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REVIEW-SYMPOSIUM

Exercise-induced modulation of neuroinflammation in ageing

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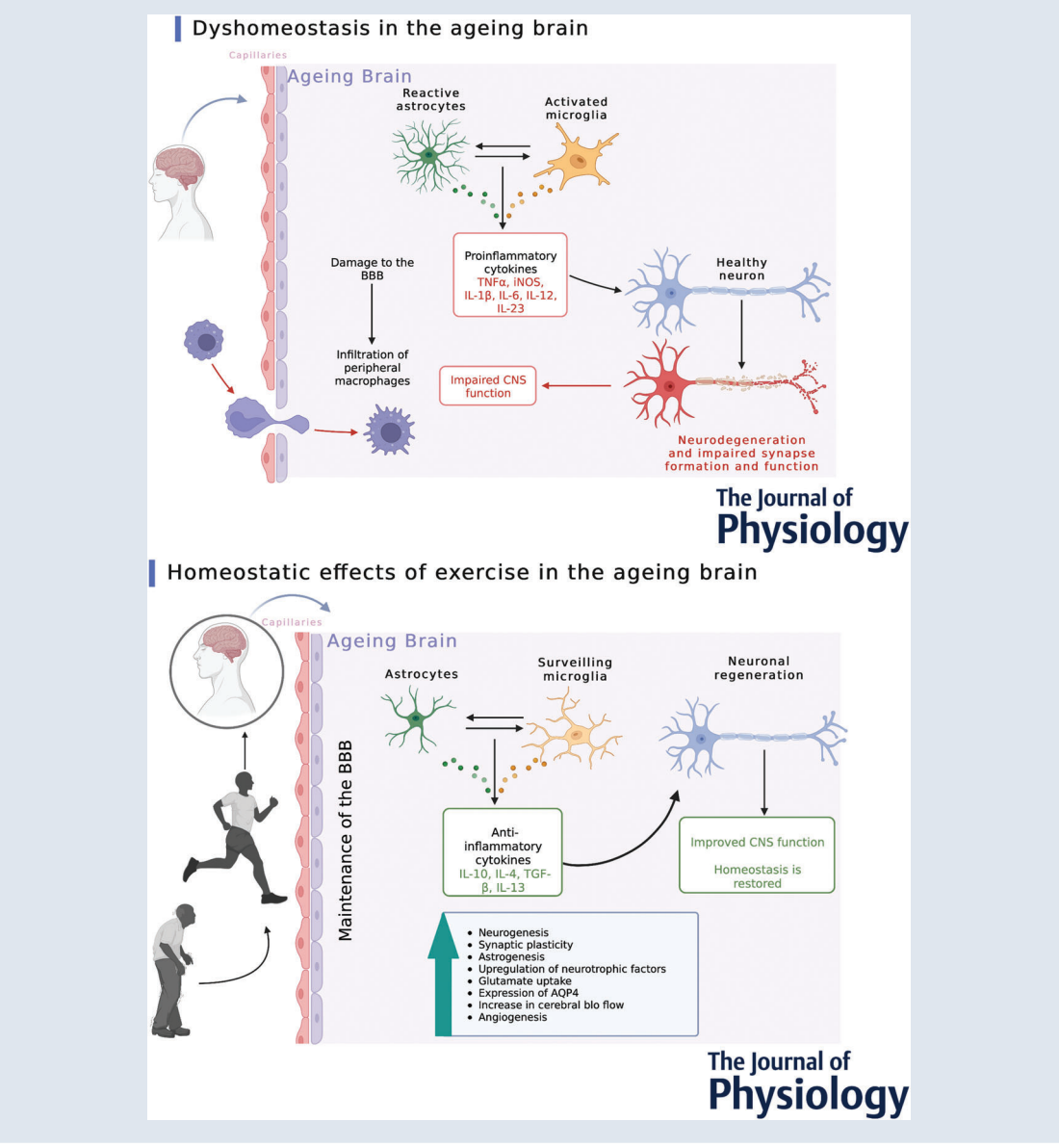

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Abstract figure legend Ageing and the associated inflammatory changes mediated by glia can lead to dysregulated homeostasis in the brain due to impairment of neuronal, and hence cognitive, function. Exercise can provide an adaptive advantage against such perturbations to homeostasis, enabling the glia to perform their normal homeostatic and protective roles within the brain.

Introduction

Engagement in regular physical activity was likely a strong driver of selection throughout much of human evolution, thus molecular, cellular and whole-body physiological processes have been shaped by and adapted to a physically active lifestyle (Booth et al., 2002; Neufer et al., 2015). Homeostasis may therefore be inherently associated with physical activity (Booth et al., 2002), especially endurance running (Bramble & Lieberman, 2004), suggesting that the evolutionarily recent emergence of a sedentary, inactive lifestyle results in disease-causing maladaptive functioning due to diminished homeostatic regulatory mechanisms in many organs, including the brain. Physical activity is associated with dynamic modulatory effects on peripheral and central nervous system (CNS) tissue with the most notable effects in the hippocampus. Studies have shown that exercise, a subset of physical activity that is planned, structured and recurrent (Caspersen et al., 1985), and specifically aerobic exercise, can improve neuroplasticity, neural development (Pedersen et al., 2009; Xing & Bai, 2020; Zhang, He et al., 2019), cognitive function (Cotman et al., 2007; Duzel et al., 2016; Pedersen et al., 2009; Wrann et al., 2013), adult hippocampal neurogenesis (Cotman et al., 2007; Lev-Vachnish et al., 2019; Trejo et al., 2001; van Praag et al., 2005; Voss et al., 2013) and cerebral angiogenesis (Cotman et al., 2007; Zhang, He et al., 2019). Some of the CNS-associated effects of exercise are likely mediated by soluble components of the immune system along with astrocytes and microglia. In this review, we highlight research findings, primarily in animal models, demonstrating the impact of aerobic exercise training on immune mediators, particularly of the innate immune system, and inflammatory states that effectively modulate brain health across the lifespan. As ageing poses a homeostatic challenge in itself, we will focus on studies examining the beneficial effects of regular, structured endurance exercise in preventing, reversing, or minimising age-associated inflammatory processes that result in impaired function of the brain.

