions.

Initial morphological observations of microglial phenotypes revealed significant heterogeneity and tightly regulated morphological changes[23]. Resting microglia are typically ramified with multiple processes, whereas activated microglia acquire an amoeboid morphology with increased soma size and shortened branches[20,24]. However, it is now clear that these activation states lie on a continuum, reflecting varying degrees of context-dependent reactivity[25,26]. Recent single-cell RNA-sequencing studies have identified transcriptional states distinguishing homeostatic microglia from various activation states found in physiological conditions, ranging from early postnatal

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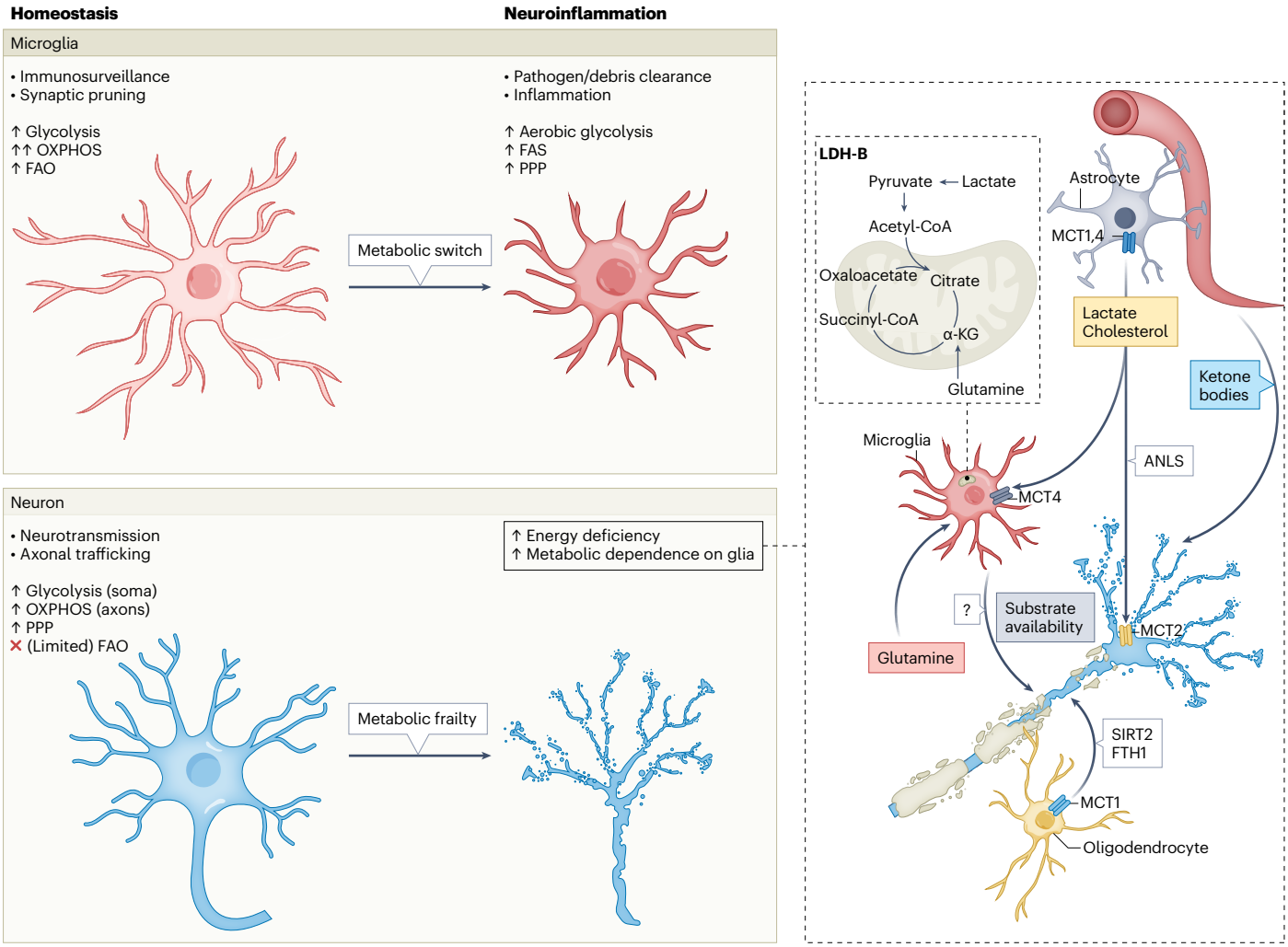

Fig. 1 | Metabolic profiles of microglia and neurons in health and disease. Under homeostatic conditions, both neurons and microglia primarily utilize OXPHOS for efficient energy production. During neuroinflammation, microglia undergo a metabolic switch, shifting to aerobic glycolysis to support rapid ATP production and their inflammatory functions. By contrast, neurons have persistently high energy demands and limited metabolic flexibility, rendering them vulnerable to fluctuations in energy supply. To maintain normal function in these conditions, neurons are metabolically supported by adjacent glial cells, such as microglia, astrocytes and oligodendrocytes (insert on the right). α-KG, α-ketoglutarate; ANLS, astrocyte–neuron lactate shuttle; FAO, fatty acid oxidation; FAS, fatty acid synthesis, FTH1, heavy subunit of ferritin; SIRT-2, sirtuin-2.

stages (proliferative-associated microglia and axon-tract-associated microglia) to ageing (white matter-associated microglia)[27].

In CNS disorders, populations of so-called disease-associated microglia (DAM) emerge and exhibit a transcriptional signature that is common across neuroinflammatory and neurodegenerative conditions[27–31]. DAM are intimately related to the expression of the triggering receptor expressed on myeloid cells 2 (*Trem2*), a lipid-binding surface molecule that is critical for phagocytosis of myelin debris, protein aggregates and apoptotic cells[32]. Specifically, DAM emerge through a two-step mechanism[29]. The first one is *Trem2* independent and causes the downregulation of microglial homeostatic genes *Cx3cr1, P2ry12, Tmem119* and *Cd33*, along with upregulation of *Tyrobp, Apoe, B2m* and ultimately *Trem2* (ref. 31). The second one depends on *Trem2* and results in the activation of lysosomal, phagocytic and lipid metabolism pathways, indicated by the upregulation of *Lpl, Axl, Cst7, Spp1* and *Itgax*[29]. While DAM are a shared feature of CNS disorders, recent research has revealed putative disease-specific microglial states, such as Alzheimer's disease-associated microglia, Parkinson's disease-associated microglia, microglia inflamed in multiple sclerosis (MIMS) and amyotrophic lateral sclerosis-associated microglia[27]. However, the precise biological functions of these distinct phenotypes remain to be fully elucidated.

Microglial metabolism. At the metabolic level, it has been shown that microglia predominantly rely on oxidative phosphorylation (OXPHOS) in homeostasis[33,34]. This highly efficient ATP production pathway provides the energy required for microglia to execute their baseline immunological functions, including the clearance of cellular debris and apoptotic cells, as well as the elimination of quiescent, less needed, or even excessive, synapses[33–35]. However, microglia also exhibit profound metabolic flexibility. They can utilize other energy substrates such as glutamine and lactate when glucose is not readily available. This adaptability endows them with the advantage of rapid adjustments to changing bioenergetic conditions (Fig. 1)[36,37].

Under neuroinflammatory conditions, microglia undergo significant metabolic reprogramming, shifting their primary energy production pathway from OXPHOS to aerobic glycolysis, a phenomenon reminiscent of the Warburg effect in cancer cells[33,38,39]. Consistently, upregulation of glycolysis and downregulation of the tricarboxylic acid (TCA) cycle have been demonstrated in murine microglia (both in vitro and in vivo) and in human induced pluripotent stem cell-derived microglia[33]. Albeit less efficient quantitatively (2 ATP molecules per glucose molecule are produced from aerobic glycolysis compared to up to 36 ATP molecules from OXPHOS), this metabolic switch rapidly

provides energy, enabling microglia to meet the heightened bioenergetic demands of a pro-inflammatory environment[33,38].

It should be noted that discrepant species-specific changes have also been observed, with a reported decrease in oxidative metabolism in mouse but not in human microglia[33]. Furthermore, differences were noted in the specific glycolytic enzymes that were upregulated, with hexokinases being prominent in mouse microglia and phosphofructokinases in human microglia[33]. Recognizing these species-specific nuances is critical and suggests that findings from murine models, while invaluable, may not always directly translate to human physiology. Microglial metabolic rewiring in response to inflammation also entails upregulation of the pentose phosphate pathway (PPP) leading to increased availability of nucleotides towards pro-inflammatory cytokine mRNA production[40,41]. Besides, fatty acid synthesis is favoured over fatty acid oxidation, which is mechanistically attributed to the TCA break at the level of isocitrate dehydrogenase with heightened levels of citrate and conversion to cytosolic acetyl-CoA serving as the principal substrate for fatty acid synthesis[38,40].

Microglial metabolic reprogramming has a key role in several human diseases and preclinical disease models. In Alzheimer's disease, amyloid-β (Aβ) triggers the switch from OXPHOS to glycolysis via the mTOR–HIF-1α pathway in acutely activated DAM[42]. However, as the disease progresses to chronicity, disruption of this bioenergetic reprogramming leads to immune tolerance with dampened phagocytosis and cytokine secretion by microglia that ultimately exacerbate Alzheimer's disease pathology[42]. In a chronic mouse model of MS, defective microglial OXPHOS caused reduced ATP production and toxic reactive oxygen species (ROS) production at the level of mitochondrial complex I, which was driven by heightened mitochondrial membrane potential and succinate oxidation[43].

