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Iron and Mechanisms of Emotional Behavior

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Abstract

Iron is required for appropriate behavioral organization. Iron deficiency results in poor brain myelination and impaired monoamine metabolism. Glutamate and GABA homeostasis is modified by changes in brain iron status. Such changes not only produce deficits in memory/learning capacity and motor skills, but also emotional and psychological problems. An accumulating body of evidence indicates that both energy metabolism and neurotransmitter homeostasis influence emotional behavior, and both functions are influenced by brain iron status. Like other neurobehavioral aspects, the influence of iron metabolism on mechanisms of emotional behavior are multifactorial: brain region-specific control of behavior, regulation of neurotransmitters and associated proteins, temporal and regional differences in iron requirements, oxidative stress responses to excess iron, sex differences in metabolism, and interactions between iron and other metals. To better understand the role that brain iron plays in emotional behavior and mental health, this review discusses the pathologies associated with anxiety and other emotional disorders with respect to body iron status.

Keywords

anxiety; dopamine; emotional behavior; GABA; glutamate; neurotransmitter; norepinephrine; oxidative stress; prefrontal cortex; serotonin

1. Introduction

Iron is required for numerous vital functions, including oxygen transport, cellular respiration, immune function, nitric oxide metabolism and DNA synthesis [1]. Iron deficiency is the most prevalent single nutrient deficiency worldwide [1,2] and results in anemia, decreased immune function, retarded growth, and impaired thermoregulation [1,3]. The metal also plays a critical role in proper brain morphology, neurochemistry, and

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bioenergetics [4]. Poor brain myelination resulting from iron deficiency in early development has long-lasting effects on behavioral functions [5-9]. Iron is vital in neurochemical circuits including monoaminergic systems [10-20] and glutamate and γ-aminobutyric acid (GABA) homeostasis [21]. Energy metabolism is also altered by brain iron status [21]. For example, cytochrome c oxidase is reduced in prenatal iron deficiency, leading to impaired hippocampal metabolic function [22]. Iron is a cofactor for tyrosine hydroxylase and tryptophan hydroxylase, enzymes that are responsible for dopamine and serotonin synthesis, respectively. Monoamine oxidase activity is also lower in humans and rats with iron deficiency anemia [23-26]. Since monoamines and GABA are involved in the regulation of mood, neuronal activity and anxiety [26-28], it is reasonable to assume that emotional behaviors are strongly affected by brain iron levels, and especially by iron deficiency conditions. Since many studies have evaluated the role of iron in motor coordination and learning/memory function, the current review focuses on emotional behavior in the context of iron status and the potential underlying molecular mechanisms.

2. Brain iron

Brain iron concentrations are highest in the substantia nigra, globus pallidus, nucleus caudate, red nucleus and putamen [29]. The rapid accumulation of iron in these areas is required for the development of the brain and may significantly contribute to behavioral organization [29]. Within the brain, iron is particularly concentrated in the basal ganglia, an area highly influenced by dopamine and GABA metabolism [26-28]. Therefore, the functions of this brain region are very susceptible to changes in iron status. Not only is the distribution of iron region-specific, the sensitivity of various brain regions to iron deficiency differs during different stages of neurodevelopment [30,31]; during the mid and late neonatal periods in rodents (equivalent to human ages 6-12 months), iron content significantly decreases by 25% in the cortex, striatum and hindbrain after a short period of feeding a low-iron diet, whereas the thalamus shows only a 5% reduction [1]. During postweaning iron deficiency, the thalamus becomes more sensitive to dietary iron, suggesting that there is a prioritization of brain iron distribution during development [1].

