Viewing Time

The program will take up to one hour to complete.

Target Audience

This program is designed for primary care physicians.

Other health care professionals working with patients and their families may also find this program of interest.

Faculty Disclosure

It is the policy of Children’s Hospitals and Clinics of Minnesota to ensure balance, independence, objectivity, and scientific rigor in all its educational programs. Our faculty have been asked to disclose to our program audience any real or apparent conflicts of interest related to the content of their presentation. They have also been requested to let you know when any product mentioned in their presentation is not labeled for the use under discussion or is still under investigation.

Faculty Disclosure

Michael K. Georgieff, MD, has disclosed no actual or potential conflict of interest in relation to this educational activity.

During this educational activity **Dr. Georgieff** will not be discussing the use of any commercial or investigational product not approved for any purpose by the FDA.

Effects of Early Iron Deficiency on the Developing Brain

Michael K. Georgieff , MD

Professor of Pediatrics and Child Psychology, Director of the Division of Neonatology and the Institute of Child Development, University of Minnesota, Minneapolis, Minnesota

Effects of Early Iron Deficiency on the Developing Brain

A lecture about the importance of iron on the developing brain and the effect of early iron deficiency in children.

Program Objectives

Upon completion of this program, participants should be able to:

- Identify periods in childhood when iron deficiency is common
- Know which brain areas and behaviors are affected by iron deficiency
- Identify which gestational conditions cause neonatal iron deficiency

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Receiving CME Credit

To receive CME credit you must view the entire program and complete the evaluation form at the end.

Early Iron Deficiency and Neurodevelopment

Children's Hospitals
Grand Rounds
2/2009

Michael K. Georgieff, M.D.
Departments of Pediatrics and Child Psychology
Head, Section of Neonatology
Director, Center for Neurobehavioral Development
University of Minnesota School of Medicine

Overview of Talk

- Basic Principles of Nutrient-Brain Interactions during Development
- Role of Iron in the Developing Brain
- Postnatal Iron Deficiency: Motor and Mental Outcomes
- Neonatal Iron Deficiency and Developing Memory Systems
- Iron Dosing and Monitoring

Early Nutrition and Brain Development: General Principle

Positive or negative nutrient effects on brain development

Based on…

Timing, Dose and Duration of Exposure

Kretchmer, Beard, Carlson (1996)

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 the developing brain
  - Cognitive and motor effects
  - Some temporary (while ID), others long-term (after iron repletion)

Why Worry about ID?

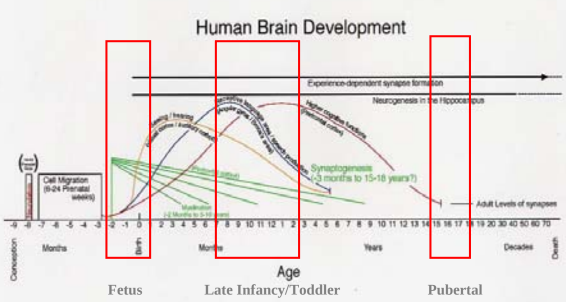
- 3 pediatric populations are at high risk for ID:
  1) Fetus and Newborn: Born to mothers with gestational severe anemia, hypertension (IUGR), diabetes mellitus, smoking
  2) Children 6 months-->2.5 years
  3) Teenage girls
- All show a wide range of motor and cognitive deficits while iron deficient, however unlike adult ID, **early ID results in neurodevelopmental alterations that persist despite iron repletion**
- Fundamental Questions:
  - Is it iron (or is it anemia?)
  - What accounts for the long-term deficits in spite of iron repletion?

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 myelin
- Cytochromes mediate oxidative phosphorylation and determine neuronal and glial energy status
- Tyrosine Hydroxylase involved in monoamine neurotransmitter and receptor synthesis (dopamine, serotonin, norepi)
- New evidence that ID affects genome while ID and long after ID is treated

The Effect of Timing of ID on Brain Development



Neurobehavioral Risks of Early ID

Postnatal ID

Fetal/Neonatal ID

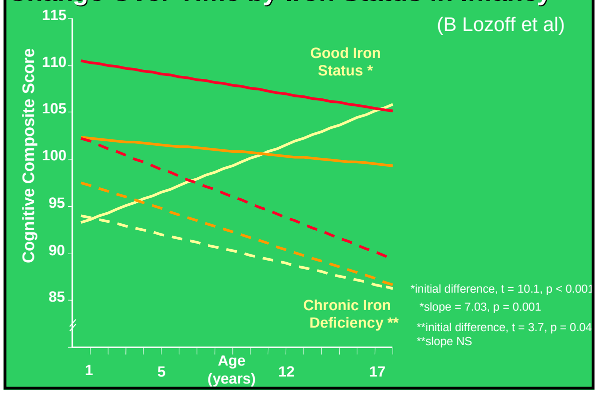
Postnatal ID: Who is at risk?