Of note, recent single-nucleus RNA-sequencing analyses of human post-mortem MS tissue revealed the presence of foamy MIMS, particularly in the rim of chronic active lesions, which are actively involved in phagocytosis of myelin[44]. Although myelin debris clearance is a fundamental step towards remyelination and repair, foamy MIMS have been implicated as mediators of disease progression through increased secretion of pro-inflammatory cytokines and ROS[44,45]. These foamy MIMS are possibly reminiscent of another microglial subtype, the lipid-droplet-accumulating microglia (LDAM)[46], which exhibit phagocytosis defects, as well as high levels of ROS and pro-inflammatory cytokines, altogether contributing to ageing and neurodegeneration[46].

Focus on neurons

Neuronal metabolism. Neurons, the primary units of information processing in the brain, exhibit remarkably high energy demands essential for executing complex functions, including the highly perplexing processes underpinning cognition. Efficient motor, sensory and especially cognitive functioning necessitate not only neuronal fitness at the single-neuron level, but also robust neuronal network integrity and synaptic efficiency to ensure effective interneuronal communication. Despite these substantial energetic requirements, neurons are metabolically limited in their capacity for energy storage: they lack significant reserves (such as glycogen) and are unable to autonomously sustain their energy needs over prolonged periods[47]. Instead, they rely heavily on substrates provided by glial cells (Fig. 1 and Box 1).

The principal energy substrate for neurons is glucose, although ketone bodies and lactate can also be utilized as alternative fuels when glucose availability is limited[48,49]. Glucose is used for ATP production, which mostly happens via OXPHOS[50,51]. Indeed, neurons are less glycolytic than other CNS cell types and exhibit low levels of 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase-3 (PFKFB3) activity due to heightened degradation by the E3 ubiquitin ligase anaphase-promoting complex/cyclosome (APC/C-Cdh1)[50,52]. However, recent evidence suggests that this neuronal preference for OXPHOS is more nuanced and spatially regulated than previously thought. Neuronal somata, for instance, exhibit increased levels of aerobic glycolysis and reduced OXPHOS compared to axonal terminals and synaptosomes, both under basal and activated conditions[52]. This distinction is reflected by elevated levels of the glycolytic enzyme pyruvate kinase 2 (PKM2) in neuronal somata compared to their terminals[53].

Of note, neuronal energy production is tightly connected to mitochondria, which are highly plastic, dynamically adjusting their morphology and localization in response to synaptic activity to meet localized energy needs[54]. Neuronal mitochondria are different from other CNS cells having a restricted ability to perform β-oxidation, mainly due to the low activity of the 3-ketoacyl-coenzyme A thiolase[55,56]. This limits the adaptability of neurons to changes in substrate abundance, which results in a rather rigid metabolic dependence on other CNS cells. Nonetheless, recent evidence suggests that nerve terminals can utilize fatty acids derived from lipid droplets through β-oxidation to support local mitochondrial ATP production in an activity-dependent manner[57]. This process requires DDHD2, a neuron-specific triglyceride lipase whose mutations are associated with hereditary spastic paraplegias[57]. In the absence of DDHD2, neuronal lipid droplets accumulate, leading to ATP depletion[57].

The PPP is also very important for both biosynthetic and, more predominantly, antioxidant purposes in neurons. Glucose molecules shunted to the PPP are primarily metabolized through its oxidative branch to produce NADPH, which in turn regenerates the reduced form of glutathione. Glutathione effectively scavenges ROS and protects neurons from oxidative stress[50,54,58].

Regional heterogeneity of neuronal metabolism. Whether the metabolic profile of neurons across brain regions resonates with specific neuronal functions remains unclear. Across brain regions, the metabolic landscape varies significantly, reflecting the diverse functional demands of neuronal subtypes and local circuitry. Untargeted metabolomic analyses combining hydrophilic interaction liquid chromatography–electrospray ionization–mass spectrometry and nanostructure imaging mass spectrometry of mouse brain tissue have demonstrated substantial regional changes[59]. This combined approach revealed substantial differences between forebrain (cortex, striatum, hippocampus) and caudal (midbrain, brainstem, cerebellum) regions, driven by metabolites such as cholesterol sulfate, carnosine, uric and sialic acids, lipoamino acids (for example, *N*-docosanoyl taurine, *N*-palmitoyl serine) and phospholipids[59]. However, it is important to note that these identified metabolites are not exclusively of neuronal origin but can also derive from astrocytes and oligodendrocytes, as well as resident or infiltrating immune cells, all contributing to a complex metabolic milieu, which is also probably influenced by the different neuronal soma-to-neuropil ratios across CNS regions.

Advanced computational analyses and neuroimaging have corroborated the notion of interregional metabolic diversity in the brain. In the mouse hippocampus, the CA3 region, which is enriched in excitatory pyramidal neurons, shows upregulation of TCA cycle and glutamate metabolism, while the white matter is enriched in gluconeogenesis, glycolysis and the Warburg effect[60]. These findings are supported by neuroimaging data in healthy adults, showing regional variation in aerobic glycolysis, with higher levels in the prefrontal and parietal cortex and lower levels in the medial temporal lobe and cerebellum[61].

Interregional heterogeneity may be further complicated by metabolic discrepancies between distinct neuronal subtypes. Albeit not extensively investigated, in vivo nuclear magnetic resonance in mice hinted to a higher TCA cycle rate in cortical compared to hippocampal glutamatergic neurons, whereas in GABAergic neurons, TCA cycle flux was higher in thalamic–hypothalamic regions and lower in the cerebral cortex[62]. Moreover, nuclear magnetic resonance characterization of hippocampal slices revealed that in resting conditions, glucose oxidation contributed more substantially to fuelling the TCA cycle in

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BOX 1

Astrocyte and oligodendrocyte heterogeneity and metabolism

- **Astrocyte heterogeneity and metabolic diversity**. Astrocytes exhibit prominent diversity based on their anatomic localization within the brain, with differences in the transcriptional signature observed between the olfactory bulb, cortex, hippocampus, brainstem and striatum[198,199]. This variation is thought to stem from close interactions with region-specific neuronal populations and is coordinated with local neuronal activity levels[200]. Astrocytes adapt their functions to provide metabolic support tailored to the demands of surrounding cells. For example, astrocytes can take up glucose from the bloodstream and convert it to lactate. Lactate is then transferred to neurons through the astrocyte–neuron lactate shuttle in an activity-dependent manner[201]. This process relies on MCTs with preferential expression on each cell type (MCT1 and MCT4 on astrocytes; MCT2 on neurons), which are critical for memory formation[202,203]. Once taken up by neurons, lactate helps sustain mitochondrial ATP production[201]. However, the absolute dependence of neurons on astrocyte-derived lactate has recently been challenged in both ex vivo hippocampal slices and in vivo studies[51].

Similarly to microglia, the cornerstone of astrocyte-mediated metabolic support for neurons is their metabolic flexibility. This flexibility encompasses a relative independence from OXPHOS and the ability to scavenge toxic metabolites such as glutamate[35], allowing them to shift their metabolic profile to meet the needs of adjacent cells.

- **Oligodendrocyte heterogeneity and metabolic diversity**. Much of the heterogeneity within the oligodendroglial population originates from oligodendrocyte precursor cells (OPCs) rather than fully differentiated oligodendrocytes[204,205]. This diversity is particularly evident during development, with OPC maturation displaying significant variations between the spinal cord and the brain. mTOR-dependent mechanisms regulating cholesterol biosynthesis have been implicated as key drivers of this regional heterogeneity[206], which is further influenced by regional differences in electrophysiological properties[207].

This functional diversity of OPCs and oligodendrocytes extends to their critical metabolic roles in supporting myelinated axons, where the axon–oligodendrocyte metabolic coupling is fundamental for preserving myelin health. Oligodendrocytes sense rapid axonal spiking linked with elevated extracellular potassium levels, which in turn increase their glycolytic rate to meet neuronal/axonal energy demands[208]. In addition, oligodendrocytes can use fatty acid β-oxidation as an energy reserve system during glucose deprivation to prevent the blockade of axonal transmission, although this compensatory mechanism does not adequately support fast spiking[209]. Finally, oligodendrocytes can traffic NAD^+-dependent enzymes such as SIRT-2 or heavy subunit of ferritin via exosomes directly to neurons, reducing oxidative damage to axons and maintaining neuronal somata[210].

- **The role of astrocyte and oligodendrocyte metabolism in cognitive impairment**. While the role of astrocyte and oligodendrocyte bioenergetics in cognitive function needs to be fully defined, recent data support their involvement in cognitive decline. Disruption of OXPHOS has been shown to drive lipid-droplet formation and acetylation of STAT33 in astrocytes (due to acetyl-CoA abundance) leading to the acquisition of a reactive phenotype[211]. Reactive astrocytes enriched with lipid droplets cause increased neuronal oxidative stress, compromise white matter integrity, and activate microglia through IL-3, exacerbating neuroinflammation[211]. Collectively, these alterations give rise to neuronal dysfunction, synaptic loss and recognition memory deficits[211]. Furthermore, it has been recently demonstrated that increased activation of indoleamine-2,3-dioxygenase 1 in astrocytes (caused by Aβ or tau aggregates) leads to elevated kynurenine levels, which dampen astrocytic glycolysis and lactate production in an aryl-hydrocarbon receptor-dependent manner[212]. These effects limit the metabolic support of neurons by astrocytes, leading to hippocampal LTP impairment and spatial memory deficits in Alzheimer's disease mouse models[212].

In oligodendrocytes, it has been shown that upregulation of dynamin-related protein 1, a mitochondrial fission guanosine triphosphatase, inhibits hexokinase 1 and causes deficient oligodendroglial glycolysis in a mouse model of Alzheimer's disease[213]. Glycolysis disruption leads to demyelination, axonal degeneration and working memory deficits[213]. Investigating the roles of these glial cell types and their interplay will provide a more comprehensive understanding of the metabolic processes underlying cognitive impairment.

glutamatergic than GABAergic neurons, but this was reversed following neuronal firing[63].

