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THE EFFECTS OF IRON DEFICIENCY ON NEUROTRANSMISSION AND COGNITIVE FUNCTION: A LITERATURE REVIEW

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ABSTRACT

Iron, though required by the body in only trace amounts, is quietly indispensable for the healthy maturation and continued function of the brain. Its passage into the central nervous system is no accident; rather, it is subject to rigorous control, with the blood–brain barrier's transferrin receptor system acting as a gatekeeper. When this delicate equilibrium is disturbed—whether by deficit or surplus—the consequences are far-reaching. Neuronal signalling falters, mitochondria become less efficient, and measurable drops in cognitive performance begin to appear. Among the neurotransmitter networks, the dopaminergic, serotonergic, and glutamatergic pathways seem especially sensitive to fluctuations in iron status, and their impairment is most evident in memory, learning, and behaviour. Infants and children, along with pregnant women and patients contending with chronic illness, are particularly vulnerable; for some, these neurodevelopmental effects may linger long after the original insult. While supplementing iron frequently reverses the deficiency, an overzealous approach can tip the scales toward toxicity. The art of clinical management lies in tailoring iron repletion to individual needs, ensuring robust neurodevelopment without courting the hazards of excess.

KEYWORDS

Iron Deficiency, Blood–Brain Barrier, Cognition, Transferrin Receptor, Neurodevelopment, Neurotransmitters, Supplementation, Neurotoxicity

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I. Introduction

Iron's biological significance is disproportionately large relative to its minute concentration within the human body. From the perspective of cellular physiology, iron is a master regulator: it quietly orchestrates electron transfers, underpins cellular respiration, and helps sustain genomic stability, not to mention its ongoing battle against the ravages of reactive oxygen species [1]. Within haemoglobin and myoglobin, iron ensures that oxygen reaches every tissue—including the energetically insatiable brain—while in mitochondria, it becomes an irreplaceable cog within iron–sulphur clusters and the respiratory chain. When these microscopic mechanisms falter due to iron deficiency, the result is a domino effect: ATP production drops, and the fundamental activities of the cell are disrupted [2,3].

Such disruptions are not merely academic. The body's delicate iron balance is essential for more than the avoidance of anaemia or overt physical decline. At the molecular level, insufficient iron undermines the cell's defences against oxidative injury and impairs the fidelity of DNA repair. These disturbances, whether acute or insidiously chronic, are particularly injurious to the nervous system. It appears that only the earliest phases of deficiency may be fully reversible; lingering shortfalls can leave enduring marks [1].

In the brain, where energy consumption is second to none, iron's importance is magnified. It is not simply a passive participant but a dynamic enabler of neural function. By acting as a cofactor for tyrosine hydroxylase and other critical enzymes, iron facilitates the biosynthesis of dopamine, noradrenaline, and serotonin—key neurotransmitters that influence mood, motivation, and cognition [4]. Reports from both bench and bedside suggest that without enough iron, neural communication falters. Patients and experimental animals alike demonstrate subtle lapses in executive function, reduced concentration, and even an increased propensity for depressive symptoms [5].

Iron's reach extends beyond neurotransmission. It is integral to the synthesis of cholesterol and essential lipids, which, in turn, are necessary for myelination—the process that dictates how swiftly nerves transmit their signals [6]. The stakes are particularly high in utero and during early childhood, when the developing brain is exquisitely sensitive to micronutrient deficits. Should iron deficiency arise at these critical stages, it can leave

permanent changes in the architecture and functioning of the cortex and hippocampus [7]. Structural neuroimaging now confirms what clinicians have long suspected: those who were iron-deficient as infants may carry deficits in grey matter volume and cognitive function years later, despite apparent biochemical resolution [5].

For adults, the threat of chronic iron deficiency is not confined to tiredness or anaemia. Increasing evidence implicates disturbed iron metabolism in the emergence of neurodegenerative diseases. For instance, Parkinson's disease has been linked to imbalances in iron and oxidative stress within the substantia nigra, while disrupted iron homeostasis and abnormal ferritin in cerebrospinal fluid have been observed in Alzheimer's disease [8,9]. The clinical community is only beginning to grasp the broader implications: iron deficiency may be a silent co-conspirator in a host of neuropsychiatric conditions, a notion now supported by mounting neurochemical and molecular evidence [10].

