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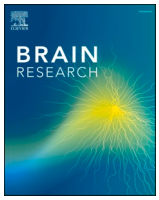

Kynurenine pathway dysregulation as a mechanistic link between cognitive impairment and brain damage: Implications for multiple sclerosis

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ABSTRACT

Cognitive impairment is a core symptom of multiple sclerosis (MS), resulting from inflammation-related brain damage and brain network dysfunction. Inflammation also causes dysregulation of the kynurenine pathway, which is the primary route of tryptophan metabolism. Kynurenine pathway dysregulation is characterised by a shift in concentrations of tryptophan catabolites, also referred to as kynurenines. Some kynurenines have neurotoxic effects that partly resemble the molecular mechanisms of MS pathophysiology underpinning brain damage and brain network dysfunction. The kynurenine pathway may therefore qualify as a mechanistic link between systemic inflammation, brain damage, and cognitive impairment in MS. This perspective article (1) provides an overview of inflammation-related kynurenine pathway dysregulation and MS-relevant neuroimmune properties of kynurenines and (2) summarises the current evidence on associations between systemic kynurenines, imaging metrics of brain structure or related markers, and cognitive performance in populations that present with kynurenine pathway dysregulation and are prone to cognitive impairment. These findings are used to (3) set a research agenda for future studies aimed at clarifying the role of the kynurenine pathway in brain damage and cognitive impairment in MS.

1. Introduction

Cognitive impairment is a core symptom of multiple sclerosis (MS) across phenotypes and disease stages and is prevalent in up to 65 % of persons with MS. The cognitive domains affected and the severity of cognitive impairment vary individually among persons with MS and most commonly include deficits in information processing speed (IPS), verbal and visual episodic memory and learning, executive functioning, and visuospatial processing, while language skills and the general intelligence remain largely unaffected (Benedict et al., 2020; Di Filippo et al., 2018). Individually or in combination, impairments in these cognitive domains are associated with reduced health-related quality of life (Ruet et al., 2013) and jeopardise independent living of persons with MS in various aspects, including employment (Clemens and Langdon, 2018), management of finances (Goverover et al., 2019), medication adherence (Bruce et al., 2010; Kalmar et al., 2008), and driving ability (Morrow et al., 2018).

MS-related cognitive impairment appears to result from an interaction of CNS inflammation and neuroaxonal damage, leading to impaired microstructural integrity, focal and diffuse inflammatory lesions, and lesion-independent atrophy of white matter, cortical grey matter, and subcortical grey matter (Manca et al., 2018; Rocca et al., 2015; Vollmer et al., 2016). The accumulating damage to widespread white matter tracts and grey matter regions impairs large-scale brain network interactions critical for behaviour, sensorimotor function, and cognitive performance (Filippi et al., 2019).

Due to the complexity of MS pathophysiology and brain network interactions, and the interdependence of cognitive domains (Benedict et al., 2020; Morelli et al., 2020), it is challenging to link individual CNS regions and white matter tracts to impairments in specific cognitive domains (Di Filippo et al., 2018). Nevertheless, the impairment of IPS has been repeatedly shown to be associated with MS-related damage to the thalamus (Batista et al., 2012; Benedict et al., 2013; Bergsland et al., 2016; Bisecco et al., 2018; Houtchens et al., 2007; Minagar et al., 2013; Schoonheim et al., 2015), orbitofrontal (Nocentini et al., 2014; Sbardella et al., 2013) and temporal cortex (Nocentini et al., 2014; Riccitelli et al., 2019), basal ganglia (i.e., caudate nucleus (Batista et al., 2012; Morelli et al., 2020; Riccitelli et al., 2019), globus pallidus (Batista et al.,

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2012; Riccitelli et al., 2019), putamen (Batista et al., 2012; Bisecco et al., 2018; Morelli et al., 2020; Riccitelli et al., 2019)), corpus callosum (Gonçalves et al., 2018; Mesaros et al., 2009; Rao et al., 1989; Riccitelli et al., 2019; Yaldizli et al., 2014), and cerebellum (Bisecco et al., 2018; Cerasa et al., 2013; Parmar et al., 2018). Impaired episodic memory has been shown to be associated with total, frontal, and parieto-occipital lesions (Rocca et al., 2015), as well as lesions (Roosendaal et al., 2009), atrophy (Sicotte et al., 2008), and demyelination (Dutta et al., 2011) of the hippocampus, which is considered a predilection site of MS-related damage (Benedict et al., 2020).

At the molecular level, manifest structural damage and brain network dysfunction are caused by an inflammation-induced aberrant cellular metabolism of neurons and glia, pathogenic glial cell activation, synaptic dysfunction and loss (i.e., synaptopathy), and disturbed neurotransmission, including glutamate excitotoxicity (Di Filippo et al., 2018; Mandolesi et al., 2015; Thompson et al., 2018).

Some of these molecular mechanisms, their contribution to structural damage, and their clinical manifestation as cognitive impairment are not unique to MS, but are also observed in other diseases and conditions that share an inflammation-related dysregulation of the kynurenine pathway (KP) of tryptophan (Trp) metabolism as a common feature. Systemic KP dysregulation became an attractive research target as tryptophan metabolites, also referred to as kynurenines, have neuroimmune properties and may thus be potential dynamic markers of inflammation-related pathophysiologies that underpin both changes in brain structure and function and cognitive impairment in various health conditions, including normotypical ageing (Sorgdrager et al., 2019) or neuropsychiatric diseases (Marx et al., 2021). Yet, associations between systemic concentrations of kynurenines, imaging metrics of brain structure, and cognitive performance have been scarcely investigated in persons with MS. Therefore, the aims of this perspective article are (1) to provide an overview of inflammation-related KP dysregulation and MS-relevant neuroimmune properties of kynurenines, (2) to summarise the current evidence on associations between systemic kynurenines, imaging metrics of brain structure or related markers, and cognitive performance in populations that present with KP dysregulation and are prone to cognitive impairment, and (3) to translate the findings to the potential role of KP dysregulation in cognitive impairment and its brain correlates in MS in order to propose a research agenda for future clinical trials.

2. The kynurenine pathway as a neuroimmune hub

2.1. Inflammation-related kynurenine pathway dysregulation

Trp is an essential amino acid that serves as a substrate for the synthesis of serotonin (5-hydroxytryptamine) and melatonin in the brain and pineal gland, respectively. Approximately 95 % of Trp is degraded along the KP, which is the major route of Trp degradation in mammals. Under physiological conditions, the KP is mainly located in the liver, where it serves to generate numerous physiologically relevant metabolites, including the *de novo* synthesis of NAD^+ for cellular energy metabolism (Badawy, 2017).

In inflammatory conditions, as present in MS, high concentrations of pro-inflammatory cytokines, such as interferon-gamma (IFN-γ) (Taylor and Feng, 1991; Werner et al., 1987), tumour necrosis factor (TNF) (Fujigaki et al., 2001), or interleukin-6 (IL-6) (Prendergast et al., 2018), increase extrahepatic KP activity by stimulating the activity of indoleamine 2,3-dioxygenase 1 (IDO1) in peripheral tissues and, to a lesser extent, in CNS tissues. IDO1 catalyses the initial cleavage of Trp to kynurenine (Kyn). Therefore, the Kyn-to-Trp ratio (KTR) is considered an index of inflammation-related KP activation. Kyn is further catabolised to either 3-hydroxykynurenine (3-HK), kynurenic acid (KA), or anthranilic acid (AA).

Systemic inflammation not only stimulates IDO1 activity, but also appears to induce the enzyme kynurenine 3-monooxygenase (KMO) both systemically and at the CNS level, as shown in IFN-γ-stimulated peripheral monocytes *in vitro* (Jones et al., 2015). In support of this, it has been shown that a peripheral immune challenge with lipopolysaccharide (LPS) increased the mRNA expression of KMO in the rat cortex and hippocampus (Connor et al., 2008). KMO fosters the formation of 3-HK, which is a substrate for other kynurenines, including xanthurenic acid (XA), 3-hydroxyanthranilic acid (3-HAA), picolinic acid (Pic), and quinolinic acid (QA) (Walker et al., 2013).

In contrast to the stimulation of IDO1 and KMO activity, inflammation downregulates the expression of kynurenine aminotransferase II (KAT II) in a region-specific manner (Parrott et al., 2016). KAT II is mainly located in astrocytes and catalyses Kyn metabolism to kynurenic acid (KA) (Kiss et al., 2003).

Moreover, inflammation downregulates the expression of 2-amino-3 carboxymuconate-6-semialdehyde decarboxylase (ACMSD), the enzyme that catalyses the formation of Pic from the 3-HAA oxidation product α-amino-β-carboxymuconate-ε-semialdehyde (ACMS) (Fig. 1). As a consequence of ACMSD downregulation, Pic formation is reduced, while the substrate availability of ACMS for QA formation is increased (Kurniati et al., 2023). This effect is partly mediated by IFN-γ, as observed in human macrophages (Braidy et al., 2016).

While Trp, Kyn, and 3-HK are transported bidirectionally across the blood–brain barrier via large neutral amino acid transporters, other kynurenines (e.g., KA, AA, 3-HAA, QA) cross the blood–brain barrier only at low rates via passive diffusion. These kynurenines are mainly produced from precursors of systemic origin and are further catabolised via neuronal and/or glial KP activity (Fukui et al., 1991; Skorobogatov et al., 2021).

2.2. Neuroimmune properties of kynurenines

At high concentrations, QA is a potent neurotoxin. QA exerts its deleterious effects through a variety of mechanisms, the most prominent of which is N-methyl-D-aspartate (NMDA) receptor-mediated glutamate excitotoxicity (Stone and Perkins, 1981). More specifically, QA stimulates the presynaptic glutamate release from neurons, inhibits the reuptake of transsynaptic glutamate by astrocytes, and restrains catabolism of glutamate to glutamine by astrocytic glutamine synthetase. The resulting excess of transsynaptic glutamate stimulates postsynaptic NMDA receptors, leading to an abnormal calcium influx, which in turn causes cellular damage and/or apoptotic death of neurons (Kelly and Burke, 1996), astrocytes (Guillemin et al., 2005a), and oligodendrocytes (Cammer, 2002) (Fig. 2).

Other neurotoxic effects of QA include the promotion of oxidative stress via the formation of reactive oxygen and nitrogen species and increased lipid peroxidation, blood–brain barrier disruption, gliotoxicity, and cytoskeletal destabilisation (Guillemin, 2012; Lugo-Huitrón et al., 2013). Underscoring its deleterious effects, it has been shown that QA injection into the prefrontal cortex of rats not only induced focal lesions at the injection site, but also disrupted cortical network activity and synaptic function in the hippocampus (Latif-Hernandez et al., 2016).

Although less well studied, 3-HK and 3-HAA appear to synergise the neurotoxic effects of QA (Guidetti and Schwarcz, 1999). 3-HK has been shown to induce the apoptosis of cortical (Chiarugi et al., 2001a) and hippocampal neurons (Okuda et al., 1996) *in vitro,* dependent or independent of its pro-oxidative effects (Reyes-Ocampo et al., 2015). Similarly, 3-HAA has been implicated as a pro-oxidant and neurotoxic agent (Okuda et al., 1998; Reyes-Ocampo et al., 2015). Both 3-HK and 3-HAA, however, also exhibit important antioxidant redox-regulatory properties (Colín-González et al., 2014; Leipnitz et al., 2007; Oh et al., 2004). Additionally, 3-HAA has been reported to have neuroprotective (Krause et al., 2011) and immunomodulatory effects, suppressing T cell activation and differentiation (Lee et al., 2013), and reducing the release of pro-inflammatory cytokines (Krause et al., 2011).

