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REVIEW ARTICLE

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Role of iron in brain development, aging, and neurodegenerative diseases

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ABSTRACT

It is now understood that iron crosses the blood-brain barrier *via* a complex metabolic regulatory network and participates in diverse critical biological processes within the central nervous system, including oxygen transport, energy metabolism, and the synthesis and catabolism of myelin and neurotransmitters. During brain development, iron is distributed throughout the brain, playing a pivotal role in key processes such as neuronal development, myelination, and neurotransmitter synthesis. In physiological aging, iron can selectively accumulate in specific brain regions, impacting cognitive function and leading to intracellular redox imbalance, mitochondrial dysfunction, and lipid peroxidation, thereby accelerating aging and associated pathologies. Furthermore, brain iron accumulation may be a primary contributor to neurodegenerative diseases such as Alzheimer's and Parkinson's diseases. Comprehending the role of iron in brain development, aging, and neurodegenerative diseases, utilizing iron-sensitive Magnetic Resonance Imaging (MRI) technology for timely detection or prediction of abnormal neurological states, and implementing appropriate interventions may be instrumental in preserving normal central nervous system function.

Abbreviations: 4-HNE: 4-hydroxynonenal; 5-HT: 5-hydroxytryptamine; α-Syn: alpha-synuclein; ADHD: Alzheimer's disease; Aβ: amyloid β-protein; ALS: amyotrophic lateral sclerosis; ADHD: attention deficit and hyperactive disorder; BBB: blood–brain barrier; BMVEC: brain microvascular endothelial cell; CSF: cerebrospinalfluid; CP: ceruloplasmin; CoQ10: coenzyme Q10; COX: cyclooxygenase; DFX: deferasirox; DFP: deferiprone; DFO: deferoxamine; DMT1: divalent metal transporter 1; DA: dopamine; DArgic: dopaminergic; DNH: dorsolateral nigral hyperintensity; ETC: electron transfer chain; ESC: embryonic stem cell; Fer-1: ferostatin-1; FPN: ferroportin; FXN: frataxin; FRDA: Friedreich's ataxia; Glu-Cys: glutamyl cysteine; GSH: glutathione; GPI-CP: glycosyl-phosphatidylinositol anchored CP; GPX4: GSH peroxidase 4; HEPH: hephaestin; HTT: Huntington; HD: Huntingto's disease; H/ROO•: hydrogen oxygen free radicals; H_2O_2: hydrogen peroxide; HO•: hydroxyl free radicals; iRBD: idiopathic rapid eye movement sleep behavior disorder; IRP: iron regulatory protein; Fe-S: iron–sulphur; LOOH: lipid hydroperoxide; L-ROS: lipid reactive oxygen species; LOX: lipoxygenase; Lip-1: liproxstatin-1; LC: locus coeruleus; MRI: magnetic resonance imaging; MDA: malondialdehyde; FtMt: mitochondrial ferritin; Mfrn1: mitoferrin 1; Mfrn2: mitoferrin 2; MSA: multiple system atrophy; mHTT: mutant HTT; MWF: myelinwater fraction; NFT: neurofibrillary tangle; NM: neuromelanin; NTBI: non-transferrin-bound iron; NE: noradrenaline; Nrf2: nuclear factor erythroid 2-related factor 2; OPC: oligodendrocyte progenitor cell; XO: oxidases; OXPHOS: oxidative phosphorylation; PD: Parkinson's disease; PolyQ: polyglutamine; PUFA: polyunsaturated fatty acid; PSP: progressive supranuclear palsy; PHD: proline hydroxylase domain; QSM: quantitative susceptibility mapping; ROS: reactive oxygen species; RC: respiratory chain; SLC39A14: solute carrier family 39 member 14; SN: substantia nigra; SNpc: substantia nigra pars compacta; $O_2^{\bullet-}$: superoxide anion free radical; SWI: susceptibility-weighted imaging; TSG: tetrahydroxystilbene-glucoside; Tf: transferrin; TFR: transferrin receptor; TBI: transferrin-bound iron; WMH: white matter hyperintensities

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Iron, an essential trace element, plays a critical role in the nervous system. It is involved in numerous physiological processes, including oxygen transport in brain tissue, DNA synthesis, energy metabolism, myelin

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synthesis, and neurotransmitter production [1]. Disruptions in iron homeostasis, either through deficiency or excess, can impair normal neurological function. Infants, particularly those born prematurely or with complications such as placental dysfunction or postpartum haemorrhage, are at increased risk of iron deficiency due to the brain's rapid development. Inadequate iron supplementation in these populations can lead to impaired brain development, with subsequent adverse effects on intelligence and social skills [2,3]. Conversely, excessive iron accumulation in brain tissue has been linked to the aging process and may increase susceptibility to neurological diseases [4]. Iron overload can catalyze the formation of reactive oxygen species (ROS), which cause significant brain damage [5,6] and are implicated in the pathogenesis of neurodegenerative disorders, such as Alzheimer's and Parkinson's diseases [7,8]. Therefore, maintaining iron homeostasis is essential for the nervous system.

This review aims to synthesize existing research on iron's role in brain development, normal aging, and the pathogenesis of neurodegenerative diseases, including Alzheimer's, Parkinson's, Huntington's, and Friedreich's ataxia. Furthermore, it will explore the potential applications of iron-sensitive MRI technology in neurology to inform novel interventions and treatments for abnormal brain development, aging, and iron-related neurological disorders.

This review explores the multifaceted role of iron in brain health and disease. Iron is essential for brain development, influencing neuronal maturation, myelin formation, and neurotransmitter function. In the aging brain, iron dysregulation, including redistribution, redox imbalance, mitochondrial dysfunction, and lipid peroxidation, contributes to age-related decline. Furthermore, iron is implicated in the pathogenesis of neurodegenerative disorders such as Alzheimer's, Parkinson's, Huntington's, and Friedreich's ataxia.

1. Brain iron metabolism

Maintaining brain iron homeostasis is crucial for nervous system function. Iron, primarily recycled from old red blood cells by macrophages, with smaller contributions from dietary absorption and liver stores, is essential for neuronal metabolism [9,10]. Iron is exported as Fe^{2+} from cells like macrophages, intestinal epithelial cells, and hepatocytes *via* ferroportin (FPN), oxidized to Fe^{3+} by ceruloplasmin (CP) and hephaestin (HEPH) [11], and regulated by hepcidin and iron regulatory protein (IRP) to maintain plasma iron levels [12,13]. It is worth noting that iron only through the blood-brain barrier (BBB) can be absorbed and utilized by brain cells, highlighting the unique nature of brain iron transport. Iron mainly passes through the blood microvascular endothelial cells (BMVECs) of the blood-brain barrier *via* the transferrin (Tf)-transferrin receptor 1 (TFR1) system. Transferrin-bound iron (TBI) is taken into endothelial cells from the blood through endocytosis mediated by TFR1, which is highly expressed on the luminal side of endothelial cells. The acidic environment of the endosome dissociates Fe^{3+} from Tf and reduces it to Fe^{2+}, which is then transported out of the endosome by divalent metal transporter 1 (DMT1). Subsequently, Fe^{2+} is then excreted from the basal side of endothelial cells, possibly mediated by FPN [14,15]. In addition, iron can be transported across the BBB *via* the non-transferrin-bound iron (NTBI) pathway [16]. Release to the side of the endothelial basement membrane can be in the form of iron transferrin or iron combined with low molecular weight molecules (such as citrate, ATP, and ascorbic acid). After that, iron can be taken up and utilized by other cells, such as neurons, astrocytes, and microglia, but the process by which these cells acquire and release iron has not been fully defined (Figure 1).