Iron deficiency is hardly a relic of the developing world; it remains a global concern, cutting across socioeconomic lines and affecting individuals at every stage of life. Diet, chronic illness, pregnancy, and childhood all contribute to this persistent challenge [2,7]. Its clinical effects are broad, extending well beyond blood counts and fatigue, to influence immunity, cognition, and emotional well-being. For clinicians and researchers alike, a deeper understanding of iron's multifaceted role in neurotransmission, neurodevelopment, and synaptic plasticity is essential. Only by clarifying these mechanisms can the medical community hope to refine prevention and treatment strategies and lessen the lasting cognitive burdens that accompany iron deficiency.

This review aims to synthesise emerging insights into how iron deficiency affects neurotransmission and cognitive function. Particular emphasis is placed on recent findings in molecular biology and neurochemistry, as well as the clinical consequences and therapeutic opportunities that follow from these advances.

Methods

This review is based on a broad and critical examination of the recent literature. The sources include not only primary research articles but also clinical trials and meta-analyses published in reputable, peer-reviewed journals. We made particular use of PubMed, Web of Science, and ScienceDirect, giving priority to studies that probe the molecular choreography of iron across the blood–brain barrier, and the fine balance maintained within neurons and glial cells. Considerable weight was given to clinical and epidemiological reports from groups at elevated risk of neurological complications from iron deficiency. Neuroimaging findings, neuropsychological test outcomes, and the results of intervention studies formed a key part of the evidence base. The synthesis aimed to move beyond mere description, with the goal of informing both practical clinical decision-making and broader public health policy on iron monitoring and intervention.

II. Iron Homeostasis in the Central Nervous System

The blood-brain barrier (BBB) is a highly selective border that precisely regulates the transport of substances from the blood to the central nervous system (CNS). Iron, as an element essential for the proper functioning of neurons and other brain cells, must be actively transported across this barrier in a strictly controlled manner. As detailed in Moos and Morgan's review, the pathway dependent on transferrin and its receptor (TfR) plays a key role in this process [11]. Proper regulation of iron levels in the brain is extremely important, as both its deficiency and excess are associated with the development of various neurological diseases.

The main mechanism of iron delivery to the brain is the transport of iron-bound transferrin (Fe^{3+}) across the transferrin receptor (TfR) present on the surface of endothelial cells of the BBB. The transferrin–TfR complex is internalized by endocytosis, after which iron is released in endosomes by acidification of the environment and then transported to the cytoplasm of endothelial cells by transporters such as divalent metal transporter 1 (DMT1). Iron is then released into the extracellular space of the brain, where it can be taken up by neurons and glial cells. Moos and Morgan emphasize that although the transferrin pathway is the dominant route of iron transport across the BBB, other potential mechanisms are the subject of intensive investigation. These include the transport of iron bound to lipoproteins or as free iron ions. However, the role of these alternative pathways in overall brain iron homeostasis is still less understood compared to the transferrin pathway [11].

Understanding the mechanisms of iron transport across the blood-brain barrier, with particular emphasis on the transferrin pathway, is crucial for understanding the pathogenesis of many neurological diseases associated with the dysregulation of iron metabolism.

Mechanism of iron uptake across the blood-brain barrier (BBB):

The mechanism of iron uptake across the blood-brain barrier (BBB) is primarily based on the uptake of the holo-transferrin complex by TfR1 receptors located on the luminal side of the cerebral vascular endothelium. After endocytosis of the complex, iron (Fe^{3+}) is reduced in the endosome to Fe^{2+} and then transported to the cytoplasm by the DMT1 transporter. From there, it can be exported to the brain (abluminal) side by ferroportin, with the participation of oxidases such as ceruloplasmin or hephaestin, which prevents toxic accumulation of free iron and oxidative stress [12]. Additional data indicate that, in addition to the classical reductive-transport pathway, there is also a possibility of transcytosis of the holo-transferrin complex across endothelial cells without the need for iron release into the cytoplasm. Such an alternative pathway may coexist and compensate for the reductive pathway depending on the metabolic needs of the brain and the local regulation of hepcidin, which affects the activity of ferroportin. Both mechanisms together provide precise control of iron distribution in the brain, minimizing the risk of toxic effects of its excess [13].

Regulation of iron transport across the blood–brain barrier (BBB):

The regulation of iron transport across the blood–brain barrier (BBB) is a complex process controlled by various mechanisms. Ferroxidases such as hephaestin and ceruloplasmin play a key role, enabling the release of iron from endothelial cells. Hepcidin inhibits this process by reducing the expression of iron transport proteins and causing its accumulation in BBB cells. In addition, astrocytes, by secreting iron-dependent signals, modulate iron release from the BBB, acting as sensors of the brain's needs. Studies in patients with restless legs syndrome indicate impaired iron regulation at the BBB level, which may be related to the improper functioning of proteins regulating iron transport in endothelial cells [14].