3. Iron deficiency

Given the susceptibility of the developing brain along with the huge prevalence of iron deficiency, it is important to understand the role of iron in behavioral and mental health. There is strong evidence that iron deficiency causes developmental delays in young children [32]. Iron deficiency is also associated with cognitive alterations in adolescents [33]. Although the condition of iron deficiency can be later corrected by supplementation, behavioral alterations persist [10]. Iron-deficient children have increased anxiety and/or depression with social and attentional problems [34]. An accumulating body of evidence has demonstrated that iron deficiency is closely associated with altered brain homeostasis in both myelination and neurotransmission, especially monoamine metabolism [1]. Studies using rodent models of iron deficiency have also revealed a strong relationship between behavioral abnormalities and altered dopamine metabolism in the striatum [10,35]. Finally, early iron deficiency can also influence the glutamatergic system and energy metabolism [22,36,37].

Human studies link anxiety-driven behavior to poor iron status. For example, increased fearfulness is found in anemic infants despite iron therapy [38]. Infants with marginal iron deficiency also have increased fearfulness [39]. However, mixed results have been reported for behavior in iron-deficient rats; anxiety is elevated [40] or unchanged in adult rats that were formerly iron-deficient [41]. Beard *et al* [40] examined anxiety-related behaviors in a light/dark box study of iron-deficient rats at 6-wk of age. This group found that iron-deficient rats moved four times more rapidly into the dark compartment, but the time spent in the dark compared with the light compartment was not different from that of control rats. The iron-deficient rats also spent less time in the center of in open field box, indicating increased fearfulness and anxiety [40]. The authors argue that the young rat is a model organism for behavioral studies to explore the influence of iron deficiency on brain function, particularly given the similarity of behaviors observed in iron-deficient children [38,42]. When examined by elevated plus maze, young male rats with dietary iron deficiency demonstrate reduced time in and entry to the open arms [20], supporting the idea that iron deficiency increases anxiety.

Ultrasonic vocalization also has been used to test anxiety in rat pups born to iron-deficient or control dams [41]. Maternal iron deficiency was associated with more distress calls, consistent with the idea that postnatal iron deficiency induces anxiety-like behaviors [40]. When supplemented with dietary iron on PND 10, the formerly iron-deficient rats did not show anxious responses on PND 99, suggesting that iron repletion can normalize anxiety-like behavior [41]. This observation contrasts with findings that early iron deficiency during the pre-weaning period followed by iron repletion results in persistent hypoactivity in an open field on PND 21 or PND 49 [17,40,43]. Eseh and Zimmerman offer potential explanations [41]. First, these differences may be explained by inadequate time for compensatory neural processes. Second, it is possible that different neural systems (e.g., dopamine and GABA) have different requirements or timing for plasticity. Finally, it must be recognized that results obtained using different methods, different levels of dietary iron, and at different developmental time periods will be inherently difficult to reconcile. For example, a decrease in stereotypic movements induced by postnatal iron deficiency was reversed by 4 weeks of iron repletion in one study [17], but not completely in another [44].

It is generally thought that the critical time window for altered emotional behaviors due to iron deficiency may be later than gestation or within the first 10 days of life in rats, equivalent in brain development to a full human gestation [41]. Neural damage during gestation may recover, whereas continued iron deficiency past a critical point could produce a lack of effect on the recuperative or compensatory process needed to reverse anxiogenic effects [41]. It is notable that iron-deficient rats given iron therapy at PND 10 still weigh significantly less than the controls on both PND 55 and PND 75 [41]. Whether the small size of the low iron group is due to decreased food intake or altered metabolism (or both) has yet to be fully examined. Ultimately, it is critical to keep in mind that the period of development during which nutritional deficiency occurs can later produce both behavioral and physiological consequences [45] – whether iron repletion can reverse the behavioral influence of iron deficiency and the mechanism(s) underlying restoration to normalcy remain important questions to be studied [46].