Astrocytes are one of the most important components of the BBB, possessing a strong ability to take in iron. However, compared to neurons and other cell types, astrocytes exhibit relatively low intracellular levels of iron or iron-related protein, which can be attributed to their lower iron demand and utilization [17]. The loss of astrocytic CP inhibits iron efflux, while iron accumulation in BMVECs of model mice reduces brain iron levels [18]. This suggests that astrocytes might serve as intermediate transporters, facilitating the movement of circulating iron from BMVECs to other brain cells. Studies have shown that astrocytes regulate brain iron influx by secreting hepcidin, which inhibits the expression of FPN1 in BMVECs [19]. Astrocytes have been reported to express transferrin receptors only in culture, but not *in vivo* [20], and primarily absorbing NTBI such as ferric ammonium citrate. DMT1 is highly expressed in astrocytic foot processes, with potential sideroreductase activity nearby [17,21]. Consequently, DMT1 may be a crucial factor mediating iron uptake in astrocytes. Additionally, astrocytes could transport NTBI *via* solute carrier family 39 member 14 (SLC39A14, also known as ZIP14) [22,23] or through the heme-related pathway involving proteins like HRG-1 and HMOX1 [17,24]. Astrocytes are the primary brain cells responsible for CP synthesis [25], and the CP they express plays a crucial role in brain iron homeostasis by influencing iron transport *via* FPN1 [18]. They transfer Fe^{2+} from ferroportin (FPN) and catalyze its oxidation to Fe^{3+} using glycosylphosphatidylinositol-anchored CP (GPI-CP)

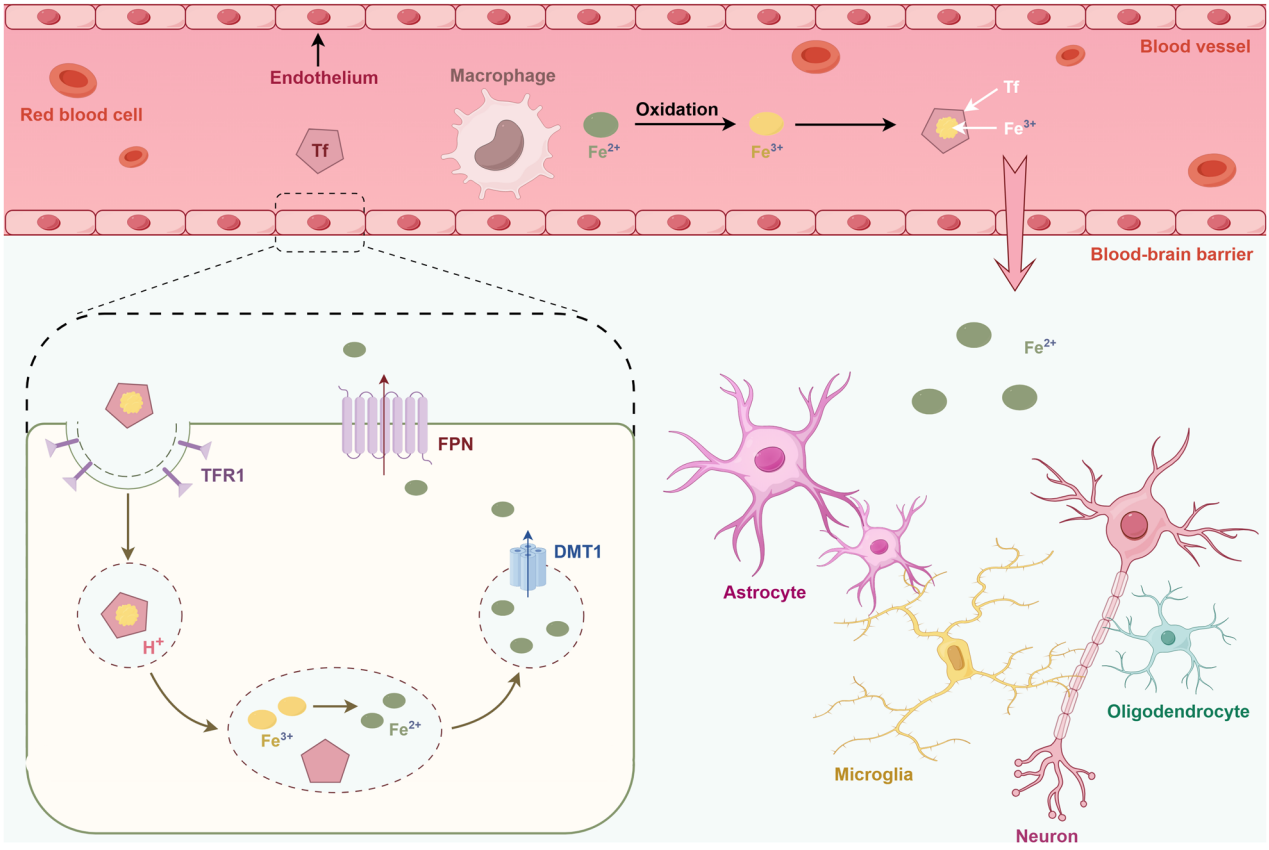

Figure 1. Iron (Fe^{2+}) is released from macrophages and oxidized to Fe^{3+}. It binds to transferrin (Tf) and enters the bloodstream. At the blood-brain barrier (BBB), Fe^{3}+-bound transferrin binds to the transferrin receptor 1 (TFR1) on endothelial cells and is endocytosed. Within the endothelial cell, Fe^{3+} is reduced to Fe^{2+} by the divalent metal transporter 1 (DMT1). Fe^{2+} is then transported across the endothelial cell by ferroportin (FPN) and released into the brain parenchyma for uptake and utilization by neurons, astrocytes, and other nerve cells.