- Most postnatal ID is due to inadequate dietary intake ± low stores at birth ± blood loss
  - Low stores at birth
    - Maternal anemia, hypertension, smoking, diabetes mellitus
  - 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)

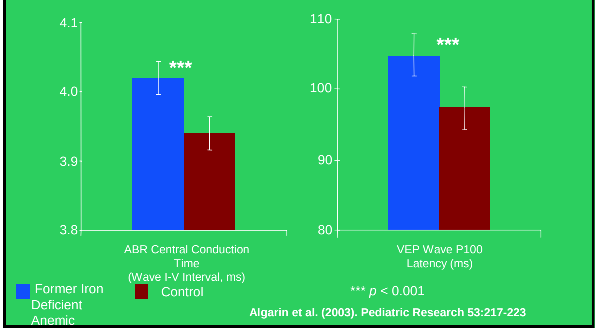
Neurobehavioral Sequelae of Early Postnatal Iron Deficiency in Humans

- Over 40 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 striatal and hippocampal 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 myelination

Level of Initial Mental Scores and Change Over Time by Iron Status in Infancy



Electrophysiologic Evidence: Evoked Potential Latencies 3 Years after Iron Rx



Neurotransmitter Effects in the Rat

- Effects on monoamines, esp dopamine, known since late 1970's (Yehuda, Youdim, Beard)
- While ID: Decreased DAT, D1R, D2R and increased SERT
  - Regional differences- Large effects in striatum
  - Changes related to timing and severity
- Following Brain Iron Repletion: Decreased striatal D2 receptors not reversed with iron supplementation after weaning (P21)

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)

(Connor, Clardy, Rao)

Summary: Postnatal ID

- Classic postnatal IDA results in motor and cognitive behavioral alterations
  - while ID (motor and cognitive)
  - after iron treatment (mostly cognitive)
- Models of early postnatal ID (P4 to P21) in the rat support effects on myelination and striatal monoamine metabolism
  - map well onto the altered behaviors and electrophysiology in humans

What Can Negatively Affect Neonatal Brain 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
  - IUGR due to maternal hypertension during pregnancy
  - 50% affected (Chockalingam et al, 1987)
  - 75,000 infants per year in US
  - 32% decrease in brain iron concentration (Georgieff et al, 1995)

What Can Negatively Affect Neonatal Brain Iron Status?

- Increased fetal iron demand for erythropoiesis
  - Chronically hypoxic fetus (IDM)
  - 65% affected (Georgieff et al, 1990)
  - 150,000 infants per year in US
  - 40% decrease in brain iron concentration (Petry et al, 1992)
- Basic principle: Iron is prioritized to RBCs over brain & other organs when fetal Fe demand exceeds fetal Fe supply

Neurobehavioral Sequelae of Fetal and Neonatal ID

- Fewer studies than in postnatal ID
- Behavioral abnormalities
  - Term infants with low neonatal iron stores have
    - poorer school age neurodevelopment (Tamura et al, 2002)
    - worse immediate and delayed recall at 3.5 y (deBoer et al, 2008)
  - Preterm infants with low iron stores at 36 weeks PCA
    - more abnormal reflexes (Armany-Sivan, 2006)
- Electrophysiologic abnormalities
  - Term neonates with ferritin concentrations <35 mcg/L have impaired auditory recognition memory processing (Siddappa et al, 2004)