Regulation of iron levels in neurons and glia:

Maintaining an appropriate concentration of iron in neurons and glial cells is essential for maintaining oxidative balance and proper metabolic functioning of the central nervous system. Neurons, due to their high energy demand and participation in the synthesis of neurotransmitters, require a precise mechanism for controlling intracellular iron levels. Glial cells, especially astrocytes, act as local iron buffers, supporting the maintenance of homeostasis in the brain microenvironment. This regulation is based on the differential expression of transferrin receptors, divalent metal transporters (DMT1), as well as proteins associated with iron storage (ferritin) and export (ferroportin). A key role is also played here by post-transcriptional regulation mechanisms, in which iron response elements (IRE) present in mRNA and iron recognition proteins (IRPs) participate, enabling dynamic adjustment of gene expression to the current metabolic needs of neurons and glial cells [13].

The importance of ferritin, transferrin, TfR receptor, ferroportin:

The central element of maintaining iron homeostasis in the central nervous system are proteins involved in its transport, storage, and export. Transferrin, as a carrier protein, binds iron in the form of Fe^{3+} and delivers it to cells by interacting with the transferrin receptor (TfR), which enables precise delivery of iron to the places of its use. Ferritin, consisting of H and L subunits, is responsible for the safe storage of iron in a biologically inactive form, protecting cells from the toxic effects of free Fe^{2+} ions and the formation of reactive oxygen species (ROS). Ferroportin, as the only known iron transporter enabling its export from cells, regulates the level of iron available in the intercellular space and cerebral circulation. The coordination of these proteins is crucial for maintaining the balance between iron availability and toxicity in the brain, preventing pathological states associated with its deficiency or excess, which may contribute to the development of neurodegenerative diseases [10].

III. Iron Deficiency – Causes and Systemic Effects

Causes of iron deficiency.

Iron deficiency can result from a variety of causes, most commonly including dietary deficiencies, increased demand, acute or chronic blood loss, and malabsorption [15,16]. There are two basic types of iron deficiency: classic iron deficiency and functional deficiency. Classic iron deficiency is associated with the depletion of iron stores and is most often the cause of microcytic and hypochromic anemia, characterized by reduced heme synthesis and reduced oxygen transport capacity of the blood. Functional iron deficiency (FID), on the other hand, occurs when iron is present in the body, but its availability is limited by pathological factors, such as chronic inflammation or chronic diseases, which lead to excessive hepcidin expression and blockage

of iron release from cellular stores. FID can manifest as anemia or other metabolic disorders without a clear deficiency of iron stores [17]. Inadequate dietary iron intake, especially in populations with limited access to animal products, leads to iron deficiency, which is essential for maintaining the body's metabolic balance. A diet poor in this nutrient is also common among vegans, populations consuming a monotonous plant-based diet, which contributes to the depletion of reserves and the consequences associated with its deficiency. Iron deficiency in nutrients occurs when physiological requirements cannot be met by the absorption of iron from the diet [18,19].

Iron is an important component of hemoglobin in red blood cells, which is responsible for transporting oxygen in the body. During bleeding, we observe a significant decrease in it. If there is a large loss of blood, iron stores in the body can be depleted, which results in iron deficiency and further anemia [18]. Its losses are often associated with acute bleeding. A study conducted in the USA assessed the incidence of subsequent iron deficiency (ID)/iron deficiency anemia (IDA) or anemia on admission to the hospital and/or during hospitalization in patients with acute gastrointestinal bleeding (GIB). 307 adult patients were followed for 3 months. The incidence of iron deficiency/anemia related to it at some point during hospitalization occurred in 92% of patients with GIB, i.e. 282/307 patients. Another study conducted in Romania in 2010 on 382 patients hospitalized due to: 51% UGIB (Upper gastrointestinal bleeding), 49% LGIB (Lower gastrointestinal bleeding) showed mild anemia (Hb ≥ 10 g/dl) in 17% (65/382), moderate (Hb 7–10 g/dl) in 39.5% (151/382) and severe anemia (Hb ≤ 7 g/dl) in 26.7% (102/382) of patients. This confirms that acute bleeding should be considered as one of the causes of iron deficiency, against the background of which anemia may develop. Many similar patients therefore require iron supplementation to treat and prevent these deficiencies [20]. It is worth adding that anemia occurs in almost all patients after severe trauma and persists even after the initial acute blood loss has subsided. The etiology is multifactorial. After acute trauma, there is a systemic inflammatory response and inhibited growth of erythroid progenitor cells, impaired iron regulation despite adequate stores, altered erythropoietin response, and prolonged mobilization of hematopoietic progenitor cells from the bone marrow to the injured tissue. Anemia is therefore not limited to those who experience trauma with acute blood loss but is common among non-injured critically ill patients as well as in those with chronic disease [21].