and soluble CP [26]. Subsequently, Fe^{3+} is captured by transferrin in the interstitial fluid and distributed to other central nervous system cells [25]. TFR1 [27,28] and DMT1 [29,30] are widely distributed in neurons, and iron deficiency significantly increases TFR1 expression in rat neurons [31]. This indicates that neurons can take up TBI *via* the TFR1-DMT1 pathway. Furthermore, neuronal cells might also absorb NTBI through pathways involving lactoferrin; however, intracellular iron levels may be difficult to regulate in this process, potentially leading to abnormal iron accumulation [32,33]. FPN has been shown to be expressed in neurons, mediating cellular iron efflux [30,34]. Both CP and HEPH can function as ferrous oxidases, facilitating iron efflux from neurons *via* FPN [35–37]. Oligodendrocytes require iron for myelin synthesis and consequently store large amounts of iron and ferritin [38]. Studies have demonstrated that oligodendrocytes lack TFR1 and primarily take up iron through heavy-chain ferritin [39]. These cells bind to H-ferritin with the assistance of the H-ferritin receptor Tim-1 (human) or Tim-2 (mouse) on the cell membrane, followed by endocytosis [40,41]. The TFR1/DMT1 pathway might also be involved in iron uptake by immature oligodendrocytes [38]. Subsequently, oligodendrocytes could employ reductases to convert Fe^{3+} stored in ferritin to Fe^{2+}, releasing the intracellular iron pool for metabolic synthesis. The FPN1/HEPH pathway is linked to intracellular iron efflux from oligodendrocytes [34]. Microglia are crucial in maintaining nervous system homeostasis, repairing damage, and defending against pathogens. Iron transport in microglia is associated with their activation state. These cells preferentially absorb NTBI in response to proinflammatory stimuli, and after upregulating the TFR1/DMT1 pathway, they engage in self-regulation and exert anti-inflammatory effects [42]. In microglia, iron efflux primarily occurs through the FPN1/HEPH pathway [34]. The interaction between IRP and iron response elements (IRE) plays a crucial role in regulating iron metabolism during this process. IRPs bind to IREs to modulate the expression of iron-related genes, such as transferrin receptors, thereby ensuring appropriate intracellular iron levels [43].

2. Iron and brain development

The first 1,000 days, spanning from fertilization to the end of the second year of life, constitute the most critical period for brain development [44]. Consequently, the developing brain requires an adequate supply of all nutrients, particularly iron. Iron is essential for numerous brain processes, including neuronal development, myelination, and neurotransmitter synthesis [45]. Iron deficiency can result in impaired brain development, affecting memory, intelligence, and social skills in newborns [46]. Moreover, it may lead to persistent neuropsychiatric problems in adulthood [47–49]. Therefore, timely iron supplementation can positively influence children's neurodevelopment [45,50–52]. This section summarizes the impact of brain iron status on brain development.

2.1. Iron and neuronal development

Iron plays a pivotal role in neuronal maturation. Ferritin levels correlate positively with the volume of the sensorimotor, mesiotemporal, and source hypocortices. Reduced peripheral iron and ferritin levels can even induce hypoplasia in the caudate nucleus and putamen, increasing the risk of seizures [53]. As the developing brain requires iron regionally and temporally, iron deficiency-induced neuronal developmental damage may exhibit region-specific characteristics. Non-anaemic iron deficiency can impair neuronal maturation in animal models. In hippocampal pyramidal neurons, basal dendrite length decreases without affecting branch complexity. Cortical neurons primarily exhibit reduced apical and basal dendrite branch complexity, with minimal impact on total neuronal length [54]. Neurons necessitate a highly integrated metabolic system to meet the energy demands of growth, differentiation, and synaptic activity. Axons transport mitochondria anterogradely for ATP synthesis at local sites. Iron deficiency impairs mitochondrial respiration and ATP production. Treatment of embryonic mouse hippocampal neurons with the iron chelator deferrioxamine (DFO) reduces mitochondrial size, movement speed, and the expression of energy-related genes, leading to chronic neuronal energy deficiency and potential impacts on neuronal connectivity and synaptic function [55]. Moreover, iron deficiency-induced loss of mitochondrial complex I activity in neurons can increase oxidative stress on proteins and lipids, further impairing neuronal development [56]. Adequate iron is essential for normal neural differentiation. Iron deficiency in embryonic stem cells (ESCs) inhibits neural differentiation, as evidenced by reduced Pax1-, Sox1-, and Tuj2-positive neuronal precursor cells and fibres, suggesting that low iron status hinders neural differentiation [57]. Dysfunctional iron regulatory proteins, such as CP [58], can cause local brain iron deficiency, affecting neuronal development and detection. Conditional knockout of the CP gene in mouse astrocytes blocks iron export to the hippocampus and cerebral cortex *via* FPN1 in BMVECs, leading to brain iron deficiency, reduced neuronal ferritin levels, and inhibited hippocampal neurogenesis [18]. HEPH, a recent homolog of CP, is one of the primary proteins that exert ferrous iron oxidase activity in neurons [37]. Inhibiting astrocytic CP secretion increases brain HEPH levels, enhancing iron release from neurons, further reducing neuronal iron concentration, and impacting neuronal development [18]. DMT1 is crucial for neuronal iron uptake. The specific knockout of the DMT1 gene in hippocampal neurons decreases neuronal iron content, alters dendritic morphology, and impairs spatial memory in mice [59]. In conclusion, both systemic and local brain iron deficiency can disrupt normal neuronal development, leading to developmental issues like memory and intelligence deficits in children. Therefore, maternal iron and related protein levels during pregnancy and postpartum require careful monitoring and timely adjustment.

2.2. Iron and myelination

Myelination during early neural development establishes the foundation for brain connectivity, contributing to the development of cognitive and behavioural functions [60]. Iron is an essential cofactor for numerous cellular enzymes involved in myelin synthesis, playing a critical role in brain structure and function development [61,62]. Iron deficiency during pregnancy and lactation, a common health issue among pregnant women and infants, can lead to brain development defects, impaired cognitive development, and mental retardation [63]. Diet-induced iron deficiency hinders myelination and triggers cellular hypoxia signalling, affecting blood vessels in a rat model and potentially leading to neurovascular impairment [63]. Regional differences may exist in myelination and functional defects caused by iron deficiency. Iron deficiency-induced reduction in myelin axon diameter can slow action potential propagation in the auditory nerve, but similar structural changes do not affect action potential propagation speed in the corpus callosum, only its signal intensity [54]. Studies have shown that functional defects in certain brain iron metabolism proteins can cause brain iron deficiency, affecting myelin development and potentially impairing myelin regeneration after injury. Astrocytic CP depletion results in iron deficiency and induces mild oxidative

damage in oligodendrocytes, leading to significant delays in oligodendrocyte maturation and insufficient myelination [64]. TFR and DMT1 are crucial for iron uptake in immature oligodendrocytes. TFR loss hinders oligodendrocyte progenitor cell (OPC) maturation and myelination [65]. DMT1-specific knockout also decreases myelin protein expression and substantially reduces the percentage of myelinated axons in the brains of model mice [66]. Oligodendrocytes require substantial iron and ferritin reserves for efficient myelination. H-ferritin deletion significantly impairs OPC maturation and myelination [67]. In conclusion, adequate iron storage is essential for early oligodendrocyte development and the myelination process. Iron deficiency can significantly disrupt normal brain myelination, leading to cognitive and intelligence-related problems.