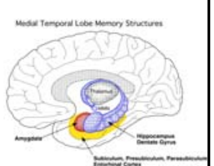
SUGGESTS SIGNIFICANT HIPPOCAMPAL IMPAIRMENT

Neonatal Iron Deficiency and Hippocampal Development

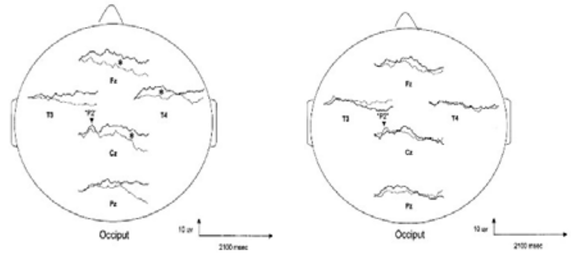
Human Data

Hippocampus and Recognition Memory

- Hippocampus resides in medial temporal lobe
- Mediates recognition memory of
  - Objects and events
  - Spatial mapping
- Develops during late fetal life and is intact at term birth
- Alters morphology and cellular signaling based on experience (experience dependent plasticity)
- Can be assessed in neonate measuring Event Related Potentials during memory task



Event related potentials (ERPs) in infants

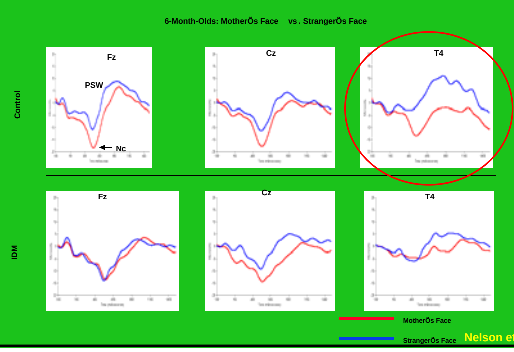


Iron Sufficient

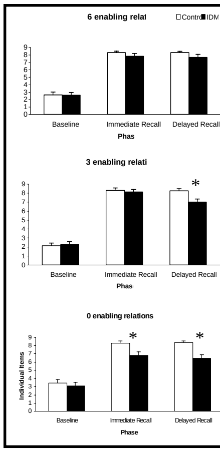
Iron Deficient

Siddappa et al., 2004, Pediatr. Res.

6 month ERPs in IDM and Control



Nelson et al, 2000



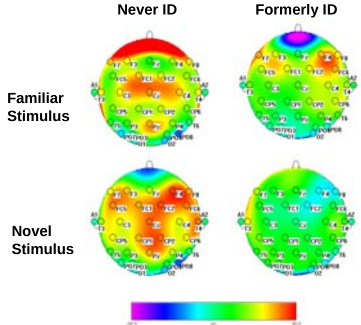
Perinatal Iron Status and Explicit Memory at 3.5 Years

1) IDM as good as control only if enabled

2) Newborn ferritin correlated with:
Immediate recall: r=0.51; p<0.01
Ordered recall: r=0.52; p<0.01
Delayed recall: r=0.40; p<0.01

DeBoer et al, 2008 under review

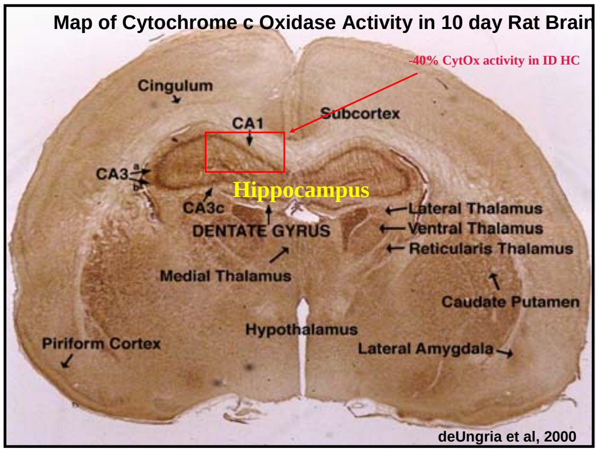
Topographic Brain Maps Based on ERPs: What structures are they using at age 3?



