Impact of Nutritional Deficiencies on Child Health and Long-term Neurobehavioral Development

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Introduction

- Assistant Professor in Division of Global Pediatrics (Medical School)
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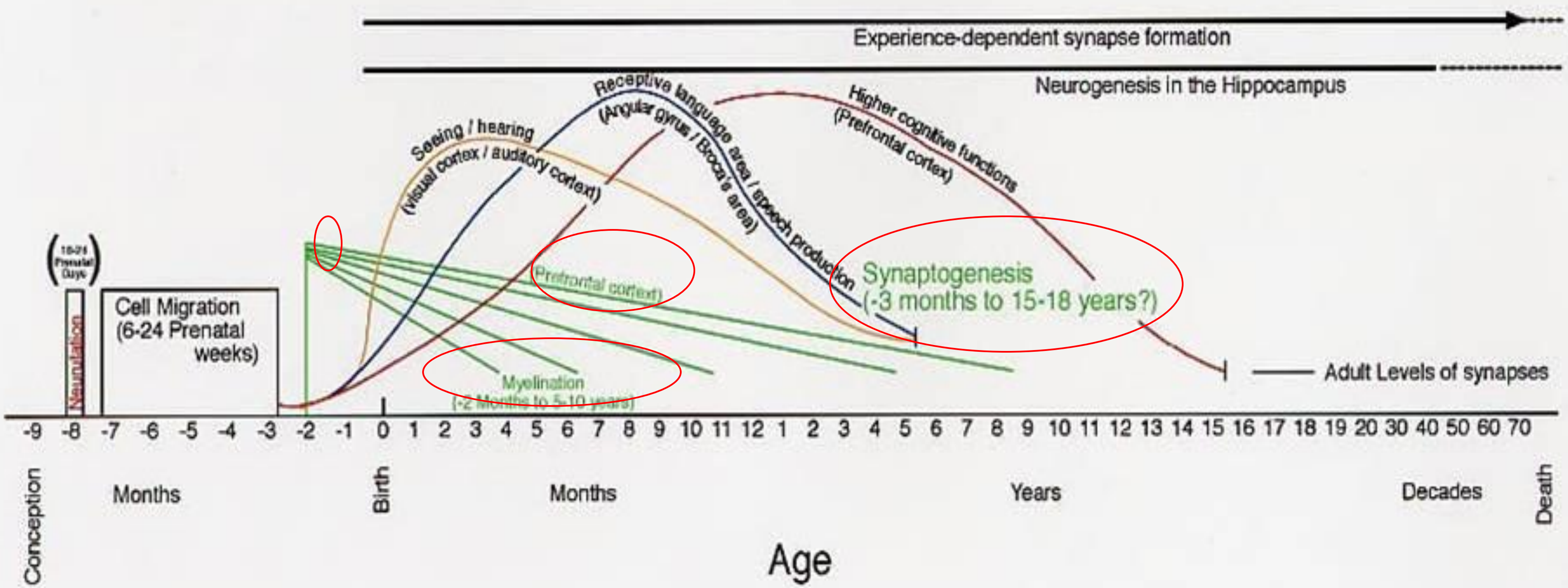
- Human Nutrition and Global Health
- Interaction of micronutrient deficiency and infectious disease → developing brain

Overview

- Basic principles of nutrient/brain interactions
- Nutrients of particular importance to early brain development
  - Protein
  - Iron
- Uganda iron and malaria study

.. “the most important stage of any enterprise is the beginning, especially when something young and sensitive is involved…. . That’s when most of its formation takes place and it absorbs every impression that anyone wants to stamp on it”. (Plato, *Republic*, 377a-b).

Human Brain Development



Nutrient-Brain Rules of Engagement

- Brain is not a homogenous organ
- Regions/processes have different developmental trajectories
  - Monoamine neurotransmitter system (mediates reward, affect, mood)→~ 35 weeks gestation to age 3 years
  - Myelination→ 32 weeks gestation to age 2 years
  - Hippocampus (recognition and spatial memory) → 32 weeks gestation to age 18 months
- The vulnerability of a brain region to a nutrient deficit is determined by
  - When nutrient deficit is likely to occur in a lifetime
  - Brain's requirement for that nutrient at that time

Nutrients with Particularly Large Effects on Early Brain Development and Behavior