2.3. Iron and neurotransmitter function

Iron serves as a critical cofactor for numerous neurotransmitter synthetases, including tyrosine hydroxylase (TH) [68], monoamine oxidase [69,70], and tryptophan hydroxylase [71]. Consequently, iron deficiency can impair neurotransmitter synthesis, leading to brain developmental issues and even neurological diseases. Low brain iron content is associated with poor cognitive performance, even in healthy young adults [72]. Iron influences dopamine (DA) metabolism by activating TH, the rate-limiting enzyme in DA synthesis [73], and DA plays a pivotal role in regulating cognition, mood, positive affect, and reward [74]. Some short- and long-term brain developmental changes associated with infant iron deficiency may be attributed to reduced DA pathway function. Children with chronic iron deficiency exhibit significantly lower overall cognitive, emotional, and motor function scores than iron-sufficient peers [75,76]. This may be linked to diminished mesencephalocortical pathway function due to insufficient DA synthesis [77]. Extensive research demonstrates that infants with iron deficiency anaemia exhibit altered social-emotional behaviour, including increased vigilance, hesitancy, unhappiness, and maternal attachment, with reduced social interactions. Iron treatment has yielded emotional benefits [78,79]. Rats with iron deficiency during pregnancy or lactation display reduced dopaminergic (DAergic) neuron function in the nigrostriatal pathway [80,81], potentially explaining motor coordination deficits in iron-deficient children [82]. Additionally, inattention and even Attention Deficit/Hyperactivity Disorder (ADHD) in iron-deficient children may result from DA dysfunction. Iron supplementation can improve ADHD-related symptoms by increasing DA transporter density and activity. Model rats with induced brain iron deficiency exhibit decreased norepinephrine (NE) and 5-hydroxytryptamine (5-HT) levels [18], leading to neurochemical disturbances, anhedonia, anxiety, and social dysfunction during early development [83]. Collectively, these findings underscore the importance of maintaining brain iron homeostasis for normal neurotransmitter function, as iron deficiency can result in neurochemical dysfunction and a range of neuropsychiatric issues.

3. Iron accumulation and brain aging

The regulation of iron homeostasis is a complex process involving systemic, cellular, and molecular mechanisms. Maintaining safe iron levels is essential for bodily function [84]. The regulation of iron absorption, circulation, storage, and metabolism mitigates the adverse effects of iron dysregulation or abnormalities [85]. With aging, brain iron deposition is associated with changes in iron regulatory proteins, including decreased transferrin [86], impaired ferritin autophagy [87], and brain-derived hepcidin overexpression [88]. Recent research has increasingly focused on the relationship between iron and aging. Modulators of iron homeostasis may contribute to delaying aging and extending lifespan. Conversely, aging-related dysregulation of iron homeostasis is often linked to age-related diseases, including bone resorption and neurodegenerative disorders [84]. This section will delineate the progression of brain iron accumulation during brain aging.

3.1. Brain iron redistribution

Iron distribution in healthy adults is markedly heterogeneous. After measuring different regions of the human brain by graphite furnace atomic absorption spectrometry, it was observed that the iron concentration is the highest in the basal ganglia (putamen, caudate nucleus and globus pallidus), and the lowest in the pons, locus ceruleus and medulla [89]. While iron levels within the basal ganglia increase linearly with age, accumulation in the thalamus, pulvinar, precentral and occipito-temporal cortices follows a quadratic or exponential trajectory [90]. It should be noted that regardless of the increasing trend followed by iron content, subcortical regions showed higher iron deposition and higher spatial variation [91]. Through brain MRI detection and brain magnetic susceptibility, it was observed that iron gradually accumulate selectively in brain regions associated with motor (precentral and postcentral, premotor cortex), cognitive (prefrontal cortex, superior temporal gyrus, insula, precuneus), and visual (occipital gyri, cuneus, posterior cingulum, fusiform, calcarine and lingual

gyrus) functions [90]. A correlation between age-related iron content variations, diffusion, and memory function has been identified. Notably, moderate to low iron levels were observed in the hippocampus and caudate, while moderate to high levels were detected in the putamen and globus pallidus [92]. This pattern suggests various stages of iron-associated gliosis, ranging from astrogliosis, potentially affecting intracellular diffusion, to microgliosis and increased vascular permeability, which can impact diffusion from multiple sources [92]. Consequently, iron accumulation has been implicated as a contributing factor to cognitive impairment in humans [91]. Iron histochemical staining of the rat brain showed that oligodendrocytes possessed the highest iron content, which may be the primary cell type affected by iron homeostasis imbalance [93]. Although oligodendrocytes undergo division throughout life, the regenerative capacity of OPCs declines with age, impairing new oligodendrocyte generation and myelin restoration and potentially leading to accelerated iron accumulation and redistribution in the brain [94,95]. Additionally, whole-brain myelin water fraction (MWF) measurements have revealed a negative correlation between myelin content and iron content across most brain regions, with males exhibiting higher iron levels than females [96]. Different regions of the aging brain showed different expression of genes closely related to neuroinflammation, suggesting that each brain region may experience different levels of neuroinflammation [97,98]. In this case, the activation of astrocytes and microglia through the release of pro-inflammatory factor, increase the iron element expression and accelerate brain iron accumulation [99]. Immunofluorescence in mouse brains showed elevated levels of markers of brain inflammation associated with iron accumulation in white matter of the corpus callosum [100]. Furthermore, the inflammatory state after iron overload had a differential effect on the regional brain iron metabolism and distribution in mice [101].

