Nutrition and the brain:
The importance of the first 1,000 days

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FIRST 1000 DAYS

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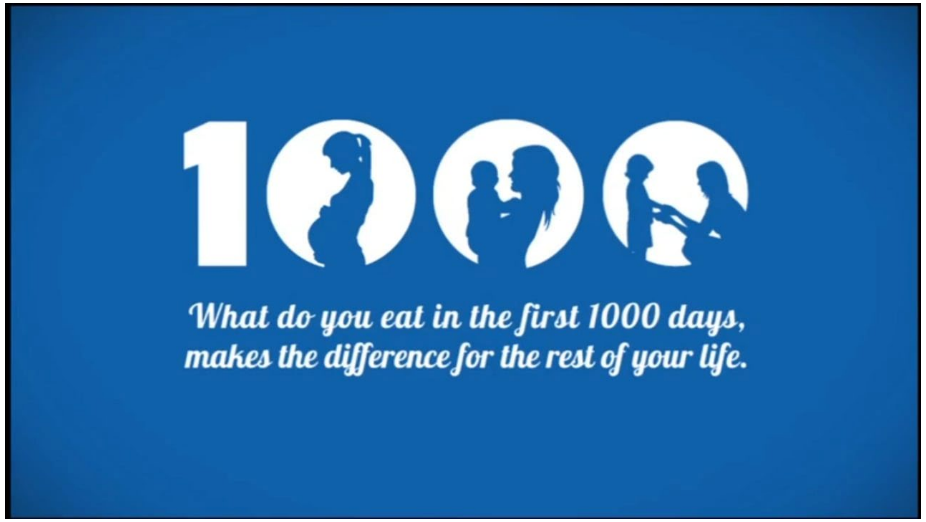
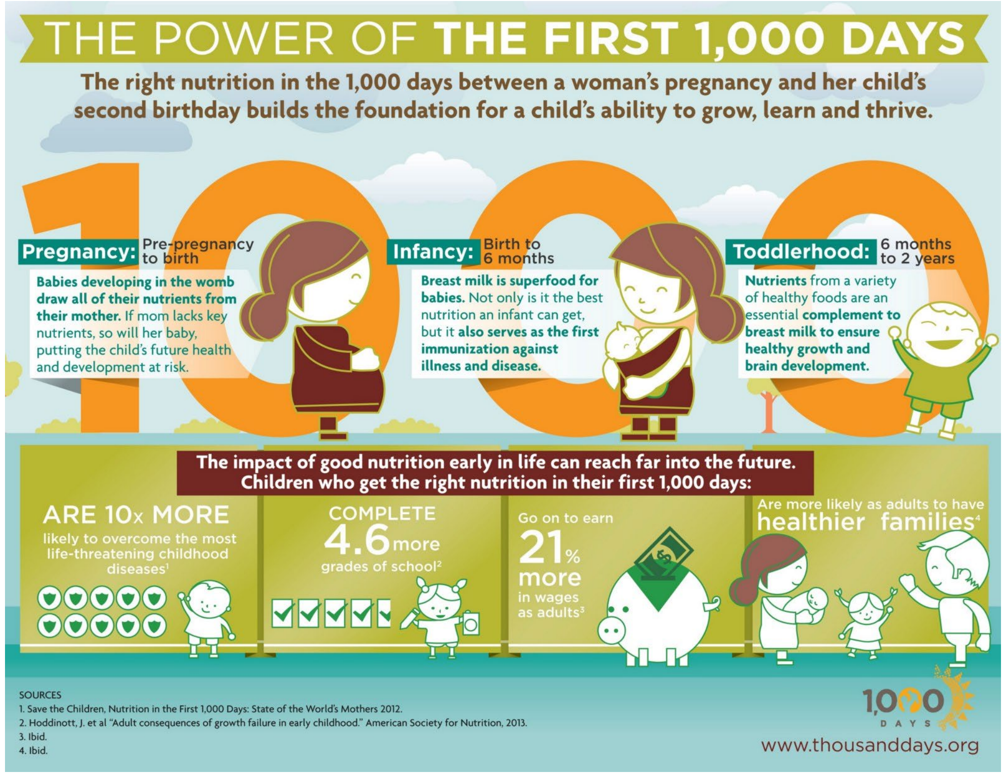