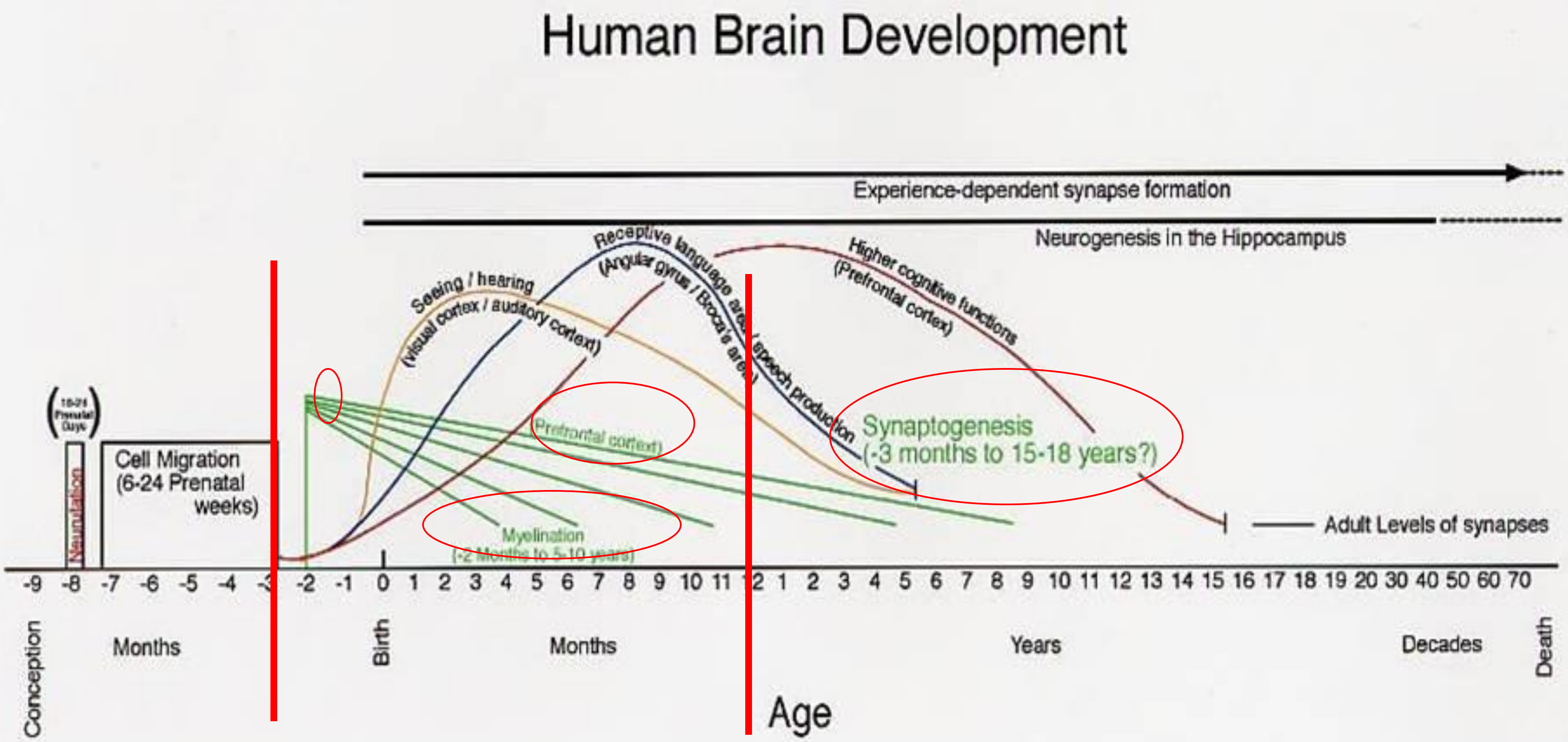
- Macronutrients
  - Protein
  - Specific fats (e.g. LC-PUFAs)
  - Glucose
- Micronutrients (vitamins and minerals)
  - Iron
  - Zinc
  - Copper
  - Iodine (Thyroid)
  - B vitamins (B6, B12)
  - Vitamin A
  - Vitamin K
  - Folate

Protein

What the Brain Does with Protein

- DNA, RNA synthesis and maintenance
- Neurotransmitter production
- Growth factor synthesis
- Structural proteins
  - Neurite extension (axons, dendrites)
  - Synapse formation (connectivity)

Protein

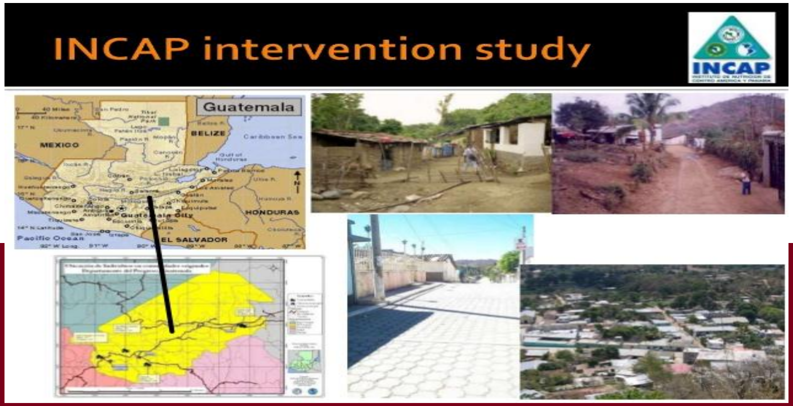

Human Brain Development
Experience-dependent synapse formation
Neurogenesis in the Hippocampus
Receptive language area / speech production
(Angular gyrus / Broca's area)
Higher cognitive functions
(Prefrontal cortex)
Seeing / hearing
(visual cortex / auditory cortex)
Prefrontal cortex)
Synaptogenesis
(-3 months to 15-18 years?)
Adult Levels of synapses
Neurulation
Cell Migration
(6-24 Prenatal
weeks)
Myelination
(-2 Months to 5-10 years)
-9 -8 -7 -6 -5 -4 -3 -2 -1 0 1 2 3 4 5 6 7 8 9 10 11 12 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 30 40 50 60 70
Conception
Months
Birth
Months
Years
Decades
Death
Age

IUGR: Experimental Evidence from Clinical Studies

- IUGR=>Poor developmental outcome
  - verbal outcome
  - visual recognition memory
  - 6.8 point IQ deficit at 7 years (Strauss & Dietz, 1998)
  - Two 2015 systematic reviews (Murray and Levine)—both concluded poorer nd outcomes with IUGR
    - Children born 35 weeks of gestation or later, those with IUGR scored 0.5 sd units lower across all neurodevelopmental assessments.