3.2. Redox imbalance

Tissue and organ function decline with aging. Senescent cells contribute to age-related pathology by producing inflammatory cytokines, proteases, growth factors, and ROS [102]. As a marker of cellular senescence, ROS is implicated in DNA damage, inflammation, lipid peroxidation, mitochondrial dysfunction, increased cell membrane permeability, and cell autolysis [103]. Elevated ROS levels directly correlate with oxidative stress caused by redox imbalance [104]. Ferritin autophagy, a lysosomal process, facilitates ferritin degradation and ferroptosis induction. Senescent cells exhibit significantly higher iron content than non-senescent or immortalized cells due to defective lysosomal ferritin autophagy [102]. Notably, exposure to various senescent cells results in substantial ferritin-bound iron accumulation, elevated labile iron levels, and increased ROS production, despite normal extracellular iron levels [105]. Neuromelanin in the substantia nigra (SN) and locus coeruleus (LC) exhibits exceptional iron storage capacity. Iron transition from stable, soluble ferritin to hemosiderin and other highly reactive iron-containing hydroxides subjects neurons to oxidative stress [106]. Iron, a crucial trace element for diverse enzymatic activities, can accelerate the reaction between oxygen and electrons in the mitochondrial electron transfer chain (ETC) and catalyze the generation of a large number of ROS, including non-free radical hydrogen peroxide (H_2O_2) and various oxygen-centred free radicals such as superoxide anion ($O_2^{\bullet-}$), hydroxyl radical ($HO^{\bullet}$), and hydroperoxyl radical ($H/ROO^{\bullet}$) [107]. H_2O_2, the most reactive ROS species, is enzymatically produced by CYP450, cyclooxygenase (COX), and various oxidases (XO). It participates in non-enzymatic oxidation *via* the Fenton reaction, heavily reliant on free iron and copper, inducing cellular aging damage [108]. $O_2^{\bullet-}$ serves as the primary ROS source. In the presence of O_2^-, H_2O_2, and iron ions, highly reactive $HO^{\bullet}$ is catalyzed, inducing oxidative damage to lipids, proteins, and nucleic acids [109]. Mitochondrial ferritin (FtMt) serves as an important iron storage protein in mitochondria with ferroxinase activity, which can reduce the labile iron pool and inhibit the generation of ROS, thus protecting cells from iron-induced oxidative damage [110]. However, in aging cells, an imbalance in iron homeostasis frequently coincides with mitochondrial protein damage, which further exacerbates ROS production [111]. Subsequently, excessive ROS induces the reduction of membrane potential and the opening of permeability transition pore, affecting the replication, transcription and translation processes of mitochondria, as well as the energy conversion and material transport function of mitochondria [112]. Moreover, ROS extensively damages biomolecules such as lipids, proteins and DNA within the cytoplasm, seriously threatening the integrity of cell membrane and the normal operation of organelles [113]. These effects suggest that ROS, as highly active signalling molecules, regulate the process of cellular senescence through a complex interplay between mitochondria and cytoplasm.

3.3. Mitochondrial dysfunction

Mitochondria are essential eukaryotic organelles that regulate diverse metabolic and signalling pathways, including energy production, calcium homeostasis,

steroidogenesis, cell growth, apoptosis, and inflammation [114]. Among them, the ETC produces cellular ATP through a series of electron transfer reactions in a process known as oxidative phosphorylation (OXPHOS). This process occurs within the inner mitochondrial membrane, involving four respiratory chain (RC) complexes (I-IV) and ATP synthase (complex V) [115]. Electron transfer is a primary source of ROS, which both promote homeostasis signalling and induce cellular oxidative stress [116]. Mitochondria undergo morphological changes with aging, characterized by reduced respiratory capacity, decreased steady-state membrane potential, and impaired OXPHOS function [117]. Diminished RC capacity and function, coupled with decreased activities of complexes I and IV, lead to reduced OXPHOS efficiency, altered ATP production, and increased ROS generation [115]. This cascade causes mitochondrial oxidative damage, impairing mitochondrial dynamics and mitophagy, ultimately resulting in mitochondrial dysfunction [118]. Mitochondria serve as regulatory hubs for iron metabolism and homeostasis. Approximately 20–50% of intracellular iron enters mitochondria, primarily involved in iron–sulphur (Fe–S) cluster biogenesis and heme synthesis [119]. Both Fe–S clusters and heme are important for normal assembly and for optimal activity of the electron transfer complexes [120]. Notably, Fe–S deficiency in senescent cells leads to an increase in labile iron within mitochondria [121,122]. Simultaneously, these senescent cells also accompanied by heme deficiency, resulting in decreased mitochondrial complex IV and disruption of iron homeostasis, finally contributing to both mitochondrial dysfunction and neuronal decay [123]. Mitoferrin 1 (Mfrn1) and its homolog mitoferrin 2 (Mfrn2), mitochondrial solute carrier family metal transporters, are essential for mitochondrial iron transport [119]. Overexpression of Mfrn1 and Mfrn2 leads to mitochondrial iron accumulation and enhanced cellular iron uptake [124,125]. In the *Caenorhabditis elegans* model, knockdown of Mfrn1 gene expression can reduce mitochondrial iron content and mitochondrial ROS level, and significantly prolong the lifespan of the nematode [126,127]. These findings provide a new perspective for understanding the regulation of mitochondrial iron metabolism in aging.

3.4. Lipid peroxidation

Recent studies have identified an iron-dependent cell death called ferroptosis, mediated by dysregulation of iron homeostasis and lipid peroxidation [128]. Oxidative stress caused by iron accumulation can induce lipid peroxidation, which impairs cellular compartmentalization and ultimately leads to cell death by compromising membrane stability [128]. Lipid peroxidation is a biochemical process where oxidants, including both free radicals and non-radical species, target lipids containing carbon–carbon double bonds. This process generates various products, such as malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), with the latter considered a potent biomarker that can accelerate oxidative stress damage [114]. Brain tissue 4-HNE concentration increases significantly with aging, reacting with DNA, proteins, and other cellular components to influence the expression of aging-related signalling pathways, including NF-κB, Nrf2, Akt/PKB, and mTOR, ultimately leading to cellular senescence [129,130]. As essential components of cell membranes, lipids contain significant amounts of polyunsaturated fatty acids (PUFAs) and free cholesterol, rendering them particularly susceptible to oxidative damage mediated by reactive oxygen species [131]. ROS react with PUFAs to form lipid free radicals ($L^{\cdot}$), initiating lipid peroxidation and generating lipid reactive oxygen species (L-ROS), which can further promote oxidative stress [132]. Iron-related lipid peroxidation originates in the endoplasmic reticulum before progressing to the plasma membrane, disrupting ion balance, increasing membrane permeability, and promoting free iron accumulation [133,134]. Iron ions can enhance lipoxygenase (LOX) or proline hydroxylase (PHD, also known as EGLN) activity, enzymes responsible for steady-state lipid peroxide and oxygen levels [135]. When intracellular L-ROS exceed normal levels, lipid peroxidation and iron accumulation are concurrently activated, inducing ferroptosis [136]. Currently, antioxidants (such as Nrf2 activators, vitamin A, vitamin E) and iron chelators (such as M-30, α-LA) can mitigate oxidative stress, iron accumulation, peroxidation, and delay cellular senescence [137–139].

4. Iron overload and neurodegenerative diseases

Iron, as a redox-active metal, is essential for neuronal metabolism and energy production. However, neural tissues are susceptible to oxidative damage in the presence of iron excess and compromised antioxidant systems [140]. Iron overload adversely affects glutathione levels, induces lipid peroxidation, stimulates ROS production, triggers ferroptosis, and accelerates inflammatory changes, ultimately leading to neurotoxicity and impaired neuronal function [7,8]. Brain iron accumulation increases with age, and elevated iron levels have been detected in pathological regions of certain

Table 1. Effects and mechanisms of iron in neurological diseases.