4. Iron overload

Excess iron in the brain is implicated in the development and pathogenesis of neurodegenerative disorders [47-51]. Iron levels in the brain increase with age [52-54]; this has been shown to occur mainly in brain regions that are affected in the disease states, including Alzheimer's, Parkinson's, and Huntington's diseases [54]. Increased iron levels promote the generation of reactive oxygen species, leading to cellular and tissue damage [55,56]. With respect to emotional behaviors, iron overload appears to alter anxiety-like behavior and mood [57-59]. Anxious responses, determined by the elevated plus maze, are observed in adult rats receiving daily intraperitoneal injections of iron [59]. Other behavioral impairments have been found in rats fed carbonyl iron diet containing 20,000 ppm iron [57]. These findings support the idea that imbalanced iron metabolism plays a pivotal role in modulating anxiety and emotional behaviors.

Neuronal damage due to iron overload may be incurred during the postnatal period and aging because the rate of iron influx into the brain is increased in both early and late stages of life [60-62]. Iron overload has been clearly shown to disrupt neurotransmitter homeostasis. Iron infusions into the substantia nigra perturb monoaminergic systems, especially the dopaminergic pathway, to promote impaired motor function resembling Parkinson's disease [63-65]. The effects of iron overload on learning and memory deficits are also well documented during postnatal development in mice [66-70]. However, there are only a few studies that have characterized the influence of iron loading on emotional behavior. In humans, iron supplementation in anemic women has been reported to alter emotional processes such as anxiety or depression [58]. Intraperitoneal injection of iron affects the emotional behavior of Wistar rats [59]; in the elevated plus maze, these iron-loaded rats spent more time in the closed arms and entered the open arms less frequently than controls, indicating that iron-treated rats display elevated anxiety. In addition, the total entries into the closed arms and activity in the maze were significantly reduced in iron overload rats compared with controls, reflecting a reduced activity and exploratory drive. Moreover, iron-loaded rats have a lower locomotion and reared less frequently in the open field [59]. These results demonstrate increased anxiety/emotional reactivity upon iron overload, which is similar to the behavioral phenotype of iron deficiency [10,19,40,71]. Since activity or exploration drive are also affected by iron overload during postnatal development [68], behavioral methods that are more anxiety-specific and less exploration/activity-dependent (e.g., conditioned place avoidance, social interaction or taste aversion tests) have been suggested to more reliably examine the effect of iron overload on anxiety [59].

The influence of iron loading on emotional behavior is dose-dependent. In contrast to intranigral iron dose of 3.0 mg/kg body weight, rats intranigrally injected with 1.5 mg iron/kg did not show a significant difference in behavioral functions compared with control rats [59]. It can be speculated that the organism, particularly the adults, can compensate for a small dose of iron supplementation [59]. Other studies reported similar results [57,68]. Sobotka *et al* [57] demonstrated a significant accumulation of iron in the brain only at the highest dose of iron overload (i.e., 20,000 ppm in diet for 12 weeks) but not at lower doses (350 and 3,500 ppm). A mechanism that protects the brain against iron overload until a

certain point, and that cannot compensate when the load exceeds this limit, has been proposed [59].

5. Potential mechanisms underlying the influence of iron status on emotional behavior

Despite a large body of evidence about iron's effect on behavioral functions from experiments using iron-deficient rodent models and observations from iron-deficient infants and children, the molecular information about the role of iron in emotional behavior is scarce. A correlation study has found interesting relationships among iron, dopaminergic system and anxiety-like behavior. Nosepokes and rate of habituation are associated with prefrontal cortical iron concentrations, whereas spontaneous activities, including locomotion and repeated movements, are better correlated with iron levels and dopamine receptor density in the ventral midbrain [40]. The regression analysis also revealed that iron levels in the ventral midbrain and prefrontal cortex are important for anxiety-like behaviors. It should be noted that other potential mechanisms could be involved in iron deficiency-related emotional behaviors and that other neurotransmitters could play significant roles in these behaviors. For example, iron deficiency alters serotoninergic [72] and GABAergic functions [73]. It is also possible that these effects are not due to direct effect by iron but may be a consequence of other factors such as metal interactions. These mechanisms are discussed below and represented in Figure 1.