Despite these key findings, a deeper level of detail in terms of precise metabolic profiles of diverse neuronal subpopulations is still warranted. For example, parvalbumin-expressing neurons, a class of fast-spiking GABAergic interneurons, exhibit remarkably high bioenergetic demands, particularly associated with the generation of network oscillations, and have been linked with behavioural–cognitive deficits in Alzheimer's disease and other neuropsychiatric disorders[64]. In a mouse model of conditional parvalbumin-specific mitochondrial dysfunction, sociability and sensory gating defects were attributed to the inability of parvalbumin interneurons to maintain their high-frequency firing patterns leading to disrupted neural circuit function[65]. These data suggest that high metabolic demands in specific neuronal subtypes may represent a critical vulnerability, readily linking cellular energy deficits to the circuit disruptions that underlie cognitive deficits.

Metabolic coupling between microglia and neurons

The dynamic metabolic shifts observed in microglia and the rather rigid metabolic profile of neurons underscore the importance of their interaction—termed metabolic coupling—in maintaining brain homeostasis. Whereas astrocytes and oligodendrocytes have long been established as critical sources of energy substrates for neurons (Box 1), the cross-talk between neurons and microglia is emerging as a central concept in neuroimmunometabolism. This interaction encompasses shared substrates, modulation of bioenergetic demands and buffering of the extracellular environment to support ion and neurotransmitter balance[36,37]. While this interaction is fundamentally bidirectional, it is often polarized in favour of neurons, reflecting their central role in higher brain functions and the metabolic flexibility of microglia[36,37].

For example, in conditions of glucose shortage, microglia can utilize glutamine as an alternative energy source via an mTOR-mediated mechanism to preserve their surveillance function[36]. In the event of

complete glucose deprivation, this microglial bioenergetic adaptation guarantees immunological clearance of waste products, damaged neurons, and excitotoxic neurotransmitters (such as glutamate), preserving extracellular equilibrium and neuronal function[66,67]. Indeed, although not detected under basal conditions, the expression of excitatory amino acid transporters, particularly EAAT1, is elevated in microglia following traumatic or ischaemic insults, providing an additional layer of neuroprotection from glutamate excitotoxicity[66,67].

During inflammation, a condition often characterized by restricted glucose availability, microglial glucose uptake is primarily mediated by glucose transporter 1 (GLUT1), which can create a direct metabolic competition with neurons[68]. However, GLUT1 has a significantly lower affinity for glucose compared to the neuronal glucose transporter GLUT3 (ref. 69). This difference in transporter affinity, combined with microglia's ability to utilize glutamine to sustain their functions, suggests that the complex metabolic changes in microglia—despite their lower numbers relative to neurons—may ultimately serve to spare glucose for neuronal use. Nonetheless, further experimental data are necessary to confirm this proposed mechanism.

Lactate can also serve as a metabolic substrate for microglia, particularly during inflammatory or ischaemic stress[37]. Microglia express the metabolic machinery to import, export and utilize lactate as an energy substrate, as evidenced by the expression of monocarboxylate transporters (MCTs) under inflammatory or ischaemic conditions, as well as lactate dehydrogenase (LDH)-B, which enables the oxidation of lactate to pyruvate for subsequent entry into the TCA cycle[37,70,71]. Thus, microglia may be able to deliver small amounts of lactate to neurons when glucose is scarce, even though this exchange is predominantly mediated by the astrocyte–neuron lactate shuttle[37].

Intriguingly, microglia also possess the ability to establish direct connections with adjacent neurons by forming tunnelling nanotubes. Through these nanotubes, microglia can share their healthy mitochondria with neurons under oxidative stress, thereby maintaining neuronal health[72]. Tunnelling nanotubes can also form in neurodegenerative diseases to reduce the burden of intraneuronal protein aggregates, further promoting neuronal survival and function[72]. Here, they serve to transfer dysfunctional mitochondrial components to microglia (transmitophagy) or reduce protein aggregate burden, promoting neuronal resilience to disease[72]. In vitro evidence with human immortalized cell lines—human neuroblastoma cell line SH-SY5Y and human microglial clone 3 (HMC3) cell lines—shed further light on this interaction proposing that it is in fact bidirectional, with a preferential transfer of aggregates from neurons to microglia and of healthy mitochondria from microglia to neurons[73].

Metabolic regulation of microglia–neuronal dynamics across the lifespan

Regulators of microglial and neuronal function in development

Microglia are key regulators of synaptic remodelling and neural circuit formation, thus shaping the developing (and adult) brain's connectivity. Under physiological conditions, the developing CNS is characterized by a dynamic sculpting of neuronal connections that is directed by neuronal activity levels, with less active or immature synapses being preferentially phagocytosed by microglia through a fine-tuned process called synaptic pruning[74–76].

There is a temporal regulation of synaptic pruning, which happens during specific critical periods of brain development[75,77]. Of note, perturbations of synaptic pruning during neurodevelopment can impact functional neuronal networks later in adulthood, because the synapses that withstand elimination by microglia will be the ones that will form the basis for future brain circuits underlying crucial behavioural/cognitive functions. For example, dysregulation of microglial synaptic pruning has been implicated in autism spectrum disorder, with evidence suggesting an excess of synaptic connections in the brain overall and more specifically in layer V pyramidal neurons in the post-mortem autism spectrum disorder temporal lobe, contributing to altered neuronal circuitry and behavioural phenotypes in adults[78,79].

Beyond their role in synaptic pruning, microglia can influence synapses through various mechanisms, including clearing of the extracellular matrix, which reduces synapse stability and facilitates their elimination[80].

However, it is important to note that some studies have reported no substantial effects on behaviour or cognition following microglial depletion (via CSF1R inhibition) in the developing mouse brain[81–84]. These findings, along with evidence that microglia are dispensable for developmental myelin ensheathment[85], challenge the prevailing view that microglia during development are vital for normal brain function. This apparent dispensability, however, is subject to limitations in current experimental models, which may not adequately distinguish between microglial deficiency and dysfunction, underestimate the contribution of blood monocytes to brain homeostasis or overlook mouse strain-specific and species-specific differences[86]. Despite these caveats, available data clearly demonstrate that the absence of microglia accelerates age-related neuropathology and disease progression, implying that their primary role is to protect against neuronal injury later in life[85,87].

To carry out their important developmental functions, microglia adopt diverse transcriptional programmes that are linked with their metabolic phenotype (Fig. 2). In mice, microglia exhibit the most notable heterogeneity during embryonal life and the very first days of postnatal life (from embryonic day 14.5 to postnatal day 5) when they are metabolically active and highly proliferative[88]. Microglia at this stage exhibit enhanced glycolysis, characterized by elevated levels of LDH-A expression, which empowers rapid ATP production to meet the increased energetic demands of proliferation[88,89].

Around the second postnatal week, microglia shift to OXPHOS to sustain a high-throughput ATP production necessary to support cAMP-dependent cytoskeleton rearrangements that fuel microglial motility and phagocytosis of immature synapses at the peak of brain synaptic pruning[75,90]. In addition, microglia enhance lactate oxidation to pyruvate entering the TCA cycle, as indicated by upregulation of LDH-B and increased mitochondrial activity[88]. This is in contrast with the elevated levels of LDH-A at earlier developmental stages, which catalyses the same biochemical reaction but in the opposite direction (that is, converts pyruvate to lactate), in congruence with the glycolytic signature of highly proliferative microglia[88]. The importance of lactate as bioenergetic substrate for microglia during the peak of synaptic pruning has been reinforced by recent evidence showing that MCT4 upregulation in microglia is essential for microglial lactate entry, where it fosters lysosomal acidification and phagocytic potential, including their ability to degrade engulfed synaptosomes[91]. Conditional knockout of *Slc16a3* (encoding MCT4) in microglia results in aberrant synaptic pruning and hyperexcitability in the hippocampus, which is manifested with anxiety-like phenotypes[91].

Lipid sensing and metabolism are also key drivers of microglial function in development. TREM2 in microglia is an indispensable receptor for phagocytosis of synaptic components. TREM2 deficiency results in surplus synapses and altered excitatory–inhibitory balance, indicating its role in maintaining proper synaptic pruning[92]. TREM2 expression is also upregulated in a subset of microglia expressing the GABAergic receptors GABBR1/GABBR2 that selectively remodel inhibitory synapses during postnatal cortical development, but do not have a direct effect on excitatory connectivity[93]. Of note, emerging data describe a distinct subset of microglia in development, called 'dark' microglia, which is TREM2 dependent and is characterized by dense cytoplasm and disrupted mitochondrial function[94]. Dark microglia display accumulated lipid droplets and glycogen, suggesting metabolic stress and a shift towards a less homeostatic, possibly dysfunctional, state[94].