Disease	Pathology	Mechanism and effect	Therapeutic agent	References
AD	Amyloid plaques formed by Aβ, NFT composed of hyperphosphorylation of Tau protein	Produce ROS to enhance oxidative stress, activate glia cells to induce neuroinflammation, and aggravate Aβ and Tau to promote neuronal death	GSH, Glu-Cys, TSG, DFO, and DFP	[145–150]
PD	Accumulation of α-Syn, loss of DArgic neurons	Induce oxidative stress, degrade proteasomes, impair mitochondrial function, promote α-Syn aggregation, and accelerate DArgic neuronal degeneration	DFO, Fer-1, and Lpx-1	[151–155]
HD	Misfolding of mHtt, degeneration of striatal neurons	Mediate oxidative stress, damage the endoplasmic reticulum and mitochondria, proliferate glial cells, and poison neurons	CoQ10, DFO, DFP, DFX, and Fer-1	[156–159]
FRDA	Recessive mutation of FXN protein gene	Produce ROS, peroxide lipid, enhance oxidative stress, and impair mitochondrial function	DFO, DFP, and Nrf2	[160–163]
ALS	Degeneration of motor neurons, proliferation of glial cells, accumulation of erroneous proteins	Induce oxidative stress, disrupt protein homeostasis, mediate neuroinflammation	Fer-1, Lip-1, DFO, DFP, Nrf2 and CuATSM	[164–169]

neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), Friedreich's ataxia (FRDA), Amyotrophic lateral sclerosis (ALS), Progressive supranuclear palsy (PSP) and Multiple system atrophy (MSA), suggesting a potential involvement of iron overload in their pathogenesis [141–144]. While the precise relationship between iron overload and neurodegenerative diseases requires further investigation, existing research strongly correlates the two, as summarized below (Table 1).

4.1. Alzheimer's disease

AD is a complex, progressive neurodegenerative disorder characterized by the extracellular accumulation of amyloid plaques composed of amyloid-β (Aβ) protein and the intracellular deposition of neurofibrillary tangles (NFTs) formed by hyperphosphorylated tau protein [170]. Aβ and tau proteins interact synergistically in AD pathogenesis, inducing neuronal destruction, apoptosis, and reduced synaptic communication, which likely underlies the memory impairment and cognitive decline observed in AD patients [145].

Iron deposition is one of the earliest reported brain chemical changes in AD patients, first discovered in 1953 [171]. Autopsy findings reveal iron accumulation in the hippocampus and frontal cortex, brain regions predominantly affected by AD proteinopathies [172]. Pathological neuronal iron accumulation in the brain of AD patients, can generatie ROS through the Fenton reaction, thereby triggering an oxidative stress response [173,174]. This oxidative stress will enhance IRP activity and increase free iron pool level, which eventually leads to neuronal damage [146]. It is noteworthy that TFR expression is decreased and ferritin expression is increased in AD brain, which may be related to cell type specificity [175–177]. Studies indicate that iron accumulation accelerates plaque and tangle formation, activates glia, and induces neuroinflammation *via* oxidative stress [147,148,178]. Iron imbalance can influence Aβ misfolding and tau hyperphosphorylation, with iron overload exacerbating Aβ and tau aggregation, ultimately contributing to AD [179,180]. MRI technology can now verify these findings [149]. Conversely, misfolded proteins can also facilitate brain iron deposition, thereby creating a vicious cycle that contributes to the progression of AD [181]. The Aβ protein exhibits a high affinity for binding iron, which enhances its redox activity and propagates neurotoxicity [182]. Additionally, hyperphosphorylated tau may further exacerbate iron accumulation in neurons by disrupting iron export mechanisms [150]. As the concentration of iron and levels of oxidative stress increase, the damage to glial cells becomes increasingly pronounced [148]. Oligodendrocytes, with their high iron content and low antioxidant levels, are particularly susceptible to oxidative stress damage [183]. In addition, activated by iron deposition, astrocytes and microglia release inflammatory mediators and aggravate oxidative stress, contributing to the progression of AD [181,184].

Glutathione (GSH) is a primary antioxidant in mammalian cells. It collaborates with glutathione peroxidase 4 (GPX4) to maintain iron homeostasis and inhibit ferroptosis [185]. Notably, glutamyl cysteine (Glu-Cys) and tetrahydroxystilbene-glucoside (TSG) supplementation restored the GSH-GPX4 antioxidant system, reducing ROS levels in AD patients and mitigating Aβ-mediated brain damage [186,187]. DFO also possesses antioxidant properties, reducing brain iron accumulation, inhibiting plaque formation, and dissolving existing Aβ sheets [188,189]. Furthermore, TFR1 knockdown alleviated iron overload and mitochondrial dysfunction in neuronal cells, while TFR1 overexpression produced opposite effects [190,191].

4.2. Parkinson's disease

PD is the second most common neurodegenerative disease after Alzheimer's disease. The most prominent pathological hallmarks are the accumulation of alpha-synuclein (α-Syn) and the loss of DAergic neurons in the substantia nigra pars compacta (SNpc) [192]. The aggregation of α-Syn is toxic [192,193], inducing selective changes in synaptic proteins, disrupting neuronal excitability and connectivity, ultimately leading to neuronal degeneration and death [151].

Numerous studies implicate oxidative stress, neuroinflammation, decreased antioxidant capacity, mitochondrial dysfunction, and lipid peroxidation damage as crucial pathways in PD pathogenesis [194–196]. α-Syn oligomers generate free radicals, inducing mitochondrial lipid oxidation and cell apoptosis, in a metal-dependent manner [197]. In the presence of iron ions, oxidative stress oxidizes Fe^{2+} to Fe^{3+}, further enhancing aggregation [152]. Iron binds to α-Syn, altering protein conformation, and iron-induced α-Syn aggregation is dose-dependent [198]. Moreover, iron regulation of α-Syn post-translational modifications influences its aggregation or oligomer formation [199]. The α-Syn-mediated reduction of Fe^{3+} to Fe^{2+}[153] increases intracellular Fe^{2+} levels, promoting α-Syn diffusion and aggregation through oxidative stress, ultimately leading to neuronal degeneration and death [200]. PD patients exhibit marked iron elevation in DAergic neurons. Neuromelanin (NM) particles, rich in iron, are found near these neurons in the SN of PD patients [201]. NM, a complex, insoluble brain pigment, binds iron ions and toxic substances, protecting DAergic neurons [202], particularly in the SNpc, LC, and vagus nerve dorsal motor nucleus, regions associated with PD's characteristic movement and performance [154]. When NM loses its iron chelating function (potentially due to iron saturation) or is released into neurons (possibly due to metabolic disorders), excess iron accumulates in DAergic neurons [193,203]. NM-mediated iron accumulation exacerbates oxidative stress, leading to proteasomal and mitochondrial dysfunction, accelerated α-Syn aggregation and misfolding, and lipid peroxide formation. TH is responsible for regulating the rate of DA synthesis, and iron is a cofactor necessary for TH activity [204]. However, excessive iron content in PD patients may overactivate TH and abnormally increase DA synthesis [198]. DA and its metabolites can be converted into toxic oxides and promote oxidative stress, causing damage to neurons [155,205]. These processes are linked to α-Syn accumulation, DAergic neuronal degeneration, and ultimately, PD [193,195].