5.1. Dopamine

A large body of evidence has indicated that impaired emotional behaviors are associated with iron deficiency through altered dopamine metabolism [14,20,74,75]. In general, there is a universal negative effect of iron deficiency on dopamine functions [11,76,77], which are specific to brain region and the stage of neural development.

Dopamine receptor 1 (D1R) expression is down-regulated in the caudate putamen and prefrontal cortex of iron-deficient rats [78]. In contrast, Beard *et al* [40] did not observe any effect of iron deficiency on D1R in both brain areas, possibly due to different specificity of ligands for D1R. Iron deficiency decreases the density of D2R in rat striatum [78] and prefrontal cortex as measured by radioactive tracer binding [40]. Western blot analysis, however, revealed no difference in D2R in the prefrontal cortex between iron-deficient and control rats [20]. While this discrepancy may reflect different approaches used to detect D2R, the region-specific response of iron deficiency to dopamine receptor density could also be due to different sensitivity to dietary iron deficiency [30,31]. Another possibility is the differential expression of receptor subtypes in different brain regions along with less specific ligands. For example, the ratio of D4R to D2/3R is greater in the prefrontal cortex than in the striatum [79]. Hence the greater binding of ligand with poor subtype specificity could result in different interpretations.

Since D2R autoreceptor regulates dopamine clearance in the synaptic cleft *via* dopamine transporter (DAT) [80,81], the negative effect of iron deficiency on D2R could result in decreased DAT activity and increased striatal dopamine [80]. A positive correlation between

D2R density and DAT density appears to support this possibility [78]. It has been proposed that iron deficiency-related “desensitization” could occur such that more dopamine is needed to stimulate DAT [78]. Iron deficiency decreases DAT density in the striatum and nucleus accumbens [16]. Effects of cocaine on DAT are reduced upon iron deficiency, implying changes in both DAT density and functioning [16]. In contrast, DAT levels are unchanged in the prefrontal cortex upon iron deficiency [20]. These observations may reflect brain region-specific regulation of the transporter by iron and/or different methods of measurement [20].

Iron is a cofactor for tyrosine hydroxylase, a critical enzyme in dopamine production; whether its activity is specifically affected in the prefrontal cortex and striatum during iron deficiency should be better explored [82]. Extracellular dopamine is elevated in the caudate putamen and nucleus accumbens upon iron deficiency [14-16,75], most likely due to decreased DAT density [15], and returns to normal levels when brain iron levels are corrected [15,75]. In contrast, extracellular concentrations of dopamine in the prefrontal cortex, determined from microdialysis samples, are lower in iron-deficient rats compared with control rats, whereas the amphetamine-evoked response is similar between iron-deficient and control rats, suggesting that the reduced basal dopamine in the prefrontal cortex could be reflected by elevated anxiety upon iron deficiency [20]. Alternatively, the amount of neurotransmitter available for evoked release may be limiting in the prefrontal cortex of iron-deficient rats [20].

5.2. Serotonin and norepinephrine

Alterations in serotonin signaling might also be responsible for emotional behaviors since it has an important role in mediating affective behaviors. However, conflicting results exist on the effects of iron deficiency on serotonin levels in rats. Iron deficiency may decrease levels of serotonin due to a down-regulation of synthetic enzymes in juveniles [13]. On the other hand, serotonin levels are elevated upon iron deficiency in adults, possibly reflecting a down-regulation of serotonin metabolism [83]. Serotonin transporter densities are reportedly reduced in the striatum of iron-deficient mice [72]. Likewise, moderate and severe gestational iron deficiency reduces serotonin uptake by brain synaptic vesicles in offspring, and this effect can be normalized with 4 weeks of iron repletion [84]. In other studies, however, iron deficiency had no effect on serotonin levels or metabolism in newborns or adults [12] and serotonin levels in the prefrontal cortex of the iron-deficient rats did not differ from controls [20].