With regard to chronic blood loss, both overt (e.g., menorrhagia, gastrointestinal bleeding) and occult forms should be taken into consideration. Notably, up to one-third of women of reproductive age experience heavy menstrual bleeding (HMB). This clinical entity is a major contributor to iron deficiency (ID), and in more severe cases, iron deficiency anemia (IDA). It is estimated that the cumulative volume of menstrual blood loss frequently exceeds 80 ml per cycle; however, accurate quantification is challenging. The downstream effects of chronic blood loss include impaired well-being, diminished quality of life, and, most importantly, compromised overall health status in women. In its mild form, iron deficiency may be clinically silent. When symptomatic, it typically manifests as fatigue, generalized weakness, exertional dyspnea, headaches, pica, alopecia, brittle nails, cold intolerance, and restless legs syndrome. Cognitive impairment is also documented, with anemia-related declines in neurocognitive performance adversely affecting occupational productivity. Therefore, both physical and cognitive functioning may deteriorate, while fatigue intensifies. Importantly, these disturbances may improve upon iron supplementation [18].

Interestingly, disturbances in iron metabolism may also result from parasitic infections such as hookworm. Adult forms of these parasites colonize the small intestine of the host and consume blood, leading to chronic iron deficiency anemia, which can ultimately impair growth and contribute to cognitive deficits [22]. Another important etiology of iron deficiency is malabsorption syndromes, such as celiac disease, Crohn’s disease, or conditions following intestinal resections. These disorders markedly restrict iron absorption in the small intestine, predominantly within the duodenum and the proximal jejunum. In celiac disease, the proximal duodenum is commonly affected, resulting in impaired absorption and subsequent iron deficiency anemia. Additionally, among celiac disease patients with refractory IDA, the incidence of enteropathy-associated T-cell lymphoma is higher compared to the general population [16]. Furthermore, chronic inflammatory states may decrease intestinal iron absorption by inducing hepcidin—a key regulator of systemic iron homeostasis—which inhibits iron release from enterocytes and macrophages, thus promoting the development of functional iron deficiency [23]. In chronic kidney disease (CKD), renal anemia is a prevalent complication, primarily due to reduced erythropoietin synthesis and impaired iron absorption, which further deteriorate over time owing to persistent inflammation. Both absolute and functional iron deficiencies play a critical role in the pathogenesis of anemia associated with CKD. Absolute iron deficiency refers to the depletion of total body iron stores, whereas functional deficiency is characterized by impaired utilization of

available iron. Contributing factors include chronic blood loss, reduced gastrointestinal absorption, and ongoing inflammation [24].

Epidemiology

Iron deficiency represents a global health issue of substantial epidemiological significance, particularly within selected population groups. Approximately one in four individuals worldwide is affected by anemia, with iron deficiency accounting for nearly 50% of all anemia cases. The risk of iron deficiency is markedly higher in developing countries [25]. Children—especially during periods of rapid growth and infancy—are particularly susceptible to iron deficiency due to increased metabolic demands and limited dietary iron intake. Iron deficiency anemia most frequently occurs in children aged 9 months to 3 years and during adolescence, periods characterized by elevated requirements that are often not fully met by dietary intake [15]. Adolescents and individuals adhering to vegan diets are also at increased risk due to the often insufficient iron content in their diets [18]. The clinical manifestations of iron deficiency range from mild, asymptomatic states to pallor, poor appetite, fatigability, lethargy, exercise intolerance, irritability, and dizziness. More severe forms may be associated with tachycardia, dyspnea, sweating, or poor capillary refill. Notably, the occurrence of anemia during early childhood can lead to neurodevelopmental impairment and cognitive deficits, which may not always be fully reversible even after iron repletion. Despite a declining incidence, iron deficiency anemia remains a common cause of anemia among young children and adolescents, particularly in developing countries. Therefore, prevention of iron deficiency in these vulnerable populations remains of paramount importance [15]. In Western countries, the prevalence of IDA is highest during two pediatric periods: between the first and third years of life (2.3–15%), and during adolescence (3.5–13% in males, 11–33% in females). Among adults, the prevalence is less than 1% in men under 50 years, 2–4% in men over 50, 9–20% in menstruating adolescent girls and young women, and 5–7% in postmenopausal women [16].