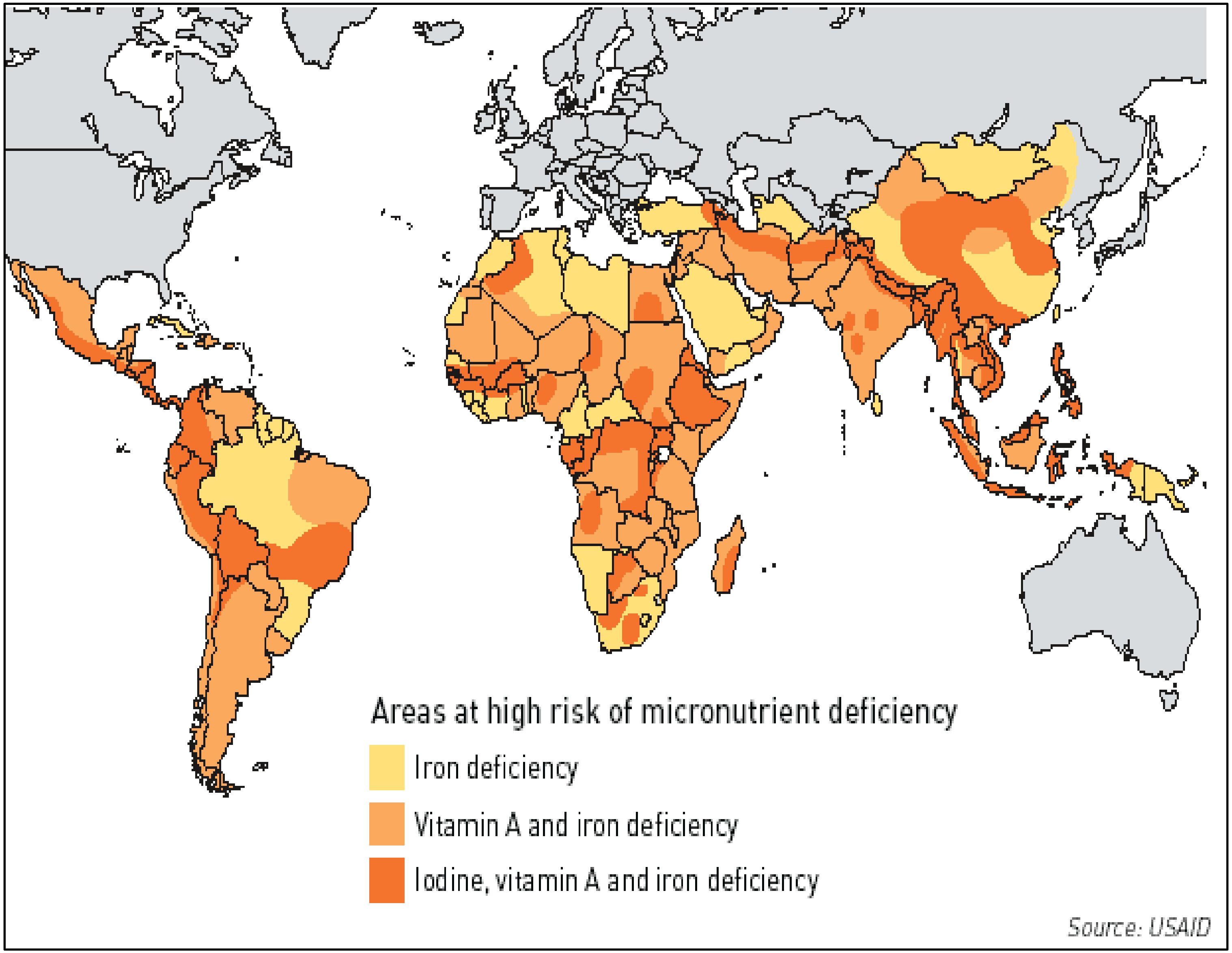
INCAP studies 1969-1977 and 1988-1989 (Pollitt et al.)

- Longitudinal study: pregnant mothers and young children in one village received beverage with protein + carbohydrates, in another village carbohydrates alone
- Adolescent children who received protein-fortified drink in utero and early childhood scored higher on tests of knowledge, numeracy, reading, and vocabulary



Thailand study
(Pongcharoen et al., 2012)

- Cross-sectional follow-up study of 9-year-old children
- Linear growth rate before, but not after, 12 months of age, and infant weight before four months of age significantly predicted child IQ at age 9.
- Child linear growth and weight after 12 months were not related to child IQ.