Extracellular norepinephrine (NE) concentrations are elevated under iron deficiency states whereas tissue levels are unchanged compared with controls [43,76,77]. Bianco *et al* found increased caudate NE concentration and further demonstrated that the activity of dopamine-β-hydroxylase, the enzyme to produce NE from dopamine, is elevated by 75% in caudate homogenates from iron-deficient rats [85]. This evidence suggests a shift to increase NE production upon brain iron deficiency, possibly compensating for altered dopamine response [85]. In addition, the brain NE transporter is down-regulated in iron deficiency [18]. The observations in serotonin and NE homeostasis are not necessarily conflicting but may hint at underlying mechanisms of the iron-monoamine relationship since the distribution of

neurotransmitters between intracellular and extracellular pools appears to be the primary site of influence of brain iron deficiency [1].

Ceruloplasmin (Cp) is a ferroxidase that converts Fe^{2+} to Fe^{3+} and contributes to cellular iron efflux. Texel *et al* have demonstrated that Cp-deficient mice exhibit increased iron deposition in the liver and spleen, whereas brain iron is reduced, especially in the hippocampus, which is accompanied by increased anxiety-like behavior with no changes in motor function or learning and memory [86]. This increased anxiety is associated with elevated levels of plasma corticosterone and decreased levels of serotonin and NE, as well as brain-derived neurotrophic factor (BDNF) and its receptor [86]. Altered hippocampal BDNF signaling is linked to changes in serotonin and NE levels. BDNF promotes the survival and differentiation of serotonin neurons [87], while NE increases BDNF and receptor activation [88]. Reduced BDNF and increased corticosterone are associated with increased anxiety [89,90]. Also, mice with hippocampus-specific deletion of BDNF display anxious behavior [91]. Tran *et al* have shown that BDNF is reduced in iron-deficient rats [92,93]. Since iron is a cofactor for the rate-limiting enzymes involved in serotonin and NE synthesis, decreased iron in the hippocampus due to Cp deficiency could result in impaired production of these monoamines and down-regulate BDNF signaling, which together promote an anxiety phenotype. These results indicate that redox properties of iron could contribute to emotional behavior by altering monoamine metabolism and BDNF homeostasis [86].

5.3. Glutamate

There are few studies about the role of iron and glutamate/GABA concerning emotional behavior. Iron deficiency in both prenatal and postnatal periods is associated with decreased activities of glutamate decarboxylase, glutamate dehydrogenase and GABA transaminase [73,94]. Brain glutamate levels are elevated in iron-deficient rats [37], suggesting either increased synthesis or decreased release from the neurons. Since excitatory glutamatergic neurotransmission accounts for >80% of the total energy expenditure in the brain [95], Rao *et al* postulated that glutamate-mediated neurotransmission is decreased due to inefficient energy metabolism in perinatal iron deficiency, leading to high intracellular glutamate levels [37]. Furthermore, glutamate binding to synaptic membranes is reduced in iron-deficient brains [96]. This evidence supports the idea that emotional responses are attenuation of glutamatergic signaling under low iron conditions.

5.4. Gaba

Altered GABA metabolism is associated with decreased iron concentrations [27,28,37,73,77,94,96]. Iron deficiency results in elevated concentrations of GABA in several brain regions, including hippocampus, striatum and globus pallidus [37,97]. The elevated GABA levels suggest an increased inhibitory drive for reducing the overall neurotransmission rates and brain activity due to insufficient energy [37]. In addition, iron deficiency enhances GABA binding to synaptic membranes [96]. Activities of GABA shunt enzymes (e.g., glutamate dehydrogenase and GABA transaminase) are reduced in rats made iron-deficient during pregnancy and lactation, and this effect is not restored by iron repletion of dams [94]. Notably, these enzymes are also decreased in postweaning iron deficiency, but this loss can be corrected upon iron supplementation [98,99].