Neuronal metabolic remodelling during development is less well characterized than microglia in vivo, but in vitro studies suggest a

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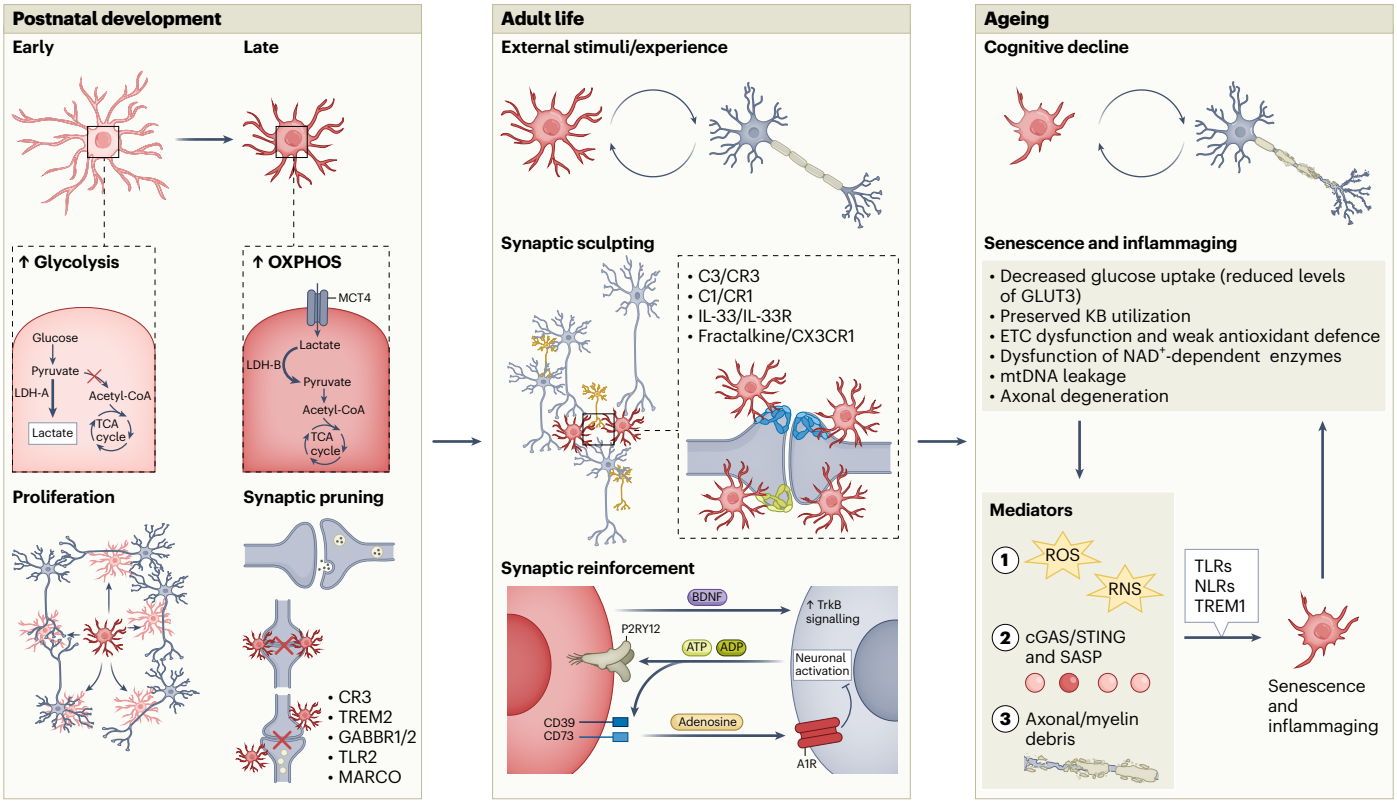

Fig. 2 | The metabolic trajectory of microglia and neurons across the lifespan. Microglia–neural interactions are tightly coupled to their metabolic state throughout life. In the early postnatal period, microglia exhibit a highly proliferative and glycolytic profile. At the peak of synaptic pruning, they undergo a metabolic switch to OXPHOS to meet the high energetic demands of synaptic sculpting. Throughout adult life, microglia maintain a predominant homeostatic OXPHOS-dependent metabolic state. This allows them to efficiently survey the brain parenchyma and mediate experience-dependent synaptic remodelling in response to environmental cues, learning and memory formation. During ageing, the brain is characterized by declining glucose utilization and growing global mitochondrial dysfunction. This environment can drive microglia towards a dystrophic, pro-inflammatory state, increasing their production of neurotoxic ROS. Both ageing microglia and neurons can also enter cellular senescence, contributing to the dysfunction of neural circuits. A1R, adenosine receptor; BDNF, brain-derived neurotrophic factor; C1/3, complement component 1/3; CR1/3, complement receptor 1/3; ETC, electron transport chain; GABBR1/GABBR2, γ-aminobutyric acid (GABA) type B receptors 1 and 2; GLUT3, glucose transporter 3; IL-33R, interleukin-33 receptor; KBs, ketone bodies; NAD^+, nicotinamide adenine dinucleotide; NLRs, nucleotide-binding and oligomerization domain-like receptors; P2RY12, purinergic receptor P2Y12; PGE2, prostaglandin E2; SASP, senescence-associated secretory phenotype; TrkB, tropomyosin-related kinase receptor B.

shift from aerobic glycolysis to OXPHOS, mediated by changes in enzymes like hexokinase 2, LDH-A and PKM isoforms, as human neural progenitor cells differentiate into mature neurons[95]. Furthermore, a transient metabolic shift involving branched-chain amino acids and glycerophospholipids has been identified in cortical neurons around postnatal day 2, which is critical for preventing aberrant neuronal excitability[96]. Branched-chain amino acids and glycerophospholipids are decreased during this short perinatal time window in the developing cortex following upregulation of SLC7A5 (the main transporter of metabolically essential large neutral amino acids), while failure to do so leads to aberrant neuronal excitability[96]. These findings highlight that specific neuronal metabolic profiles during development are integral to healthy circuit formation and pruning, although comprehensive understanding of these bioenergetic alterations in the developing brain remains an area of ongoing research.

In summary, in the developing brain microglia and neurons undergo profound metabolic shifts driven by a combination of intrinsic cellular programmes and the local microenvironment. One possible driver is the need to support high energy demands associated with key maturational processes necessary for the rapid acquisition of visual, motor and somatosensory skills after birth. At the whole-brain level, changes in the utilization of polyamines and lipids to support time-dependent specialized processes (such as myelination) may be the drivers of local metabolic microenvironments that ultimately affect cellular functions[97,98]. Uncovering these metabolic adaptations during development may lead to a better understanding of disrupted neuro-immune processes associated with neurodevelopmental disorders.

Regulators of microglial and neuronal function in the adult life

Throughout adult life, the brain maintains remarkable plasticity, continuously adapting to new experiences and stimuli. An emerging and crucial concept regulating this process is the link between brain metabolism and neuronal network function. The core principle behind this idea is that a delicate equilibrium between neuronal network energy expenditure and communication efficiency must be maintained[99–101]. In this sense, neuronal architecture is exquisitely refined to ensure efficient information processing within the brain while simultaneously optimizing metabolic economy[99–101].

During adult life, experience-dependent neurotransmission takes place within local microcircuits. This information is then integrated across large-scale neural networks to guide specific functions, a process that occurs despite the differential metabolic costs of long-range versus local signalling[102,103]. It is postulated that this metabolic cost rises proportionally with the number of connections and the anatomical distance between involved regions. This renders central network nodes, or 'connector hubs', which are highly interconnected, particularly vulnerable to metabolic changes due to their higher energetic expenditure, primarily reflecting synaptic activity[102,103]. Therefore,

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BOX 2

Role of cytokines and complement in synaptic remodelling

Key immune regulators of synaptic remodelling identified to date include fractalkine (CX3CL1), C3, IL-33 and CD47, among others[75,76,92,93,214–217]. These molecules work in concert with microglial metabolic adaptations to ensure precise synaptic sculpting, which is crucial for establishing and maintaining neural networks to support cognitive function.

- **CX3CL1:** This chemokine expressed by neurons signals to its receptor CX3CR1 on microglia. Of note, electrophysiological recordings in *Cx3cr1* knockout mice have revealed decreased synaptic strength and plasticity during postnatal development, closely linked to a delay in the maturation of brain connectivity. This highlights the importance of this chemokine–receptor interaction in regulating neuron–microglia communication in normal circuit development[75].
- **Complement cascade (C3 and CR3):** The complement system has a pivotal role in directing synaptic pruning. Briefly, less active synapses are preferentially 'tagged' with C3, which is then recognized by CR3 on the microglial surface. This recognition triggers the phagocytic engulfment and elimination of tagged synapses by microglia, ensuring efficient circuit refinement[76].
- **IL-33:** A more recently described regulator, IL-33 is secreted by astrocytes and guides microglia-mediated synapse engulfment by acting on its cognate receptor IL1RL1 on the microglial surface[216]. This interaction enhances the activity of stimulus-dependent transcription factors, including AP-1/FOS, and increases the expression of pattern recognition receptors, such as TLR2 and the scavenger receptor MARCO, which collectively favour excitatory synapse refinement[217]. In addition, IL-33 promotes microglial clearance of the extracellular matrix, which can affect the synaptic turnover in the hippocampus[215].
- **Other molecular brakes:** Synaptic pruning is a tightly regulated process requiring 'molecular brakes' to prevent excessive or aberrant elimination. CD47, a 'don't eat me' signal, has such a role. It safeguards synapses from excessive microglial engulfment following binding to its receptor SIRPα (signal regulatory protein-α) on microglia. Simultaneously, CD47 also helps regulate neural-activity-dependent synaptic pruning by preferentially tagging active inputs, ensuring that only appropriate synapses are maintained[214].

understanding the coupling between brain metabolism and neuronal networks at organ level can significantly increase our understanding of cognitive functioning.

However, the capacity for learning, memory and flexible cognition is not solely a neuronal endeavour: it is shaped by the vigilant surveillance and active remodelling orchestrated by microglia. Beyond their traditional role in synaptic pruning, microglia exert a profound influence on neuronal function through a bidirectional dialogue, underpinned by metabolic and signalling interactions essential for brain homeostasis[104].

This finely tuned microglial–neuronal cross-talk is mediated by a complex array of signalling molecules. For instance, heightened neuronal activity, often indicated by increased production of neurotransmitters (like glutamate) or through the fractalkine–CX3CR1 pathway, elicits a rapid microglial response, increasing their motility and promoting direct contact with dendritic spines[105,106]. This interaction is crucial for synaptic plasticity, along with the central role of complement cascade proteins in tagging weak or dysfunctional synapses observed during neurodevelopment (Box 2)[104,107,108]. Furthermore, microglial secretion of brain-derived neurotrophic factor and subsequent activation of tropomyosin-related kinase receptor B in neurons promote dendritic spine formation, a process that is fundamental for motor learning[109].