Areas at high risk of micronutrient deficiency
Iron deficiency
Vitamin A and iron deficiency
Iodine, vitamin A and iron deficiency
Source: USAID

Worldwide impact of micronutrient deficiencies

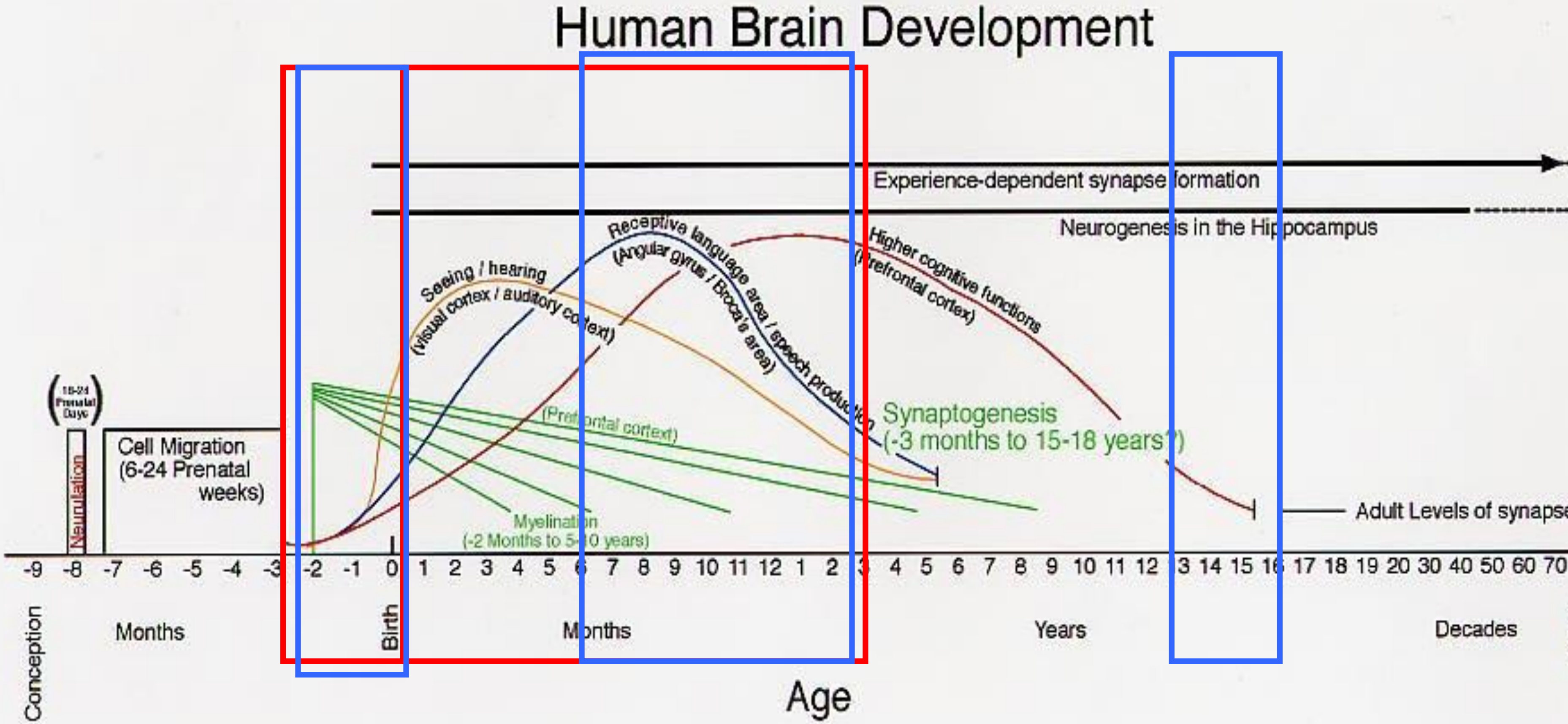
- Iron
  - 2 billion people (1/3 of world's population) are iron deficient
  - Also causes low thyroid hormone state
- Zinc
  - 1.8 billion people are zinc deficient
  - Usually co-morbid with protein deficiency
- Iodine
  - 600 million people world-wide are deficient
  - I Deficiency =>thyroid hormone deficiency =>cretinism (global delays)

ELIMINATION OF THESE MICRONUTRIENT DEFICIENCIES WOULD INCREASE THE WORLD'S IQ BY 10 POINTS (Morris 2008)

Iron

Iron: a critical nutrient for the developing human brain

- Iron containing enzymes and hemo-proteins are involved in developing brain
  - Delta 9-desaturase, glial cytochromes control myelin production
    - » Iron Deficiency=> Hypomyelination
  - Cytochromes mediate neuronal and glial energy status
    - » Iron Deficiency=> Impaired neuronal growth, differentiation
  - Tyrosine Hydroxylase involved in monamine neurotransmitter synthesis (dopamine, serotonin, norepi)
    - » Iron Deficiency=> Altered affect, mood, motor control



Fetus Late Infancy/Toddler Pubertal

Table 2: The timing of brain demand and risk of deficiency for iron*

	Period of high brain demand for iron?	Period of high risk for iron deficiency?	Neurodevelopmental impact?
Fetal period	Yes	Yes	Yes
Infancy (0-6 mos)	Yes	No	No
Toddlerhood (6-36 mos)	Yes	Yes	Yes
Middle Childhood (3y -12y)	No	No	No
Teens (13y-)	No	Yes	No

*When the period of high brain demand for iron coincides with a period of high risk for iron deficiency, as in the fetal and toddler periods, neurodevelopmental consequences result. Accordingly, these periods are optimal for iron intervention.