5.5. Oxidative stress

Iron overload enhances reactive oxygen species [55], and iron-treated rats show increased iron in brain regions involved in emotional processes, including the frontal cortex, basal ganglia, hippocampus, and cerebellum [59]. To account for the effects of iron exposure on behavior, Maaroufi *et al* [59] proposed the hypothesis that increased oxidative stress due to iron overload impairs monoamine functions. Administration of a small amount of iron for only a few days (3.0 mg/kg for 5 consecutive days) promotes iron accumulation in the substantia nigra of an adult brain, where iron may generate cytotoxic free radicals. Such oxidative stress can impair dopaminergic signaling and monoamine function, consequently leading to the behavioral impairment [100,101]. However, while several studies have shown an association between brain iron loading and oxidative stress in neurodegenerative disorders [47-51], the exact role of iron overload in emotional behavior remains to be determined.

6. Sex differences in iron metabolism and emotional behavior

There is a significant influence of sex on anxiety behavior in adulthood; females are less anxious than males based on elevated plus maze results [41]. Other studies reached similar conclusions [102,103]. Estrogen effects on dopaminergic function in the context of iron deficiency have been reported [78], possibly by transcriptional regulation of DAT and receptors [19]. Estrogen also modifies D2R expression [104,105]. Sex differences also exist in spatial memory performance [106].

Latency to startle response is attenuated in female, but not in male, iron-deficient rats [19]. The expression of monoamine transporters and D1R is also different between male and female [18,72]. In males, iron-deficient rats have lower DAT levels in several brain regions, including caudate putamen and nucleus accumbens. However, female rats do not show a difference in DAT levels between iron deficiency and control diets. D1R is another example: while iron-deficient rats show a significant reduction in D1R in nucleus accumbens and substantia nigra, female rats increase D1R compared with control of the respective gender [19]. Overall, it appears that male mice are more sensitive to the effect of iron deficiency than are female mice [72]. Studies using rats also showed a similar pattern [19]. Finally, it has been noted that brain iron levels are also dependent upon gender and iron diet [43].

7. Other metals

Although iron has been most studied in emotional behavior and neurotransmitter metabolism, abnormal levels of other metals, whether essential or not, also significantly contribute to mental disorders and here we briefly discuss several metals.

7.1. Zinc and selenium

As an essential metal, zinc plays an important role in brain function and energy metabolism. The metal is involved in controlling emotional behavior, and mood disorders and depression are associated with reduced zinc concentrations in serum [107] while zinc supplementation improves anger and depression [108]. Likewise, zinc-deficient rats display anxiety-like

behavior [109] and zinc treatment provides anxiolytic activity in rodents [110]. The role of zinc in cognitive and emotional behavior mediated by glutamate and glucocorticoid signaling under stressful circumstances has been reviewed [111]. Selenium, a metalloid mineral, provides anti-oxidant activity to protect the body from oxidative stress. Human studies show that selenium supplementation improves mood [112-114].

7.2. Manganese and copper

Manganese is required for several critical enzymes, including superoxide dismutase, glutamine synthetase and arginase [115,116]. When over-deposited in the brain, however, manganese promotes neurotoxicity characterized by memory loss, impaired motor coordination and psychotic behavior resembling Parkinson's disease [117-119]. Impaired dopamine and cholinergic systems participate in manganese-mediated psychological disorders [120-122]. Similarly, abnormal tissue accumulation of copper, observed in Wilson's disease, is also associated with impaired emotional behavior and neurological problems [123,124].

7.3. Lead and mercury

Heavy metals have long been recognized as neurotoxicants. Emotional problems associated with lead exposures in neonates [125] or adults [126] affect mental health, although not always [127]. Social and emotional dysfunction in children correlate with pre- and postnatal lead exposures [128]. Studies in mice show lead-associated behavioral effects could be mediated, at least in part, by increased corticosterone levels [129]. Other possibilities include disruption of monoamine metabolism in the basal ganglia [130] and formation of hydroxyl radicals [131].