Conclusion: Infants who were iron deficient as newborns have a differently wired brain and process memory events differently even after iron repletion

Iron Deficiency and Hippocampal Development

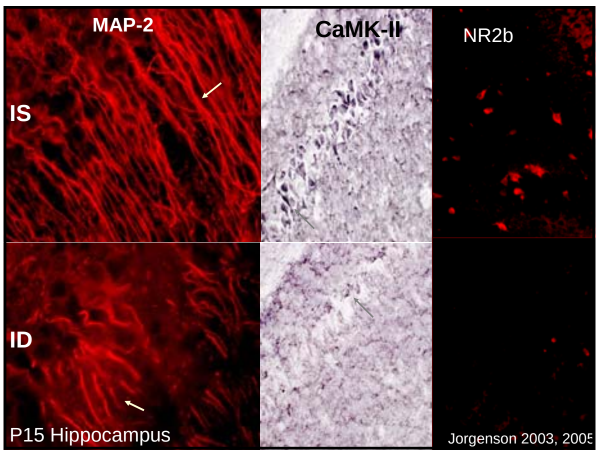
Rodent Data



Dendritic Arborization in Hippocampal Area CA-1

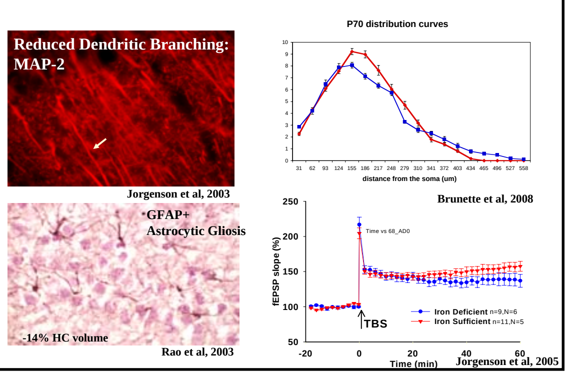
- Dendritic arborization increases rapidly between P15 and P25 in the rat
- Arborization is dependent on
  - Adequate neuronal energy status
  - Glutamate mediated stimulation
- Both processes compromised by ID

Rao et al, 2003
Jorgenson et al, 2005



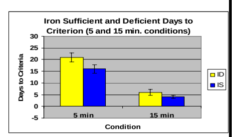
Persistence of Abnormalities after Iron Repletion

Structural Abnormalities, Astrocytosis & Reduced LTP in Adult CA1 (P65-70) after Early ID



Rat Dietary ID: Behavioral Consequences

- Altered performance on hippocampus-mediated behaviors
  - Radial arm maze *Schmidt et al., 2007 Behav Neurosci.*
    - Longer time to criteria



  - Morris Water Maze *Felt & Lozoff, 1996 J Nutr.; Felt et al., 2006 Behav Brain Res.*
    - Longer swim distances; less time in target quadrant
  - Trace Conditioning *McEchron et al.,2007, Dev Neurosci.; Gewirtz et al, 2008 Brain Res.*
    - Less fear-potentiated startle

Genomic Alterations in IDA Rat Hippocampus

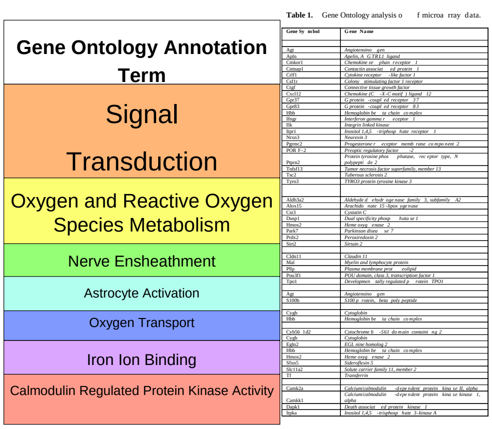
A new approach to IDA

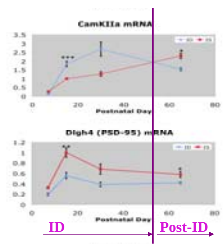
Could these account for long-term changes in structure and function?

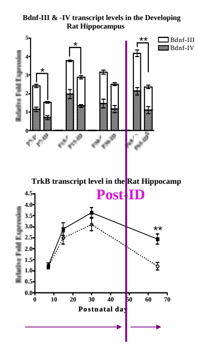
Expression Studies in Hippocampus of Rats w/Dietary ID

(ES Carlson et al, 2007)

- Affymetrix R230A genechip (~9000 genes)
  - 468 transcripts with altered expression due to iron deficiency (FDR < 0.04)
- 25 genes tested over development with qPCR, 10 had long-term changes at P65
- Changes were detected in genes related to iron metabolism, energy metabolism, dendrite morphogenesis, synaptogenesis and plasticity