According to the current understanding, the kynurenines AA, XA, and Pic have similar Janus-faced roles. AA acts as an antioxidant and

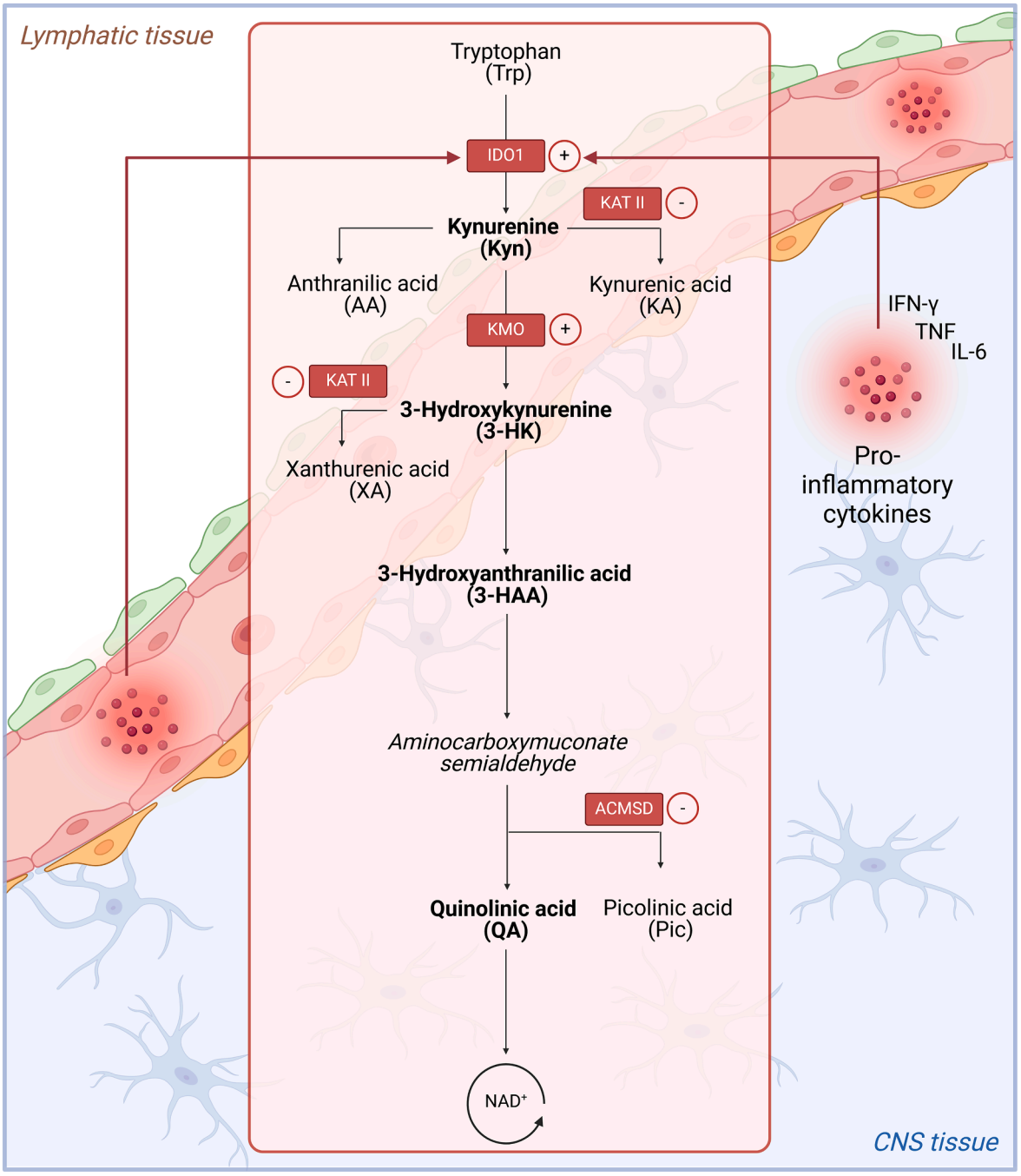

Fig. 1. Pro-inflammatory cytokines modulate kynurenine pathway activity at the systemic and CNS level. Schematic concept of kynurenine pathway dysregulation due to chronic low-grade inflammation. Pro-inflammatory cytokines, such as interferon-gamma (IFN-γ), tumour necrosis factor (TNF), or interleukin-6 (IL-6), stimulate the expression of indoleamine 2,3-dioxygenase 1 (IDO1) and kynurenine 3-monooxygenase (KMO), while downregulating the expression of kynurenine aminotransferase II (KAT II) and 2-amino-3 carboxymuconate-6-semialdehyde decarboxylase (ACMSD). As a result of inflammation-related changes in the expression of key enzymes of the kynurenine pathway, the degradation of tryptophan (Trp) and the formation of kynurenine (Kyn), 3-hydroxykynurenine (3-HK), 3-hydroxyanthranilic acid (3-HAA), and quinolinic acid (QA) are increased. In contrast, the formation of kynurenic acid (KA), xanthurenic acid (XA), and picolinic acid (Pic) is reduced. Please note that this illustration is a schematic construct that is not intended to depict the anatomical proximity/location of the tissues/vessels shown. This figure was created with Biorender.com.

inhibitor of the enzymatic machinery that produces QA, but may also negatively affect neuronal survival through its iron-chelating properties (Chobot et al., 2015; Darlington et al., 2010). XA modulates transsynaptic glutamate availability and thus influences QA-related glutamate excitotoxicity. On the one hand, XA is an agonist at the metabotropic glutamate receptor, increasing postsynaptic glutamate uptake (Fazio et al., 2017). On the other hand, XA inhibits the presynaptic vesicular glutamate transport (Neale et al., 2013), limiting extracellular glutamate availability. In addition, XA has been shown to act as a potent antioxidant by scavenging free radicals (Pérez-González et al., 2015; Ramírez-Ortega et al., 2017). Pic is considered a neuroprotective kynurenine. Although Pic does not attenuate QA-mediated NMDA excitotoxicity, it has been shown to ameliorate at least some of the neurotoxic effects of QA in rat models (Beninger et al., 1994; Cockhill et al., 1992; Jhamandas et al., 1998). Moreover, Pic exerts immunomodulatory effects. While suppressing the proliferation and

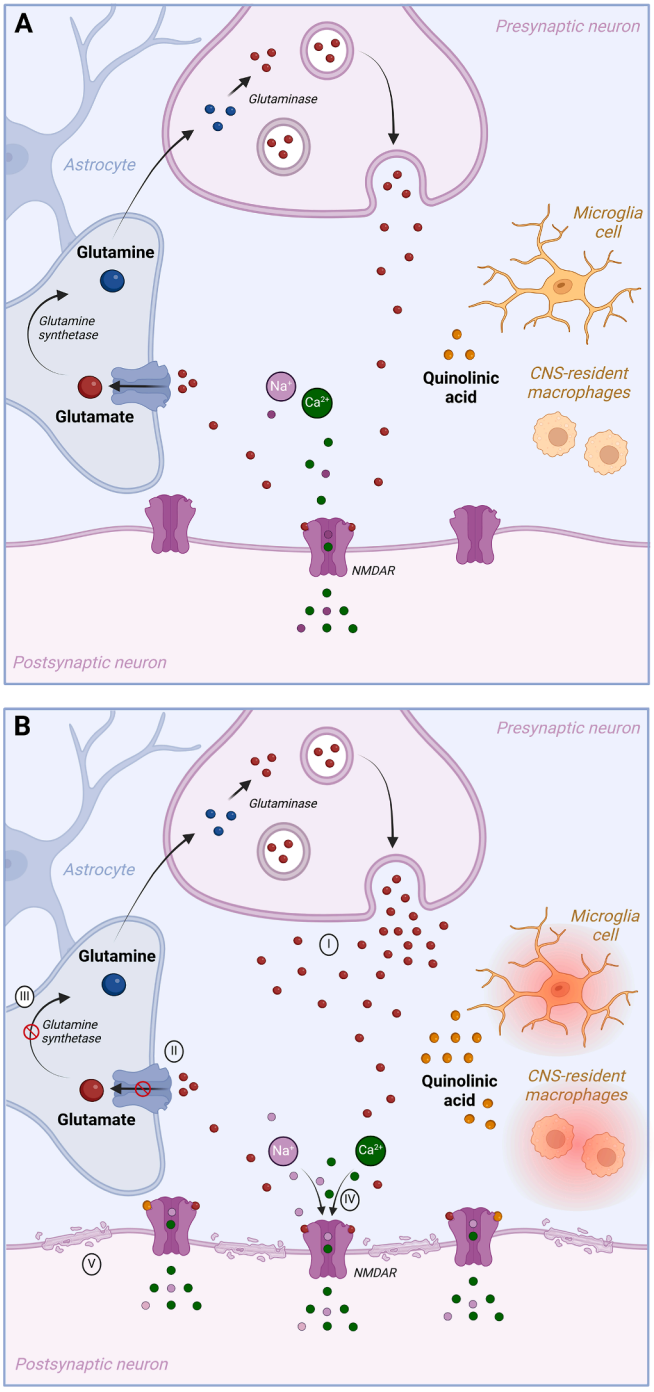

Fig. 2. Simplified overview of the mechanisms of quinolinic acid-induced glutamate excitotoxicity. Quinolinic acid (QA) modulates glutamatergic neurotransmission. **A** Glutamatergic neurotransmission under physiological conditions. **B** CNS inflammation stimulates QA formation in activated microglia and CNS-resident macrophages. (I) Abnormal concentrations of QA increase presynaptic glutamate release, (II) reduce astrocytic glutamate reuptake, and (III) inhibit astrocytic glutamate-glutamine recycling by glutamine synthetase. (IV) Both transsynaptic glutamate and QA bind to N-methyl-D-aspartate receptors (NMDARs). Increased NMDAR activation leads to excessive calcium (and sodium) influx, resulting in postsynaptic overstimulation and (V) damage and/or apoptosis of the postsynaptic neuron. This figure was created with Biorender.com.

metabolism of T cells (Prodinger et al., 2016), Pic has been shown to stimulate the secretion of inflammatory chemokines (Bosco et al., 2000).

KA is considered to be a neuroprotective kynurenine through a variety of mechanisms (Guillemin et al., 2001; Parrott and O'Connor, 2015). For instance, KA exerts an antagonistic effect on NMDA and alpha7 nicotinic acetylcholine (α7nACh) receptors (Hilmas et al., 2001). The inhibition of NMDA and α7nACh receptors causes a reduction in the transsynaptic glutamate concentration (Carpenedo et al., 2001; Grilli et al., 2006; Rassoulpour et al., 2005; Wu et al., 2010). The effects of KA on ionotropic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors are concentration-dependent. While low concentrations of KA stimulate AMPA receptors, high concentrations of KA have been shown to inhibit AMPA receptors in the rat hippocampus (Prescott et al., 2006). Dynamic interactions of KA with glutamate, gamma-aminobutyric acid (GABA), acetylcholine, and dopamine homeostasis highlight its extensive involvement in neurotransmission (Amori et al., 2009; Beggiato et al., 2014; Carpenedo et al., 2001; Grilli et al., 2006; Rassoulpour et al., 2005; Zmarowski et al., 2009). Additionally, at physiological concentrations, KA has antioxidant effects, reducing lipid peroxidation and scavenging reactive oxygen species (Albuquerque and Schwarcz, 2013; Sandi et al., 2021; Stone and Darlington, 2013). Thus, KA counteracts several mechanisms of QA-mediated neurotoxicity and gliotoxicity, including glutamate excitotoxicity and the promotion of oxidative stress, thereby contributing to neuronal and glial viability as the cellular basis for cognitive function.

The effects of most kynurenines (e.g., AA, XA, Pic) on cognitive performance are poorly understood. Previous research mainly focused on KA and QA and their respective balance. KA appears to be a double-edged sword in relation to cognitive performance. Studies in rodent models showed that a high concentration of KA in the brain is associated with poor cognitive performance in the domains of spatial working memory (Chess et al., 2007), set-shifting ability (Alexander et al., 2012), learning and memory (Chess and Bucci, 2006; Chess et al., 2009; Oliveros et al., 2017; Peyton et al., 2019), and sensorimotor processing (Nilsson et al., 2006). In support of this, an intracerebroventricular injection of KA into the rat hippocampus reduced the local extracellular glutamate concentration and impaired spatial learning and memory, whereas blockade of KA formation via KAT II inhibition resulted in an increase in extracellular glutamate and an improvement in spatial learning and memory (Pocivavsek et al., 2011). This suggests glutamatergic hypofunction as a potential mechanism underpinning the deleterious effects of KA on cognitive performance, as proposed in the context of schizophrenia pathophysiology (Wu et al., 2014). In addition, these findings highlight the importance of a homeostatic balance between molecules, rather than shifts in individual concentrations of kynurenines and/or neurotransmitters *per se*, as critical for optimal physiological function and behaviour.