Nepalese studies

(Christian, Murray-Kolb et a., 2010-2012)

Pregnancy	Post-natal 12-36 months	Age 7-9 years Psychometric tests
Iron supplementation		
✗	→	Better intellectual, motor, executive functioning
	✗ →	No benefit
✗	✗ →	No additional benefit

Postnatal Iron Deficiency

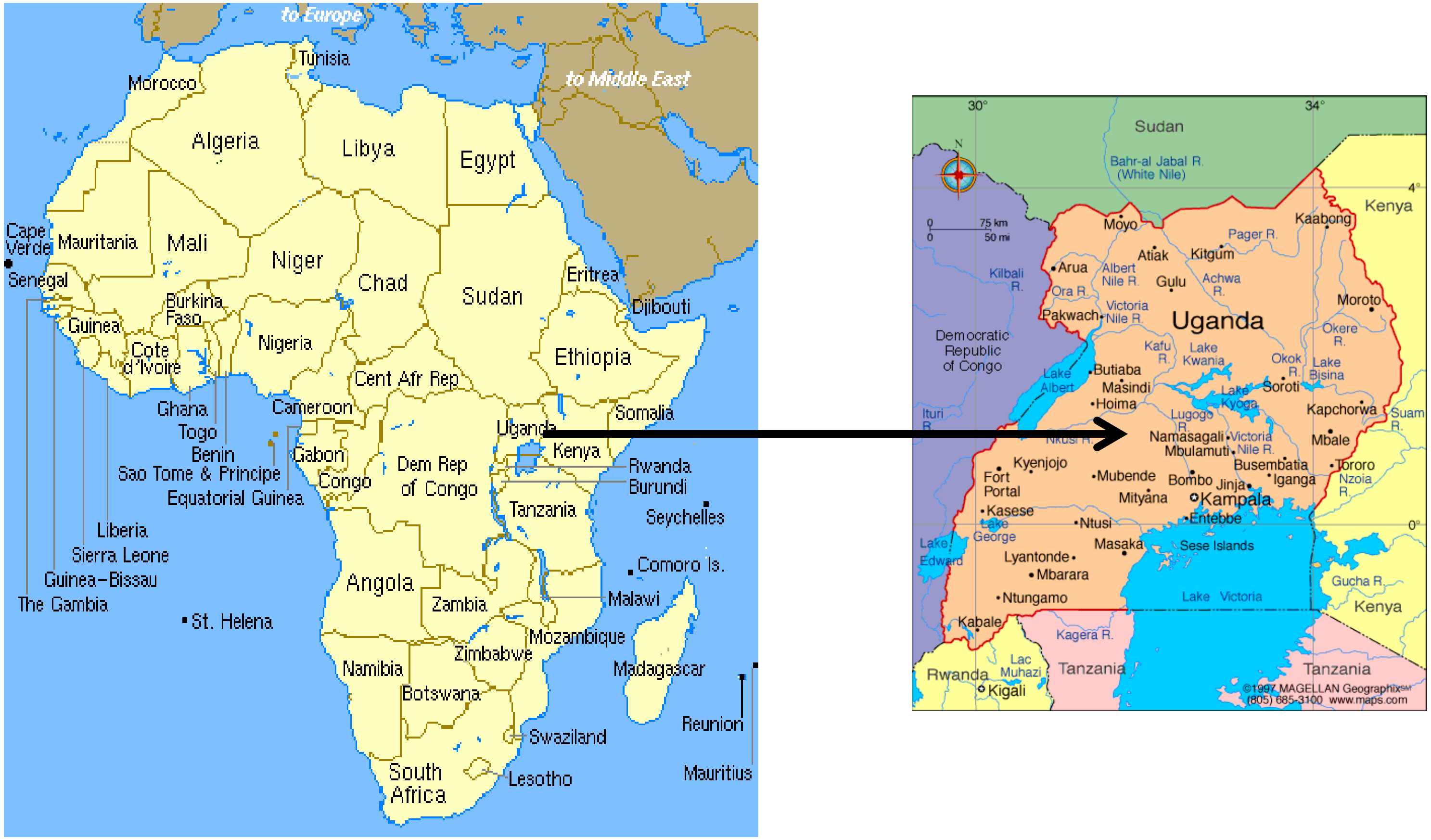
Early Childhood

- Social-emotional behaviors

<u>Dopamine related behaviors:</u>

- – Positive responsively
- – Reward responsiveness
- – Sensitivity to novelty

Uganda iron and malaria study



Frequency of cognitive deficits in Ugandan school-aged children with cerebral malaria at 24-mo follow-up

	Cerebral malaria, n=38 (%)	Community controls, n=79 (%)	Chi-square p
At least one impairment	26.3	7.6	0.006
Working memory	7.9	5.1	0.680
Attention	18.4	2.5	0.005
Tactile learning	7.9	1.3	0.100

John et al. Pediatrics 2008

Is iron deficiency part of the problem?

