The Specific Role of Iron in Early Brain Development

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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 because iron is prioritized to red cells before the brain when iron supply does not meet iron demand (Georgieff et al, 1992; Petry et al, 1992)
    - **ANEMIA IS A POOR SCREEN FOR RISK OF BRAIN ID**
- Main reason to worry is the effect on the developing brain
  - Cognitive and motor effects
  - Some temporary (while ID), others long-term (after iron repletion)

Why Worry about Iron and Neurodevelopment?

3 pediatric populations are at high risk for ID:

1) **Fetus and Newborn**

2) **Children 6 months-->2.5 years**

3) Teenage girls

All show a wide range of motor and cognitive deficits while ID

Unlike in adolescence, **early-life ID results in neurodevelopmental alterations that persist despite iron repletion**

Iron: A Critical Nutrient for the Developing Brain

- One of the most studied nutrients in brain development
- Iron is found in proteins involved in brain development and function
- Also directly regulates genes in the brain

Iron: A Critical Nutrient for the Developing Brain

- **Myelin**= fatty coating on nerves that mediates Speed of Processing
  - Critical period: 32 weeks gestation to 2 years
- **Energy** => complexity of brain structures, which in turn supports Learning and Memory
  - Critical period for hippocampus: 28 weeks gestation to 18 months
- **Dopamine**= mediates reward, affect, memory, motivation
  - Critical period: mid-gestation to 3 years

Concordant Studies of Short and Long-Term Effects on Myelin, Energy & Dopamine

Human (>50 studies)

- Slower Speed of Processing
  - While ID (Roncagliolo et al, 1998)
  - Long term (Algarin et al, 2003)
- Reduced Learning and Memory
  - While ID (Siddappa et al, 2004)
  - Long term (Riggins et al, 2009)
- Hesitancy, wariness, poor social interaction
  - While ID (Lozoff et al, 2008)
  - Long term (Lukowski et al, 2010)
- Poorer motor coordination (Lozoff et al, 2008)

Animal (>250 studies)

- Abnormal myelin fat and long-term myelin gene expression (Ortega et al, 2004; Clardy et al, 2006)
- Abnormal long-term hippocampal structure, synaptic plasticity, gene expression (Carlson et al, 2009; Tran et al, 2009)
- Abnormal midbrain and frontal lobe monoamine regulation
  - While ID (Beard & Connor, 2003)
  - Long term (Unger et al, 2013)

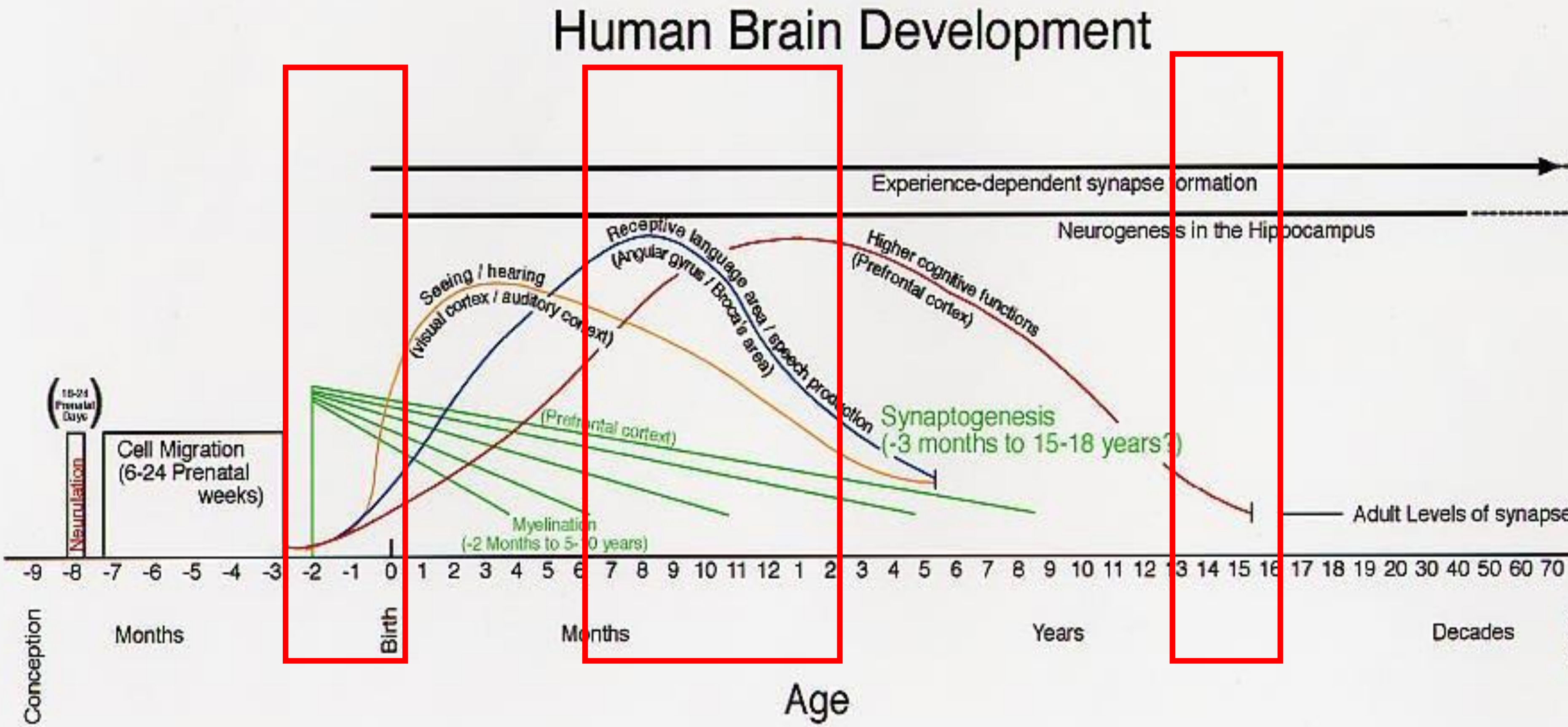
Nutrient->Brain->Behavior Relationships: Why Timing of ID is Important