The metabolic aspects of the neuron–microglial interplay are particularly important. Neuronal firing, an energetically demanding process, leads to the release of ATP into the extracellular space (Fig. 2)[20,110,111]. Then, ATP acts as a potent chemoattractant for microglia, engaging their P2RY12 receptors and initiating rapid extension of microglial processes and migration towards active neurons[20,110,111]. This immediate metabolic sensing allows microglia to localize sites of intense neuronal activity. Critically, these extracellular ATP and ADP molecules are swiftly metabolized by microglial ectoenzymes CD39 and CD73 into adenosine[111,112]. Adenosine then acts on neuronal adenosine A1 receptors, effectively dampening neuronal excitability. This negative-feedback loop has been implicated as a protective mechanism against anomalous neuronal excitation and hyperactivity, which can perturb the fine balance required for a proper function of neuronal networks and behaviour.

An additional layer of protection against network hyperexcitability and hypersynchronous activity provided by microglia lies in the preservation of inhibitory G_i-dependent signals that also sustains microglial motility and patrolling of the brain[113]. This continuous metabolic exchange underscores the deeply integrated nature of neuronal and microglial function in maintaining brain homeostasis.

Ageing and the shifting metabolic landscape of the brain

As the brain transitions from adult life into ageing, the homeostatic mechanisms that govern neuronal–microglial interactions and metabolic balance undergo significant alterations. Cognitive abilities tend to diminish, yet there is heterogeneity in the rate and severity of cognitive impairment, as well as in the specific cognitive domains affected[114]. This variability is influenced by a combination of genetic and environmental factors, including dietary intake and energy expenditure (for example, basal metabolism and exercise)[115]. Ultimately, the hallmarks of ageing (that is, dysregulated energy metabolism, mitochondrial dysfunction, perturbed redox balance with intracellular accumulation of oxidatively damaged macromolecules and chronic inflammation, among others) collectively contribute to the age-related decline in brain function[114].

The general hypometabolic state reported in the ageing brain can significantly impact both structural and functional connectivity. The vulnerability of connector hubs to metabolic changes is further exacerbated in the aged brain, where even subtle metabolic changes can lead to aberrant network synchrony[116]. Compared to young individuals in whom a substantial proportion of glucose is directed towards central nodes in frontal regions, in older individuals glucose allocation shifts predominantly to posterior brain hubs[117]. This age-related rearrangement of metabolic network topology has been directly correlated with poorer cognitive performance[117]. Accordingly, functional connectivity studies in humans revealed decreased connectivity within nodes of critical networks such as the default mode network, salience network and executive/attention networks in ageing[114,118].

At the cellular level, neurons in the ageing brain exhibit significant metabolic alterations that increase their vulnerability to oxidative damage (Fig. 2). A hallmark of neuronal ageing is the development of insulin resistance and the downregulation of glucose transporters (for example, GLUT3, predominantly expressed in neurons), leading to decreased neuronal glucose utilization[18,114,119]. In stark contrast, the utilization of ketone bodies (for example, β-hydroxybutyrate and acetoacetate) appears to be remarkably preserved in the ageing brain, suggesting a potential compensatory mechanism[120].

Further compounding these issues, ageing is associated with impaired mitochondrial biogenesis and electron transport chain dysfunction in neurons, which are coupled with weakened antioxidant defence systems resulting in heightened production of ROS and reactive nitrogen species (RNS), including superoxide anion, hydroxyl radical and nitric oxide[114,121]. The decline in neuronal mitochondrial activity in ageing has been related to reduced levels of the coenzyme NAD^+, eventually leading to suboptimal activity of NAD^+-dependent enzymes, mainly the cyclic ADP-ribose synthases CD38 and CD157, poly(ADP-ribose) polymerases and deacetylases of the sirtuin family[122].

Ageing also leads to an increased susceptibility to nuclear and mitochondrial DNA damage in microglia and neurons[123]. Cytosolic DNA released from dysfunctional mitochondria in aged microglia activates the cGAS–STING signalling cascade, which shifts the microglia to a DAM-like phenotype driving neurotoxicity and impaired spatial memory[124]. Similarly, neurons bearing DNA double-strand breaks enter a late-stage DNA damage response and adopt a senescence-associated secretory phenotype through nuclear factor (NF)-κB-mediated upregulation of senescent and antiviral immune pathways, which can further induce a neuroinflammatory response[125].

Finally, it is important to note that the regenerative potential of myelin is also diminished with ageing, and white matter integrity is progressively compromised[126]. These age-related white matter changes constitute a major stimulus for the activation of microglia, which cluster together and form nodules characterized by the presence of lipofuscin-like lysosomal inclusions[126–128]. Altogether, these cumulative metabolic and molecular changes contribute to a chronic, sterile, low-grade inflammation, termed 'inflammaging', ultimately compromising neuronal resilience and cognitive fitness[115,129].

Global bioenergetic disruption in ageing myeloid cells, including microglia, manifests as an energy-deficient state marked by reduced glucose metabolism and impaired mitochondrial respiration, ultimately leading to maladaptive immune responses[130]. The cyclooxygenase-2-derived lipid messenger prostaglandin E2 has been found elevated in ageing macrophages where it dampens metabolic activity following binding to the prostaglandin E2 receptor 2 (EP2) receptor (which is also markedly increased in ageing)[130]. Importantly, inhibition of the PGE2–EP2 signalling pathway revitalized bioenergetic function and reversed spatial and recognition memory deficits in aged mice, thus providing a potential therapeutic target[130].

In ageing microglia, it has been recently shown that TREM1 synergizes with Toll-like receptor (TLR) signalling and NOD-like receptors to amplify innate immune signalling cascades and promote inflammation[131,132]. Interestingly, TREM1 deficiency in aged mice has been shown to restore ribose-5-phosphate (ribose-5P) to youthful levels preserving hippocampal-dependent spatial memory[133]. This appears to be linked to the upregulation of the transcription factor Nrf2, which drives genes regulating the antioxidant response as well as enzymes of both the oxidative and non-oxidative branches of the PPP, ultimately resulting in increased levels of ribose-5P[133]. This steady supply of ribose-5P is critical not only for purine and pyrimidine synthesis, but also to provide glycolysis intermediates. Enhanced glycolysis, in turn, increases pyruvate and acetyl-CoA, thereby fuelling the TCA cycle and mitochondrial respiration[133]. This highlights a direct metabolic pathway linking microglial TREM1 signalling to cellular bioenergetics and cognitive function in ageing.

More recently, dysfunctional lipid metabolism has also been implicated in the ageing brain, as shown by the accumulation of lipid droplets within microglia, especially in LDAM[46]. LDAM exhibit a unique transcriptional profile and key drivers of lipid-droplet formation, including genes previously linked to autosomal-dominant forms of neurodegeneration (for example, *Slc33a1*, *Snx17*, *Vps35*, *Cln3*, *Npc2* and *Grn*)[46]. LDAM can comprise over 50% of all microglia in the aged hippocampus and are associated with attenuated phagocytic function, increased ROS production and heightened production of pro-inflammatory cytokines[46]. Although their full characterization is ongoing, LDAM are believed to be major mediators in age-related neuroinflammation and concurrent neuronal dysfunction, underscoring the critical role of lipid metabolism in microglial ageing and its impact on overall brain health. However, whether these microglial metabolic changes stem solely from local, CNS-confined processes or are also influenced by ageing-related systemic peripheral inflammation still remains an active area of investigation[114,134].

Metabolic regulation of microglia–neuronal dynamics in disease

Microglial activation and cognitive impairment in metabolic disorders

Metabolic disorders such as obesity, diabetes and non-alcoholic fatty liver disease have been associated with compromised brain function[135]. Preclinical models of these diseases provide compelling evidence for a link between microglial activation and cognitive impairment[135]. In mice, obesity induced by either a high-fat diet (HFD) or a high-sucrose diet impairs hippocampal-dependent memory, a deficit closely associated with increased microglial activation[136]. This often includes an increase in the phagocytosis of synaptic components that leads to substantial dendritic spine loss, thereby impinging on neuronal integrity and function[136]. Notably, in HFD-fed mice, the microglial free fatty acid receptor 4 acts as an intrinsic metabolic sensor that modulates microglial activation through downregulation of NF-κB–interferon-β (IFNβ) signalling, mitigating cognitive deficits induced by HFD[137].

In experimental models of diabetes, cognitive impairment frequently arises as a consequence of neuronal dysfunction attributed to toxic lipids (lipotoxicity), advanced glycation end products, and oxidative damage due to elevated reactive aldehyde levels that cause peroxidative membrane injury[138]. In vitro studies have compellingly demonstrated that not only chronically high glucose levels but also acute glucose fluctuations (in either direction) can activate microglia, leading to the secretion of pro-inflammatory mediators that subsequently compromise neuronal function[139,140]. This in vitro evidence is further supported by in vivo observations, which show a clear association between recurrent moderate hypoglycaemia and microglial activation, oxidative injury of the hippocampal CA1 region and spatial memory deficits in diabetic rats[141]. This underscores the sensitivity of microglia to both hyperglycaemic and hypoglycaemic episodes in the periphery, highlighting the importance of tight glycaemic control for brain health.

Peripheral metabolic signalling may also have a key role in regulating brain function and inflammation. For example, succinate, an intermediate of the TCA cycle[142], accumulates under metabolic stress—such as mitochondrial dysfunction—and can be released extracellularly. Once in the extracellular space, succinate binds to its G-protein-coupled receptor, GPR91 (SUCNR1), which is expressed in neurons and microglia[143]. In peripheral tissues, succinate–SUCNR1 signalling modulates inflammation and contributes to metabolic disease[143]. Whether this metabolic signalling pathway has any role in neuroinflammation (and cognitive decline) still remains elusive.