Exercise, immune mediators and homeostasis in the CNS – a question of timing?

In addition to its conventional host defence role, the innate immune system regulates responses to non-pathogenic environmental or homeostatic challenges (Rankin & Artis, 2018) via the action of soluble molecules, particularly pro- and anti-inflammatory cytokines. Furthermore, immune components participate in a wide range of biological processes relevant to healthy nervous system function such as proliferation, neurogenesis, synaptic pruning, metabolic regulation or synaptic potentiation (Borst et al., 2021; Ferro et al., 2021; Medzhitov, 2021), and are vital mediators of the response to damage or disease. Tissue damage and subsequent dysfunction can be minimised by promoting a favourable balance of pro- and anti-inflammatory molecules within the brain parenchyma, and regular endurance exercise has generally been reported to have beneficial anti-inflammatory effects in the CNS (Gleeson et al., 2011; Ostrowski et al., 1999). While the effects of exercise on baseline cytokine expression may be modest or even absent in young healthy animals (Olah et al., 2009; Tong et al., 2001), robust anti-inflammatory effects are revealed in the context of infection, pathology or age.

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Evolutionary and anthropological theories combined with experimental data suggest that life-long physical activity may be necessary for homeostatic functioning of the CNS, but evidence shows that short-term structured exercise training protocols or interventions in humans can also have prophylactic or therapeutic effects in combatting pathological processes that affect the CNS, including psychiatric and neurological diseases (Pedersen & Saltin, 2015). Rodent models have been used to explore the potential underlying mechanisms at a cellular level; accordingly, prophylactic exercise can provide an adaptive advantage against subsequent infectious and non-infectious perturbations to brain homeostasis in both young (Agudelo et al., 2014; Benson et al., 2015; Chennaoui et al., 2015; Ding et al., 2005; Funk et al., 2011; Mota & Kelly, 2020; Nickerson et al., 2005; Zaychik et al., 2021) and aged rodents (Barrientos et al., 2011; He et al., 2017; Littlefield et al., 2015). Regular daily running for the duration of between two and six weeks in either a voluntary or involuntary manner increases pathogen clearance (Nickerson et al., 2005) while minimising CNS dysfunction as evidenced by improved spatial memory (Barrientos et al., 2011; Mota & Kelly, 2020), reduced depression and anhedonia (Agudelo et al., 2014), reduced anxiety, decreased amyloid-β (Aβ) deposition (He et al., 2017), smaller infarct size in ischaemic-reperfusion models (Ding et al., 2005), attenuated cell death by neurotoxins (Funk et al., 2011), or even delayed disease progression in experimental autoimmune encephalomyelitis models of multiple sclerosis (Benson et al., 2015; Zaychik et al., 2021). A key common finding of these animal studies is that prior exercise training altered the expression and/or secretion of perturbation-induced soluble immune molecules relative to sedentary controls, highlighting the role of inflammatory components in the exercise-associated functional advantages and suggesting a potential causal link between them. Immune challenge with whole bacteria or their purified toxins is associated with elevation of central concentrations of the canonical pro-inflammatory cytokines, interleukin-1β (IL-1 β), interleukin-6 (IL-6), and tumour necrosis factor-α (TNF- α), that can be modulated by regular, moderate intensity prophylactic exercise in an age- and brain region-dependent manner (Barrientos et al., 2011; Littlefield et al., 2015; Mota & Kelly, 2020; Nickerson et al., 2005). It may be argued that modulation of the immune response to bacterial toxins by exercise may not be beneficial, given the need for a robust immune response to resolve potentially damaging inflammation – hence the region-specificity of the response is key. Prior endurance exercise can reduce hippocampal IL-1β expression and secretion upon immunological challenge in both aged and young rodents concomitant with preserved memory function (Barrientos et al., 2011; Mota & Kelly, 2020), but enhance IL-1β in the hypothalamus and pituitary in young rats (Nickerson et al., 2005) enabling the synthesis of glucocorticoid hormones (Berkenbosch et al., 1987; Besedovsky et al., 1986; Engström et al., 2012) that are essential for generation of the febrile response and other symptoms of sickness behaviour crucial to the resolution of infection. Both exercise-induced responses might be said to optimise homeostasis and thus survival of the affected organism.

