Iron Deficiency and the Developing Brain

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Learning Objectives

Define the common causes of iron deficiency in newborn infants and toddlers

Identify the regions of the brain that are particularly vulnerable to early childhood iron deficiency

Characterize the behaviors that are affected by early life iron deficiency

Overview

Why worry about iron?

Nutrient-brain interactions- why the brain needs iron

Iron needs in infancy
- Sequelae of iron deficiency

Fetal and neonatal iron
- Term and preterm infants
- Sequelae of iron deficiency

Why Worry About Iron Deficiency?

2 billion people world-wide are iron deficient (WHO)
- 30-50% of pregnant women

Every cell/organ system needs iron for proper development and subsequent function

Iron deficiency anemia is associated with clinical symptoms
- Due to tissue level ID
- Symptoms occur prior to anemia

Main reason to worry is the effect on <u>the developing brain</u>
- Cognitive and motor effects
- Some temporary (while ID), others long-term (after iron repletion)
- **The long-term effects are the real cost to society**
  - **Increased depression, anxiety, risk of schizophrenia, autism**
  - **Loss of job and educational potential**

Early Nutrition and Brain Development: General Principles

Positive or negative nutrient effects on brain development

Based on…

Timing, Dose and Duration of Exposure

Kretchmer, Beard, Carlson, 1996

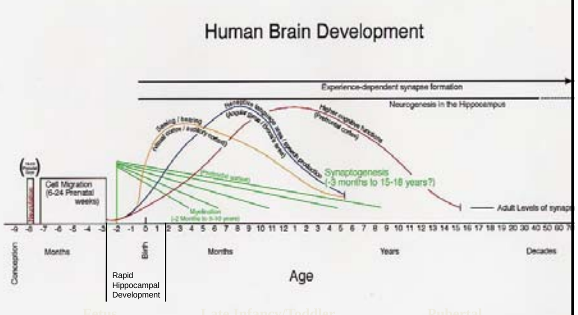
Nutrient-Brain-Behavior Relationships

Various brain regions/processes have different developmental trajectories

The vulnerability of a brain region to a nutrient is based on

- When nutrient deficit/overload is likely to occur
- Brain's requirement for that nutrient at that time

Behavioral changes must map onto those brain structures altered by the nutrient effect



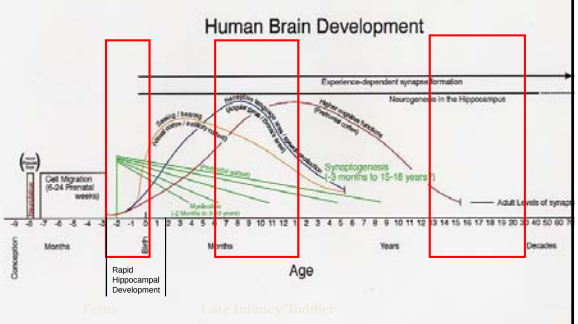
From Nelson and Thompson, 2001

Iron:
A Critical Nutrient for the Developing Brain

Iron containing enzymes and hemo-proteins are involved in important cellular processes in developing brain

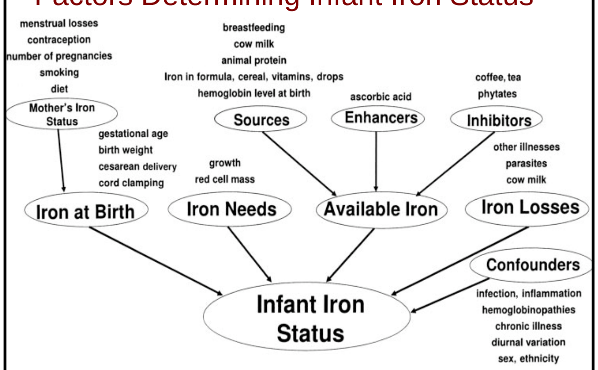
- Delta 9-desaturase, glial cytochromes control oligodendrocyte production of <u>myelin</u>
- Cytochromes mediate oxidative phosphorylation and determine neuronal and glial <u>energy</u> status
- Tyrosine Hydroxylase involved in <u>monoamine neurotransmitter</u> and receptor synthesis (dopamine, serotonin, norepi)
- ID affects <u>genome</u> while ID and long after ID is treated