Pregnant women constitute another high-risk group due to the increased iron demand associated with fetal development and maternal blood volume expansion [7]. Pregnancy exerts a significant impact on maternal iron status, even in well-resourced populations that are generally supplemented with iron. Iron deficiency affects a substantial proportion of pregnant women worldwide, with potentially serious consequences for both perinatal and neonatal outcomes. The prevalence of iron deficiency (ferritin <15 μg/L) increases with gestational age—by 4.5%, 13.7%, and 51.2% at 15, 20, and 33 weeks of gestation, respectively. Therefore, it is recommended that women undergo early pregnancy screening for iron status, with a suggested ferritin target concentration of >60 μg/L [26].

In the elderly, iron deficiency is associated with increased morbidity and mortality. It frequently coexists with chronic diseases (such as heart failure and inflammatory conditions [18]), malabsorption syndromes, and dietary changes, all of which increase the risk of anemia and its clinical complications. In the European population aged ≥70 years, the prevalence of iron deficiency reaches 27% [27]. According to WHO data, iron deficiency affects over 1.6 billion people globally, making it one of the leading causes of anemia and impairment of physiological function worldwide.

IV. The Impact of Iron Deficiency on Neurotransmission

Iron plays a fundamental role in the synthesis and metabolism of key neurotransmitters, directly affecting the proper functioning of the nervous system and cognitive processes [4]. Numerous neurotransmitter systems interact in the human body, with most of them being modulated, to a greater or lesser extent, by each other. Some of these systems are significantly more dependent on iron levels than others.

Dopamine

Dopamine is a catecholamine neurotransmitter synthesized primarily in neurons and the adrenal medulla. Its direct precursor, levodopa (L-DOPA), is produced from tyrosine by tyrosine hydroxylase, with oxygen, iron (Fe^{2+}), and tetrahydrobiopterin as cofactors, or indirectly from the amino acid phenylalanine via phenylalanine hydroxylase and the same cofactors. Furthermore, iron serves as a cofactor for monoamine oxidase (MAO), the enzyme responsible for the degradation of dopamine and other monoamines, which further regulates neurotransmitter homeostasis. Dopamine regulates the reward system, sleep, motor functions, and cognition, and plays a key role in certain pathological states, such as psychosis. Iron deficiency anemia alters dopaminergic neurotransmission in specific brain regions, resulting in dysregulation of these functions [28,29].

Serotonin

Similarly to dopamine, the synthesis of serotonin requires iron as a cofactor for tryptophan hydroxylase, the enzyme converting tryptophan to 5-hydroxytryptophan (5-HTP), a precursor of serotonin. Serotonin regulates mood, anxiety, depression, emotional stress responses, as well as sleep and pain perception. Most serotonin in the human body is found in the peripheral pool and is produced by enterochromaffin cells in the gut [4]. Iron deficiency can result in decreased serotonin levels, reduced serotonin transporter density, or impaired regulation of serotonin metabolism, potentially leading to dysregulation of mood, emotional processes, and cognitive functions [30].

GABA and Glutamate

Iron indirectly affects the GABAergic (γ-aminobutyric acid) and glutamatergic neurotransmitter systems, which are the principal inhibitory and excitatory transmitters in the central nervous system, respectively. Disruption of iron homeostasis can impact the activity of enzymes involved in the synthesis and metabolism of these neurotransmitters, as well as modulate the expression of their receptors, ultimately disturbing the balance between inhibitory and excitatory neurotransmission. This imbalance may result in cognitive deficits and an increased risk of neurotoxic states [4,30]. Notably, iron serves as an essential enzymatic cofactor for, among others, tyrosine and tryptophan hydroxylases, which are required for the synthesis of catecholamines and serotonin [4]. Its deficiency leads to decreased GABA synthesis, as observed in animal models, particularly in the hippocampus—a brain region crucial for memory and learning.

