



Published in final edited form as:

*Nutr Rev.* 2011 November ; 69(Suppl 1): S43–S48. doi:10.1111/j.1753-4887.2011.00432.x.

## Long-term Brain and Behavioral Consequences of Early Iron Deficiency

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### Abstract

Early iron deficiency (ID) not only affects brain and behavioral function during the period of ID but long after treatment. The mechanisms include long-term alterations in dopamine metabolism, myelination and hippocampal structure and function. Recent studies demonstrate long-term genomic changes suggesting that the regulation of brain function is fundamentally altered.

### Introduction

Iron deficiency (ID) is the most common micronutrient deficiency in the world. In early life, there are three peak times of risk for ID large based on perturbations in the balance between iron supply and iron demand. These times periods are late fetal/early neonatal life, toddlerhood, and adolescence, particularly in females. The clinical conditions that lead to ID during each of these time periods have been extensively characterized. Each is associated with poorer brain performance during the period of ID. Interestingly and importantly, however, treatment with iron appears to completely reverse cognitive symptoms only in the latter group. In contrast, early ID, defined as ID occurring in either fetal/neonatal or toddler time periods, results in long-term, and potentially permanent, neurobehavioral impairments.

It is not surprising that the brain does not function normally while it is iron deficient. Iron is absolutely necessary for normal neuronal and glial energy metabolism, neurotransmitter production and myelination<sup>1</sup>. A large number of studies in humans and in animal models demonstrate that early ID has a negative effect on these brain processes with concurrent behavioral abnormalities. It remains less clear, however, why relatively prompt early and complete iron repletion fails to reverse the genomic, neurochemical, structural and behavioral effects of early ID. This chapter reviews the evidence for long-term consequences of fetal/neonatal and toddler ID in humans and considers the animal data supporting the premise that these long-term consequences are due to improper development during critical periods of development.

### Long-term Effects of Early ID in Humans

A striking aspect of early ID is the failure of relatively prompt treatment and recovery from ID to completely reverse the behavioral abnormalities<sup>1,2</sup>. Multiple studies demonstrate long-term motor, cognitive and socio-emotional behavioral deficits in children and young adults following a period of ID early in life (reviewed in <sup>1</sup>). The majority of these long-term studies follow-up infants who were iron deficient during infancy and toddlerhood, although there is an increasing body of literature suggesting that fetal-neonatal ID also confers long term risks to brain function (reviewed in <sup>3,4</sup>).

## Neonatal ID

Newborn ID occurs as a consequence of maternal gestational conditions that limit the iron supply or increase the iron demands of the fetus. Processes that limit iron availability to the fetus include severe maternal ID anemia, maternal hypertension that restricts placental nutrient flow, maternal cigarette smoking and premature birth<sup>5</sup>. Increased fetal iron demand occurs during pregnancies complicated by maternal diabetes because chronic intrauterine hypoxia driven by chronic fetal hyperglycemia and hyperinsulinemia augments erythropoiesis. Each additional gram of fetal hemoglobin that is synthesized requires 3.5 additional milligrams of iron<sup>6</sup>. Acute neurobehavioral effects of neonatal ID include altered temperament and child-mother interaction<sup>7</sup>, slower neural conduction velocity<sup>8</sup>, higher prevalence of abnormal neurologic reflexes<sup>9</sup>, and poorer discrimination memory<sup>10</sup>.

The recovery from neonatal ID has not been extensively defined although one small study showed that infants born with low cord serum ferritin concentrations have normal, although statistically lower, ferritin concentrations at 9 months of age<sup>11</sup>. Follow-up neurobehavioral studies of infants born with low iron stores have not assessed iron status at the time of behavioral testing. Nevertheless, a number of studies suggest that children born with low iron stores have abnormal neurobehavioral processing at follow-up<sup>12,13</sup>. Newborn infants with the lowest quartile of cord serum ferritin (<76 mcg/L) have more school performance problems than infants with ferritins from the middle quartiles<sup>12</sup>. Studying a cohort of infants of diabetic mothers and control infants at 3.5 years of age, Riggins et al (2009) demonstrated poorer immediate recall memory, delayed recall memory, and working memory inversely related to the cord serum ferritin concentration<sup>13</sup>. Enabling the infants during the memory tasks alleviated many of these deficits, suggesting that the learning deficits are not absolute and are amenable to alternative learning approaches<sup>13</sup>. High density electrophysiology neuroimaging of the infants during task performance using event related potentials (ERP) confirmed a relationship between brain and behavioral findings. Overall, although the body of the literature is small, the available data suggest that long-term general and cognitive behaviors remain affected well after the likely resolution of neonatal ID.