Physical activity and, specifically, structured aerobic exercise programmes also have potential therapeutic capacity in conditions affecting the CNS (Booth et al., 2002; Duzel et al., 2016), although results of randomized control trials investigating the impact of physical activity, including supervised moderate to high intensity aerobic and strength exercise interventions, on the cognitive skills of people with dementia are somewhat contradictory (Lamb et al., 2018). While pre-disease homeostatic set points may not be fully restored by rehabilitative exercise, physical activity is beneficial in increasing the ability of an organism to adapt to the new internal environment, increasing 'apparent vigour' (Ayres, 2020). Early moderate intensity treadmill running of even a few days' duration after ischaemia-reperfusion injury in rats reduces neuronal death, improves motor skills and dampens inflammation via modulation of the innate immune system (Lu et al., 2021; Zhang et al., 2016). Meanwhile, a large amount of literature shows downregulation of pro-inflammatory cytokines and compounds by long-term, regular treadmill running in several rodent models of Alzheimer's disease (AD) in which Aβ-associated pathology develops early and prior to exercise onset (Leem et al., 2011; Zhang et al., 2022; Zhang, Lee et al., 2019).

While inflammatory responses are necessary for the restoration of homeostasis in the immune-challenged brain, uncontrolled and unresolved responses threaten the integrity and function of its constituent cells. Even without the presence of overt pathology, ageing is accompanied by chronic, low-grade inflammation, termed inflammaging (Franceschi & Campisi, 2014; Franceschi et al., 2018) reinforced by the growing number of dysfunctional, senescent immune cells over time (Yousefzadeh et al., 2021). However, as excellently reviewed and discussed elsewhere (Duggal et al., 2019), the modern sedentary lifestyle is an inevitable contributor to gradual immune dysfunction in ageing as it is inconsistent with evolutionary adaptive biological processes. While ageing results in inflammation and cytokine imbalance in the CNS of rodents housed with no access to exercise, endurance running reverses these effects (Connolly et al., 2022; Dallagnol et al., 2017; Gomes da Silva et al., 2013; Lovatel et al., 2013; Mela et al., 2020), resulting in amelioration of memory impairments. Alterations in hippocampal cytokine expression display

a 'dose response' to exercise (Connolly et al., 2022), but even a short duration (less than two weeks) of 30 min of daily low-intensity treadmill exercise can favourably shift the ratio of pro- to anti-inflammatory cytokines in the hippocampus of aged rats (Gomes da Silva et al., 2013), suggesting that even short-term improvements to a sedentary lifestyle can yield positive benefits to the brain. Given their central role in neuroimmune function, attention has focused on how glia may mediate at least some of these effects of exercise on the brain.

Homeostasis and the response of microglia and astrocytes to exercise

Homeostasis in the brain depends on communication between microglia, astrocytes, neurons and blood vessels (Fig. 1). This communication is largely maintained by the release and expression of different soluble mediators, including growth factors, ATP, neuro- and gliotransmitters, inflammatory cytokines, chemokines, nitric oxide and reactive oxygen species (Drago et al., 2017; Marinelli et al., 2019), many of which are involved in neuroimmune signalling.

Microglia, the principal resident innate immune cells in the CNS parenchyma, are long-lived, heterogeneous, self-renewing, phagocytic cells that constantly survey their environment with the help of ramified processes (Nimmerjahn et al., 2005). They are critically involved in the maintenance of CNS homeostasis and function throughout life by regulating neurogenesis (Vukovic et al., 2012), preserving the integrity of the extracellular matrix (ECM), neurons and macroglial cells via release of trophic factors such as brain-derived neurotrophic factor (BDNF) and insulin-like growth factor-1 (IGF-1), activity-dependent synaptic remodelling, enzymatic and mechanical ECM modulation, or phagocytosis of apoptotic cells and debris (Crapser et al., 2021; Schafer & Stevens, 2015). Equipped for multidirectional interaction with other CNS cell types as well as ECM components, they sense and quickly respond to environmental changes (Hickman et al., 2013), and as such are potential candidates to proactively respond to systemic signalling molecules (Althammer et al., 2021; Erny et al., 2015), including exerkines secreted from active skeletal muscle and other metabolically active tissues during exercise (Madore et al., 2020; Pluvinage & Wyss-Coray, 2020). Indeed, several exerkines, including IL6, lactate, BDNF and cathepsin B, have been demonstrated to influence inflammatory processes (Rody et al. 2022) and, for example, increased peripheral expression of irisin,

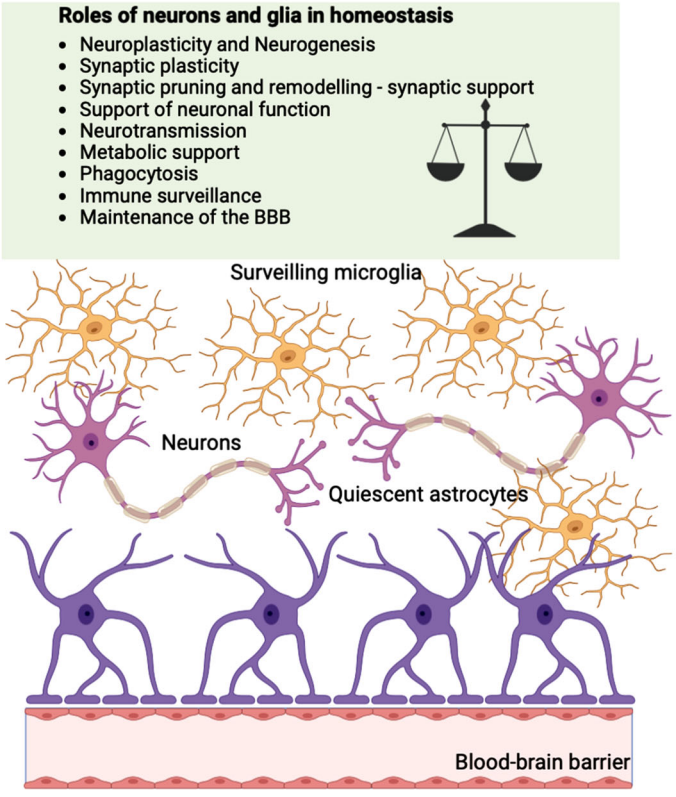

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Figure 1. Roles of glial and non-glial cells in brain homeostasis
Roles of glial and non-glial cells in brain homeostasis.