The Differential Effect of Timing of ID on Brain Development



Iron Deficiency in the Infant or Toddler (6-24 months)

Factors Determining Infant Iron Status



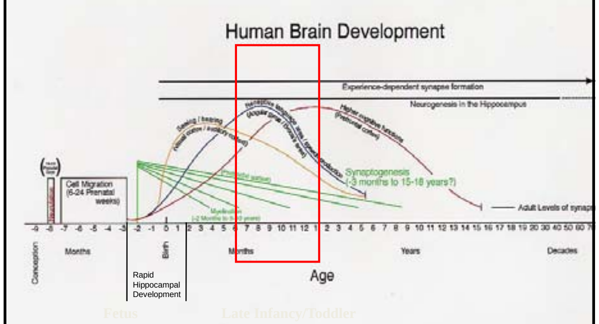
Courtesy of B. Lozoff, MD

ID in Infancy: Who is at risk?

Most postnatal ID is due to inadequate dietary intake ± low stores at birth ± blood loss

- Low stores at birth
- Inadequate dietary intake
  - Low iron formula
  - Breast milk
  - Early change to cow milk
- Blood loss
  - Hemorrhage at birth (anemia)
  - Parasitic infection, food intolerance (GI loss)

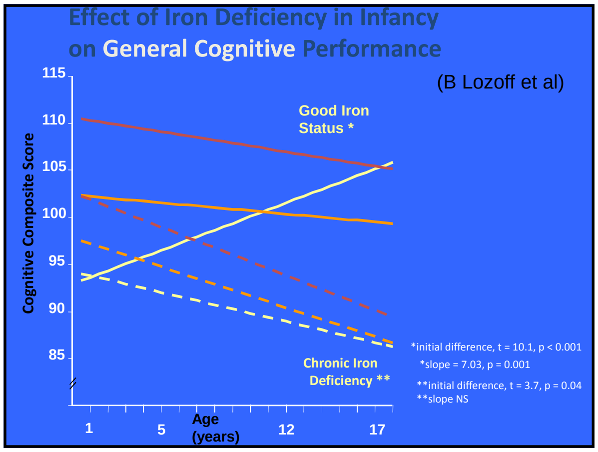
Brain Development Affected by ID in Infancy



Neurobehavioral Sequelae of Early Postnatal Iron Deficiency in Humans

Over 50 studies demonstrate dietary ID between 6 and 24 months leads to:

- Behavioral abnormalities (Lozoff et al, 2000)
  - Motor and cognitive delays while iron deficient
  - Cognitive delays 19-23 years after iron repletion
    - Arithmetic, writing, school progress, anxiety/depression, social problems and inattention (Lozoff et al, 2000)
  - Characteristic of <u>monoamine</u> and <u>hippocampal</u> dysfunction
- Electrophysiologic abnormalities (delayed ABR latencies)
  - At 6 months while iron deficient (Roncagliolo et al, 1998)
  - At 2-4 years after iron repletion (Algarin et al, 2003)
  - Characteristic of impaired <u>myelination</u>



Effect of Iron Deficiency in Infancy on **Affect and Engagement**

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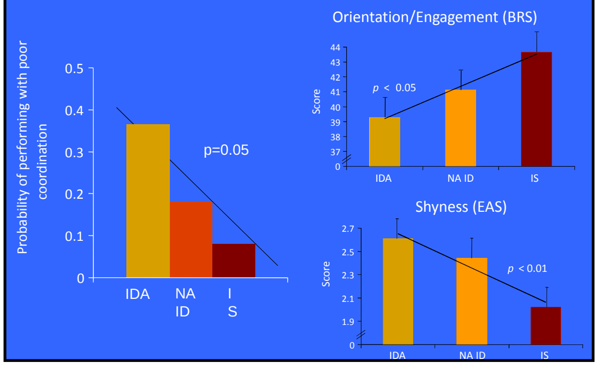
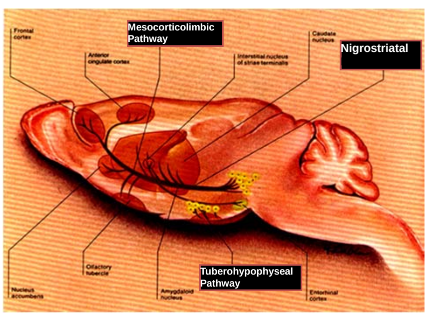
Motor Coordination and Affect in Human Toddlers: a Dose Response Effect (Lozoff et al, 2008)