Since glutamate is essential for cognitive function and thus glutamatergic receptors are widely distributed throughout the brain, the neuroactive effects of kynurenines could be considered a whole-brain phenomenon. However, there is some evidence that especially frontal, hippocampal, thalamic, striatal, and pallidal neurons are susceptible to QA-mediated damage (Guillemin, 2012; Schwarcz and Köhler, 1983; Schwarcz et al., 2012). Their particular high vulnerability may be related to a high density of glutamatergic NMDA and AMPA receptors, which determine the memory-forming capacity of neurons via long-term potentiation (Nakazawa et al., 2004; Wang et al., 2005). In support of this, immunochemistry revealed an abundance of IDO1 and QA in the hippocampi of individuals with Alzheimer's disease (Guillemin et al., 2005b). This regional specificity of QA accumulation may be due to the low activity of the QA-degrading enzyme quinolinate phosphoribosyltransferase (QPRT) in the hippocampus, striatum, and frontal cortex (Foster et al., 1985). Another post-mortem study demonstrated that the caudate and putamen revealed particularly high concentrations of KA in individuals with Alzheimer's disease, which has been interpreted as a counterregulatory mechanism against QA-mediated neurotoxicity and

gliotoxicity (Jacobs et al., 2019). In addition, animal models suggest that systemic KP modulation results in a region-specific accumulation of some kynurenines in the CNS. For instance, peripheral immune challenge with LPS stimulated IDO1 and KMO expression, and increased the 3-HK/KA ratio in the rat hippocampus (Parrott et al., 2016).

2.3. Peripheral manipulation of the kynurenine pathway modulates cognitive performance

The neuroimmune properties of kynurenines likely have important (patho-)physiological implications for cognitive performance, as discussed in Section 2.2. In Section 2.3, research is reviewed that aimed to manipulate CNS KP activity, using pharmacological inhibition and knockout of KP enzymes, to study the involvement of the KP in neuronal damage and performance in cognition-related behavioural tasks in rodent models.

2.3.1. IDO1 inhibition

In an Alzheimer's disease mouse model, the daily oral administration of the synthetic non-competitive IDO1 inhibitor coptisine (50 mg/kg) for one month reduced microglial and astrocytic activation, and associated neuronal loss. This neuroprotective effect was accompanied by an improvement in spatial memory and learning to the performance level of wild-type mice, as assessed by the Morris water maze test (Yu et al., 2015). Corroborating this finding, Alzheimer's disease mice daily treated with the IDO1 inhibitor DWG-1036 (80 mg/kg) by oral gavage for ten days showed improved spatial memory performance compared to vehicle-treated mice, as assessed by the Barnes maze test (Fertan et al., 2019).

2.3.2. KMO inhibition and knockout

KMO inhibition has been investigated as an alternative approach to reduce the neurotoxic effects of kynurenines by shifting the KP activity towards an increased KA formation. Zwilling et al. studied a seven-day oral administration of the KMO inhibitor JM6 (100 mg/kg) in wild-type mice. Although JM6 did not cross the blood–brain barrier, it increased the concentration of KA in the CNS and decreased the extracellular glutamate concentration in the prefrontal cortex of mice. In the next step, the effects of JM6 on cognitive performance were studied in Alzheimer's disease mice. Oral administration of JM6 (75 mg/kg) for 120 days prevented the disease-associated synaptic loss in the cortex and hippocampus of presymptomatic Alzheimer's disease mice and, at the behavioural level, preserved spatial memory performance compared to control mice, as assessed by the Morris water maze test. The neuroprotective effects of KMO inhibition via oral JM6 treatment (7.5 or 25 mg/kg) were reproduced in a Huntington's disease mouse model. After eight weeks of JM6 treatment, Huntington's disease mice showed a decrease in markers of cortical and striatal synaptic loss, consistent with reduced microglial activation (Zwilling et al., 2011).

Heisler and O'Connor studied the effect of peripheral immune challenge with LPS on novel recognition memory in IDO1 and KMO knockout mice compared to wild-type and saline-treated knockout mice. Knockout of IDO1 or KMO prevented the development of novel recognition memory deficits following the LPS challenge. As a result, knockout mice showed similar performance in the novel object recognition test as saline-treated mice (Heisler and O'Connor, 2015). Erhardt et al. moreover demonstrated that KMO knockout resulted in higher CNS KA concentrations in the cerebrum and cerebellum of mice. However, in contrast to the pro-cognitive effects of KMO knockout reported by Heisler and O'Connor, a lower contextual memory performance was observed in KMO knockout compared to wild-type mice, as assessed with a passive avoidance paradigm task (Erhardt et al., 2017).

2.3.3. KAT II knockout

The effects of KA as a 'cognitive depressor' have been studied in KAT II knockout models (Szalardy et al., 2012). In support of this hypothesis, KAT II knockout mice exhibited subphysiological concentrations of hippocampal KA, which were associated with higher hippocampal extracellular glutamate concentrations, and showed superior performance in cognitive tests related to contextual memory, as assessed by a passive avoidance paradigm task, and spatial memory, as assessed by the T-maze test, compared to wild-type mice. In addition, electrical stimulation of hippocampal cells *ex vivo* induced greater NMDA-dependent long-term potentiation in KAT II knockout mice compared to wild-type mice *ex vivo* (Potter et al., 2010). A single oral dose of the KAT II inhibitor BFF-816 (30 mg/kg) transiently reduced extracellular KA concentrations in the prefrontal cortex, hippocampus, and striatum of wild-type rats, while increasing striatal dopamine and glutamate concentrations in the prefrontal cortex and hippocampus *in vivo*. In a subsequent experiment, the same dose of BFF-816 administered by oral gavage 90 min prior to the Morris water maze test, repeated over five consecutive days, additionally improved spatial memory performance (Wu et al., 2014). Similar results were obtained by Kozak et al. who showed that subcutaneous administration of the KAT II inhibitor PF-04859989 (32 mg/kg) to wild-type rats transiently reduced the KA concentration in the prefrontal cortex and, when administered 60 min before cognitive testing, improved the performance in a sustained attention task compared to rats receiving the vehicle alone (Kozak et al., 2014). Of note, these studies focused on the acute effects of KAT II inhibition on cognitive performance following a single or repeated dose (i.e., five consecutive days) of KAT II inhibitors. Compared to the approaches of IDO1 and KMO inhibition described above, the long-term effects of daily KAT II inhibitor administration over weeks and months on neuronal damage and cognitive performance have not been studied. Nevertheless, some research efforts have been made to develop KAT II inhibitors as 'cognitive enhancers' (Stone and Darlington, 2013).

2.3.4. Manipulation of kynurenine pathway enzymes in rodent models of MS

Potential pro-cognitive effects of peripheral KP manipulation have not yet been investigated in MS. However, research has focused on potential neuroprotective effects of IDO1 and KMO inhibition in experimental autoimmune encephalomyelitis (EAE), the most commonly used animal model of MS, which exhibits features of inflammation and demyelination. Sundaram et al. showed that daily intraperitoneal injection of the IDO1 inhibitor 1-methyl-tryptophan (100 mg/kg) for seven days reduced brain and spinal cord IDO1 expression in symptomatic EAE mice in parallel with an improvement in clinical severity and KP dysregulation induced by EAE (Sundaram et al., 2020). Although not investigated, these findings may be attributed to reduced glial cell activation and neuronal loss in light of the above-mentioned findings in a mouse model of Alzheimer's disease (Yu et al., 2015). Consistent with the findings of Sundaram et al., Zarzecki et al. report that IDO1 inhibition by daily oral administration of epacadostat (200 mg/kg) for 25 days reduced the expression and activity of both IDO1 and KMO, as well as the concentrations of 3-HK and QA in the prefrontal cortex, hippocampus, and spinal cord of EAE mice, resembling a reversal of EAE-induced KP dysregulation (Zarzecki et al., 2020). Sundaram et al. additionally demonstrated that a daily intraperitoneal administration of the KMO inhibitor Ro 61–8048 (100 mg/kg) for seven days decreased CNS KMO expression, while increasing CNS KAT expression and the KA/QA ratio in both the cerebrospinal fluid (CSF) and plasma (Sundaram et al., 2020). In another study, intraperitoneal injection of two doses of the same KMO inhibitor (100–300 mg/kg), 15 h and 3 h before sacrifice, reduced QA and 3-HK concentrations in spinal cord homogenates, while the EAE-induced increases in Kyn and KA concentrations in the blood, spinal cord, and forebrain continued (Chiarugi et al., 2001b). These findings suggest that CNS KP activity in EAE mice can be effectively manipulated via pharmacological IDO1 and KMO inhibition, with putative neuroprotective effects that may be relevant to cognitive performance. However, evidence for the latter is still lacking.

In contrast to IDO1 inhibition, studies have also investigated the

effects of IDO1 boosting in EAE, given that peripheral immune cells show an IDO1-induced immunomodulatory response to inflammatory stimuli, which is considered an endogenous immunosuppressive mechanism to counteract autoimmunity (Vécsei et al., 2013). For instance, IFN stimulation has been shown to induce IDO1 in plasmacytoid dendritic cells, which in turn promoted the priming of regulatory T cells, resulting in an increased release of anti-inflammatory cytokines in EAE mice (Cauwels et al., 2019). Co-treatment with intravenously injected DNA nanoparticles, which stimulate IFN and activate IDO1, and the intraperitoneal administration of the KAT II inhibitor PF-04859989 (40 mg/kg) or the 3-hydroxyanthranilate 3,4-dioxygenase (HAAO) inhibitor 4-chloro-3-hydroxyanthranilic acid (125 mg/kg) for 12 days following disease onset suppressed EAE progression (Lemos et al., 2020). Consistent with the concept of IDO1 boosting to induce immunosuppressive effects, there is some evidence suggesting detrimental effects of IDO1 depletion. For example, Yan et al. showed that IDO1 knockout mice developed a more severe course of EAE, accompanied by an increased number of pro-inflammatory T cells and a greater IFN-γ production in the spleen of IDO1 knockout compared to wild-type mice (Yan et al., 2010). In addition, the daily subcutaneous injection of the IDO1 inhibitor 1-methyl-tryptophan (5 mg, ~ 250 mg/kg) for 47 days worsened disease progression in EAE mice compared to vehicle-treated EAE mice following the onset of the acute phase of EAE (Kwidzinski et al., 2005). Based on a previous study showing that IDO1 is depleted in peripheral blood mononuclear cells of persons with relapsing-remitting MS (Negrotto and Correale, 2017), Mondanelli et al. investigated the effects of IDO1 boosting on inflammation and neuroaxonal damage in EAE mice by intraperitoneal injection of the serotonin metabolite N-acetylserotonin (10 mg/kg) on alternate days for 25 days. N-acetylserotonin treatment reduced both the immune cell infiltration and the demyelination in the spinal cord of wild-type but not IDO1 knockout mice with EAE at 25 days postimmunisation, indicating IDO1-mediated immunosuppression. Moreover, N-acetylserotonin treatment induced an increase in the concentration of anti-inflammatory IL-10, while reducing concentrations of pro-inflammatory cytokines, such as IFN-γ. In a follow-up experiment involving the same animals, Mondanelli et al. showed that the injection of N-acetylserotonin caused an IDO1-dependent increase in the systemic Kyn concentration. This increase in Kyn was thought to promote neuroprotection via aryl hydrocarbon receptor signalling, as treatment with N-acetylserotonin resulted in an amelioration of pathological signs only in wild-type mice, but not in aryl hydrocarbon receptor knockout mice (Mondanelli et al., 2020).