the cleaved and secreted form of the exercise-induced membrane-bound protein FNDC5, has been shown to reduce microglial activation (Islam et al 2021).

As brain-resident macrophages, microglia express pattern recognition receptors that enable the detection of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). Upon binding PAMPs and DAMPs, microglia become activated and adjust their function to enable pathogen clearance and subsequently resolve any structural and functional damage (Borst et al., 2021; Salter & Stevens, 2017). As such, microglia are also a source of inflammatory mediators such as cytokines. Chronic, extensive and dysregulated activation of microglia, however, is thought to underlie several pathological states such as neurodegenerative conditions associated with age (Borst et al., 2021), hence understanding how microglia function may be fine-tuned by various factors throughout life, including lifestyle factors such as exercise, is of potential therapeutic importance.

Recently, it was reported that late-life physical activity levels in humans, determined using actigraphy monitoring, both correlated with cognitive resilience in life and was negatively correlated with microglial activation in brain tissue post-mortem (Casaletto et al., 2022). Studies in rodents have also shown convincingly that microglia proliferation, activation and function may be modulated by endurance exercise in a manner associated with improved function. After eight weeks of wheel running, numbers of new microglia increase in the cortex (Ehninger & Kempermann, 2003) or hippocampus (Olah et al., 2009; Vukovic et al., 2012) of young mice while, in contrast, microglial proliferation is reduced in the hippocampus of aged mice (Kohman et al., 2012), pointing to the possibility of differential exercise modulation of microglia subpopulations reflective of age-dependent phenotypes and functions. In fact, effects are not limited to changes in microglia number or proliferation. Studies suggest that, either via influencing the differentiation of new microglia or by transcriptomic reprogramming of existing microglia, exercise facilitates alterations in the proportion of microglia subpopulations. Shifts in the number of microglia associated with 'neuroprotective' *vs*. 'neurotoxic' phenotypes have been described in several studies (Kohman et al., 2012; Kohman et al., 2013; Littlefield et al., 2015); these changes were distinct in the sexes and were dependent on age and brain region (Kohman et al., 2013). Exercise-associated changes in microglia phenotype and function are more apparent following subsequent perturbations such as infection- or ageing-related inflammation. Bacterial stimulation elicits transcription of pro-inflammatory cytokines in microglia, but prior short-term daily treadmill running at a moderate intensity blunts this response in the young mouse (Mota & Kelly, 2020) as does voluntary running-wheel access in the aged rat (Barrientos et al., 2011). Exercise effects are not limited to the brain microglia; two months of wheel running was shown to reverse an age-related decline in motor unit number while downregulating microglia activation markers in the spinal cord, suggesting that the effects of exercise may be mediated by the favourable changes in microglia (Giorgetti et al., 2019).

Astrocytes are a heterogeneous and abundant subtype of neuroglia (Allen & Eroglu, 2017; Chaboub & Deneen, 2013) that are primarily responsible for promoting brain homeostasis by ensuring that ionic, neurotransmitter, synaptic and metabolic balance is maintained (Allen & Lyons, 2018; Matejuk & Ransohoff, 2020). They are also responsible for preserving the blood–brain barrier integrity and protecting and repairing the brain after damage or insult (Bush et al., 1999; Pekny & Pekna, 2014). They can provide energy supply or metabolites to neurons (Belanger et al., 2011; Cali et al., 2019) and can monitor and alter synaptic function (Chung et al., 2015) by actively controlling the formation and remodelling of synapses (Matejuk & Ransohoff, 2020) via mechanisms involving TNF-α (Matejuk & Ransohoff, 2020) and interleukin-33 (IL-33)-driven increases in microglial phagocytic activity (Vainchtein et al., 2018). This complex cytokine-mediated glia-to-neuron communication may contribute to balancing the number of synapses required during brain development and in adulthood.

The astrocytic response to CNS damage is complex and highly context-dependent, as reactive astrocytes can have both neuroprotective and neurotoxic effects while responding to an insult or injury to the CNS (Cho et al., 2005; Pekny & Pekna, 2014). Reactive microglia release a cocktail of classical inflammatory factors, such as IL-1β, TNF- α and IL-6, that can change astrocytic activity by modulation of purinergic signalling (Gao et al., 2013; Shinozaki et al., 2017) and the NF-κB pathway (Jiang & Cadenas, 2014). In the aged brain, astrocytes are associated with an increase in oxidative stress due to the accumulation of ROS, causing the neuronal damage (Bellaver et al., 2017) that is a common feature of ageing and neurodegeneration (Ishii et al., 2017). Dysfunction of glia in the aged brain limits their ability to mediate healthy homeostatic responses, contributing to chronic neuroinflammation and exacerbating age-related functional decline.