Recently, signalling metabolites originating from the gut–brain axis have gained prominence in regulating CNS inflammation and cognitive function. These metabolites include short-chain fatty acids (SCFAs) and fermentation products derived from host microbiota. SCFAs have been implicated in the regulation of microglial homeostasis, with germ-free mice exhibiting microglial abnormalities including an immature phenotype[144]. Recent studies in patients with Alzheimer's disease and mouse models of Alzheimer's disease are rather inconsistent, with increased or decreased levels of certain SCFAs in biofluids and faecal samples compared to healthy control individuals[145]. One aspect that has to be elucidated is whether a perturbed balance of SCFAs overall compromises neuronal function, or if distinct SCFAs are primarily responsible for any deleterious effects. Moreover, a key

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Table 2 | Human imaging studies showing correlation between microgliosis, neuronal dysfunction and cognitive decline (in chronological order)

Ref.	Clinical condition	Methodology	Key finding(s)
Barletta et al.[190]	MS	Combined [^{11}C]-PBR28 PET and synthetic MRI	• Information processing speed assessed with SDMT was negatively correlated with microglial activation in white matter lesions and perilesional areas
Braga et al.[158]	COVID-19 with persistent depressive and cognitive symptoms	[^{18}F]FEPPA PET	• Increased $TSPOV_T$ in dorsal putamen correlated with greater severity of motor slowing • No significant correlation between hippocampal $TSPOV_T$ and the magnitude of self-perceived cognitive deficits
Malpetti et al.[156]	Frontotemporal dementia	[^{11}C]PK11195 PET and structural MRI	• Faster cognitive decline was associated with increased microglial activation in frontal regions • Microglial activation and grey matter volume were negatively correlated in frontal regions
Chen et al.[153]	AD MCI	• T1-weighted MP RAGE • CSF and plasma $A\beta_{42}/A\beta_{40}$ • CSF and plasma p-tau181 • CSF sTREM2 and PGRN	• Baseline brain volumes were decreased in the hippocampus, entorhinal cortex and middle temporal lobe and at the whole-brain level overall in AD and MCI • CSF sTREM2, CSF and plasma p-tau181, can predict longitudinal cognitive decline in individuals with positive AD pathology
Tondo et al.[154]	MCI	[^{11}C]-(R)-PK11195 and [^{18}F]FDG-PET	• Microglia activation is present in the prodromal MCI phase of different underlying aetiologies • There is spatial overlap between brain hypometabolism and increased TSPO signal
Zou et al.[155]	Adults aged 50 years or older with known amyloid pathology status	[18F]-florbetaben PET, [^{11}C]-PBR28 PET and [18F]-MK-6240 PET	• In amyloid-positive control individuals, binding of [^{11}C]-PBR28 in neocortical regions and [^{18}F]-MK-6240 in medial temporal cortex was higher than in amyloid-negative control individuals • Microglial activation is independently associated with amyloid positivity and memory impairment
Malpetti et al.[152]	AD	[^{18}F]-AV-1451 PET, [^{11}C]-PK11195 PET and structural MRI	• Tau burden in temporoparietal regions and neuroinflammation in the anterior temporal lobe can serve as imaging predictors of cognitive decline in AD
Herranz et al.[157]	MS	^{11}C-PBR28 MR-PET	• Microglial activation was more prominent in the frontoparietal, temporal and occipital regions, right cingulate cortex, thalamus, hippocampus and NAWM • Microglial activation was greater in secondary progressive MS than relapsing–remitting MS and was associated with decreased information processing speed as well as memory and executive function deficits

CSF, cerebrospinal fluid; [^{11}C]-PBR28, *N*-((2-(methoxy-^{11}C)-phenyl)methyl)-*N*-(6-phenoxy-3-pyridinyl)-, [^{11C}]PK11195, 1-(2-chlorophenyl)-*N*-[^{11}C]methyl-*N*-(1-methylpropyl)-3-isoquinoline carboxamide, [^{18}F]-AV-1451, flortaucipir; [^{18}F]FDG, [^{18}F]fluoro-D-glucose; [^{18}F]FEPPA, fluorine F 18–labelled *N*-(2-(2-fluoroethoxy)benzyl)-*N*-(4-phenoxypyridin-3-yl)acetamide; [^{18}F] MK-6240 PET, 6-(fluoro-18F)-3-(1^{H}-pyrrolo[2,3-c]pyridin-1-yl)isoquinolin-5-amine; PGRN, progranulin; p-tau181, phosphorylated-tau at threonine 181; MRI, magnetic resonance imaging; NAWM, normal appearing white matter; SDMT, symbol digit modalities test; sTREM2, soluble TREM2; $TSPOV_T$, translocator protein distribution volume; T1-weighted MP RAGE, magnetization-prepared rapid gradient echo.

question is which CNS cell populations are mainly impacted by SCFAs. Of note, a microbiota-dependent accumulation of the metabolite N^6-carboxymethyllysine has also been found in microglia (in aged mouse and human brains), mediating mitochondrial dysfunction, decreased ATP production and a surge of ROS[146].

Neuroimmunometabolism in chronic neurodegenerative and neuroinflammatory disorders

Microglial activation, once considered a mere consequence of neuronal damage, is now recognized as a major, active contributor to neurodegeneration driving neuronal dysfunction and eventually neuronal loss[147–151]. The specific triggers of neuroinflammation may vary across diverse pathologies—such as the accumulation of distinct protein aggregates in Alzheimer's disease or Parkinson's disease, or autoimmune insults in MS. Discrete transcriptional states of microglia, other than the more widely known DAM, have been described in several CNS disorders, including MS and amyotrophic lateral sclerosis, although their functional/biological relevance still remains unclear[27]. Despite differences in the causal factors driving neuroinflammation and microglial transcriptional changes in these diseases, aberrant microglial activation represents a congruent and central feature across neurodegenerative and neuroinflammatory disorders[149,150].

Human imaging studies using positron emission tomography (PET) with the microglial activation marker 18-kDa translocator protein TSPO ligand have consistently demonstrated a correlation between heightened microglial activation and cognitive decline across a spectrum of neurodegenerative and neuroinflammatory conditions (Table 2). This has been shown in Alzheimer's disease, mild cognitive impairment (MCI), frontotemporal dementia, Parkinson's disease dementia and MS[152–157]. Another PET study in people with persistent cognitive and depressive symptoms as later sequelae of mild-to-moderate coronavirus disease 2019 (COVID-19) infection, revealed increased microglial activation within the brain, which was more pronounced in the ventral striatum and dorsal putamen compared to in healthy control individuals[158].

At the cellular level, alterations in the metabolic programme of microglia under chronic neuroinflammatory and neurodegenerative conditions are increasingly identified as key drivers of neurotoxicity and defective synaptic organization (Fig. 3)[159]. Under stress, microglia undergo a metabolic switch and secrete pro-inflammatory cytokines as well as extracellular ROS/RNS (primarily nitric oxide, peroxynitrite, superoxide and hydrogen peroxide)[160]. Notably, NOX2, the catalytic subunit of the NADPH oxidase enzyme complex, and mitochondrial reverse electron transport are central players in microglial ROS production, exerting direct neurotoxic effects on neighbouring neurons following release into the extracellular space[43,160–162].

A further mechanism underlying microglial-mediated neurotoxicity is the excessive secretion of excitatory amino acids, predominantly glutamate, by abnormally activated microglia[163]. More precisely, activated microglia exhibit significantly enhanced glutamine uptake and upregulation of glutaminase, the enzyme that converts glutamine to glutamate, resulting in excessive glutamate production causing

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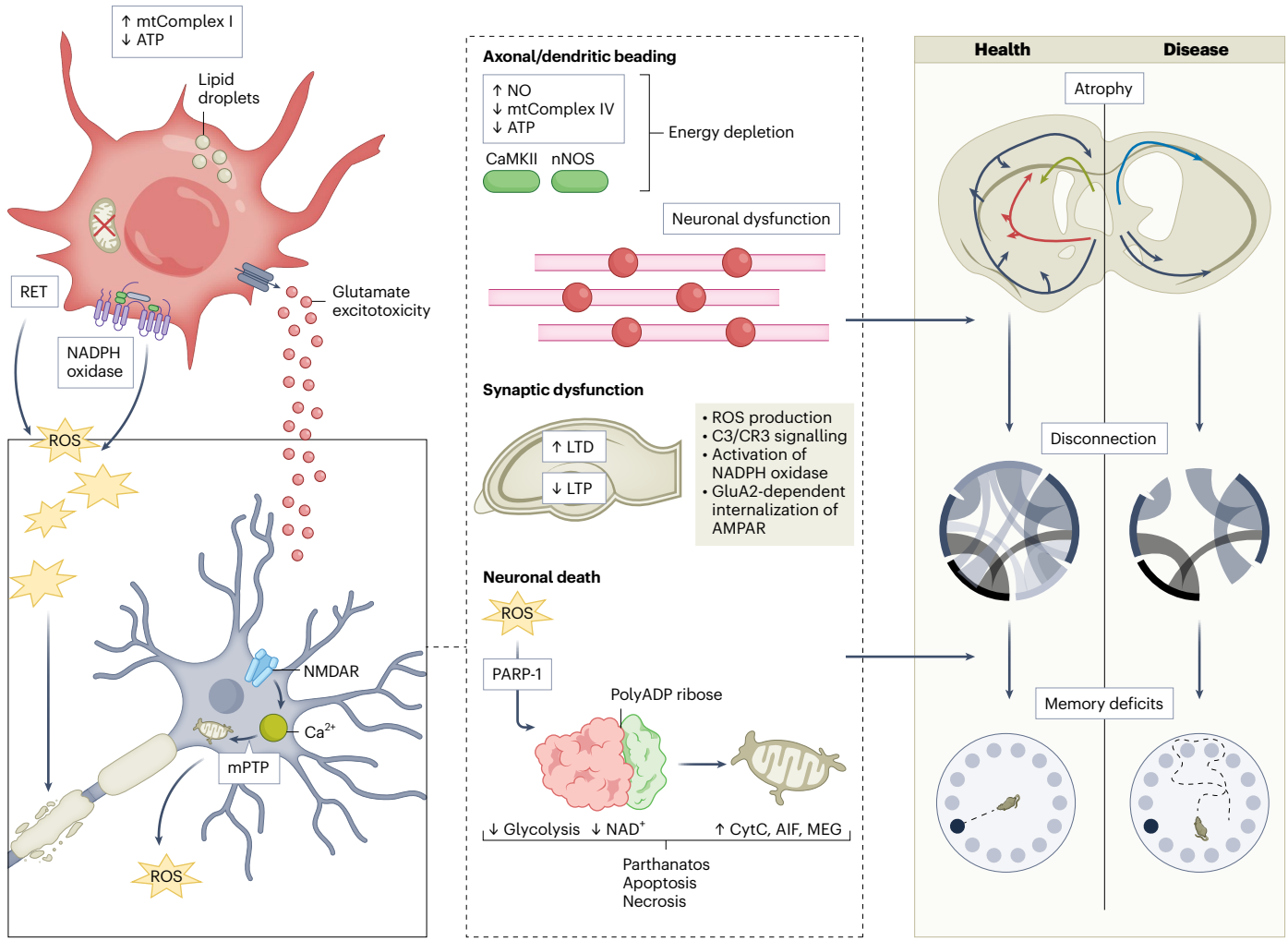