Altogether, studies using enzymatic inhibition and/or knockout of key KP enzymes yielded some discrepant results. For example, injection of the IDO1 inhibitor 1-methyl-tryptophan in symptomatic EAE mice ameliorated the clinical severity of EAE mice (Sundaram et al., 2020), while in another study mice injected with the same IDO1 inhibitor showed greater clinical deterioration compared to vehicle-treated EAE mice (Kwidzinski et al., 2005). These findings suggest that dose (100 mg/kg vs. ~250 mg/kg), route of administration (i.e., intraperitoneal vs. subcutaneous), and duration of the intervention (i.e., seven days vs. 47 days) may be critical factors in treatment protocols that determine the effects of inhibition or knockout of key enzymes on KP activity, neuroimmunomodulation, and clinical severity. The conflicting results obtained from IDO1 inhibition and IDO1 boosting experiments further highlight the complex involvement of IDO1 in neuroimmunomodulation, including the IDO1-mediated immunosuppression via Trp depletion and aryl hydrocarbon receptor ligand formation (i.e., Kyn, KA) (Lemos et al., 2020), and the CNS accumulation of neurotoxic kynurenines, such as QA and 3-HK (e.g., Chiarugi et al., 2001b). In line with this, Zarzecki et al. argue that inflammation-related IDO1 induction in MS may, on the one hand, mediate beneficial anti-inflammatory effects (e.g., through the suppression of T cell responses) and, on the other hand, contribute to neurodegeneration via the accumulation of deleterious kynurenines, such as QA (Kwidzinski and Bechmann, 2007; Zarzecki et al., 2020).

The paucity of evidence on the effects of inhibition and/or genetic manipulation of key KP enzymes, such as IDO1 and KMO, in relation to cognition in animal models of MS may be explained by the limited availability of standardised behavioural tests to assess cognitive performance when pronounced motor impairment is present (Aharoni et al., 2019). Thus, it is necessary to develop appropriate behavioural tests or adapt established tests (e.g., T-maze test, Morris water maze test) that allow for cognitive performance testing independent of motor capabilities. Still, challenges remain in translating findings from cognitive performance tests in rodents to persons with MS.

Given the knowledge gaps in rodent models of MS, it is also not surprising that *human studies* aiming to investigate associations between systemic concentrations of kynurenines, cognitive performance, and its brain correlates in persons with MS are lacking.

3. Associations between systemic kynurenine pathway dysregulation, brain structure or related markers, and cognitive performance

3.1. Framework and rationale for synthesising evidence in populations other than MS

Due to the paucity of evidence in MS, we provide a narrative review of research focusing on associations between systemic concentrations of kynurenines, imaging metrics of brain structure or related markers, and/or the performance in MS-relevant cognitive domains in populations that exhibit inflammation-related KP dysregulation and are prone to cognitive impairment. MS-relevant cognitive domains were selected based on established cognitive test batteries in MS, including the Brief Repeatable Battery (BRB) (Boringa et al., 2001), the Minimal Assessment of Cognitive Function in MS (MACFIMS) (Benedict et al., 2002), and the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) (Langdon et al., 2012). Accordingly, studies investigating IPS, visual and visuospatial memory, verbal memory, executive function and cognitive flexibility, working memory, and sustained attention were considered. As this perspective article focuses on chronic inflammation-related conditions, including age-related cognitive decline and neuropsychiatric diseases, studies on acute-onset viral diseases (e.g., SARS-CoV 2, HIV) or recent neurotrauma (e.g., stroke or post-stroke cognitive impairment, perioperative settings, sports-related concussion) are not reviewed. Details on study characteristics are provided in Suppl. Tables 1–5.

3.2. Ageing and age-related cognitive decline

The ageing process is associated with the manifestation of chronic low-grade inflammation, which is referred to as 'inflammageing'. Inflammageing is thought to induce chronic activation of the KP (Franceschi et al., 2000). Accordingly, the KTR and Kyn concentration at both the systemic and CNS level appear to increase as a function of normotypical ageing (Bakker et al., 2024). To gain insight into the mechanisms of age-related changes in brain structure and progressive cognitive decline, systemic concentrations of kynurenines have been studied in older adults across a wide range of cognitive performance levels, including those with intact cognitive performance, mild cognitive impairment, and manifest Alzheimer's disease.

As an indirect measure of increased Trp degradation and reduced metabolism to 5-hydroxytryptamine, Willette et al. demonstrated that a greater serum-derived Kyn/5-hydroxytryptamine ratio was associated with lower orbitofrontal cortical thickness and hippocampal grey matter volume, as well as higher peripheral concentrations of TNF, C-reactive protein, matrix metalloproteinases, and numerous mainly pro-inflammatory cytokines in cognitively intact older adults and individuals with mild cognitive impairment or Alzheimer's disease who were part of the community-based *Alzheimer's Disease Neuroimaging Initiative (ADNI)* cohort. No correlations were observed between the

serum-derived KTR or Trp and Kyn serum concentrations and cortical thickness or grey matter volumes (Willette et al., 2021). Consistent with these findings, Vints et al. reported no associations between serum Kyn or IL-6 concentrations and total grey matter volume or regional grey matter volumes of the dorsolateral prefrontal, medial temporal, primary sensorimotor, dorsal posterior cingulate, or hippocampal cortex in a cohort of cognitively intact older adults. However, the serum Kyn concentration was associated with the accumulation of neurometabolites in some of these brain regions, as determined by proton magnetic resonance spectroscopy. Specifically, a higher Kyn concentration was associated with stronger myo-inositol signalling in the sensorimotor cortex and stronger total choline signalling in the dorsolateral prefrontal cortex. Both metabolites have previously been proposed as potential indices of inflammation-related glial proliferation (Vints et al., 2022). Moreover, Parker et al. reported that a greater plasma-derived KTR and a higher plasma Kyn concentration at baseline, and increases in both measures over two years, were associated with higher baseline plasma concentrations and increases in plasma concentrations of glial fibrillary acidic protein, a measure of astrogliosis (Abdelhak et al., 2022), and neurofilament light chain, a measure of neuroaxonal damage (Benkert et al., 2022), in the community-based *Physical Performance Across the Lifespan* (PALS) cohort. The plasma Trp concentration was inversely associated with both the glial fibrillary acidic protein concentration and the neurofilament light chain concentration at baseline and over the two-year study period (Parker et al., 2023). In line with this, Chatterjee et al. demonstrated positive associations between the plasma-derived KTR (Chatterjee et al., 2019) and plasma Kyn concentration (Chatterjee et al., 2021) and plasma neurofilament light chain concentration. Building on these findings, they also reported positive associations between plasma KA, 3-HK, AA, and QA concentrations and plasma neurofilament light chain concentration in older adults from the KARVIAH cohort (Chatterjee et al., 2019).

In terms of cognitive performance, and in line with the magnetic resonance imaging findings obtained in the ADNI cohort, a greater Kyn/5-hydroxytryptamine ratio was found to be associated with poorer cognitive status (i.e., mild cognitive impairment and Alzheimer's disease diagnosis), and a lower performance in the domains of verbal memory and executive functioning. Similarly, a greater KTR was associated with a lower verbal memory performance across all cognitive performance groups (Willette et al., 2021). The findings obtained in the ADNI cohort are corroborated by the results from the community-based *Hordaland Health Study* (HUSK). In more detail, Solvang et al. reported an inverse association between a greater KTR and a lower performance in visuospatial learning. The quadratic associations between Kyn and visuospatial learning and between Kyn and executive functioning suggest that both particularly high and low systemic Kyn concentrations are detrimental to cognitive performance (Solvang et al., 2019). In an ADNI subcohort of cognitively impaired elderly individuals, Nho et al. observed a positive correlation between the serum Kyn concentration and memory performance. However, kynurenines other than Kyn were not studied (Nho et al., 2021). Some evidence suggests a negative association between the systemic QA concentration and cognitive performance. For example, a negative association was identified between the serum QA concentration and a composite score for attention and executive functioning in older adults with memory impairment (Küster et al., 2017). Similarly, Gulaj et al. reported that, in individuals with Alzheimer's disease, a higher serum QA concentration was associated with a lower performance in the Clock Drawing Test, which is a combined measure of executive, visuospatial, and constructional abilities (Gulaj et al., 2010).

In summary, the current evidence in ageing and age-related cognitive decline does not support associations of systemic kynurenines with cortical thickness or grey matter volumes in cohorts of elderly individuals with varying degrees of cognitive performance. However, cross-sectional and longitudinal studies reported associations between the systemic KTR, Trp, and several kynurenines with neurometabolic signalling or blood-derived markers of neuropathology, including glial proliferation (myo-inositol, choline), astrogliosis (glial fibrillary acidic protein), and neuroaxonal damage (neurofilament light chain). With regard to cognition, a greater KTR and a higher QA concentration have most consistently been reported to be associated with poorer cognitive performance, while associations between Kyn and cognitive performance may be concentration-dependent.

3.3. Neuropsychiatric diseases

In neuropsychiatric diseases, including schizophrenia and mood disorders (e.g., major depressive disorder and bipolar disorder), pathophysiological and clinical features partly overlap. As such, schizophrenia, major depressive disorder, and bipolar disorder are all characterised by various degrees of cognitive impairment, similar structural (Cheon et al., 2022) and functional (Ma et al., 2020) abnormalities of the brain, and inflammation-related KP dysregulation (Marx et al., 2021). However, the cognitive domains affected, the severity of cognitive impairment (Bakkour et al., 2014), and the patterns of KP dysregulation (Marx et al., 2021) likely differ. Disease-specific differences have also been observed in the interactions between systemic kynurenines and both imaging metrics of brain structure and cognitive performance. For instance, Liang et al. recently showed that although KP dysregulation was associated with fronto-striatal disconnectivity across diagnostic groups, the associations between plasma concentrations of kynurenines and connectivity metrics were of complex, disease-specific nature. Similarly, working memory performance was found to be both disease-specific (healthy individuals > major depressive disorder > bipolar disorder > schizophrenia) and differentially associated with plasma concentrations of kynurenines. More specifically, lower working memory performance was associated with high dimensional canonical correlations of a greater KTR and higher 3-HK, Trp, XA, 3-HAA, and AA concentrations in healthy individuals, higher 3-HK concentration and a greater 3-HK/KA ratio in individuals with major depressive disorder, and higher XA and 3-HAA concentrations in schizophrenic individuals (Liang et al., 2024). In another study, a higher plasma QA concentration revealed to be associated with slower IPS and lower working memory performance only in the subgroup of schizophrenic individuals, but not in the comparison group composed of persons diagnosed with major depressive disorder (Cathomas et al., 2021). These findings emphasise the need for a distinguished approach when considering the potential role of the KP in brain morphology and cognitive performance in these neuropsychiatric diseases.

3.3.1. Schizophrenia

Cognitive impairment is a debilitating and poorly understood symptom of schizophrenia that is assumed to evolve from disturbed dopaminergic and glutamatergic neurotransmission and CNS inflammation (Sapienza et al., 2022). Distinct alterations in KP activity between schizophrenic and healthy individuals have been comprehensively reported in meta-analyses (Cao et al., 2021; Marx et al., 2021) and are increasingly investigated in relation to schizophrenia-related cognitive impairment and brain structure abnormalities (Sapienza et al., 2022). Underpinning the associations of inflammation-related KP dysregulation with imaging metrics of brain structure and cognitive performance, Kindler et al. demonstrated that a greater plasma-derived KTR was associated with both reduced rostral middle frontal gyrus volume, that is an anatomical subregion of the dorsolateral prefrontal cortex, and reduced attention only in participants presenting with pronounced systemic inflammation (i.e., a pro-inflammatory cytokine cluster with high mRNA expression of IL-18, IL-1β, IL-6, and IL-8). The same association was not observed in participants with low systemic inflammation or in healthy individuals. Moreover, participants with pronounced systemic inflammation were found to have a greater KTR compared to both other groups, and together with schizophrenic participants with low systemic inflammation, revealed lower rostral middle frontal gyrus volume compared to healthy participants. In a