Exercise can impact on the functions of astrocytes as well as microglia, though most of the evidence here has been derived from experiments in young rats and mice and in mouse models of AD. In young rodents, treadmill running for between one and four weeks increases astrocyte projections and proliferation as well as the expression of glial fibrillary acidic protein (GFAP) in specific brain regions that are associated with cognitive function (Fahimi et al., 2017; Saur et al., 2014; Uda et al., 2006). Importantly, these cells were shown to contribute

to exercise-induced neuroplasticity, neurogenesis and cognitive function by improving neural circuitry, as well as learning and memory (Fahimi et al., 2017; Saur et al., 2014; Uda et al., 2006). Longer periods of exercise (12 weeks of moderate intensity treadmill running) in rats can increase astrocytic uptake of neuron-derived glutamate, indicating that astrocytes play a role in controlling potential neuronal damage by avoiding excitotoxic effects at the synaptic level (Santin et al., 2011). Several studies have assessed the capacity of exercise to modulate astrocyte function in mouse models of AD. In the APP/PS1 model, either 10 weeks of voluntary wheel running (Tapia-Rojas et al., 2016) or five months of treadmill running (Zhang et al., 2018) reduced activation of hippocampal astrocytes. In the 5xFAD model, astrocyte remodelling has been linked with cognitive improvements induced by six months of voluntary wheel running (Belaya et al., 2020); interestingly, no change in microglial activation in response to exercise was observed in these mice.

Exercise thus modulates the function of glia in a manner that appears to enhance their ability to support neuronal and hence cognitive function (Fig. 2), with the weight of evidence thus far supporting a more important role for microglia when compared with astrocytes, at least in ageing. Recent experiments are shedding light on the mechanisms by which exercise may achieve these effects – and cellular bioenergetic regulation may be one of the contributing mechanisms.

Fuelling the glial regulation of brain homeostasis

The brain has a high energy demand, accounting for 25% of glucose utilisation, and neurons and astrocytes coordinate metabolic reactions to match energy supply to demand. Activation leads to alterations in energy demand that can be investigated by assessment of metabolic pathways and metabolic flexibility. Microglia and neurons use mainly oxidative phosphorylation to generate energy, whereas astrocytes use glycolysis; nonetheless metabolic pathways and contributions are subject to age- and state-dependent transient or chronic modulation/changes (Herrero-Mendez et al., 2009; Itoh et al., 2003). Astrocytes store glucose in the form of glycogen, allowing the transport of lactate to neurons during cerebral activation through the astrocyte-neuron lactate shuttle (ANLS) (Bordone et al., 2019; Dienel, 2017; Suzuki et al., 2011). Exercise is associated with increased lactate consumption by neurons in an activity-dependent manner (Nalbandian & Takeda, 2016); it is suggested that exercise contributes to the normal functioning of the ANLS (Tsai et al., 2016), helping to promote brain homeostasis via astrocytic activity. Thus, understanding how the astrocyte-neuron shuttle responds to the high energy demand in the brain during exercise may help unravel some of the mechanisms associated with this communication during ageing and disease. Recent *in vitro* findings suggest that while acute activation of astrocytes is accompanied by the upregulation of glycolysis, chronic activation leads to the depletion of glycogen stores, reduction of glycolytic capacity and a compensatory increase in mitochondrial oxidative phosphorylation (Robb et al., 2020). Ageing, perhaps owing to the chronic inflammatory milieu, was also shown to be associated with an elevated reliance on oxidate phosphorylation in astrocytes (Jiang & Cadenas, 2014). Since the neuroprotective capacity of astrocytes is largely dependent on their high glycolytic rate and the concomitant lactate efflux, chronic activation- or age-dependent metabolic reprogramming could compromise astrocyte function and ultimately CNS equilibrium (Xiong et al., 2022).

Cellular metabolic reprogramming occurs upon activation of peripheral macrophages (Galván-Peña & O'Neill, 2014; Mills & O'Neill, 2016) and microglia (Gimeno-Bayón et al., 2014; Holland et al., 2018; Kong et al., 2019; Rubio-Araiz et al., 2018; York et al., 2021), with pro-inflammatory stimuli inducing a transient shift towards aerobic glycolysis and tricarboxylic acid cycle and downregulation of oxidative phosphorylation. Although glycolysis is less energetically efficient than oxidative metabolism, it is considerably more rapid; from a homeostatic perspective, this enables the necessary fast, adaptive response to activation (Lynch, 2020). In parallel with this reprogramming, accumulating metabolites, as well as organelles such as mitochondria, are repurposed to enhance the production of cytokines (Kelly & O'Neill, 2015) and reactive oxygen species (Mills et al., 2016). Acute changes in microglia function in response to bacterial lipopolysaccharide stimulation are underpinned by metabolic reprogramming via activation of the HIF-1α pathway and the production of IL-1β. While this is critical for resolving inflammation, it has been shown to impact on neuronal function by inhibiting synaptic plasticity (York et al., 2021). Microglia dysfunction in chronic disease and age-related senescence, however, has also been linked with heightened microglia activation and chronic dysregulation of microglia metabolism (Baik et al., 2019; McIntosh et al., 2019; Mela et al., 2020) as long-term reliance on energetically inefficient glycolysis may lead to cellular exhaustion and hence compromise fundamental homeostatic microglia functions (Lynch, 2020; McIntosh et al., 2019). Regular exercise may therefore counteract maladaptive energetic changes in microglia.