- Brain regions have different developmental trajectories

- Vulnerability of a region to ID is based on
  - **Timing** of when ID is likely to occur during the lifespan
  - Brain region **requirement** for iron at that time

- Behavioral changes seen with ID map onto those brain regions

The Effect of Timing of ID on Brain Development



Fetus **Late Infancy/Toddler** **Pubertal**

Defines likely period of ID

Neurobehavioral Sequelae of Early Life ID in Humans: The Differential Effect of Timing

- Prenatal ID: (Siddappa et al, 2004; Amin et al, 2010;Nelson et al, in press; Insel et al, 2010)
  - **Learning and Memory**
  - **Speed of Processing**
  - **Long-term Organizational Skills**
  - **Hyperactivity/Attention Deficits**
  - **Higher risk of Schizophrenia in Adulthood**
- ID in Infancy: (For Review, see Grantham-McGregor, 2001; Walker et al, 2007; 2011; Lozoff, 2008; Lukowski, 2010)
  - **Speed of Processing**
  - **Paucity of Movement**
  - **Sleep Disorders**
  - **Hesitancy/Wariness**
  - **Higher risk of Depression in adulthood**

Is it Really the Lack of Iron? The Classic Rat IDA Dietary Model

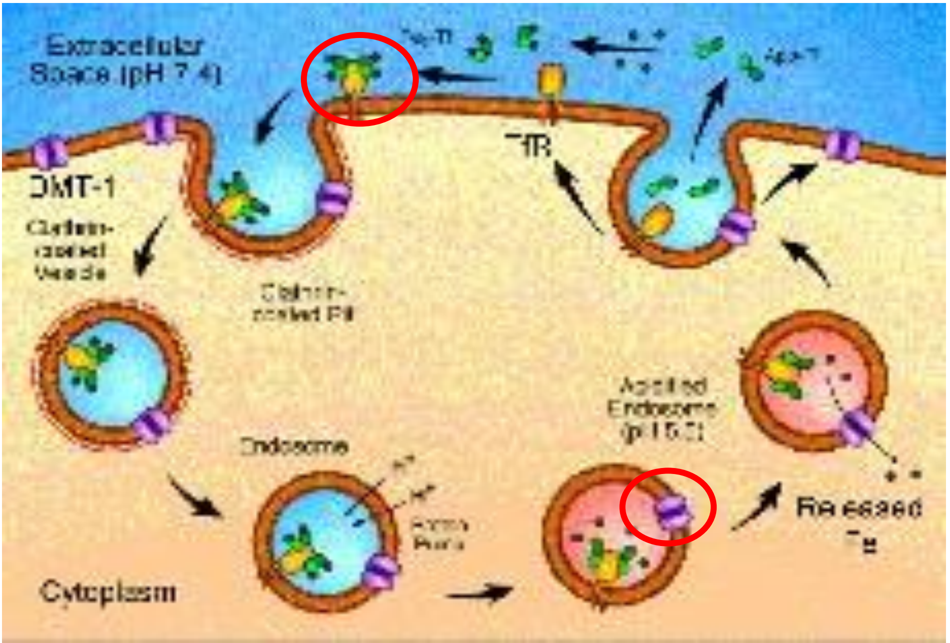
- Strengths
  - Backbone of ID modeling for over 40 years (eg, Youdim, Dallman, Beard)
  - Models "the human condition" of ID anemia