post-mortem cohort, Kindler et al. additionally analysed brain tissue homogenates of schizophrenic individuals with regard to concentrations of kynurenines and cytokines, and the mRNA expression of KP enzymes, clustered according to a similar cytokine pattern. Here, an increased mRNA expression of tryptophan-2,3-dioxygenase, KAT I, and KAT II mRNA, and a greater KTR were found in the dorsolateral prefrontal cortex subregion of participants with pronounced systemic inflammation when compared to the schizophrenic participants with low systemic inflammation and healthy controls. KMO mRNA expression levels did not differ between groups (Kindler et al. 2020). These findings suggest that inflammation, both systemic and localised in the dorsolateral prefrontal cortex, stimulates the expression of key KP enzymes, thereby promoting an enhanced Trp degradation towards KA in the dorsolateral prefrontal cortex, a brain region involved in working memory and other cognitive domains with particular relevance in schizophrenia (Smucny et al., 2022). In another study, a greater plasma-derived KTR and a higher plasma Kyn concentration were reported to be associated with lower grey matter volume of the insula and anterior cingulate gyrus of schizophrenic individuals, respectively. Grey matter volumes of both the insula and anterior cingulate gyrus were found to be reduced in schizophrenic participants compared to healthy controls (Zhou et al., 2022). In contrast to the evidence for a potential role of the systemic KTR and Kyn concentration in schizophrenia-related differences in brain structure and cognitive performance, Huang et al. did not show any associations between serum KA or QA concentrations and global cortical thickness in schizophrenic individuals. Neither were the KA concentration or the KA/QA ratio associated with the regional grey matter volumes of the hippocampus, amygdala, pallidum, putamen, caudate, or thalamus (Huang et al., 2021). Chiappelli et al. studied plasma concentrations of kynurenines in relation to white matter fractional anisotropy, which is a measure of microstructural integrity, as well as glutamatergic signalling. In this study, a lower plasma Trp concentration was associated with a lower tract-averaged and regional fractional anisotropy of the corona radiata and genu corpus callosum in schizophrenic participants, but not in healthy controls. While not being associated with the tract-averaged or regional integrity metrics in either group, a greater plasma-derived KTR revealed to be associated with lower prefrontal glutamatergic signalling in the entire study cohort. The study additionally investigated IPS and working memory performance. However, no associations were found between plasma concentrations of Trp and kynurenines or plasma-derived ratios and the performance in these cognitive domains (Chiappelli et al., 2016). This finding is in contrast with the results of other studies. For instance, Fazio et al. reported associations between a higher serum Trp concentration and better working memory performance, and between a higher serum Kyn concentration and slower IPS. While an inverse association between the serum concentration of AA and visual memory was the only significant finding among multiple-episode participants, the first-episode participants revealed several associations between systemic kynurenines and cognitive performance domains. As such, a higher serum Trp concentration was not only associated with better working memory performance, but also revealed positive associations with sustained attention and visual memory. In addition, higher Kyn, KA, and QA serum concentrations were associated with slower IPS, while a higher serum concentration of 3-HAA was inversely associated with lower performance in the domains of sustained attention and working memory in the first-episode participants (Fazio et al., 2015). Despite not having classified participants according to episode frequency or inflammatory status, two studies demonstrated that higher systemic QA and KA concentrations were associated with slower IPS and lower attention, respectively (Cathomas et al., 2021; Huang et al., 2020). In contrast to the findings of Fazio et al., Więdłocha et al. did not show any associations between the serum Kyn concentration and different domains of cognitive performance. This group, however, demonstrated that a higher serum concentration of N-formylkynurenine, which is the direct precursor of Kyn, was associated with lower working memory performance in schizophrenic individuals (Więdłocha et al., 2023).

Taken together, the available evidence on the potential associations between systemic kynurenines, imaging metrics of brain structure, and cognitive performance in schizophrenia is inconclusive. The assessed brain structure outcomes vary considerably. Inflammatory status and episode frequency appear to be important discriminants of systemic KP metabolite profiles in subgroups of schizophrenic individuals. Some evidence supports associations between a greater systemic KTR and a lower dorsolateral prefrontal cortex volume in the presence of substantial systemic inflammation, as well as between a greater KTR and a higher Kyn concentration and lower subcortical grey matter volumes. Systemic KA and QA concentrations were not associated with imaging metrics of brain structure, but were repeatedly shown to be related to lower performance in different cognitive domains, including IPS and attention. The findings in schizophrenic individuals are thus consistent with the hypothesis that KA might act as a 'cognitive depressor' in schizophrenia (Section 2.2). However, they require cautious interpretation, given that only CSF, but not systemic KA concentrations have been reported to be altered in schizophrenic compared to healthy individuals (Cao et al., 2021; Marx et al., 2021) and that antipsychotic medication substantially affects systemic concentrations of kynurenines (Cao et al., 2021).

3.3.2. *Major depressive disorder*

In major depressive disorder, KP dysregulation has been discussed as a mechanistic link between inflammation and neurobiological hallmarks of the disease, including serotonin depletion, dysregulation of the hypothalamic–pituitary–adrenal axis, and excitotoxic damage that impairs hippocampal neurogenesis (Troubat et al., 2021). KP dysregulation in major depressive disorder is partly characterised by a reduction in the systemic KA concentration, accompanied by a reduction of the KA/QA ratio (Marx et al., 2021).

In this respect, a lower systemic KA/QA ratio was found to be associated with lower grey matter volumes of the hippocampus (Paul et al., 2022; Savitz et al., 2015a) and the amygdala (Paul et al., 2022; Savitz et al., 2015a) in individuals with major depressive disorder. The plasma KA concentration was also reported to be positively associated with hippocampal subiculum subfield volume (Doolin et al., 2018). In contrast, a greater serum-derived KTR and a higher Kyn concentration have been shown to be associated with reduced striatal grey matter volume (Savitz et al., 2015b). Similar observations were made by Zheng et al. who investigated associations of serum kynurenines with measures of microstructural integrity. In this study, positive associations were observed between the serum-derived KA/QA ratio and the fractional anisotropy of the fornix, superior thalamic radiation, corpus callosum, and cingulum, while inverse associations were found between the KA/QA ratio and serum C-reactive protein concentration. Moreover, when considered individually, a higher serum KA concentration was associated with a higher fractional anisotropy, while a higher serum QA concentration was associated with a lower fractional anisotropy of selected white matter fibre bundles (Zheng et al., 2022). In addition to the inverse associations observed between the serum QA concentration and white matter microstructural integrity, Wei et al. reported that a higher plasma Kyn concentration was associated with a lower number of white matter fibres between the right fusiform gyrus and right inferior temporal gyrus (Wei et al., 2022). Other studies focused on the systemic KA concentration in relation to the concentrations of kynurenines other than QA. Doolin et al. reported that a greater plasma-derived KA/Kyn ratio was positively associated with the volumes of the hippocampal subiculum and the cornu ammonis 1 subfield (Doolin et al., 2018). Savitz et al. demonstrated that a combined pattern of Trp, Kyn, and KA serum concentrations, which are all reduced in major depressive disorder (Marx et al., 2021), was positively associated with hippocampal volume in a combined sample of unmedicated individuals with major depressive disorder and healthy individuals. Additionally, the combined Trp, Kyn, and KA pattern and the serum-derived KA/QA ratio were associated with higher amygdalar volume in participants with major depressive disorder (Savitz et al., 2015a). In another study of this group, both the log-transformed KA/QA ratio and the KA/3-HK ratio mediated

the association between the diagnosis of major depressive disorder and cortical thickness of the right Brodmann area 32. Moreover, the KA/3-HK ratio was identified as a mediator between systemic inflammation, as indicated by higher log-transformed C-reactive protein concentration, and lower cortical thickness of the right Brodmann area 32 (Meier et al., 2016). In support of the above findings and consistent with the antagonistic roles of KA and QA in neurotransmission, associations with glutamatergic signalling have been studied in major depressive disorder and revealed that a higher plasma KA concentration and a greater plasma-derived KA/QA ratio were associated with lower glutamatergic signalling of the basal ganglia, whereas a higher plasma QA concentration was associated with stronger glutamatergic signalling (Chen et al., 2021). Additionally, higher plasma concentrations of Kyn and 3-HAA were associated with stronger striatal total choline signalling in a study cohort of melancholic adolescents with major depressive disorder (Gabbay et al., 2010). The above approaches to studying associations between systemic kynurenines and imaging metrics of brain structure and neurometabolic signalling are complemented by complex functional magnetic resonance imaging and connectivity analyses, which are not discussed in detail here (Chen et al., 2021; DeWitt et al., 2018; Kamishikiryo et al., 2022; Liang et al., 2024; Okamoto et al., 2020).

With regard to the performance in cognitive domains, systemic kynurenines have been less well studied in major depressive disorder. Previous studies mainly focused on a few kynurenines (i.e., Kyn, KA, QA) and ratios (i.e., KTR, QA/KA ratio, KA/Kyn ratio). Among these, a greater serum-derived KTR was shown to be associated with lower immediate and delayed verbal recall, and a lower performance on the Trail Making Test, a combined measure of attention, visual search, IPS, set-shifting, and cognitive flexibility, in the entire study cohort of individuals with major depressive disorder and healthy individuals. Notably, although individuals in the healthy cohort did not have a diagnosis of major depressive disorder, they also had symptoms of depressed mood and/or fatigue (Hestad et al., 2017). Zhou et al. reported associations between a higher serum-derived KTR and a lower performance in the domains of visual memory, verbal memory, and IPS in female individuals with major depressive disorder. In this study, a higher serum Kyn concentration was also associated with lower verbal learning (Zhou et al., 2019). The findings of Chirico et al. do not support the above associations between the KTR and Kyn concentration and memory or IPS. However, an inverse association was found between the plasma-derived QA/KA ratio and visual associative memory (Chirico et al., 2020).

In summary, research on the associations between systemic kynurenines and imaging metrics of brain structure has consistently shown that higher systemic concentrations of KA alone, or concentrations of KA in relation to the putatively neurotoxic kynurenines QA, Kyn, or 3-HK, are positively associated with volumes of several subcortical brain regions, white matter microstructural integrity, and lower glutamatergic signalling of the basal ganglia in individuals with major depressive disorder. Furthermore, the balance between KA and 3-HK has been identified as a mediator between the C-reactive protein concentration and a lower regional cortical thickness, supporting the hypothesis of kynurenines as a potential mechanistic link between systemic inflammation and brain structure abnormalities. Based on fewer investigations of cognitive performance, there is some evidence for associations between a greater KTR, a higher Kyn concentration, and a greater QA/KA ratio, and lower memory performance and IPS in major depressive disorder.

3.3.3. *Bipolar disorder*

Bipolar disorder is a heterogeneous disease characterised by fluctuating mood states between depressive, manic, and euthymic episodes, with associated changes in symptoms and inflammatory profiles (Jones et al., 2021). KP dysregulation in bipolar disorder mostly resembles the characteristic patterns observed in major depressive disorder, that are reduced systemic concentrations of Trp and KA, and a reduced KA/QA ratio, irrespective of the mood state (Marx et al., 2021). In a direct comparison, however, Comai et al. demonstrated that inpatients with bipolar disorder during a depressive episode had greater systemic inflammation (e.g., higher plasma concentrations of TNF and IL-1β), a greater plasma-derived KTR, and a higher plasma concentration of Kyn compared with inpatients with major depressive disorder. In addition, fractional anisotropy of several white matter tracts differed between individuals with major depressive disorder and bipolar disorder. Specifically, the fractional anisotropy of the corpus callosum, corticospinal tract, external capsule, and inferior fronto-occipital fasciculus was lower, while the fractional anisotropy of the posterior corona radiata and retrolenticular limb of the internal capsule was higher in participants with bipolar disorder compared to those with major depressive disorder. In inpatients with bipolar disorder only, associations between a higher plasma Trp concentration and a higher fractional anisotropy of the corpus callosum, and between a greater KTR and a lower white matter fractional anisotropy of the corpus callosum, external capsule, inferior fronto-occipital fasciculus, and corticospinal tract were identified. The KTR had a moderating effect on the association between a higher plasma concentration of the pro-inflammatory mediator IL-1β and a lower fractional anisotropy of the inferior fronto-occipital fasciculus in participants with bipolar disorder (Comai et al., 2022). The results reported by Poletti et al. are consistent with these findings and also show that a greater plasma-derived KTR was associated with lower fractional anisotropy of the corpus callosum. This observation was exclusively made in individuals during a depressive episode of bipolar disorder (Poletti et al., 2019). Another study of this group revealed that in individuals during a depressive episode of bipolar disorder, a higher plasma KA concentration was associated with a higher microstructural integrity of numerous white matter structures (e.g., anterior thalamic radiation, anterior corona radiata, corpus callosum, inferior fronto-occipital fasciculus, cingulum), as indicated by a lower mean and radial white matter diffusivity (Poletti et al., 2018). Distinct associations between kynurenines and white matter integrity have been observed in individuals with bipolar disorder during a manic episode. In these participants, a higher plasma Kyn concentration was associated with a higher fractional anisotropy of the cingulate gyrus and several white matter tracts, including the external capsule, inferior fronto-occipital fasciculus, and posterior corona radiata. Differences according to mood state were also observed for associations between plasma kynurenines, cortical thickness, and regional grey matter volumes. For example, individuals during a manic episode revealed an inverse association between the KTR and grey matter volumes of the superior temporal gyrus, amygdala, Brodmann area 11, and insula, whereas individuals during a depressive episode showed an inverse association between the KTR and a lower cortical thickness of the precentral gyrus and the precuneus, as well as grey matter volumes of the amygdala, fusiform gyrus, and precuneus (Poletti et al., 2019). Interestingly, findings obtained by Savitz et al. do not support associations between the KTR and grey matter volumes of the hippocampus and amygdala in individuals with bipolar disorder. However, a greater serum-derived KA/3-HK ratio was associated with a higher hippocampal volume in the study cohort of medicated and unmedicated individuals with bipolar disorder during a depressive episode (Savitz et al., 2015c).