Brain hypometabolism is a prominent feature of AD in humans, and experiments in a rodent AD model suggest that long-term exercise can modify brain, and specifically microglia, glucose metabolism in association with alleviating symptoms commonly associated with the disease in humans (Zhang et al., 2022). In addition,

a recent study (Mela et al., 2020) showed that exercise can combat specific metabolic changes in microglia in aged mice. Chronic, age-related upregulation of glycolysis in microglia, in which phagocytic and chemotactic capacity was decreased and expression and release of IL-1β was increased, was associated with increased markers of senescence and spatial memory deficits. A two-week-long regimen of daily moderate intensity treadmill running corrected this microglia metabolic dysregulation, decreasing their glycolytic rates; this was

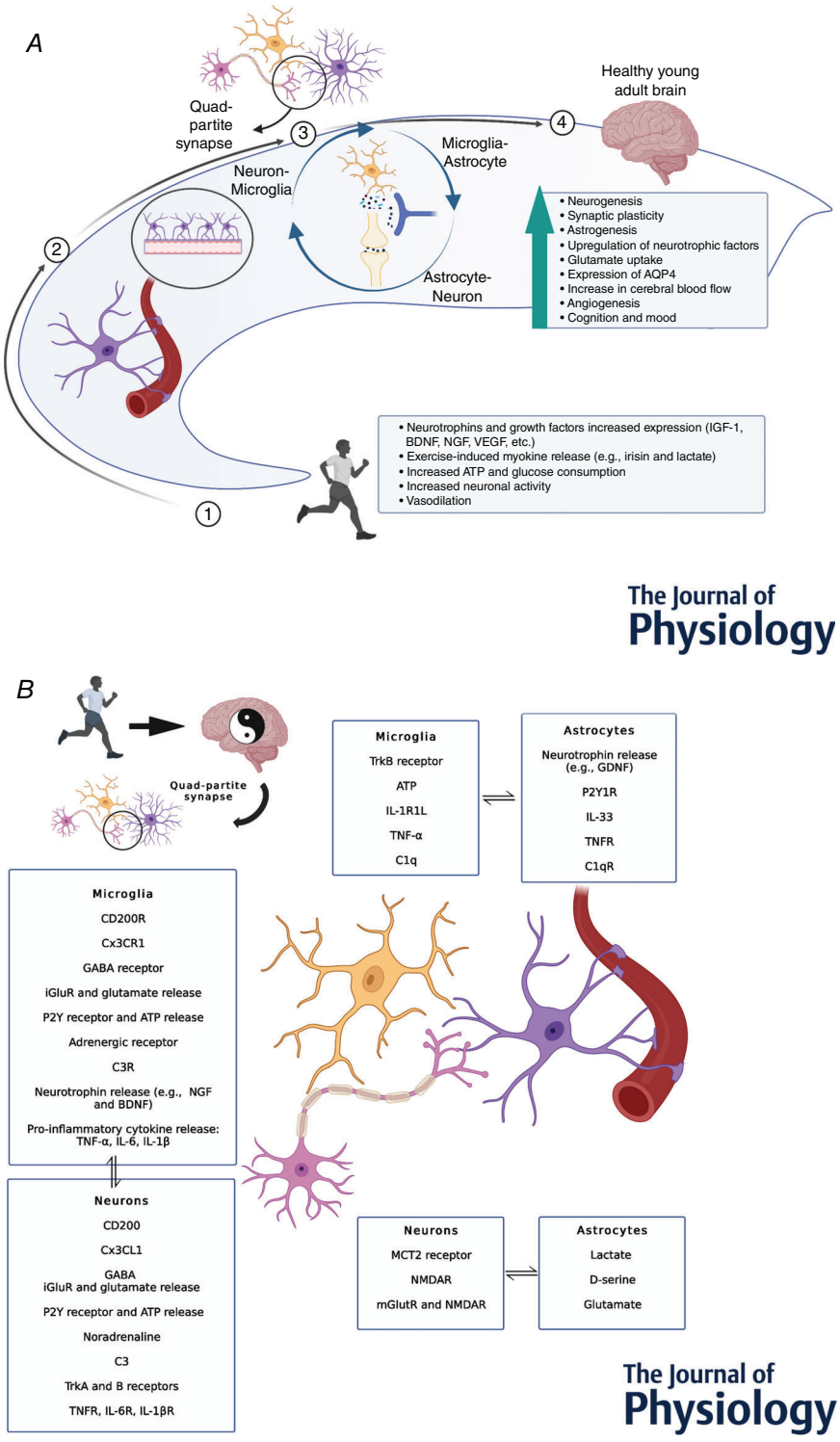

Figure 2. Exercise influences intercellular communication, supporting homeostasis in the CNS
A, brain homeostasis is supported by exercise. (1) Regular physical activity is associated with the release of soluble factors, such as neurotrophic and growth factors, metabolites and myokines, contributing to (2) the maintenance of the blood–brain barrier via astrocytic end-feet communication. (3) The tight relationship between neuroglia and neurons forms the quad-partite synapse. (4) Homeostatic conditions are maintained to promote brain health. *B*, crosstalk between neuroglia (i.e. microglia and astrocytes) and neurons during exercise.
CD200R, CD200 receptor; Cx3CR1, Cx3 chemokine receptor 1; Cx3CL1, Cx3 chemokine ligand 1; iGluR, ionotropic glutamate receptor; mGluR, metabotropic glutamate receptor; NMDAR, N-methyl-D-aspartate receptor; P2YR, purinergic receptor; ATP, adenosine triphosphate; CR3, complement receptor 3; C3, complement component C3; C1q, complement component 1q; C1qR, C1q receptor/complement component C1q receptor; NGF, nerve growth factor; VEGF, vascular endothelial growth factor; BDNF, brain-derived neurotrophic factor; GDNF, glial cell-derived neurotrophic factor; TrkA/B, tyrosine kinase receptor A and B; TNF-α, tumour necrosis factor alpha; TNFR, tumour necrosis factor receptor; GABA, γ-aminobutyric acid; IL6, interleukin 6; IL6R, interleukin 6 receptor; IL-1β, interleukin 1 beta; IL-1βR, interleukin 1 beta receptor; IL-33, interleukin 33; IL-1R1L, interleukin 1 receptor-like 1; MCT2, monocarboxylate transporter 2; AQP4, aquaporin 4.

coupled with improved microglia function, an increase of proliferative microglia, and ultimately enhanced spatial memory compared with age-matched sedentary control mice. Similar exercise-driven metabolic reprogramming was also reported in Kupffer cells, resident macrophages of the liver (Zhang et al., 2021), suggestive of ubiquitous exercise-induced mechanisms modifying cellular metabolism in tissue-resident macrophages. If true, this opens an exciting possibility of exercise-mediated correction of dysregulated macrophage/microglial function across multiple tissues.

Of note, microglia possess high metabolic flexibility and can use various fuel sources *in vivo* (Bernier et al., 2020). Furthermore, accumulating evidence indicates that metabolites, such as those derived from microbiota, shape microglia function by way of cell signalling mechanisms and epigenetic regulation (Erny et al., 2021; O'Riordan et al., 2022). Given that many metabolites and complex lipids are released into the systemic circulation following exercise on variable timescales (Contrepois et al., 2020; Rai & Demontis, 2021), including following acute, short ramp-treadmill aerobic exercise performed to maximal exercise capacity (Contrepois et al., 2020), it is plausible that exercise-related metabolites may contribute to the environmental influence on microglia function and activity, and that some of these effects are brought about via modulation of microglia cellular metabolism, ultimately leading to the reprogramming of microglial phenotypes (Fig. 3). Extensive muscle activity, on the other hand, also results in the acute release of stress- and