- Prevalence of iron deficiency among Ugandan children 6 mo- 5 yr = ~60% (WHO)
- Iron deficiency also has established harmful effects on memory and attention.
- Does iron deficiency play a role in the neurodevelopmental impairment observed in children with severe malaria?
- Expected effect of iron supplementation?

Pemba Island Study 2002

Pemba study

- Determine the effects of iron/folic acid +/- zinc supplementation on severe morbidity and mortality
  - 30,000 children aged 1-35 mo
- Began February 2002
- Iron-containing arms stopped by DSMB in August 2003
- 12% increased risk of hospitalization or death among children who received iron
- No increased risk with iron in parallel study in Nepal
- Sub-study showed that ZPP level modified risk from iron
  - High ZPP > Benefit from iron
  - Normal ZPP > Potential harm from iron

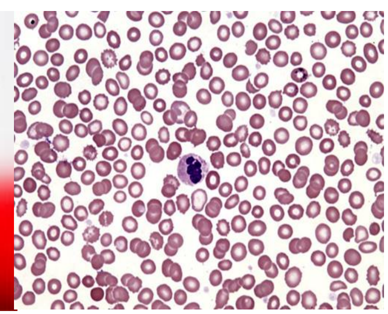
WHO recommendation 2007

- Iron deficiency prevention:
  - Universal iron supplementation no longer recommended in malaria-endemic areas.
  - Screen for iron deficiency before giving iron.
- Iron deficiency treatment:
  - Daily iron therapy for 3 months with food along with measures to prevent and control malaria
  - Antimalarial treatment plus iron therapy for children with malaria and iron deficiency