α-synuclein is functionally linked to iron and lipid metabolism, suggesting a potential interaction between dysregulated α-synuclein and PD pathological markers related to ferroptosis. By regulating labile iron pool and inhibiting ferroptosis, DFO nanotablets can effectively reduce DAergic neuron loss and related behavioural disorders, which is expected to be a potential drug for the treatment of PD [206]. Notably, although the iron-chelating agent Deferiprone (DFP) can also reduce iron levels in the brain, it did not show a significant improvement in PD progression in clinical trials [207]. In addition, specific inhibitors of ferroptosis, such as ferrostatin-1 (Fer-1) and liproxstatin-1 (Lip-1), exhibit neuroprotective effects on dopaminergic neurons [208].

4.3. Huntington's disease

HD is an autosomal dominant neurodegenerative disorder characterized by an expanded polyglutamine (polyQ) repeat within the Huntington (HTT) gene [156]. Misfolded mutant HTT (mHtt) protein forms inclusion bodies, leading to progressive degeneration of striatal neurons in the basal ganglia, accompanied by glial proliferation, resulting in striatal atrophy and lateral ventricle enlargement, the neuropathological hallmarks of HD [157,209]. Quantitative magnetic susceptibility imaging reveals increased iron deposition in the basal ganglia of HD patients compared to healthy controls [210,211]. Notably, brain iron accumulation correlates with disease severity [158]. The basal ganglia exhibit high sensitivity to iron changes. Increased brain iron accumulation promotes mHtt aggregation, while iron overload-induced excessive ROS exacerbate oxidative stress, damaging the endoplasmic reticulum and mitochondria [212]. Mhtt-induced neuronal death activates microglia and glial cells, driving neuroinflammation and neuronal toxicity [213]. Iron is sensitive to inflammatory signals, increasing its expression in inflammatory environments [212]. Microglia in model mice exhibit increased labile iron, and conversely, high iron levels enhance microglial activation and neurodegeneration [159]. Iron overload-induced ferroptosis contributes to HD pathogenesis. Inhibiting ferroptosis-associated molecules and signalling pathways can significantly ameliorate HD symptoms and pathology. For instance, coenzyme Q10 and DFX alleviate symptoms and improve HD pathological manifestations [214]. Additionally, the ferroptosis inhibitor Fer-1 and its derivatives demonstrate efficacy in preventing cell death in HD brain slice models [19].

4.4. Friedreich ataxia

FRDA is an autosomal recessive inherited neurodegenerative disease caused by recessive mutations in the

frataxin (FXN) protein gene [215,216]. FXN is a mitochondrial protein involved in Fe–S cluster biogenesis, maintenance, and repair, effectively regulating oxidative stress [160]. Consequently, decreased FXN expression and levels in FRDA lead to mitochondrial dysfunction, oxidative stress, ROS accumulation, and ultimately, progressive nervous system damage.

FXN is a mitochondrial protein with a high affinity for iron, capable of storing this element and facilitating mitochondrial Fe–S cluster biogenesis [161]. Fe–S clusters are essential cofactors in mitochondrial respiration, widely present in ferredoxin and mitochondrial respiratory complexes. They regulate gene expression in response to oxidative stress, oxygen levels, and iron levels, and are integral to mitochondrial ROS production [217]. Consequently, FXN and Fe–S clusters are crucial for maintaining iron homeostasis and metabolism, acting as key regulators to prevent ferroptosis [218]. Inhibition of FXN expression accelerates free iron accumulation, mitochondrial iron overload, Fe–S cluster deficiency, and respiratory chain dysfunction, leading to excessive ROS production and significantly increased cellular ferroptosis [218]. Research on FRDA animal models has revealed elevated ROS levels, oxidative stress, and lipid peroxidation, mirroring observations in FRDA patients [162]. In this disease, free iron generates excessive ROS through the Fenton reaction, inducing oxidative stress. Additionally, FXN deficiency decreases intracellular cysteine, GSH synthesis, and GPX4 activity, resulting in harmful lipid hydroperoxide (LOOH) accumulation and further ROS overproduction [219].

Therapeutic strategies for Friedreich's ataxia primarily focus on increasing FXN levels or mitigating FXN loss, with antioxidants playing a crucial role [220]. Nrf2 is a key transcription factor regulating oxidative stress response. By modulating the expression of genes associated with ferroptosis and oxidative damage, Nrf2 promotes cell defense, accelerates iron storage, inhibits iron absorption, and reduces lipid and ROS synthesis [163]. Nrf2 downregulation in FRDA diminishes antioxidant gene expression and increases cellular susceptibility to oxidative stress, while Nrf2 inducers help prevent ferroptosis-mediated neurodegeneration [221]. Additionally, FRDA-induced labile iron accumulation in mitochondria suggests the potential therapeutic application of iron chelators [220].

4.5. Amyotrophic lateral sclerosis

ALS is the most prevalent motor neuron disease, typically characterized by simultaneous impairment of upper and lower motor neuron function, resulting in muscle weakness, muscle atrophy, and eventual paralysis [222]. The neuropathological manifestations are atrophy of nerve cells in the anterior segment of the spinal cord, reactive gliosis in the anterior horn, and protein aggregates containing various cytoplasmic inclusions [164]. Although the precise mechanism underlying motor neuron degeneration remains unknown, it has been established that multiple brain regions in ALS patients have increased tissue iron loading, most notably motor cortex, globus pallidus, and SN [165].