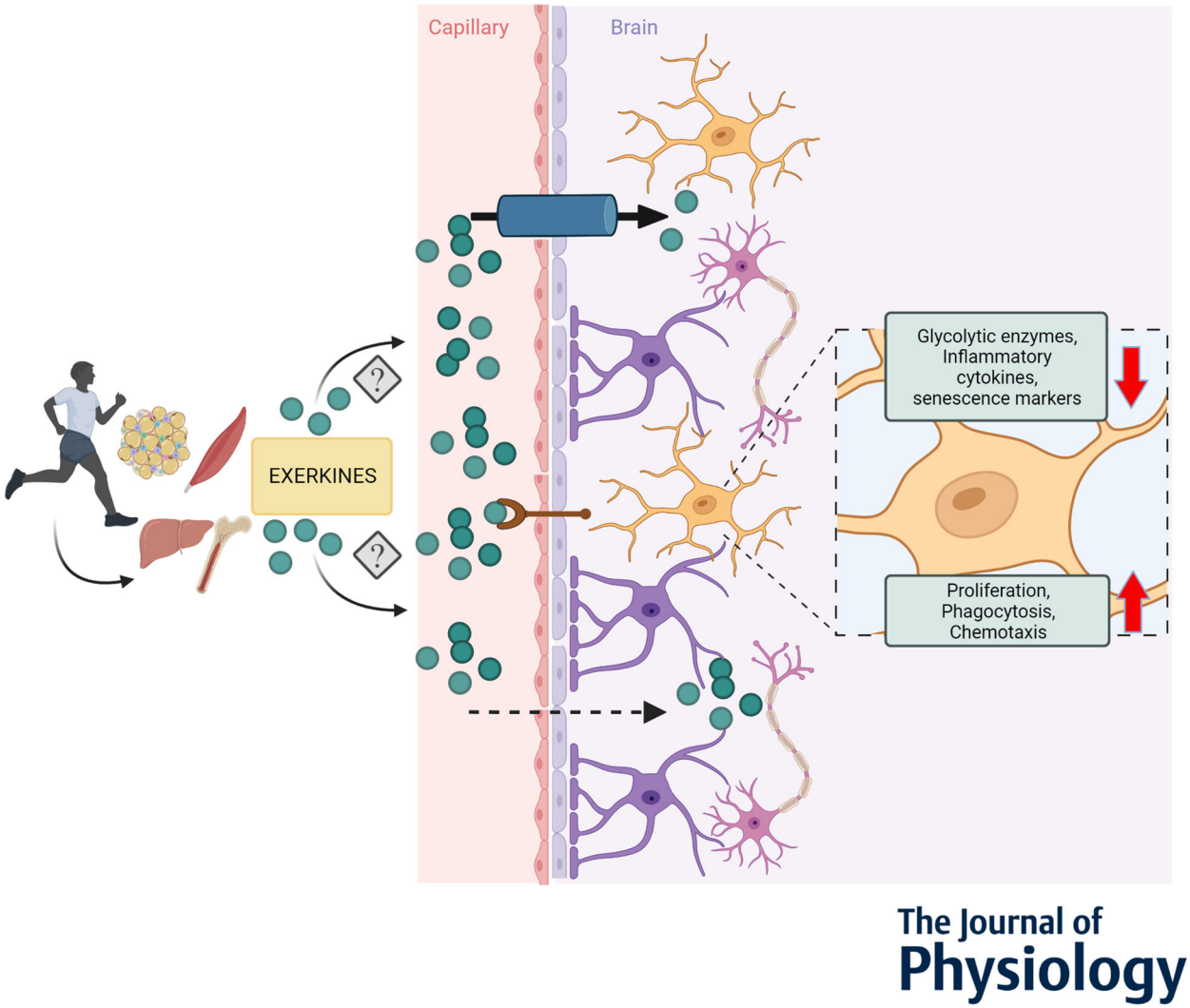

Figure 3. Fuelling the glial regulation of brain homeostasis
Endurance exercise has been shown to modulate microglia glucose bioenergetics, impacting microglial function in a manner conducive to enhanced cognitive performance in aged rodents. Several lines of research suggest that systemic exercise-derived factors may act as inter-organ signalling mediators in these processes.

damage-associated factors, alarmins. Nonetheless, the repetitive, low-level exposure to alarmins may provide an adaptive advantage to the innate immune system (Goh et al., 2020), including resident immune cells of the CNS. Collectively, it is reasonable to speculate that the cumulative, life-long regular exposure to exercise-related compounds can significantly modify microglia function with wide-reaching implications for CNS homeostasis. Microglia have a myriad of functions in the CNS in the steady state that are pivotal for structural and functional integrity across the lifespan, and the data explored here overwhelmingly suggest that exercise exerts a considerable influence on how microglia fulfil these functions.

Pushing the field forward – and why sex matters

Several exerkines have been proposed to modulate brain function (Chow et al., 2022), including via regulation of inflammatory processes (de Miguel et al., 2021; Islam et al., 2021). The question of whether these may mediate any anti-inflammatory effects of exercise via direct action on brain tissue, and/or via the modulation of systemic inflammation remains to be fully determined. Similarly, the role of exercise-induced biomolecule-carrying exosomes (Whitham et al., 2018) on neuroinflammation remains underexplored, though their ability to modulate the metabolism of target cells is intriguing in light of the discussion above. Large-scale, multi-omics investigations will advance our understanding of the inter-organ molecular transducers (Sanford et al., 2020) and cellular players involved. A further limitation of basic research in this and many other fields is the disproportionate use of male rodents, and the lack of incorporation of sex as a biological variable into fundamental research questions (Rechlin et al., 2022). Sex hormones have a regulatory impact on physical activity in humans and rodent models (Lightfoot, 2008), with oestrogen being a driver of voluntary physical activity in female rodents resulting in cyclical activity patterns (Krause et al., 2021; Ladyman et al., 2021; Slonaker, 1924). Oestrogen levels decline after menopause in women, which is also associated with reduced physical activity with drastic metabolic consequences and increased susceptibility to AD (Krause et al., 2021). Therefore, it is crucial to consider system-wide interactions when elucidating