Studies on the relation between systemic kynurenines and cognitive performance revealed that a higher plasma KA concentration was associated with better IPS in both depressed and manic individuals with bipolar disorder (Hebbrecht et al., 2022). In individuals with bipolar disorder during an euthymic episode, associations were observed only in male subjects, and included an inverse association of the 3-HK/KA ratio and a positive association of the Kyn/3-HK ratio with verbal learning and memory (Platzer et al., 2017).

Besides major depressive disorder and bipolar disorder, potential relations between the serum-derived KTR and serum concentrations of Trp and Kyn with cognitive performance have been studied in individuals with panic disorder. These individuals presented with a

greater serum-derived KTR than healthy individuals. There was an inverse association between the KTR and the performance in the Digit Span Task, a measure of short-term visual and working memory (Quagliato et al., 2019).

Taken together, current evidence supports inverse associations between the systemic KTR and cortical or subcortical grey matter volumes, and between the systemic KTR and white matter integrity in individuals with bipolar disorder, although associations differed by mood state. The KTR moderated the association between systemic inflammation and lower white matter microstructural integrity. In addition to the moderating effect observed between systemic inflammation and regional cortical thickness in participants with major depressive disorder, these findings may suggest an involvement of systemic KP dysregulation in more subtle inflammation-related brain damage. Associations between systemic kynurenines and cognitive performance in bipolar disorder have been scarcely investigated. Available studies do not show associations of most kynurenines with IPS, attention, or memory performance. Results of a single study suggest a positive association between the plasma KA concentration and IPS. The KTR has not been investigated in combination with cognitive performance in bipolar disorder.

3.4. Learnings from research in ageing and neuropsychiatric diseases

Most studies linking systemic concentrations of kynurenines with gross structural brain imaging metrics in elderly individuals, without or with varying degrees of cognitive impairment, did not demonstrate significant associations between Trp, kynurenines, or related ratios and cortical thickness or regional brain volumes. Findings in schizophrenic individuals are inconclusive. The systemic concentration of KA – alone or in relation to concentrations of QA, Kyn, or 3-HK – revealed several positive associations with brain morphology in major depressive disorder and bipolar disorder, including regional grey matter volumes and measures of white matter microstructural integrity.

Transdiagnostically, a greater systemic KTR and higher systemic concentrations of QA have most consistently been reported to be associated with lower cognitive performance in several MS-relevant cognitive domains (e.g., IPS, verbal memory). Associations between the systemic concentration of KA and cognitive performance might differ between individuals with schizophrenia and those with mood disorders.

4. Implications for MS

4.1. Kynurenine pathway dysregulation in rodent models of MS

Extrapolation of the above findings to persons with MS requires an extensive review of the current state of knowledge on KP dysregulation in MS in order to propose a research agenda for future MS studies. As outlined in Section 2.1, fundamental hallmarks of KP dysregulation include the inflammation-related induction of IDO1 and KMO, and the inhibition of KAT II and ACMSD, resulting in a chronically elevated Trp degradation and an increased formation of 3-HK, 3-HAA, and QA over KA, respectively. Experimental MS models support the presence of these characteristic hallmarks in MS. For example, Sundaram et al. showed that the induction of EAE increased the IDO1 gene expression in CNS tissues in parallel with an increase of the KTR in the brain, spinal cord, and plasma of EAE mice compared to control mice. Similarly, KMO was shown to be upregulated in the CNS of EAE mice, while CNS KAT I and KAT II expression were found to be downregulated. Consistent with KAT downregulation, both the KA concentration and the KA/QA ratio were reduced in the brain and spinal cord of mice upon EAE induction. Interestingly, a gradual decrease of the KA/QA ratio was observed during the progression of EAE. The results of Sundaram et al. further show that ACMSD gene expression was downregulated in the CNS of EAE mice compared to control mice, presumably causing the observed reduction in the CNS Pic/QA ratio in EAE mice. The EAE-induced changes in KP enzymatic activity and concentrations of kynurenines were associated with the progression of disability (Sundaram et al., 2020). The findings of Zarzecki et al. indirectly confirm the results of Sundaram et al. by showing that IDO1 inhibition prevented an EAE-induced upregulation of IDO1 and KMO in several CNS regions, including the prefrontal cortex, hippocampus, and spinal cord, and in peripheral tissues, including the spleen and lymph nodes (Zarzecki et al., 2020). Distinct changes were observed in the progressive MS mouse model of cuprizone-induced demyelination. Here, the oral administration of cuprizone toxin over five weeks resulted in gradual changes in concentrations of Trp and several kynurenines (i.e., KA, 3-HK, AA) in the cortex, hippocampus, brainstem, and plasma in parallel with progressive demyelination and glial cell activation. Interestingly, reductions in plasma concentrations of KA, XA, and 3-HK, and the striatal 3-HK concentration were already observed after one week of cuprizone treatment, prior to the manifestation of substantial myelin damage, and normalised during the remyelination period after cuprizone treatment was stopped (Polyák et al., 2023).

Overall, the findings in the EAE model are broadly consistent with *in vitro* and *in vivo* evidence on inflammation-related KP dysregulation (Section 2.1). Moreover, both animal models of MS (i.e., EAE model, cuprizone-induced model) showed dynamic changes in KP enzyme activity and concentrations of kynurenines at the CNS and systemic level as a function of pharmacologically induced pathological features, suggesting associations between KP dysregulation and molecular mechanism of MS pathophysiology. These associations may have clinical implications for MS symptoms beyond motor disability. Finally, differential changes in enzymatic activity and kynurenine concentrations between EAE and cuprizone-induced animal models suggest that KP dysregulation is dependent on the animal model studied or, in other words, distinct intoxication-induced inflammatory or demyelinating processes that mimic aspects of relapsing-remitting or progressive MS pathophysiology.

4.2. Kynurenine pathway dysregulation in persons with MS

Kynurenines and key KP enzymes have also been investigated in human studies in order to characterise KP dysregulation in persons with MS, as recently reviewed (Fathi et al., 2022). The included studies examined different body fluids (i.e., CSF, plasma, serum) and cell lines (i.e., peripheral blood mononuclear cells, red blood cells) and mostly focused on KTR, Trp, Kyn, KA, QA, and IDO1. According to the current evidence, persons with MS do not show differences in systemic concentrations of Trp or Kyn compared to healthy individuals. Equivocal findings are reported regarding differences in the systemic KTR and KA concentration between persons with MS and healthy individuals (Isık et al., 2023; Lim et al., 2017; Mancuso et al., 2015; Tömösi et al., 2020). However, available studies consistently showed a greater serum-derived QA/KA ratio and a higher serum concentration of QA in persons with MS compared to healthy individuals (Isık et al., 2023; Lim et al., 2017; Tömösi et al., 2020). These findings align with observations in the EAE model (Section 4.1) and may suggest the QA/KA ratio and the systemic QA concentration as proxies for neurotoxic damage, given their association with corresponding CNS concentrations and CNS-derived ratios that have been demonstrated in both animal models (Sundaram et al., 2014) and human MS studies (Lim et al., 2017). A greater QA/KA ratio and a higher systemic QA concentration further suggest an upregulation of IDO1 and/or KMO activity. While human studies in MS do not allow validation of CNS KP enzyme expression *in vivo*, it has been shown that persons with relapsing-remitting MS during clinical remission have lower systemic IDO1 mRNA expression in peripheral blood mononuclear cells compared to healthy individuals (Huang et al., 2005; Mancuso et al., 2015; Negrotto and Correale, 2017). These observations have been made in cohorts with unmedicated participants with MS (Huang et al., 2005; Mancuso et al., 2015) and in cohorts also including participants on disease-modifying treatment (Negrotto and Correale, 2017).

Due to the important immunoregulatory role of peripheral IDO1 activity, IDO1 boosting has been studied in the EAE model of MS, as reported in Section 2.3. To the best of the authors' knowledge, KMO mRNA expression has not yet been studied in individuals with MS. However, there is some evidence for an increased peripheral KAT expression during MS relapses, based on a study showing that KAT I and KAT II mRNA expression in red blood cells was higher in individuals with MS one to three days after relapse onset compared to healthy individuals (Hartai et al., 2005). Of note, the study lacked a comparison group of participants with MS during clinical remission. Consistent with the increase in KAT expression, persons with MS during a relapse were shown to have higher plasma (Hartai et al., 2005) and CSF (Rejdak et al., 2007) concentrations of KA compared to healthy individuals, which could be interpreted as a counterregulatory mechanism against neurotoxic damage.

4.3. Associations between systemic kynurenines and clinical outcomes in MS: Where are we now?

It remains unclear whether a greater systemic QA/KA ratio or a higher QA concentration, observed irrespective of clinical status (relapse vs. remission) or phenotype, or a higher KA concentration, observed during an MS relapse, are related to brain damage and brain network dysfunction that are causal to MS-related cognitive impairment. Most human MS studies focused on associations between systemic kynurenines and disease severity, with inconclusive results (Isık et al., 2023; Kupjetz et al., 2023; Lim et al., 2017; Saraste et al., 2022). There is one single study that investigated serum concentrations of Trp and kynurenines in relation to white and grey matter volume, lesion volume, thalamic volume, and microglial activation using positron emission tomography. Neither Trp concentration nor concentrations of Kyn, KA, AA, 3-HK, XA, 3-HAA, Pic, or QA were associated with the obtained imaging metrics. However, an inverse association was identified between the serum concentration of 3-HK and [^{11}C]PK11195 DVR, a measure of microglial activation, in the normal-appearing white matter and the thalamus (Saraste et al., 2022). Another study investigated serum concentrations of Trp, Kyn, KA, and QA in relation to plasma neurofilament light chain concentration and cognitive performance. Interestingly, a greater QA/KA ratio and a lower KA/Kyn ratio were found to be independently associated with higher plasma neurofilament light chain concentration, slower IPS, and lower visuospatial memory performance in persons with MS (Joisten et al., 2021).

4.4. Research gaps and methodological challenges

In light of these promising preliminary findings, it seems reasonable to orientate on the more comprehensive base of evidence available in populations that are also characterised by inflammation-related KP dysregulation and are prone to cognitive impairment in order to guide future research in MS. It is important to note that, although KP dysregulation is present in all of the health conditions reviewed, individual differences in KP dysregulation exist between (aged) healthy individuals and individuals with Alzheimer's disease, schizophrenia, major depressive disorder, and bipolar disorder (Section 3.2–3.4). Similarly, KP dysregulation in MS likely follows a distinct disease-specific pattern. Limited comparability also applies to disease-specific alterations in brain structure and cognitive performance, as indicated by the results of a recent study (Liang et al., 2024). Accordingly, brain imaging metrics and related markers (e.g., dorsolateral prefrontal cortex in schizophrenia) and validated cognitive tests and batteries (e.g., CERAD battery in Alzheimer's disease) have been selected depending on the population of interest in previous studies (Suppl. Tables 1–5).