P7= Proliferative Phase
P15,30= Differentiative Phase
P65= Adult Synaptic Plasticity Phase
Carlson et al, 2007

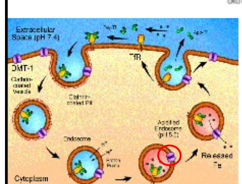
BDNF is critical for dendritic morphogensis during development and maintaining synaptic plasticity during adulthood
Tran et al, 2008

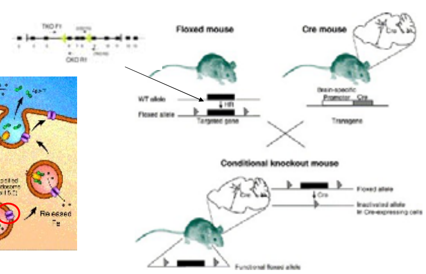
But, those animals were anemic!

How do we know it is iron?

Does non-anemic ID cause neurodevelopmental problems?

Conditional Gene Targeting of DMT-1 during Late Gestation

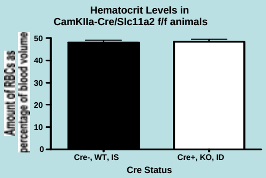




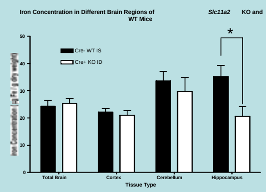
Carlson et al, 2008

Conditional gene targeting in the mouse nervous system: Insights into brain function and diseases.
Gaveriaux-Ruff and Kieffer, 2007, Pharmacol. Ther.

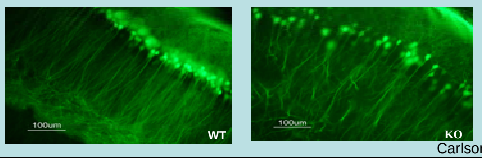
DMT-1 KO is not anemic



DMT-1 KO has a 40% HC iron loss

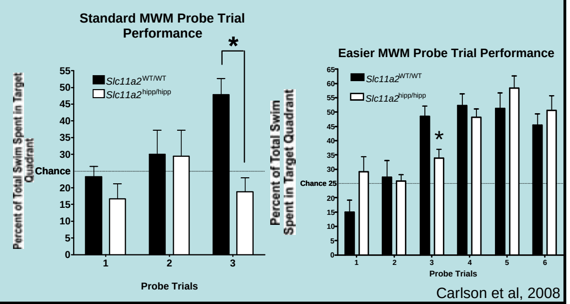


DMT-1 KO has abnormal dendrites



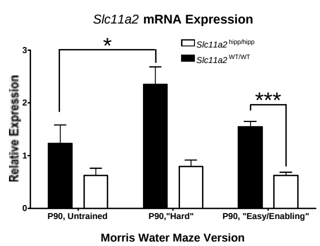
Carlson et al, 2008

Adult DMT-1 KO has Impaired Learning on Morris Water Maze, BUT CAN LEARN WHEN ENABLED



Carlson et al, 2008

Iron Uptake is Important for Learning and Memory



Carlson et al, 2008

Iron Dosing for Neonates and Infants

• Term AGA	• 1 mg/kg daily
• Term SGA	• 2 mg/kg daily
• Preterm >30 w EGA	• 2 mg/kg daily
• Preterm <30 w EGA	• 4 mg/kg daily
• Preterm on rhEpo	• 6 mg/kg daily

Monitoring Iron Status

- AAP recommends hemoglobin screening at 9 months of age
  - Earlier screening for premies, SGAs
  - sTfR, ZnPP, MCV might screen pre-anemia
    - sTfR, ZnPP not available everywhere, lacking standards for < 12 month olds
- Ferritin is good pre-anemic screen
  - But, infant cannot have acute illness (acute phase reactant)
- NHANES and CDC testing sTfR/Heme ratio

Summary

- Iron plays a critical role in early neurodevelopment
- Early iron deficiency without anemia disrupts form and function of the hippocampus
  - Alteration of genes involved in morphogenesis and synaptogenesis
  - Alterations persist into adulthood
  - ID children can perform normally on cognitive testing when enabled (e.g., teaching strategies)
- Early detection of at risk infants is crucial for brain health
  - Need new tools to detect pre-anemic ID

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Comments

and

Questions

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