## Postnatal ID

Term infants that are born with normal iron stores do not typically become iron deficient in the first 6 postnatal months because the stored iron combined with a small amount of dietary intake matches the needs of the growing infant<sup>14</sup>. After six months of age, infants' risk for ID increases because the neonatal iron stores have been utilized, the low amount of iron in human milk is insufficient, and non-meat complimentary foods have limited iron bioavailability<sup>15</sup>. These factors may combine in certain populations with an increase in intestinal iron loss because of blood loss due to parasites or allergic response to cow milk protein to place the infant in significantly negative iron balance.

Neurodevelopmental studies of iron deficient infants and toddlers begin with assessments as early as 6 months of age<sup>16</sup> and continue into early pre-school age. Over 50 studies now demonstrate that ID causes abnormal neurobehavioral processing while the infant is ID<sup>17</sup>. While many of these studies concentrate on the abnormalities of the currently iron deficient individual, several large and small-scale studies demonstrate that these abnormalities continue beyond the period of resolution of the ID. The studies highlight the effects of early ID on general functioning, cognitive ability, socio-emotional functioning, motor capacity, and brain electrophysiological function. The long-term outcome studies of infants and toddlers have assessed two fundamental questions; whether there is a positive developmental outcome related to iron treatment of anemic children and children at risk for ID and whether there are residual neurodevelopmental deficits in spite of iron treatment. The studies attempt to link the observed behaviors to neurologic processes that were likely to have been affected

during the period of ID as predicted by animal models (see below). These processes include effects ascribable to alterations in dopamine metabolism, myelination and neuronal energy metabolism and are developmentally sensitive to how the effects of ID are modulated by the timing, dose and duration of ID<sup>2,18</sup>.

Studies that assess whether iron deficient children respond to iron typically show improvements in long-term outcomes in the treated group<sup>19</sup>. Similarly, most randomized studies that assess whether iron supplementation prevents ID also demonstrate improved iron status and developmental outcome in the supplemented group<sup>20,21</sup>. However, in spite of these positive findings, there is an interesting and robust body of literature that shows that early ID results in long-term brain and behavior consequences. Although it is difficult to control for all potential confounders, several of these studies are well designed in that ID appears to be the only risk factor to neurodevelopment<sup>22</sup>. Moreover, the participants in one of these cohort studies are now in their 30's which will allow for even longer-term follow-up. In terms of general cognitive performance, iron deficient toddlers not only have a lower mean developmental quotient at initial testing but have a lower intelligence quotient in adolescence<sup>23</sup>. Indeed the gap in general cognitive function widens between the iron sufficient and iron deficient group as they age<sup>23</sup>. More specifically, virtually all of the neurologic domains affected acutely by ID in toddlerhood show residual long-term negative effects even after treatment. For example, motor abnormalities are evident during the period of ID particularly during sleep<sup>24</sup> and persist well after treatment<sup>25</sup>. In the cognitive domain, formerly iron deficient children demonstrate poorer mathematical and writing abilities consistent with long term alterations in hippocampal and higher cortical functions<sup>22</sup>. In the socio-emotional behavioral domain, currently iron deficient toddlers demonstrate more hesitancy and wariness particularly in novel situations<sup>26</sup>. In follow-up, formerly iron deficient infants show lower levels of physical activity, positive affect, and verbalization during structured tasks at 5 years of age, despite iron therapy that corrected their ID anemia in infancy<sup>27</sup>. Furthermore, formerly iron deficient children demonstrate more anxiety-depression symptoms at 11 to 14 years of age<sup>28</sup>. These findings are consistent with long-term alterations in striatal-nigral and striatal-frontal dopaminergic circuitry. Other frontal lobe-mediated functions are also affected since formerly iron deficient adolescents show greater attention problems, poorer planning ability and lack of inhibitory control<sup>22,23</sup>. The temporally-and anatomically-distant frontal lobe findings are particularly interesting from a neurodevelopmental perspective because, unlike the striatum and the hippocampus, the frontal lobes are not undergoing rapid development in the time period when the infants were iron deficient<sup>24</sup>. Thus, they should not be at particularly high risk from the lack of an early life nutritional substrate<sup>2,18,29</sup>. The poorer frontal lobe development in children with early ID may be due to suboptimal connections being formed from primary areas (eg, striatum, hippocampus) that in fact are profoundly affected by ID, instead of direct effects on the neurons and neurochemistry of the frontal lobes themselves. The frontal effects have been understudied in animal models and certainly deserve further exploration.