What is the Biology? Major Dopamine Pathways Connecting to Prefrontal Cortex



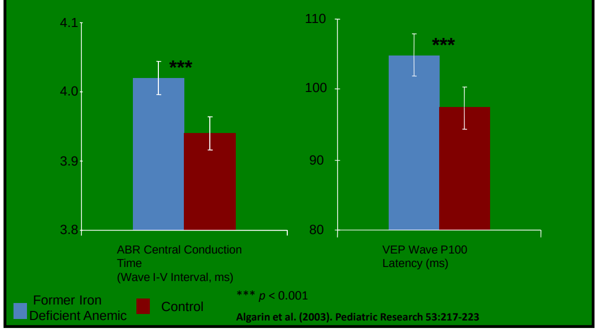
Courtesy of B. Lozoff

Neurotransmitter Effects in the Rat

Effects on monoamines, esp dopamine, known since late 1970's
(studies by Yehuda, Youdim, Beard)

While ID: Decreased DAT, D1R, D2R and increased SERT
- Regional differences- Large effects in striatum, ventral midbrain
- Changes related to timing and severity (E Unger et al, 2012)

Slower Nerve Conduction Velocity:
Evoked Potential Latencies 3 Years after Iron Rx



*** $p < 0.001$

Algarin et al. (2003). Pediatric Research 53:217-223

What is the Biology?
Myelin Effects in the Rat

Altered fatty acid profile in myelin fraction

Decreased myelin proteins, including myelin basic protein

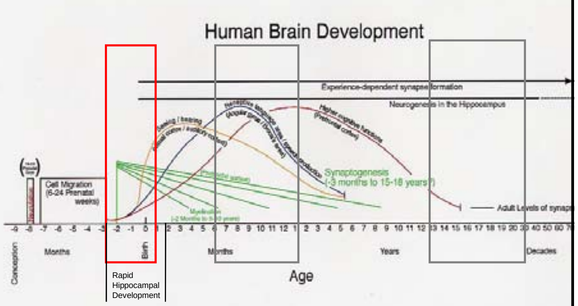
Decreased oligodendrocyte proliferation

Transcripts for myelin basic protein affected

- short term (while ID)
- long term (at P180 after iron repletion)

(Studies by Connor, Clardy, Rao)

Brain Development Affected by Fetal/Neonatal ID



Fetal Iron: Endowment and Distribution

Fetuses have 75mg of elemental iron per kilogram body weight during 3rd trimester

- Term infant: 250mg
- **24 weeker (500g): 37.5 mg**

Majority is in the RBCs (55mg/kg)

Liver storage pools are relatively large at term (12 mg/kg); serum ferritin >40 mcg/L

Non-storage tissues, including brain, heart, skeletal muscle account for the rest (8 mg/kg)

What Can Negatively Affect Neonatal Iron Status?

Decreased maternal iron supply

- Fetus with very iron deficient mother (Hgb<8.5)
- Common (>30%) in developing countries
- No studies of newborn brain iron status

Decreased placental iron transfer during gestation

- Prematurity
  - Iron accreted during third trimester
  - Generally negative iron balance during NICU stay
- IUGR due to maternal hypertension during pregnancy
  - 50% affected
  - 75,000 infants per year in US
  - 32% decrease in brain iron concentration (Georgieff et al, 1995)
- Early cord clamping

Term Infants:
What Can Negatively Affect Neonatal Iron Status?