Changes in Neurotransmitter Receptor and Transporter Expression

Iron deficiency has been associated with alterations in the expression of receptors for neurotransmitters, such as dopamine (D1, D2), serotonin, GABA, and glutamate receptors. Research indicates that iron deficiency can reduce the density of dopamine receptors, thereby disrupting signaling within the limbic system and cerebral cortex [4,28,29]. Similar changes in the expression of neurotransmitter transporters, responsible for reuptake, can disrupt synaptic homeostasis, contributing to cognitive and emotional deficits [29,31]. Iron modulates the transcription and translation of membrane proteins responsible for monoamine transport, and its deficiency may impair the efficiency of dopaminergic and serotonergic pathways [4].

Impact of Iron Deficiency on Mitochondrial Function and Oxidative Stress

Iron is crucial for normal mitochondrial function—organelles responsible for cellular energy production. It is indispensable for the function of respiratory chain enzymes such as NADH:ubiquinone oxidoreductase, succinate dehydrogenase, and cytochromes. These proteins contain prosthetic groups in the form of iron–sulfur (Fe–S) clusters or heme, the activity of which is severely compromised in the absence of iron. Loss of these functions leads to reduced oxidative phosphorylation efficiency, limiting ATP production and decreasing the cell's overall energetic capacity [31]. Moreover, iron deficiency impairs the biosynthesis of Fe–S clusters themselves, resulting in mitochondrial enzyme instability and disruption of electron transport in the respiratory chain. Consequently, the production of reactive oxygen species (ROS), such as superoxide anion and hydrogen peroxide, increases, exerting toxic effects on proteins, membrane lipids, and mitochondrial DNA. Such damage is significantly involved in the pathogenesis of neurodegenerative disorders, including Alzheimer's and Parkinson's disease [35,36].

Beyond proteins directly participating in cellular respiration, iron is a key cofactor for diiron monooxygenases and Fe(II)- and 2-oxoglutarate-dependent dioxygenases. Examples include members of the ALKBH protein family (ALKBH1, ALKBH7), which regulate cell death processes and mitochondrial tRNA modifications. Iron scarcity impairs their activity, disturbing cellular homeostasis and mitochondrial translation quality [35].

In iron deficiency anemia, erythropoiesis is limited, leading to decreased oxygen-carrying capacity of the blood and secondary tissue hypoxia. This directly reduces the activity of iron-dependent enzymes not only in mitochondria but also in skeletal muscle, liver, and heart, thereby impairing oxygen utilization in these tissues [37]. Mitochondrial morphology is also altered: mitochondria become enlarged, rounded, and their cristae become shallower. These structural changes impact the organelle's bioenergetic efficiency, promoting further metabolic dysfunction. Studies have also demonstrated increased mitochondrial DNA fragmentation under conditions of both iron deficiency and overload, highlighting the extraordinary sensitivity of mitochondrial genomes to iron homeostasis disturbances [38,39].

V. Consequences of Iron Deficiency for Cognitive Function

It is well established that iron deficiency leads to alterations in both behavioral and developmental domains through its impact on neurotransmitters such as serotonin, norepinephrine, and dopamine [31,32]. Moreover, studies in rodent models have shown that behaviors mediated by dopamine—such as neophobia during periods of reduced brain iron—can be persistent and may not resolve completely even after iron repletion. Increased responsiveness to novel stimuli has been attributed to permanent damage to dopaminergic pathways. Additionally, it has been suggested that changes within the striatal dopaminergic system may affect the development of the basal ganglia, a structure essential for motor, cognitive, and memory-related functions [32]. Iron deficiency induces behavioral changes that may become apparent as early as infancy and, if left uncorrected, can have long-lasting effects extending into adulthood [31,32].

There is mounting evidence that brain iron deficiency during early life has numerous consequences for neurochemistry and neurobiology. Although the biological basis of behavioral and cognitive developmental delays observed in infants with iron deficiency is not yet fully elucidated, abnormalities in neurotransmitter metabolism, impaired myelin formation, and altered cerebral energy metabolism are all implicated. Recent studies indicate that iron deficiency slows neuronal processing in the central nervous system, which is a key component of neuronal dysfunction associated with this condition [32].

The mechanisms by which iron deficiency affects behavior include disruptions in the hippocampus, striatum, and key neurotransmitters. The hippocampus is essential for memory, learning, and other higher cognitive processes. In contrast, the striatum participates in executive functions such as planning, inhibitory control, sustained attention, working memory, emotion regulation, memory storage and retrieval, motivation, and reward. It is now recognized that iron deficiency alters both behavioral and developmental aspects via its effects on neurotransmitters, particularly serotonin, norepinephrine, and dopamine [31].