Beyond the behavioral assessments, electrophysiologic abnormalities also persist in these infants. Auditory brain stem evoked potential latencies are longer in iron deficient 6 month olds<sup>16</sup> and in iron deficient preterm infants<sup>8</sup>. Slower conduction velocities in these studies have been ascribed to abnormalities in myelin formation. In follow-up, formerly iron deficient 4 year old children demonstrate longer latencies on visual evoked potentials than never anemic controls<sup>30</sup>; a finding potentially consistent with persistent myelination deficits. As with the long-term hippocampal, frontal lobe and monoamine effects implied by the behavioral studies, these electrophysiologic abnormalities are consistent with known ID neuropathologies uncovered in animal models.

## Long-term Effects of Early Life ID in Model Systems

The acute and long-term neurologic effects of early ID have been explored a number of models including mice, rats and non-human primates, but the vast majority of the literature has been in rats. In most studies, early life ID is induced during early gestation by feeding the mother an iron deficient diet until either postnatal day 7 or postnatal day 21 after which they are placed on iron sufficient diets or by placing weaned pups on an iron deficient diet at day 21. The first approach models gestational ID without postnatal ID in the human since the rodent brain at postnatal day 7 approximates the maturity of a term human infant. The second models gestational-lactational ID while the third models ID in the post-weaned toddler. All model common time periods for ID in humans. While the timing, dose and duration regional vulnerability theory suggests that there may be differential regional effects on the rapidly developing brain, the fact is that there is a good deal of overlap among these paradigms because of the relatively long time that it takes to replete the brain after the period of ID. Thus, in reviewing the animal work, it is probably best to categorize the entire body of work as “early ID.” Studies using these experimental paradigms date back to the 1970’s and first described the long-term biochemical and behavioral abnormalities. The laboratories of Youdim, Dallman and others established three fundamental neural processes that were profoundly affected by early ID; dopamine metabolism, energy metabolism, and myelination<sup>31-33</sup>. While these effects are largely driven by the failure to incorporate iron post-translationally into iron containing enzymes and hemoproteins, more recently there has been more interest in potential effects of ID on long-term brain gene expression<sup>34-37</sup>.

The largest body of work on long-term effects lies within the domain of dopamine, and more generally monoamine, neurotransmitter metabolism. Seminal work by Youdim’s and Beard’s groups have demonstrated that these neurotransmitters systems are highly vulnerable to ID at least in part by affecting iron dependent synthetic enzymes such as tyrosine hydroxylase<sup>31,33</sup>. While most of the studies have concentrated on brain regions where iron is highly concentrated (eg, striatum, substantia nigra, ventral midbrain), dopamine is found in many areas of the brain driven through the meso-cortico-limbic pathway, the nigro-striatal pathway and the tuberohypophyseal pathway. Large regional differences in dopamine metabolism are seen in response to the timing and severity of ID. If iron treatment begins later than postnatal day 4 in the ID rat, long-term behavioral and neurochemical effect are seen<sup>38</sup>. Neurochemical effects include decreased striatal D2 receptors and alterations in striatal metabolism related to myelination and energy metabolism<sup>39,40</sup>. The findings reinforce that importance of timing of ID in conferring long-term behavioral risk. Long-term behavioral effects include less exploration and fear of novel situations; findings that map well onto similar behaviors in the human (see above)<sup>41</sup>. Non-human primate models, where more human-like behaviors can be assessed, show that prenatal IDA leads to more impulsive behavior while postnatal IDA results in more passive, withdrawn behavior that is reminiscent of the findings in humans<sup>42</sup>.

Myelin synthesis is iron dependent for a number of defined and likely several as yet undefined mechanisms. Myelin is synthesized by oligodendrocytes and begins prenatally in rodents and humans. Oligodendrocytes are highly metabolic cells. ID, which compromises cellular energy status, likely reduces their capacity to generate energy and thus restricts cellular capabilities. Moreover, iron containing enzymes are involved in the synthesis of fatty acids contained in myelin. Early ID alters the fatty acid profile of myelin<sup>43</sup> as well as genes that code for structural proteins involved in myelin generation such as myelin basic protein<sup>34</sup>. Metabolomic analyses of the hippocampus and the striatum demonstrate long-term abnormalities in myelin pre-cursors<sup>40,44</sup>. The myelin effects on the metabolome are a primary driver of the abnormalities in striatally based procedural memory induced by early

ID in rats<sup>44</sup>. These long-term myelin effects likely underlie the slower neural conduction speeds observed in children following recovery from early ID<sup>30</sup>.