Fig. 3 | Pathological cross-talk: how dysfunctional microglia can compromise neuronal function and cognition in neurological disorders. In CNS diseases, dysfunctional microglia may contribute to cognitive impairment by compromising neuronal health through several interconnected pathways. Excessive glutamate secretion can perturb Ca^{2+} homeostasis causing mitochondrial dysfunction in neurons, increased ROS and lower ATP production. Mitochondrial dysfunction in microglia also sustains RET and ROS release, which is exacerbated by microglial NADPH complex activity. In addition, specific microglial states with altered metabolism and pro-inflammatory secretome, such as LDAMs, can also disrupt neuronal function. Collectively, these insults cause dendritic/axonal beading, synaptic dysfunction and, ultimately, neuronal death. At the whole-brain level, this widespread neuronal damage manifests as progressive atrophy and the disconnection of neural circuits critical for cognition, resulting in memory deficits and cognitive impairment. AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; CaMKII, calcium/calmodulin-dependent protein kinase II; C3, complement component 3; CR3, complement receptor 3; CytC, cytochrome C; GluA2, glutamate ionotropic receptor AMPA type subunit 2; LTD, long-term depression; MEG, matrix protein endonuclease G; mPTP, mitochondrial permeability transition pore; mtComplex I, mitochondrial complex I; NAD^+, nicotinamide adenine dinucleotide; NADPH, nicotinamide adenine dinucleotide phosphate hydrogen; NMDAR, *N*-methyl-D-aspartate receptor; nNOS, neuronal nitric oxide synthase; NO, nitric oxide; PARP-1, poly(ADP-ribose) polymerase-1; RET, reverse electron transport.

neuronal excitotoxicity. Overabundance of glutamate in the microenvironment then leads to increased Ca^{2+} influx, mainly through the NMDARs in neurons[164].

Early in the neurodegenerative process, neurons exhibit 'neuritic beading'—a focal swelling along dendrites and neurites[161,165]—that may precede irreversible damage and neuronal death of neurites[161,165]. Neuritic beading therefore represents a potential therapeutic window[161]. In vitro neuron–microglia co-culture systems suggest that the underlying mechanistic basis involves Ca^{2+}/calmodulin-dependent protein kinase activation after increased Ca^{2+} influx[165]. Intracellular Ca^{2+} accumulation amplifies nitric oxide production by neuronal nitric oxide synthase, which in turn directly inhibits mitochondrial complex IV and hinders ATP production.

When Ca^{2+} overload overwhelms the buffering capacity of mitochondria, it triggers the prolonged opening of the mitochondrial permeability transition pore. This results in severe mitochondrial membrane depolarization and a detrimental shift from ATP synthesis to heightened ROS production[164,166,167]. In turn, increased mitochondrial permeability can cause progressive osmotic swelling and rupture of mitochondrial membranes, leading to the release of pro-apoptotic factors like cytochrome C, apoptosis-inducing factor (AIF) and matrix protein endonuclease G, leading to apoptotic or necrotic neuronal death[168,169].

Critically, mitochondrial ROS production triggered by Ca^{2+} accumulation in response to glutamate excitotoxicity also leads to poly(ADP-ribose) polymerase-1 activation[170]. Poly(ADP-ribose) polymerase-1 activation is further promoted by the aberrant formation of peroxynitrite during mitochondrial permeability transition with bursts of superoxide production, as well as by DNA damage due to oxidative or nitrosative stress[170,171]. Poly(ADP-ribose) inhibits glycolysis after binding to hexokinases, thus contributing to NAD^+ depletion and further exacerbating the overall neuronal energetic collapse

under these conditions[172]. Mechanistically, poly(ADP-ribose) also interferes with the interaction of AIF with the outer mitochondrial membrane, leading to release of AIF from mitochondria and translocation to the nucleus. This triggers extensive DNA fragmentation and chromatin condensation, driving caspase-independent neuronal death (or 'parthanatos')[168].

Linking neuroimmunometabolism and cognition: lessons from Alzheimer's disease

The main body of evidence on the signalling cascades and metabolic pathways involved in neurodegeneration-associated cognitive impairment refers to Alzheimer's disease. The pathological hallmarks of Alzheimer's disease are the extracellular accumulation of Aβ plaques and the intracellular aggregation of hyperphosphorylated tau protein, both of which drive neuronal dysfunction and ultimately cause neuronal loss and cognitive decline.

One key insight comes from studies on β-site amyloid precursor protein cleaving enzyme-1 (BACE-1). Targeted deletion of *Bace1* in microglia enhances their phagocytic potential and promotes the acquisition of a DAM-1 signature[173]. The increased phagocytic activity towards Aβ clearance requires an extensive reorganization of the cytoskeleton, which in turn increases the energy demand of microglia. Indeed, it has been demonstrated that microglial response to Aβ is accompanied by a metabolic switch from OXPHOS to aerobic glycolysis[42]. BACE-1 deficiency potentiates this metabolic switch, allowing microglia to utilize energy via aerobic glycolysis, which is essential to support the increased engulfment of Aβ in acute inflammatory conditions[174]. Mechanistically, *Bace1* deletion promotes glycolysis through upregulation of the PI3K–mTOR–HIF-1a pathway, a critical signalling axis for metabolic reprogramming[174]. In the in vivo setting, BACE-1 deficiency in microglia rescues impaired synaptic plasticity in the hippocampus of 5xFAD mice and leads to improved performance in working memory and contextual fear conditioning tasks[174]. The translational potential of BACE-1 modulation is high, with preclinical mouse studies already demonstrating that delivery of small interfering RNA against BACE-1 and curcumin via specific nanoparticles can promote microglia-mediated phagocytic clearance of Aβ and rescue spatial memory deficits in amyloid precursor protein/PS1 mice[175].

Further emphasizing the central role of glycolysis in microglial function in Alzheimer's disease, recent work uncovered a glycolysis–histone H4 lysine 12 (H4K12) lactylation–PKM2 positive feedback loop in microglia of 5xFAD mice[176]. Disruption of this loop through PKM2 inhibition ameliorates Aβ pathology and mitigates spatial memory deficits[176]. Additionally, hexokinase 2 deficiency in microglia, which impacts the first step of glycolysis, is associated with heightened ATP levels, thus promoting Aβ phagocytosis and lessening spatial memory deficits in 5xFAD mice[177].

Apart from changes in glycolytic function, mitochondrial dysfunction is a pervasive feature in Alzheimer's disease and profoundly impacts cognition. For instance, impairment of short-term spatial working memory and decreased motivation levels have been observed following the loss of the redox-active [2Fe–2S] mitochondrial-associated protein mitoNEET (CISD1) in global *Cisd1*$^{-/-}$ mice, where they have been associated with diminished c-Fos expression in the CA1 region of the hippocampus and the overlying cortex[178].

Moreover, mitochondrial disruption in microglia, particularly due to pathogenic tau protein, can lead to mitochondrial DNA leakage into the cytosol[179]. This leaked mitochondrial DNA is then sensed by cGAS, eliciting the activation of the cGAS–STING–type I interferon signalling pathway, which drives a pro-inflammatory microglial state[179]. Ablation of *Cgas* in p.Pro301Ser tauopathy mice abrogates type I interferon activation in microglia and critically upregulates the myocyte enhancer factor 2c (*Mef2c*) transcriptional network in neurons, which is strongly implicated in cognitive resilience. These alterations protect against synapse loss, restore synaptic plasticity in the hippocampus and improve spatial memory in p.Pro301Ser mice.

Lipid dysregulation in microglia is also increasingly recognized as a critical factor that interferes with neural circuit dynamics in Alzheimer's disease, ultimately affecting cognition. In vitro mechanistic evidence suggests that the accumulation of lipid droplet within APOE4-expressing microglia shifts them towards a dysfunctional, pro-inflammatory phenotype, impairing their ability to properly sense neuronal activity[180]. Concomitantly, APOE4 microglia exhibit compromised lipid influx, and the ensuing extracellular lipid accumulation, particularly cholesterol, can suppress neuronal activation. This occurs through the potentiation of inwardly rectifying potassium (Kir) currents that lead to hyperpolarization of the resting membrane potential and a reduced overall number of calcium transients in APOE3 spheroid cultures. Moreover, recent work in mouse 5xFAD and human Alzheimer's disease brains revealed an increased activity of diacylglycerol *O*-acyltransferase 2 (DGAT2), an enzyme that converts free fatty acids to triacylglycerols in microglia following exposure to Aβ leading to the formation of LDAM, heightened plaque burden and neuronal dysfunction[181].