Memory, learning, and concentration deficits

Shah et al. demonstrated that iron deficiency induces changes in the hippocampus, corpus striatum, and monoamine levels that lead to anxiety, depression, sleep disorders, and psychotic disorders [40]. Furthermore, a recent study by Korczak et al. confirmed the long-term effects of early iron deficiency on neurodevelopment, showing that cognitive and behavioral deficits may persist even years after the initial deficiency has been corrected [41]. Beard's classic work indicated that iron deficiency is associated with impaired memory, learning, and concentration, which can be partially—but not always fully—reversed by later iron supplementation [31].

Cognitive development in children

It has been demonstrated that iron deficiency in infants is associated with an increased risk of mild to moderate intellectual impairment, as well as a negative impact on neurobehavioral development [32,41]. Chronic iron deficiency in children has been linked to significantly lower scores in language, environmental sound perception, and motor skills compared to infants with adequate iron status [41]. Furthermore, young adults who experienced chronic and severe iron deficiency in early childhood were found to have persistent deficits in executive functioning and recognition memory [41]. Iron deficiency in children may affect both neuropsychological and socio-emotional functioning, and in some cases may contribute to the development of antisocial behavior. The timing of deficiency is critical; if it occurs early in life, it can lead to developmental delays. Research has shown that even iron supplementation may not yield expected benefits if the deficiency was present early and persisted for an extended period. The most frequently observed behaviors in infants and young children with iron deficiency include wariness and hesitation in social interactions, reduced expression of positive affect, and decreased social engagement [32,41].

Long-term vs. Reversible deficits

Available studies indicate that the effects of iron deficiency on neuronal functioning can be irreversible. If deficiency occurs very early in life or persists for a significant duration, its consequences are not reversible, even with iron supplementation [41]. This was confirmed by a study conducted by Lukowski et al., which evaluated the long-term impact of early iron deficiency on executive functions and recognition memory. Neurocognitive assessments included tests of inhibitory control, cognitive flexibility, planning, selective attention, and working memory. Results showed that, despite 20 years having passed since iron deficiency treatment in early childhood, specific cognitive deficits remained evident in participants. These difficulties are consistent with dysfunction of frontostriatal circuits and the hippocampus.

This study suggests that disruptions in neurological development during the first two years of life may have a significant impact on long-term cognitive functioning, including recognition memory. Additionally, it underscores the importance of iron deficiency prevention beginning in the prenatal period, as long-term consequences may persist even if the deficiency is detected and treated early [41].

Clinical Presentation and Evidence from Research (e.g., Neuropsychological, fMRI, EEG Studies)

Studies have shown that the hippocampus—a brain region responsible for learning and memory processes—is particularly sensitive to iron deficiency [40]. The use of neuroimaging techniques such as event-related potentials (ERP) has enabled the assessment of brain function. Utilizing this non-invasive method of recording electrical brain activity, it has been demonstrated that infants with adequate iron status display electrophysiological signatures of maternal voice recognition, whereas such responses are absent in infants with fetal or neonatal iron deficiency [32]. These results indicate that early-life iron deficiency adversely affects recognition memory and highlight the unique vulnerability of the developing hippocampus to iron deficiency.

Another study by Lien et al. also demonstrated the impact of iron deficiency on the hippocampus in the developing brain. It was shown that DNA methylation—a process critical for neuronal differentiation and maturation in the developing central nervous system—also plays a key role in memory and cognitive functions in the adult brain. This was the first study to provide evidence that DNA methylation may serve as an epigenetic mechanism contributing to dysregulated gene expression in the hippocampus of young animals with iron deficiency. However, it should be noted that this study was conducted exclusively in an animal model.

VI. Interventions and Therapeutic Options

In response to growing awareness of the impact of iron deficiency on nervous system function and cognitive processes, a range of therapeutic strategies has gained significant importance in clinical practice. The most commonly used treatment modality is oral iron supplementation. However, for selected patient groups—such as individuals intolerant to oral formulations or those with chronic illnesses—intravenous iron supplementation is recommended. Food fortification with micronutrients is another possible alternative.