Dallman's group was instrumental in uncovering the effects of ID on metabolic function in the brain<sup>32</sup>. ID reduces cytochrome c concentrations in the brain<sup>32</sup> and cytochrome c oxidase activity<sup>45</sup>. These findings led to the hypothesis that brain regions with high metabolic demands would be most affected by this "metabolic brown-out." The brain is not metabolically homogenous with certain areas such as the hippocampus, prefrontal cortex and anterior cingulate cortex demonstrating greater iron dependent metabolic activity early in life than other areas<sup>45</sup>. This higher metabolic rate occurs during periods of rapid cellular differentiation; in the rat the hippocampus is rapidly differentiating in the early postnatal period<sup>46</sup>. The hippocampus affected by early ID anemia exhibits altered neurometabolism and gene expression, decreased energy availability and growth factor expression, abnormal dendritogenesis, decreased long-term potentiation (LTP), and abnormal hippocampus-based learning and memory<sup>35,44,45,47,48</sup>. The deficits persist into adulthood in spite of complete brain and blood iron repletion<sup>35,36, 49-52</sup>.

Although studies using the rat model have yielded many insights into the effects of early ID anemia, the model has limitations with respect to addressing the specific role of iron in these neural processes because of the potential wide-spread confounding effects of brain and body ID (e.g., hypoxia, uptake of other divalent metals, glucocorticoid activation, poor maternal care). We recently addressed this issue by generating a genetic mouse model in our laboratory; a non-anemic mouse with a hippocampal neuron-specific, late gestation knock-out of the gene for the iron transporter DMT-1 (Slc11a2). It shares multiple (but not all) of the phenotypic and genomic characteristics with the ID anemic rat<sup>53</sup> suggesting that it is the specific lack of iron, as opposed to the anemia or other confounders, that is responsible for the abnormal recognition memory seen in iron deficient rodents. Indeed, in the wild-type control, the amount of iron transporter expression in the hippocampus was directly related to the difficulty of the task being learned<sup>53</sup>. Based on the findings of acute and long-term deficits exhibited by this non-anemic mouse model of ID, we concluded that iron has a critical role in normal learning and memory<sup>53</sup>. The long-term cognitive deficits seen in formerly iron deficient adolescents<sup>22</sup> are likely in part due to the long-term changes in hippocampal structure and function seen in these models.

The new frontier in ID research is on its long-term effects on the genome. Important whole brain genomic effects 6 months after early ID anemia in the rat include reductions in myelin basic protein expression and microtubule associated protein-2, which codes for a scaffolding program important for cytoskeletal stability<sup>34</sup>. The effects appear to be regional as well. Early ID anemia acutely altered genes involved in synaptic efficacy, neurotransmitter release, determination of structure and neurotrophic factors<sup>35</sup>. All point to long-term dysregulation of brain processes that are critical for normal adult synaptic plasticity.

Finally, although it convenient to use animal models to isolate specific long-term pathologic processes induced by early ID, ultimately abnormal behaviors are a complex product of the integration of multiple brain processes that work in cooperation or in competition<sup>54</sup>. Early ID appears to have differential magnitudes of effect on the various systems involved in cognition, thus potentially disturbing the balance of their relative contributions to normal behavior. Unbalancing of memory systems can be induced by targeted genomic disruption of iron uptake in a single brain region (eg, hippocampus). When this is done, not only is hippocampal based recognition memory compromised<sup>53</sup>, but extra-hippocampal effects in the striatum are seen<sup>55</sup>. This "unbalancing" of developing brain systems is thought to potentially underlie later-appearing developmental psychopathologies<sup>56</sup>. For example,

children born to iron deficient mothers are more likely to develop schizophrenia later in life in a dose-dependent manner related to the degree of maternal ID<sup>57</sup>.

## Summary

A robust parallel literature in humans and animals models strongly supports the premise that early ID causes long-term neurobehavioral abnormalities in spite of relatively prompt diagnosis and treatment. The abnormalities span important neurologic domains, including dopamine metabolism, myelination and energy metabolism, whose proper function is critical for optimal brain health in adulthood. Adult neurobehavioral dysfunction not only serves as a personal behavioral risk in terms of educational achievement and job placement, but also a but also a risk to the following generation.

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