the impact of physical activity on brain health. At the cellular level, microglia are intrinsically sexually dimorphic in the mouse adult brain, possibly owing to the perinatal androgen surge and subsequent aromatization to oestradiol in the male brain (Villa et al., 2018), and show sex-dependent alterations in transcriptomic, morphological and metabolic regulation in neurodegenerative diseases (Guillot-Sestier et al., 2021). Furthermore, exercise has been demonstrated to specifically modulate microglia in the hippocampus of aged mice in a sex-dependent manner (Kohman et al., 2013). Evidence shows an increase in the expression of markers of inflammation in older females compared with males, indicating a higher microglial and astrocytic activation (Mouton et al., 2002); this may be a contributing factor to the phenomenon that neurodegenerative diseases appear to affect females at a higher rate than males, notwithstanding the longer lifespan generally enjoyed by females. Finally, disparate research findings warrant further investigation and greater methodological consistency. The type, intensity, timing or duration of exercise, are potential confounding variables (Calverley et al., 2020; Duglan & Lamia, 2019; Gabriel & Zierath, 2019; Sanford et al., 2020; Wolff & Esser, 2019), and methodological differences in exercise regimens may underlie disparities in results or differences in the magnitude of effects on the CNS in animal models. Designing exercise protocols in animal models to fine-tune the activity of glia in the face of the homeostatic challenges posed by ageing may have translational value to human health, aiding our understanding of the role of physical activity in preserving brain health and function throughout the lifespan.

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Additional information

Competing interests

None declared.

Author contributions

Zsuzsanna Barad: Conception or design of the work; Drafting the work or revising it critically for important intellectual content; Final approval of the version to be published; Agreement to be accountable for all aspects of the work. Joana Augusto: Conception or design of the work; Drafting the work or revising it critically for important intellectual content; Final approval of the version to be published; Agreement to be accountable for all aspects of the work. Áine Kelly: Conception or design of the work; Drafting the work or revising it critically for important intellectual content; Final approval of the version to be published; Agreement to be accountable for all aspects of the work. All authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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Supporting information

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