Studies have shown that the nervous system of ALS patients may detect elevated levels of lipid peroxidation products, as well as the antioxidant enzyme activity change, the change of the related parameters of the oxidative stress prompts the iron accumulation may participate in ALS pathologic process [223]. Furthermore, microglial stress mediated by ferroptosis induces non-cell autonomous neuronal death and accelerates the progression of ALS [224]. Brain MRI has found that the motor cortex of ALS patients has low signal intensity, which is related to the iron accumulation of microglia [166]. Spinal cord tissue examination has revealed increased ferritin and microglia activation in white and grey matter regions of ALS patients [225]. A possible link between microglial iron accumulation and neuronal degeneration is that iron is released after neuronal degeneration and death, and microglia maintains iron homeostasis in the brain by removing excess iron and storing it as ferritin [225]. Similarly, iron deposition and expression of iron-related proteins have been observed in both motor neurons and glial cells within ALS mouse models [167]. Neurons and glial cells may accumulate iron through different mechanisms: glial cells through TFR and ferritin, while neurons through DMT1 and other mechanisms; In addition, intracellular iron accumulation may also be associated with disruptions in axonal transport and mitochondrial dysfunction [167]. *In vivo* and *in vitro* studies have confirmed that protein misfolding in motor neurons can disrupt intracellular antioxidant systems, thereby promoting ferroptosis in neurons [226]. The inhibition of GPX4 activity has been shown to lead to motor neuron degeneration and subsequent paralysis [227]. Conversely, the overexpression of GPX4 can significantly delay the onset of symptoms in mice and enhance their motor function [168].

Ferroptosis-related inhibitors represent a promising therapeutic strategy for the treatment of ALS, as evidenced by numerous studies. Fer-1, Lip-1 and DFO can effectively inhibit lipid peroxidation and attenuate neuronal ferroptosis in ALS [228,229]. DFP has demonstrated favourable safety profiles and efficacy in preclinical mouse models as well as preliminary clinical

trials [230]. The Nrf2 activator is capable of upregulating the protein expression of GPX4, thereby inhibiting ferroptosis and alleviating neuronal degeneration associated with ALS [169]. Furthermore, CuATSM—a free radical trapping antioxidant—also modulates lipid peroxidation and ferroptosis, positioning it as a potential clinical candidate for ALS treatment [231].

5. Iron-sensitive MRI technology in the application of the nervous system

Iron-sensitive MRI techniques, primarily R2* relaxation imaging, susceptibility-weighted imaging (SWI), and quantitative susceptibility mapping (QSM), enable the non-invasive characterization of iron deposition within tissues. R2* relaxation imaging, a rapid and versatile relaxation measurement technique, exploits the paramagnetism of iron compounds, inducing local magnetic field inhomogeneities that increase tissue R2* values. This property allows for quantitative tissue iron content estimation through linear fitting. SWI, a magnetic resonance imaging sequence sensitive to local magnetic field changes, significantly enhances image contrast between tissues with different magnetic susceptibilities. It highlights paramagnetic materials (e.g. hemosiderin or deoxygenated haemoglobin) and diamagnetic materials (e.g. calcium), finding broad application in clinical diagnosis and treatment [232]. QSM, derived from SWI, employs dual-phase signal or gradient echo sequences to generate quantitative susceptibility maps for most tissues. Iron-sensitive MRI technology offers non-invasive quantitative tissue iron content assessment, representing a burgeoning research field within magnetic resonance (NMR) with promising applications in neural studies.

Brain iron accumulation is a critical factor in neurodegenerative diseases, yet brain iron levels are difficult to correlate with peripheral iron levels or iron regulatory proteins. Analyses of cerebrospinal fluid, serum, or plasma from PD patients reveal only minor and inversely related serum iron changes compared to autopsy brain substantia nigra iron levels [233]. In healthy individuals, substantia nigra SWI imaging demonstrates dorsolateral nigral hyperintensity (DNH) and bilateral hypointensity, resembling a 'swallow tail'. Increased brain iron deposition in PD patients results in DNH signal loss on SWI imaging, serving as a highly accurate PD diagnostic marker [234–236]. This phenomenon aids in early PD identification. Idiopathic rapid eye movement sleep behaviour disorder (iRBD), a PD prodrome, exhibits DNH signal loss in approximately 60% of patients [237]. Additionally, R2* relaxation imaging and quantitative susceptibility mapping (QSM) can assess substantia nigra iron content, supporting PD diagnosis and disease progression tracking [238,239]. Iron-sensitive MRI can differentiate various PD subtypes [239] and distinguish between aging manifestations, essential tremor, and other diseases [240,241]. Similarly, iron-sensitive MRI serves as a non-invasive complementary tool for Alzheimer's disease clinical diagnosis and treatment. R2* relaxation imaging and QSM measure cortical iron accumulation in AD patients [242] potentially aiding in novel AD therapy efficacy assessment [243]. Additionally, QSM's diamagnetic component measurement tracks AD-related indicators like Aβ accumulation, white matter demyelination, and cerebrospinal fluid (CSF) changes [244]. In addition, iron-related neuroimaging detects iron deposition in the nucleus accumbens (chronic migraine and migraine-related dysfunction biomarkers), white matter hyperintensities (WMH) associated with brain iron loss (aiding in cerebral small vessel disease diagnosis related to cognitive deficits), and other nervous system disease biomarkers [245–248]. This imaging modality assesses brain changes due to early infant and child iron deficiency [249,250] and tracks brain iron accumulation to evaluate cognitive and memory function changes during physiological aging [92,251].

While magnetic susceptibility changes can be used to determine iron accumulation, the method lacks specificity as brain tissue magnetic susceptibility is primarily influenced by iron [252,253]. Consequently, the application of iron-sensitive MRI in neurology remains limited [254], and faces challenges such as the standardization of data acquisition and processing, as well as the safety evaluation of contrast agents. Future research could focus on optimizing imaging technologies and developing novel contrast agents. For example, the development of Ferroptosis-targeted MRI agents suitable for the nervous system [255,256] to bind intracellular iron ions could significantly increase local magnetic susceptibility, providing more accurate imaging of neurological lesions. To fully realize the potential of iron-sensitive MRI in the neurological field, future research should establish precise correlations between iron-sensitive MRI data and iron-related neurological diseases. This can be achieved by correlating MRI susceptibility changes with disease-specific biomarkers and integrating R2*, SWI, QSM, and other neuroimaging data within a multi-centre collaborative framework.

6. Summary and prospect

Iron and iron-related proteins participate in diverse brain processes, from neonatal development to aging-related pathologies. However, the mechanisms regulating brain iron metabolism vary across brain regions,

developmental stages, and disease states, necessitating further investigation. Comprehending regional brain iron metabolism changes during development and aging is crucial for early detection and intervention of neurodevelopmental disorders, aging-related cognitive decline, and the development of targeted therapies. Research on brain iron alterations during neurodegenerative disease progression can inform the development of specific treatments, such as selective iron chelators. Iron-sensitive MRI technology holds promise for mapping brain iron distribution, enhancing our understanding of the nervous system and facilitating clinical diagnosis and treatment of iron-related neurological disorders. Nonetheless, further refinements in iron-sensitive MRI resolution and specificity are required.

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Authors contributions

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Compliance with ethics requirements

This article does not contain any studies with human or animal subjects.

Disclosure statement

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Data availability

Data availability is not applicable to this article as no new data were created or analyzed in this study.

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