Oral iron supplementation remains the first-line intervention. Clinical studies demonstrate that even in women without overt anemia but with iron deficiency, a one-month course of supplementation (80 mg elemental iron daily) significantly reduces fatigue [42]. The effectiveness of oral supplementation has also been confirmed in children, where improvements in mental development test scores and intelligence quotient (IQ) have been observed, particularly in those with iron deficiency or anemia [43]. A meta-analysis of 32 clinical trials involving over 7,000 children aged 6–12 years showed a positive effect of supplementation on cognitive function, concentration, and intelligence [44].

Currently, many patients struggle with inflammatory bowel disease, have undergone bariatric surgery, or do not tolerate oral preparations. In such cases, intravenous iron administration is a recommended alternative. A randomized clinical trial demonstrated that administration of 800 mg intravenous iron (iron(III)-hydroxide sucrose complex) significantly reduced fatigue in premenopausal women with ferritin ≤50 ng/mL and normal hemoglobin. The greatest effect was observed in women with ferritin <15 ng/mL [45]. Another study found that iron-deficient, non-anemic patients showed significant improvement in fatigue just four weeks after intravenous supplementation, with sustained improvement after 12 weeks of therapy [46].

In summary, although oral supplementation is the first-line method due to its availability and low cost, intravenous preparations are an effective and safe alternative in complex or refractory cases.

Iron plays a critical role as early as the fetal stage—it is necessary for neurogenesis, neuronal differentiation, and the development of brain structures such as the hippocampus and prefrontal cortex. Maternal iron deficiency during pregnancy can lead to abnormal neuronal organization and impaired neurotransmission, even if the newborn shows no signs of anemia at birth [47,48]. Neuroimaging studies of children born to mothers with low third-trimester ferritin levels reveal reduced hippocampal volume and decreased prefrontal cortex activity [47]. Iron supplementation during the second and third trimesters led to improved cognitive function in children at four years of age, especially in those born to mothers with iron deficiency [49].

The first two years of life are particularly crucial for brain development. Iron deficiency during this time can result in permanent neurological deficits, even if anemia is later corrected [47].

Iron is an essential element for nervous system function, but excess iron can have serious neurotoxic consequences. Free iron ions (Fe^{2+}) can initiate the formation of free radicals via the Fenton reaction, leading

to damage of membrane lipids, proteins, and DNA [50]. Disturbed iron homeostasis is implicated in the pathogenesis of neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis. In Parkinson's disease, a local increase in iron concentration is observed in the substantia nigra, correlating with the loss of dopaminergic neurons [10]. The risk of neurotoxicity is particularly important in individuals with metabolic disorders such as hemochromatosis. Nevertheless, caution is warranted even in patients without such conditions—especially with intravenous supplementation. Exceeding the required dose can result in non–transferrin-bound iron (NTBI), which is biologically active and can cross the blood–brain barrier [51].

Cohort studies have shown that high plasma ferritin in older adults correlates with reduced hippocampal volume and worse performance on cognitive function tests [52].

In summary: Iron supplementation should be closely monitored and individually tailored. Both iron deficiency and excess can negatively affect the nervous system. The prenatal period and the first years of life are especially sensitive to disturbances in iron metabolism. Intravenous supplementation is an effective alternative but carries a higher risk of adverse effects and requires careful supervision.

VII. Summary and Conclusions

This literature review confirms the essential role of iron as a trace element required for the proper functioning of the central nervous system. Iron deficiency significantly impacts neurotransmission, particularly affecting the synthesis of dopamine and serotonin as well as the balance of GABAergic and glutamatergic systems. Children and pregnant women are especially vulnerable to iron deficiency. Early diagnosis and iron supplementation are crucial to avoid the negative consequences of deficiency; however, iron excess may induce neurotoxicity, underscoring the necessity of precise therapeutic monitoring.

Despite numerous studies, many areas require further in-depth investigation. Among these, attention should be directed toward the molecular mechanisms linking iron deficiency to disturbances in neurotransmission and their specific manifestations across different brain regions. Data on the long-term effects of supplementation are also lacking, especially with regard to interactions with other micronutrients and environmental factors. Further research is needed to develop new diagnostic methods for the early detection of subclinical deficits, as well as to optimize therapeutic strategies that minimize the risk of neurotoxicity.

The introduction of systematic monitoring of iron metabolism, especially in at-risk groups, may substantially improve outcomes and cognitive function in these patients. Prevention of iron deficiency, including nutritional education, should be an integral part of care. Furthermore, clinicians should be aware of the potential neurotoxic consequences of excessive supplementation, which requires an individualized approach to therapy.

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