Concurrent antimalarial treatment and iron therapy

Antimalarial Treatment

+

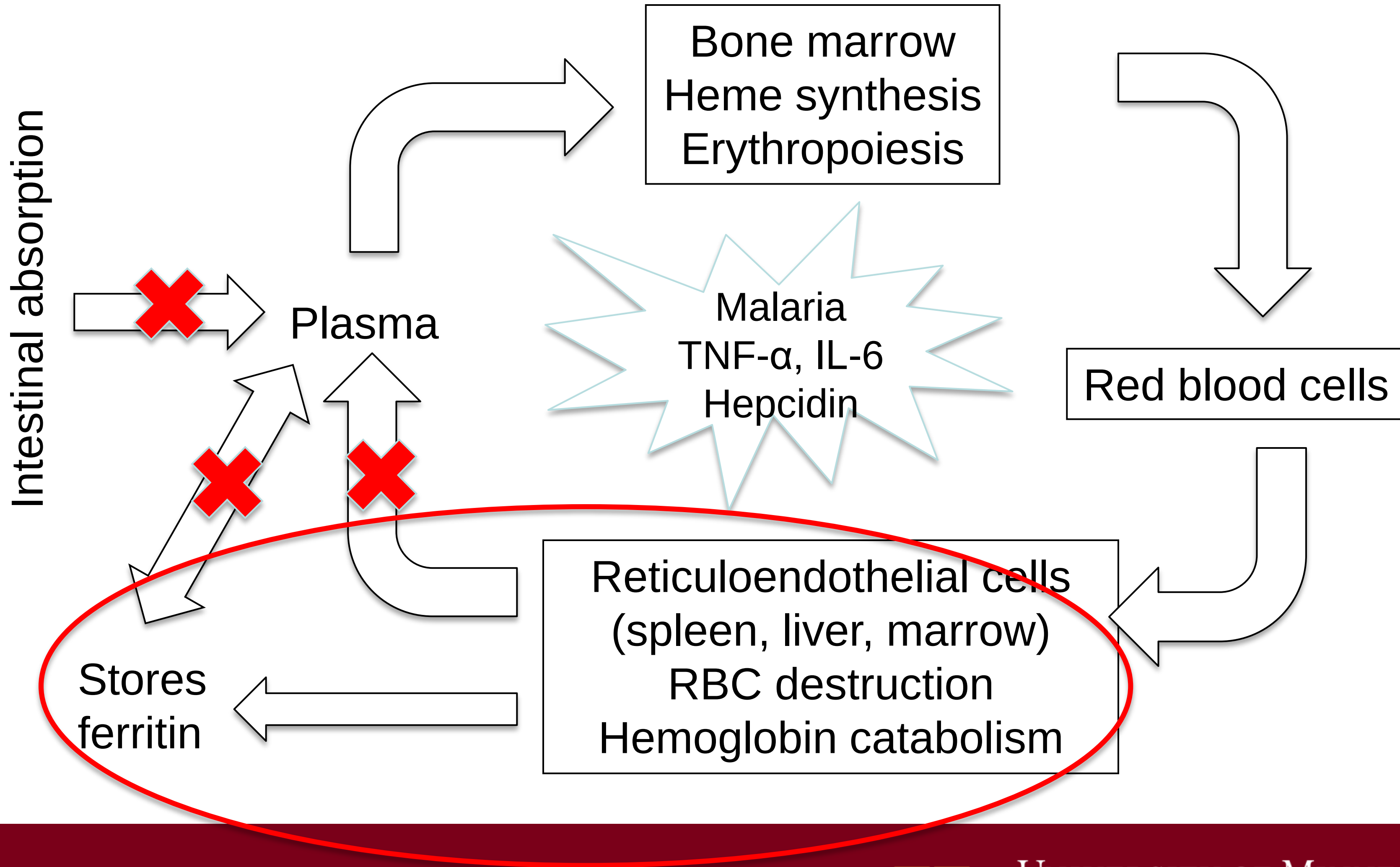


Unresolved anemia

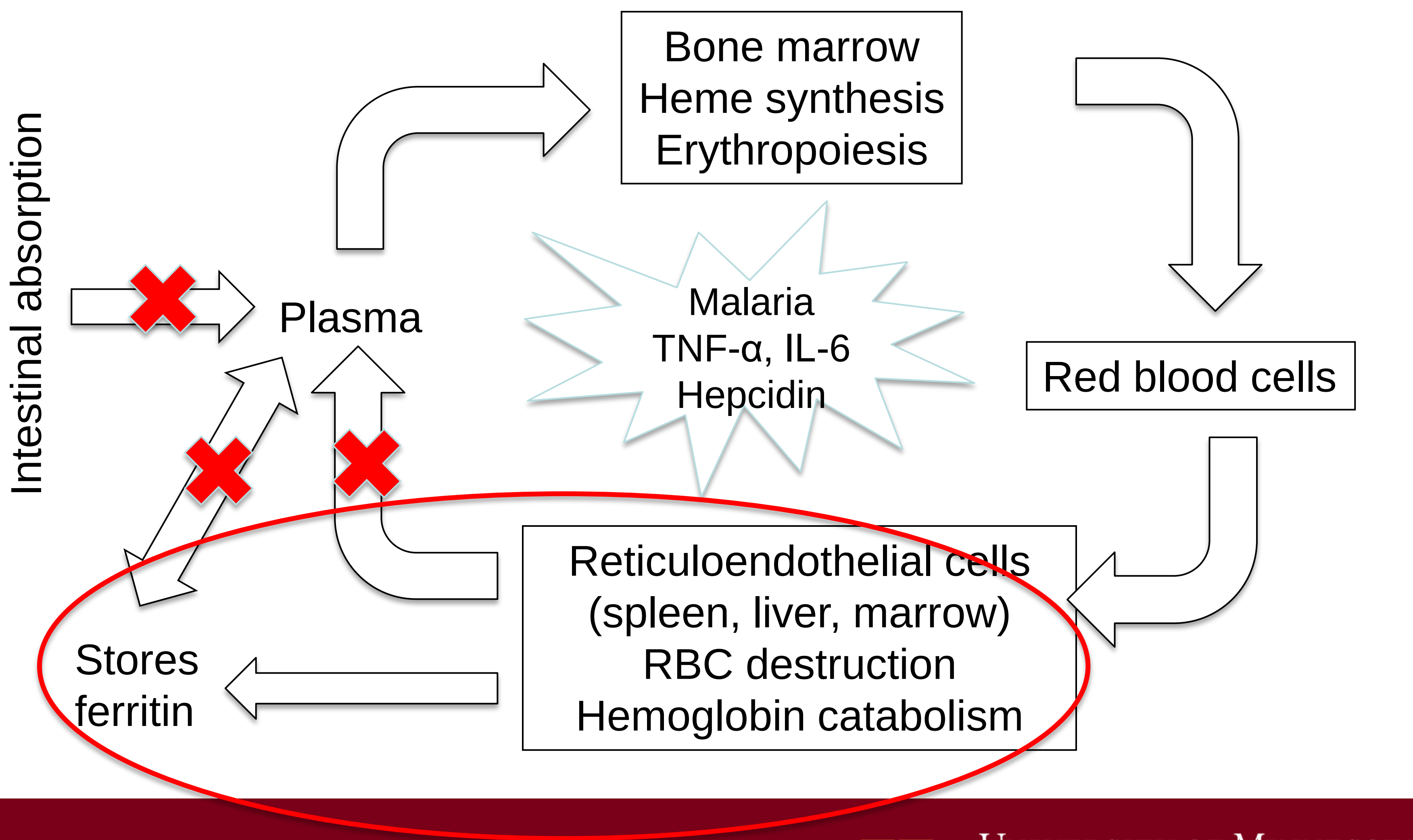
Persistent iron deficiency

More frequent clinical malaria episodes

Iron absorption, metabolism, and storage



Iron absorption, metabolism, and storage



Immediate vs. delayed iron

- Hepcidin declines 4 weeks after anti-malarial treatment (Doherty et al. 2008, deMast et al. 2009)
- Delaying start of iron by 4 weeks after anti-malarial treatment may lead to improved iron absorption and utilization
- Will iron given 4 weeks after malaria episode lead to:
  - **Improved iron status and better resolution of anemia**?
  - **Fewer malaria episodes** (iron supplied when parasitemia cleared)?
  - **Better cognitive & behavioral outcomes?**

Kampala Iron Study, Uganda 2010-2014

- Children (18 mo – 5 y) with severe malaria [cerebral malaria (CM), severe malarial anemia (SMA)] and community children (CC)
- Children with high ZPP randomized to start 3-mo of iron with antimalarial treatment at baseline (immediate group) or 4 weeks later on Day 28 (delayed group)
- Outcomes: anemia and iron status at 6 and 12 months, frequency of clinical malaria episodes, neurobehavioral development