Adding up to the disease-specificity of cognitive tests and batteries used in the reviewed studies, the assessment of MS-related cognitive impairment still remains a challenge in clinical practice and research. Although primarily attributed to MS pathophysiology *per se*, MS-related cognitive impairment is a highly complex phenomenon that, in addition to the large interindividual variability in neuroaxonal damage, is influenced by a variety of MS-specific factors, including other MS symptoms or comorbidities, sociodemographic factors, such as age, and an individual's cognitive reserve, that is the preservation of cognitive status by the engagement in cognition-stimulating daily-life activities and intellectual enrichment (Margoni et al., 2023). In particular, depression and fatigue, which partly overlap in symptomatic expression, may interfere with cognitive performance in MS, with as yet conflicting results (Chiaravalloti and DeLuca, 2008; Golan et al., 2018). Sleep disturbances have also been shown to be associated with cognitive impairment and exacerbate both fatigue and depression (Hughes et al., 2018), highlighting the intricate interaction between MS symptoms. Further complicating, persons with MS reveal a higher prevalence of comorbid neuropsychiatric diseases, including bipolar disorder (Joseph et al., 2021; Marrie and Horwitz, 2010) (Section 3.3). The presence of potential comorbid neuropsychiatric disorders and the co-occurrence of age-associated cognitive decline hinder the attribution of cognitive impairment to MS. The constellation of apparent and latent MS-related, comorbid, and/or co-occurring factors is characteristic to the individuality of MS-related cognitive impairment, yet challenges any investigation on causality.

Taking into account the aforementioned limitations regarding disease- or condition-specific differences, the reviewed studies suggest that, for example, systemic inflammation (e.g., Kindler et al., 2020), clinical status (e.g., Poletti et al., 2019), and medication (e.g., Cao et al., 2021) influence KP activity (Section 3.2). These variables may also affect KP dysregulation in MS, given that concentrations of kynurenines appear to differ between studied MS models (Section 4.1), MS phenotypes (Lim et al., 2017), and clinical states (relapse or remission) (Section 4.2), all of which are related to the extent of systemic and CNS inflammation. Consequently, disease-modifying treatment and steroid administration, which are intended to suppress inflammatory activity, may not only shape the inflammatory microenvironment but also likely modulate KP dysregulation. The variety of available pharmacological treatments (i.e., disease-modifying, symptomatic, and steroid treatment), including differences in mechanisms of action and treatment frequency, are a methodological challenge to overcome in MS studies that focus on pathways related to neuroimmunomodulation, such as the KP. Inflammation also likely influences the mutual interaction of systemic and CNS concentrations of kynurenines. Kita et al. showed that both a peripheral and a CNS-localised immune challenge with LPS increased the formation of Kyn and the QA metabolite quinolate in the CNS of gerbils. Interestingly, the sources of Kyn and quinolate varied depending on the site of administration. For example, the peripheral LPS challenge increased the striatal formation of quinolate from blood-derived Kyn, whereas the intrastriatal LPS challenge increased the formation of quinolate from locally produced Kyn. Additionally, the intrastriatal LPS challenge increased the quinolate concentrations in the serum and several peripheral tissues, including the liver, spleen, and lung of gerbils (Kita et al., 2002). Notably, these observations concerning the intercompartmental exchange of kynurenines have been made in animal models with intact blood–brain barrier integrity. However, persons with MS present with varying degrees of inflammation-induced blood–brain barrier disruption, which likely affects the intercompartmental exchange of kynurenines. First, the reduced integrity of the blood–brain barrier allows for increased trafficking of immune cells, such as autoreactive T helper (T_H) cells, into the CNS (Dendrou et al., 2015). Upon CNS invasion, these blood-borne immune cells may stimulate the KP activity of CNS-resident cells, such as microglia, via the release of pro-inflammatory cytokines. Second, the reduced integrity of the blood–brain barrier may allow for the CNS entry of blood-derived kynurenines, such as QA, KA, or 3-HK, which cross the blood–brain barrier to a limited extent under physiological conditions (Section 2.2,

Fig. 3). While the concordance of systemic (i.e., serum or plasma) and CSF concentrations of kynurenines has been partly confirmed (Section 4.2), the intercompartmental exchange of kynurenines may be as individual as the extent of inflammation-related blood–brain barrier disruption. However, the extent of blood–brain barrier disruption and local CNS inflammation in early and late MS remains difficult to assess.

KP dysregulation is increasingly understood in ageing (Bakker et al., 2024) and neuropsychiatric diseases (Cao et al., 2021; Marx et al., 2021), allowing for studies that investigate associations between kynurenines, brain imaging metrics, and cognitive performance within

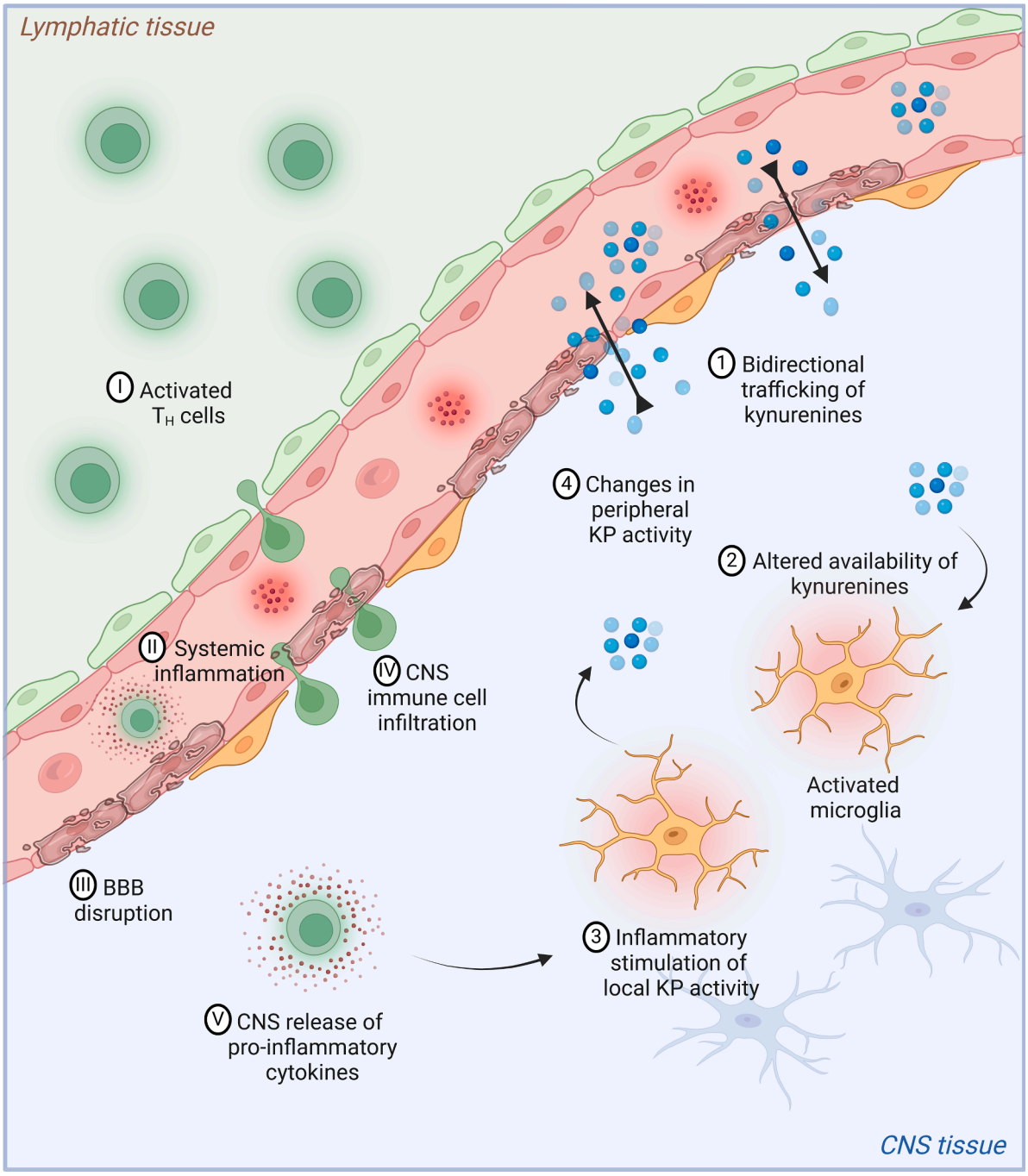

Fig. 3. Simplified illustration of the potential role of MS-related blood–brain barrier disruption in kynurenine pathway dysregulation. MS-related blood–brain barrier disruption may affect the kynurenine pathway (KP) activity at the systemic and CNS level, and the intercompartmental exchange of kynurenines across the blood–brain barrier. Roman numbers (left): (I) Activation of autoreactive T helper (T_H) cells in lymphatic tissue, (II) T_H cells enter the systemic circulation. Systemic inflammation results from an orchestrated action of various immune cells and pro-inflammatory mediators. (III) Inflammation-induced disruption of the blood–brain barrier (BBB) allows (IV) immune cell infiltration into the CNS. (V) Blood-borne immune cells contribute to local CNS inflammation, for example, by releasing pro-inflammatory cytokines. Arabic numbers (right): (1) The inflammation-induced reduction of BBB integrity alters the exchange of kynurenines across the BBB. Kynurenines of systemic origin that poorly cross the BBB under physiological conditions may enter the CNS and vice versa. (2) The altered availability of kynurenines affects the activity of the KP in CNS-resident cells (e.g., microglia). (3) At the same time, CNS inflammation stimulates the KP activity in CNS-resident cells. (4) CNS-derived kynurenines cross the disrupted BBB and alter systemic concentrations of kynurenines. Please note that this illustration is a schematic construct that is not intended to depict the anatomical proximity/location of the tissues/vessels shown. This figure was created with Biorender.com.

primary objectives. However, KP dysregulation in MS is still incompletely understood and current evidence is inconclusive (Sections 4.1, 4.2).

Evidence on KP dysregulation in persons with MS is limited by studies with (1) small sample sizes, (2) incomplete KP metabolite profiling and gene expression analyses, and (3) a limited stratification of participants concerning relevant participant characteristics, as for example MS phenotype and pharmacological treatment.

4.5. A research agenda for future MS studies

This perspective article summarised the evidence on structural brain abnormalities and molecular mechanisms that are causal to cognitive impairment in MS and provides a rationale to investigate the KP as a mechanistic link between brain damage and cognitive impairment in MS (Section 1). Cognitive test batteries validated for the use in MS were retrieved to inform the evidence-based selection of relevant cognitive domains (Section 3.1). In the next step, evidence obtained in populations other than MS was reviewed to provide an overview on the associations between systemic KP dysregulation and brain imaging metrics or related markers, and between systemic KP dysregulation and cognitive performance in domains relevant to MS.

The translatability of previous findings is limited by disease-specific differences in KP dysregulation (e.g., a reduced systemic KA concentration as a hallmark of KP dysregulation in major depressive disorder), alterations in brain structure (e.g., the role of the dorsolateral prefrontal cortex in schizophrenia), and clinical manifestations as cognitive impairment (e.g., reduced attention in schizophrenia) (Section 4.4). Therefore, this evidence does not allow drawing any conclusions to MS. Yet, it provides valuable insight into the potential role of the *systemic* KP in brain pathologies and associated cognitive impairment, and stimulates future study designs in terms of outcome selection.

While cortical thickness, lesion load, and volumes of cortical regions or subcortical structures may represent interesting outcomes in MS, given their association with impairments in IPS and/or episodic memory (Section 1), the studies reviewed in Section 3 did not consistently show associations of Trp, kynurenines, or related ratios with gross imaging metrics. Rather, systemic concentrations of kynurenines were associated with measures of white matter integrity (e.g., fractional anisotrophy), neurometabolic signalling (e.g., myo-inosital or choline compound signalling), or blood-derived markers (e.g., neurofilament light chain, glial fibrially acidic protein), suggesting that kynurenines may act as dynamic markers of distributed and/or subvisible disease pathology. These measures may therefore represent more appropriate diagnostic adjuncts to depict the role of the KP in molecular aspects of MS pathophysiology, including pathogenic glial cell activation, synaptopathy, and glutamate excitotoxicity.