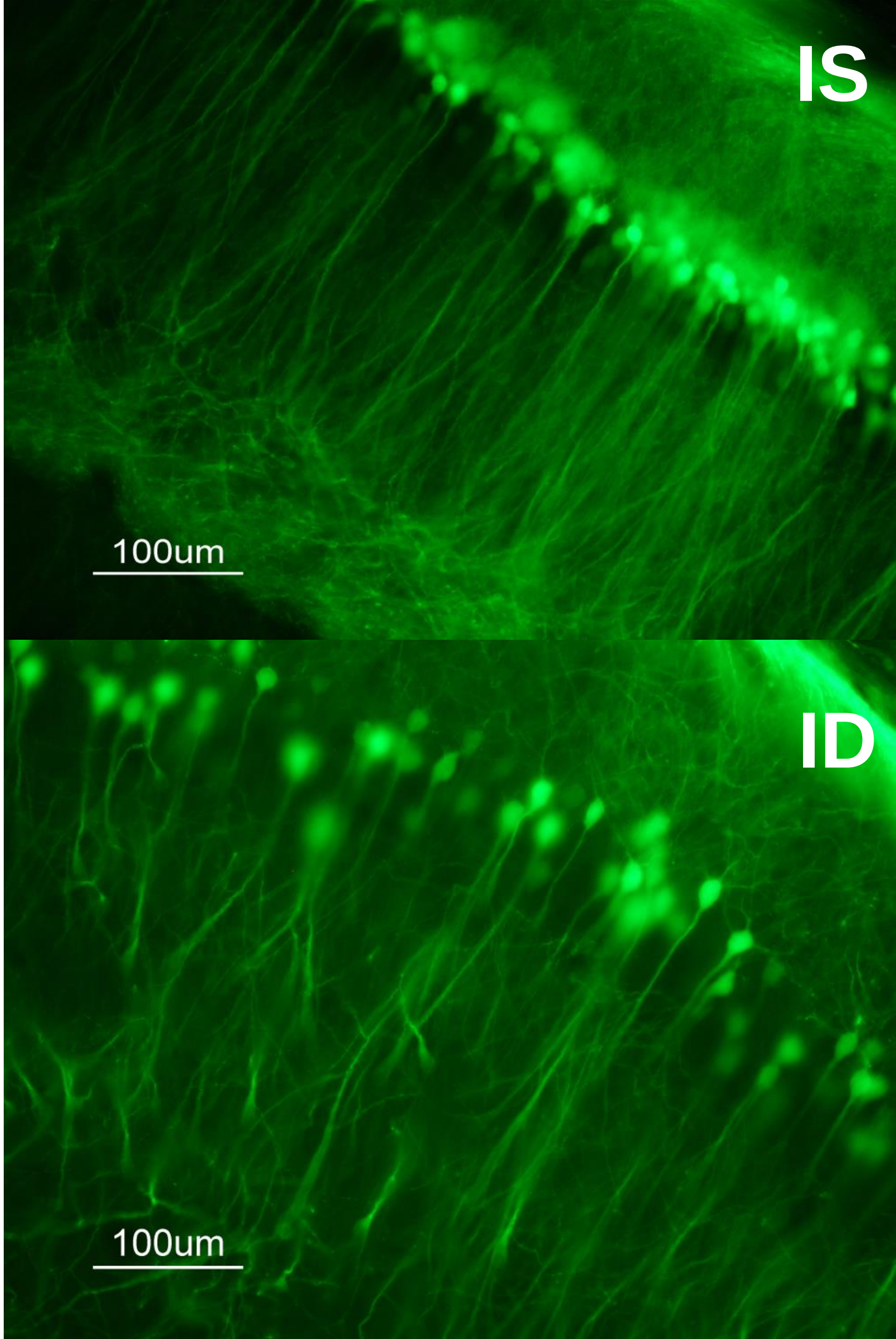
- Limitations (same as in human studies)
  - **Not able to define specific role of iron in neuron development and function**
  - Confounds (many are same as human):
    - Anemia =>Tissue Hypoxia Effects
    - Brain toxicity from uptake of other divalent metals (Zn, Cu, **Mn, Pb**)
    - Activation of stress response

Isolating the Role of Iron: Non-Anemic, Neuron Specific ID Mice:

<u>DMT-1 KO</u>

- *slc11a2* KO (exons 6-8)
- E18.5
- Hippocampus-specific





Why is this Important?

- Non-anemic ID is 3x more common than ID anemia
- Non-anemic brain ID in newborn humans reduces recognition memory (Siddappa, 2004)
- Non-anemic ID in toddlers reduces motor and affective domain function (Lozoff, 2008)

Summary

- Iron plays a critical role in early neurodevelopment
- Multi-layer investigations demonstrate that the behavioral deficits are due specifically to the lack of iron
- Early iron deficiency <u>without anemia</u> affects brain function
- ID brain/behavior alterations <u>persist</u> into adulthood
- Early detection of at risk infants is crucial for brain health
- Need new tools to detect pre-anemic iron deficiency