Behavioral deficits are reported in rats upon perinatal methylmercury exposures [132]. In humans, chronic subtoxic levels of inorganic mercury produced heightened distress, anxiety and psychoticism without alterations in general intellectual functioning and motor skills [133]. In studies using zebrafish, Maximino *et al* have proposed that oxidative stress induced by methylmercury produces mitochondrial dysfunction and inhibits tryptophan hydroxylase, thereby altering serotoninergic systems [134].

8. Conclusions

A strong body of evidence demonstrates altered metabolism of iron and other metals modifies emotional behaviors. Conversely, people with psychological disorders appear to have reduced iron status; for example, serum iron levels are lower in schizophrenics than in controls [135]. Subjects with major depression have lower hematocrit and serum transferrin [136]. Interestingly, these patients also display lower zinc levels [137]. Moreover, the amount of selenium in the diet is inversely associated with reports of anxiety, depression, and tiredness, which are improved by selenium supplementation [113]. These findings suggest a possibility that individuals with mood symptoms may have insufficient vitamins and minerals [113] and therefore may need more micronutrient supplementation than healthy subjects [138].

Effects of iron in emotional behavior are determined by many physiological/biological properties and spatial/temporal factors; these include intracellular and extracellular concentrations of neurotransmitters, brain iron levels, different brain regions (e.g., density and affinity of neurotransmitter receptors/transporters/enzymes), regulation of these molecules, iron exposure period and timing, route of exposure, animal species, sex, nutritional status and disease state. Different methods of behavioral measurements and the influence of other metals produce different behavioral outcomes. More systematic and controlled studies are warranted to better understand the underlying mechanism of iron-associated emotional behavior and mental health. It is necessary to improve our understanding of the pathologies associated with anxiety and other psychiatric disorders to develop therapies to alleviate emotional dysfunction.

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Abbreviations

BDNF	brain-derived neurotrophic factor
Cp	Ceruloplasmin
D1R	dopamine receptor 1
DAT	dopamine transporter
GABA	γ-aminobutyric acid
NE	norepinephrine
PND	postnatal day

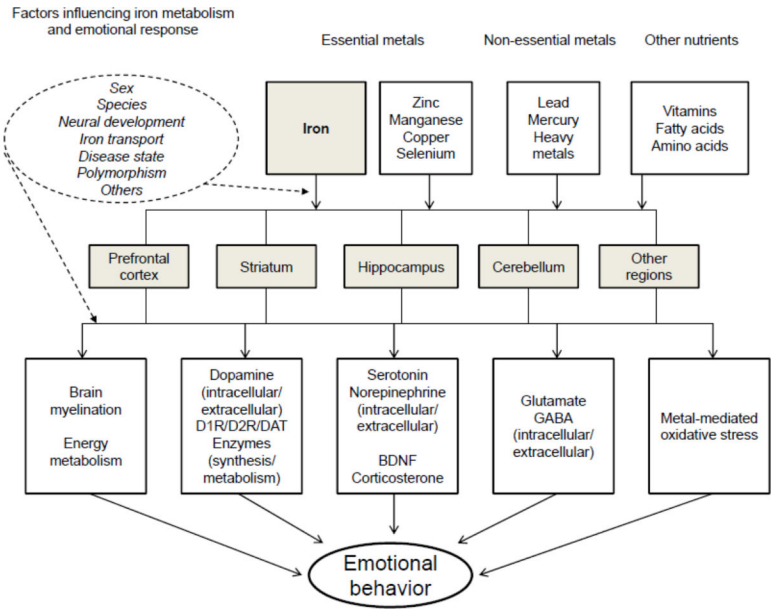

Figure 1. Potential mechanisms of iron-dependent emotional behavior

Shown are proposed mechanisms of anxiety and emotional behavior with a focus on iron metabolism. Effects of factors that can control iron metabolism and emotional behavior are indicated by dotted arrows.