Diabetes Mellitus during pregnancy

- Chronically hypoxic fetus (IDM)=> Increased erythropoeisis
- 65% affected
- 150,000 infants per year in US
- 40% decrease in brain iron concentration (Petry et al, 1992)

Basic principle:

Iron prioritized to RBCs over brain & other organs when Fe demand> Fe supply

Factors that Determine Preterm Infant Iron Status in the NICU

<u>Negative Iron Balance</u>
- Low Endowment (IUGR)
- Phlebotomy Losses
- Iron Rx at 2 months
- Iron Rx < 2mg/kg/d
- rhEpo Rx
- Rapid Postnatal Growth

<u>Positive Iron Balance</u>
- Older gestation & AGA
- RBC Transfusion
- Iron Rx at 2 weeks
- Iron Rx @ 2-4 mg/kg/d
- Iron Rx @ 6mg/kd/d c rhEpo
- Parenteral Iron
- Slow Postnatal Growth Rate

Preterm infants have elevated ZnPP at 34 weeks PCA (Winzerling &Kling, 2001)

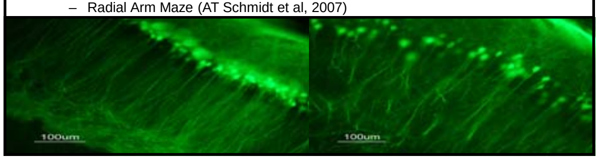
Neurobehavioral Sequelae of Fetal and Neonatal ID

Fewer studies than in postnatal ID
- Decreased maternal iron status
  - increased risk of schizophrenia in offspring (Insel et al, 2008)
  - increased risk of autism in offspring (Schmidt et al, 2014)
- Term infants with low neonatal iron stores have
  - impaired auditory recognition memory processing (Siddappa et al, 2004)
  - poorer school age neurodevelopment (Tamura et al, 2002)
  - worse immediate and delayed recall at 3.5 y (Riggins et al, 2009)
- Preterm infants with now iron stores at 36 weeks PCA
  - more abnormal reflexes (Armany-Sivan, 2006)
  - longer conduction times on BAER (Amin et al, 2010)
- Early iron supplementation in preterms => higher mental processing composite score at 5.3 years (Steinmacher et al, 2007)

SUGGESTS SIGNIFICANT <u>HIPPOCAMPAL</u> AND MYELIN IMPAIRMENTS

What is the Biology? Hippocampal Effects: Rodent Models

- Short and long-term genomic changes (ES Carlson et al, 2007)
  - Dendritic structure, synaptic efficacy, oxidative metabolism
- Reduced energy status (M deUngria et al, 2000)
- Glutamate and GABA sequestration (R Rao et al, 2003)
- Altered dendritic morphology (ES Carlson et al, 2009)*
- Long-term suppression of BDNF and its receptor (P Tran et al, 2009)
- Reduced LTP (long-term potentiation) (Pisasnsky et al, 2013)
- Reduced learning and memory
  - Morris Water Maze (B Felt and B Lozoff, 1996)
  - Radial Arm Maze (AT Schmidt et al, 2007)



Summary

- Iron plays a critical role in early neurodevelopment
- Early iron deficiency <u>without anemia</u> affects brain function
- ID brain/behavior alterations persist after resolution of ID
- Early detection of at-risk infants is crucial for brain health
- Need new tools to detect pre-anemic iron deficiency

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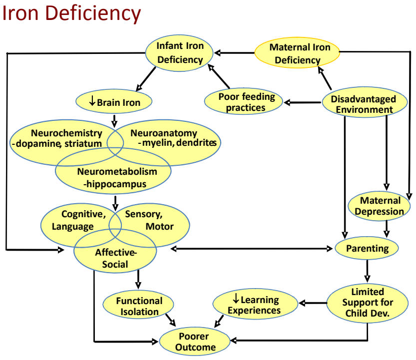
Conceptual Model of Neurodevelopmental Effects of Early Iron Deficiency



From Lozoff et al, 2006