The intracellular signalling molecule spleen tyrosine kinase (SYK) has also garnered notable attention due to its heightened activation observed in microglia of amyloidopathy mouse models[182]. Selective *Syk* deletion in microglia of 5xFAD mice exacerbates Aβ accumulation in the hippocampus, cortex and thalamus, in tandem with worsened spatial memory[183]. Loss of SYK signalling in microglia limits LPL expression (a DAM marker) and reduces their phagocytic potential towards Aβ clearance, while paradoxically promoting lipid-droplet formation and more prominent ROS production, leading to neuronal damage[183].

Altogether, this evidence provides crucial insights into how dysregulated cellular metabolism in glia, particularly microglia, directly drives cognitive decline in chronic neurodegenerative conditions.

Linking neuroimmunometabolism and cognition: a new perspective in MS?

MS is a chronic inflammatory and neurodegenerative disease of the CNS characterized by demyelination, axonal damage and progressive neurological decline. Beyond motor and sensory deficits, cognitive impairment affects a significant proportion of patients with MS, profoundly impacting their quality of life[184,185].

A growing body of literature supports the concept that MS is akin to many mitochondrial diseases, where bioenergetic deficits within microglia and neurons contribute significantly to neuronal vulnerability and subsequent neurodegeneration[186,187]. Indicators of oxidative stress, a direct consequence of mitochondrial dysfunction, are elevated in the brains of patients with MS, while increased levels of ROS, lipid peroxidation products and protein carbonyls are consistently observed in both acute lesions and normal appearing white matter[188]. This oxidative environment strains neuronal energy production, rendering neurons more susceptible to excitotoxicity and apoptotic cell death. Neuronal dysfunction and death in the grey matter due to oxidative stress may underlie cognitive deficits in MS, as tissue loss and cortical lesion load represent structural changes associated with cognitive impairment even at early stages[189]. PET studies, while less extensive than in Alzheimer's disease, are starting to provide in vivo evidence of heightened microglial activation showing a correlative link with information processing speed and memory impairment in MS[157,190].

Although these seminal clinical studies suggest a putative role of microglia and their metabolism in MS, there is still a paucity of direct evidence specifically detailing the role of metabolic perturbations and molecular dynamics in MS-related cognitive impairment. The few studies that have investigated cognition in this context at molecular and mechanistic levels have largely utilized the experimental autoimmune encephalomyelitis (EAE) mouse model, offering critical, albeit limited, insights.

BOX 3

Outstanding questions

- **Temporal dynamics and reversibility of dysregulation**: At what specific stage of neurodegenerative, neuroinflammatory and metabolic disorders do cognitive decline and neuroimmunometabolic disruption occur? Furthermore, if detected early, are these dysregulations reversible, offering a critical therapeutic window? This leads to a more granular question: is it the neurons or the glial cells that exhibit a dysregulated metabolic profile first, or is it a simultaneous and interdependent process?
- **Sex-specific differences and systemic interplay:** Are there sex-specific differences in neuroimmunometabolic regulation that influence vulnerability or resilience to cognitive impairment, which could inform personalized therapeutic strategies? Moreover, what is the intricate role of peripheral immune cell bioenergetics and their interplay with neuronal and non-neuronal CNS cells in driving or modulating cognitive impairment?
- **Metabolic network–neuronal network link:** Is there a direct relationship between the metabolic network and neuronal network organization in the brain? If so, which specific metabolic pathways drive this crucial association, and how does this relationship become perturbed in cognitive decline? This extends to identifying if there are common neuroimmunometabolic perturbations that underpin cognitive dysfunction across different neurodegenerative disorders, suggesting shared fundamental mechanisms.
- **Precision metabolic phenotyping and heterogeneity:** How can we non-invasively detect specific metabolic shifts (for example, the Warburg effect, mitochondrial dysfunction, altered lipid metabolism) in distinct brain cell types (neurons, microglia, astrocytes) in vivo? Can advanced imaging techniques or novel biomarkers identify these specific metabolic alterations and correlate them with different trajectories of cognitive decline? This precision is crucial for understanding (1) microglial diversity and how specific microglial metabolic pathways differentially contribute to synaptic/neuronal dysfunction across various pathologies, as well as (2) how precise metabolic deficits in specific neuronal populations unfold.
- **Targeting specific metabolic pathways for therapeutic gain:** A major challenge lies in achieving specificity in targeting distinct metabolic pathways in specific CNS populations to avoid unwanted off-target effects. What are the optimal combinatorial approaches to address multiple dysregulated metabolic pathways simultaneously, and how can we ensure optimal brain delivery and bioavailability of these metabolic modulators? Beyond pharmacology, how can dietary patterns, exercise and metabolite-based therapeutics be optimized to influence specific microglial and neuronal metabolic states?

In the hippocampus of EAE mice, memory impairment is linked to local microglial activation within the dentate gyrus and disruptions in GABAergic transmission, which is mediated by various mechanisms including interleukin (IL)-1β signalling[191,192]. IL-1β increase is parallelled with a rise in NADPH oxidases (NOX) and subsequent oxidative stress in hippocampal neurons, contributing to deficits in synaptic plasticity. Importantly, independent administration of minocycline (a microglia inhibitor) and apocynin (a NOX inhibitor) was able to restore hippocampal long-term potentiation (LTP) and alleviate learning deficits in the hole-board test, underscoring the contribution of microglial activation and associated oxidative stress to cognitive dysfunction[193].

Apart from the dentate gyrus, impaired LTP due to elevated NOX activity and ROS production in hippocampal microglia has also been shown in CA1 hippocampal neurons, further solidifying the link between microglial oxidative metabolic processes and hippocampal synaptic plasticity. Relevant to this, marked expression of complement component 3 has been reported in the dentate gyrus of EAE mice and has been implicated in driving the pathological phagocytosis of synapses[194].

Recent studies reveal that in both EAE and human progressive MS tissue, microglia exhibit impaired mitochondrial OXPHOS, leading to a pro-inflammatory state characterized by ROS production—particularly at the level of mitochondrial complex I[43]. Restoring microglial mitochondrial function through genetic or pharmacological means—such as agents modulating succinate dehydrogenase activity—has been shown to ameliorate disease outcomes[43]. In chronic MS lesions, microglia/macrophages can also develop an iron-laden profile due to phagocytosis of myelin debris leading to intracellular iron overload and subsequent generation of ROS via Fenton chemistry within their lysosomes[195,196]. This 'ferroptotic' stress can impair microglial function and contribute to sustained inflammation and axonal damage[195,196].

However, further research is needed to understand how microglial metabolic status in MS can dictate their phenotype and impact on neurons affecting their complex functions. Admittedly, direct metabolic alterations in neurons themselves remain poorly understood in MS. For example, it has recently been demonstrated, that accumulation of PFKFB3 within neurons due to an IFNγ-mediated reduction in proteasome activity, results in heightened neuronal glycolysis, reduced PPP and ultimately oxidative damage and ferroptosis[197]. Inhibition of PFKFB3 (or of the immunoproteasome subunit, proteasome 20S β 8), either through neuron-specific genetic ablation or after pharmacological inhibition, has a neuroprotective effect in vitro and in the EAE mouse model in vivo[197]. However, the extent to which this specific neuronal metabolic change drives neuronal pathology across the heterogeneous stages and subtypes of human MS remains to be determined.

Ultimately, it is tempting to speculate that correcting these intricate metabolic failures within the CNS will be paramount to halt the progression of disability and associated cognitive decline in MS.

Outstanding questions and future directions

The emerging field of neuroimmunometabolism is revolutionizing our understanding of brain health and disease, revealing the intricate, bidirectional communication between cellular metabolism and immune responses in the CNS. We now appreciate that microglia, far from being simple bystanders, are fundamental regulators of cognitive function throughout the lifespan, orchestrating synaptic refinement and actively shaping neuronal network function. While neurons undoubtedly remain at the core of cognition, the evidence strongly suggests that the dynamic neuron–microglia metabolic cross-talk, rather than neurons in isolation, ultimately dictates cognitive performance. This paradigm shift underlines a move beyond purely neuron-centric therapeutic approaches.

Halting cognitive decline in neurodegenerative, neuroinflammatory and metabolic disorders represents one of the most formidable challenges in contemporary clinical practice. A comprehensive understanding of the complex neuro–immune–metabolic interactions, coupled with insights into neurocognitive network organization, is paramount to achieving this goal. The fundamental premise of these new neuroimmunometabolic treatment approaches lies in the prevention or rectification of the aberrant metabolic reprogramming that occurs in neuronal and immune cells under inflammatory CNS conditions. The ultimate objective will be to preserve cognitive abilities by mitigating neurotoxicity, neuronal dysfunction and synaptic

compromise. Yet, significant outstanding questions remain before these discoveries can be fully translated to clinical practice (Box 3).

The pursuit of these outstanding questions demands interdisciplinary collaboration, leveraging cutting-edge tools (such as single-cell multi-omics, advanced metabolic imaging, holistic neuronal network activity interrogation and sophisticated computational modelling). Developing selective treatments with minimal off-target effects and identifying effective combinatorial strategies for simultaneous modulation of multiple metabolic pathways will be also crucial.

In conclusion, the field of neuroimmunometabolism has the potential to unlock new therapeutic avenues, aiming to salvage neuronal health, restore synaptic integrity and preserve the precious cognitive abilities that define human nature.

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Competing interests

S.P. is founder, CSO and shareholder (>5%) of CITC. The other authors declare no competing interests.

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