Center for Neurobehavioral Development Behavior Rating Scales

- Inattention/hyperactivity
  - Negative affect, cooperation, social responsiveness, hyperactivity
- Fearfulness
  - Fear, exploration, social initiation
- Positive affect
  - Positive affect, engagement/interest

Functional Isolation Hypothesis

Undernutrient- micronutrient deficiency (ID)

↓

Altered socio-emotional behavior

↓

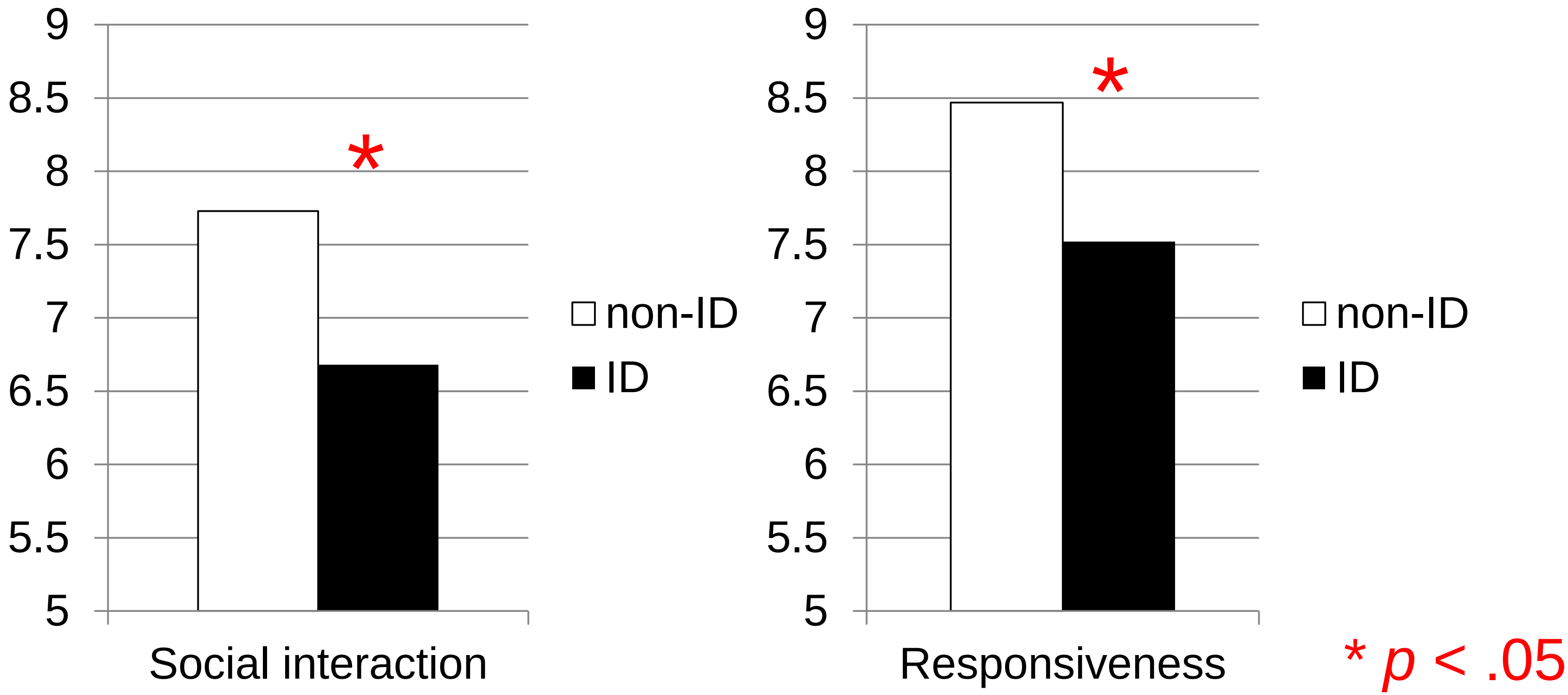
Negative effects on caregiving environment

↓

Poorer developmental outcomes

Differences Based on ID groups

- All children (*N* = 160)



* $p < .05$

Summary

- Certain nutrients have high impact on early brain development
  - Protein, fats, iron, zinc, iodine, vitamins A, folate
  - More impact in fetal and neonatal time period
- Nutrient effects depend on timing, dose and duration
  - Timing in terms of brain development process
  - Timing in terms of prevalence of nutrient deficit in population
  - Early identification and correction is essential

Policy implications

- Recognize that nutritional policy is transgenerational
  - Maternal pre-conceptional nutrition status affects fetal health
  - Concentrate on young women
    - Own growth needs + additional stress of pregnancy
  - Early prenatal care
    - Address nutritional status
    - Address maternal diseases that affect fetal nutrient status
      - Diabetes, hypertension, malaria

Policy Implications

- Policy should **prevent** long-term nutritionally based brain deficits
  - Screen for maternal/neonatal nutrients that particularly affect early brain development
  - Ensure adequate dietary supply or supplement these nutrients in mother
  - Nutritional surveillance during early childhood


LEVI'S