Indeed, inflammation-induced glutamate excitotoxicity has recently been reinforced as one central pathophysiological mechanism driving neuronal and glial damage and death, as well as altering brain network activity in MS via excessive cytosolic and nuclear calcium influx, oxidative stress, and lipid peroxidation (Woo et al., 2024). All three mechanisms are, at least in part, amplified by an abnormal CNS concentration of QA, as shown in preclinical models (Section 2.2, Fig. 2). Moreover, brain network activity changes due to CNS ion imbalance have been proposed to underpin cognitive impairment in MS (Woo et al., 2024). In this regard, results obtained in different animal experiments showed that KP manipulation is linked to changes in both glutamatergic neurotransmission and cognitive performance. For instance, both KMO inhibition and KAT II knockout modulated the extracellular glutamate concentration in the prefrontal cortex and hippocampus, and improved memory performance in mice (Section 2.3). Consistent with these findings, the systemic KTR and concentrations of QA and KA have been reported to be associated with glutamatergic signalling of the prefrontal cortex and basal ganglia in individuals with schizophrenia and major depressive disorder, respectively. Aside from glutamatergic signalling, the systemic KTR, Kyn concentration, and 3-HAA concentration have been shown to be associated with myo-inositol and/or choline compound signalling in cognitively intact elderly individuals and individuals with major depressive disorder (Sections 3.2, 3.3). Both neurometabolites indicate inflammation-induced activation of astrocytes and microglia, and correlate with disease severity in MS (Chang et al., 2013). Finally, a greater KTR and higher systemic concentrations of several kynurenines (e.g., 3-HK, QA) have been shown to be associated with higher concentrations of plasma neurofilament light chain and glial fibrillary acidic protein in large community-based cohorts of cognitively intact and cognitively impaired elderly individuals. Neurofilament light chain is associated with the ageing process, but is also a well-established fluid-based marker of neuroaxonal damage in neurological diseases, including MS. Plasma and CSF neurofilament light chain concentrations are particularly elevated during inflammatory relapses and, especially in early disease, serve as a predictive marker of clinical worsening (Woo et al., 2024). Moreover, neurofilament light chain was shown to be a predictive marker of IPS decline in persons with active MS over a three-year period (Barro et al., 2023). Glial fibrillary acidic protein indicates reactive astrogliosis, and complementary to neurofilament light chain, reflects neurodegenerative aspects of MS even in early disease (Woo et al., 2024).

Altogether, these findings emphasise that markers of neurotransmitter homeostasis, astrocytic and microglial activation, and neuroaxonal damage may be utilised as outcomes when studying the involvement of kynurenines in MS pathophysiology in combination with validated cognitive test batteries (Section 3.1, Fig. 4). Given that neurofilament light chain and glial fibrillary acidic protein are established markers that reflect MS pathophysiology, disease severity, and/or disability progression, including cognitive impairment, further investigations on their relationship with systemic kynurenines appear to be particularly worthwhile.

Our research agenda ultimately calls for action to expand preclinical and clinical research. As a first step, *animal studies* need to be conducted that (1) use behavioural tests allowing for the assessment of cognitive performance irrespective of motor capabilities, (2) differentiate between rodent models of MS (e.g., EAE, cuprizone-induced model), and (3) consider critical determinants of treatment protocol design, including dose, frequency, route of administration, and duration of the intervention, to evaluate the role of the KP in MS-related cognitive impairment. As a second step, large-scaled *human studies* are needed that comprehensively characterise KP dysregulation in MS. These studies will need to (1) investigate both systemic and CSF concentrations of kynurenines, accounting for variable degrees of MS-related blood–brain barrier disruption, and (2) KP enzyme expression and activity in different cell lines and tissues. (3) Cognitive performance testing should be performed using cognitive tests and batteries validated for the use in MS. (4) To depict the role of the KP in molecular aspects of MS pathophysiology and brain damage, white matter integrity, neurometabolic signalling, or blood-derived markers, such as neurofilament light chain, should be selected as preferred measures over gross metrics of brain morphology. (5) Finally, participants in future studies need to be comprehensively characterised according to individual contributors to MS-related cognitive impairment, such as relevant sociodemographics (e.g., age), symptomatic manifestations (e.g., fatigue), comorbidities (e.g., bipolar disorder), or the individual cognitive reserve, in line with rigorous stratification of participants according to systemic inflammation, pharmacological treatment (disease-modifying, symptomatic, and/or steroid treatment), clinical status (relapse vs. remission), and MS phenotype, all of which may contribute to the complexity of both MS-related cognitive impairment and/or systemic KP dysregulation in MS.

5. Conclusions and final remarks

In this perspective article, we summarised research findings from animal and human studies on associations between inflammation-

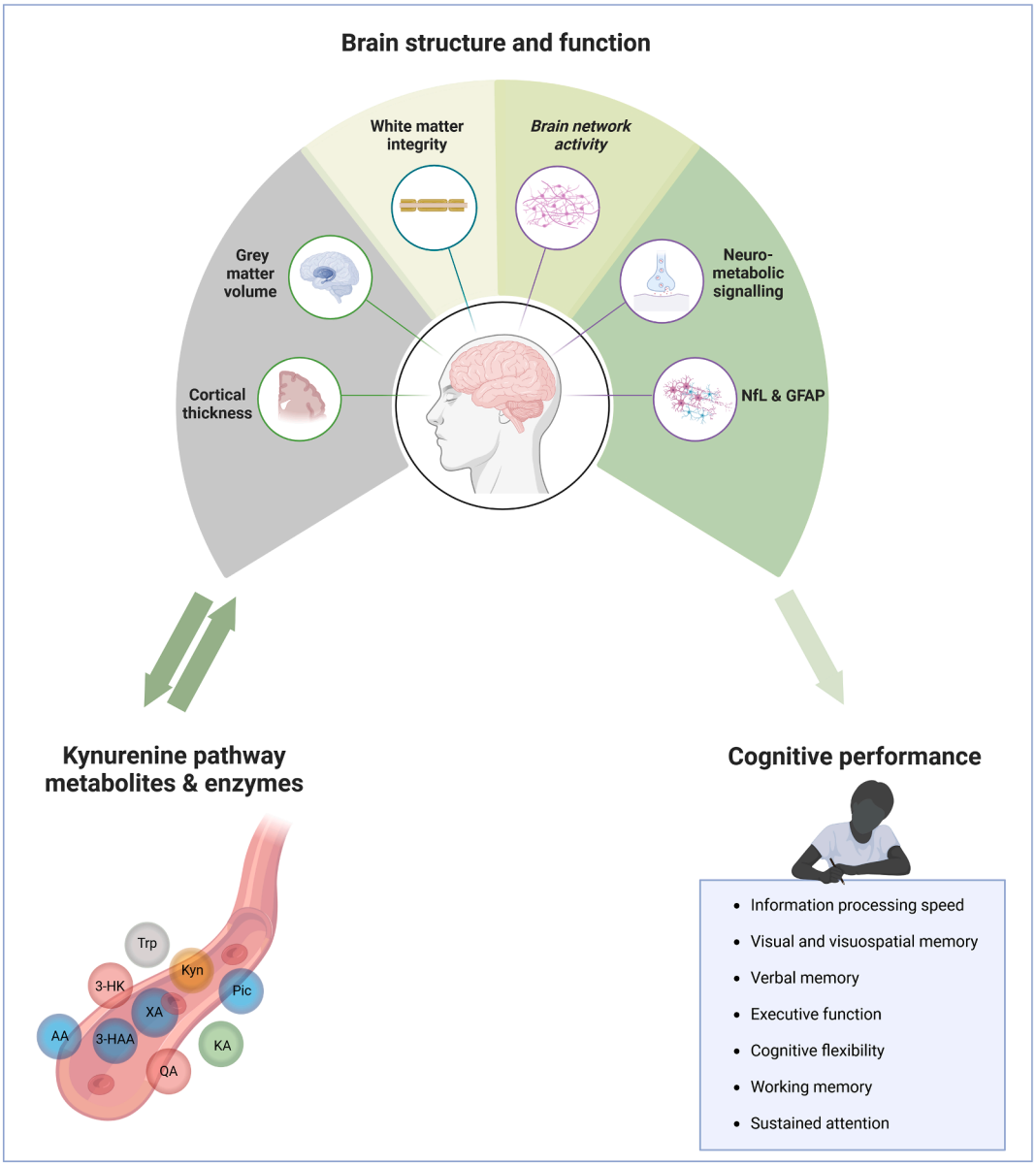

Fig. 4. Outcome selection in future trials. Overview of the proposed outcomes for future studies aimed at investigating the role of the kynurenine pathway in MS pathophysiology, MS-related brain damage, and cognitive impairment. Measures of white matter integrity or brain network connectivity (not reviewed in detail), dynamic imaging markers related to neurotransmission and glial cell activation (e.g., neurometabolites), and/or markers of neuroaxonal damage or astrogliosis (e.g., neurofilament light chain (NfL) or glial fibrillary acidic protein (GFAP)), coloured in green, may be preferable to gross brain imaging metrics (e.g., cortical thickness, grey matter volume of cortical or subcortical regions), coloured in grey. Cognitive domains have been derived from validated test batteries for the use in MS. AA = anthranilic acid; KA = kynurenic acid; Kyn = kynurenine; Pic = picolinic acid; QA = quinolinic acid; Trp = tryptophan; XA = xanthurenic acid; 3-HAA = 3-hydroxyanthranilic acid; 3-HK = 3-hydroxykynurenine. This figure was created with Biorender.com.

induced KP dysregulation, brain damage, and cognitive impairment in order to identify research gaps and methodological challenges of the current evidence, and to define a research agenda for future studies aimed at investigating KP dysregulation as a mechanistic link between MS pathophysiology and cognitive impairment in MS.

Inflammation-induced KP dysregulation is associated with a shift in the activity of key KP enzymes, leading to changes in concentrations of individual kynurenines and their respective balance. Kynurenines have neuroimmunomodulatory properties that influence neuronal survival and cognitive performance, as evidenced by animal studies. Human studies found equivocal associations between systemic concentrations of kynurenines and gross imaging metrics of brain structure.

However, some consistent associations have been observed between systemic concentrations of kynurenines and dynamic imaging markers related to neurotransmission and glial cell activation, as well as concentrations of blood-derived markers of neuroaxonal damage. The systemic KTR, QA concentration, and KA concentration were most frequently studied and showed the most robust associations with the performance in cognitive domains commonly affected in persons with MS (e.g., IPS, verbal memory). These studies included healthy cohorts during normative ageing and individuals with Alzheimer's disease, schizophrenia, major depressive disorder, and bipolar disorder.

Both animal and human studies suggest the presence of KP dysregulation in MS. While there is some evidence for a greater systemic QA/KA ratio and a higher QA concentration in persons with MS, the exact differences in KP metabolite profiles and enzymatic activity compared to healthy individuals are incompletely understood. Animal and human studies investigating systemic kynurenines in combination with

clinically relevant outcomes in MS are mostly limited to disease severity, whereas associations with cognitive performance have scarcely been examined.

Therefore, we propose a research agenda encouraging future trials to address the identified research gaps in MS. As a first step, future studies in *animal models* are needed to investigate MS-related KP dysregulation in relation to cognitive performance, taking into account differential effects depending on the MS model studied, the treatment protocol used, and the behavioural test selected. As a second step, *human trials* need to be conducted that comprehensively assess systemic and CSF concentrations of kynurenines and KP enzyme expression, together with validated cognitive tests and batteries for the use in MS and rather dynamic markers of MS pathophysiology and brain damage, such as neurofilament light chain. In the design of future trials, it will be necessary to comprehensively characterise participants in relation to MS- and participant-specific factors, such as symptomatic manifestations or potential comorbidities, which may contribute to the complexity of both MS-related cognitive impairment and systemic KP dysregulation in MS.

The mechanistic approaches in animal studies and the clinically oriented approaches in human MS studies will help to elucidate the role of KP dysregulation in MS pathophysiology and MS-related cognitive impairment, and may potentially contribute to the development of treatment strategies to maintain or improve cognitive performance in persons with MS by tackling KP dysregulation.

CRediT authorship contribution statement

Marie Kupjetz: Writing – original draft, Visualization, Methodology, Data curation, Conceptualization. **Tiffany Y. Wences Chirino:** Writing – original draft, Visualization, Data curation. **Niklas Joisten:** Writing – review & editing, Methodology, Conceptualization. **Philipp Zimmer:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Declaration of competing interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brainres.2024.149415.

Data availability

No data was used for the research described in the article.

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