The brain in the first 1,000 days

- Reduction of toxic stress and inflammation
- Presence of strong social support and secure attachment
- Provision of optimal nutrition

Georgieff et al., Acta Paediatrica 2018

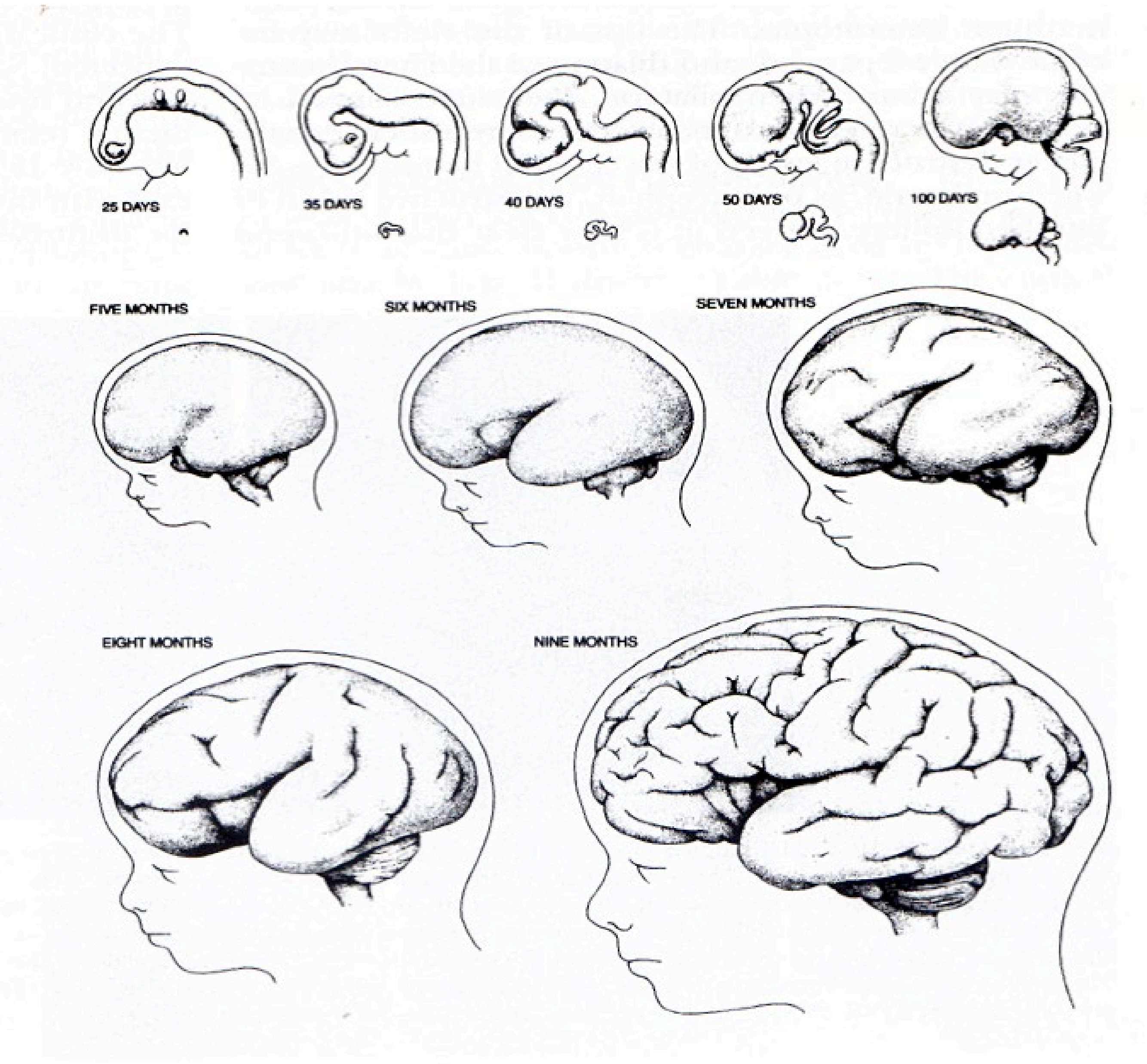
Global perspective

- At least 200 million children fail to reach their developmental potential each year.
- Four primary causes (Walker SP et al. Lancet, 2007):
  - Inadequate cognitive stimulation
  - Stunting
  - Iron deficiency anemia
  - Iodine deficiency

Outline

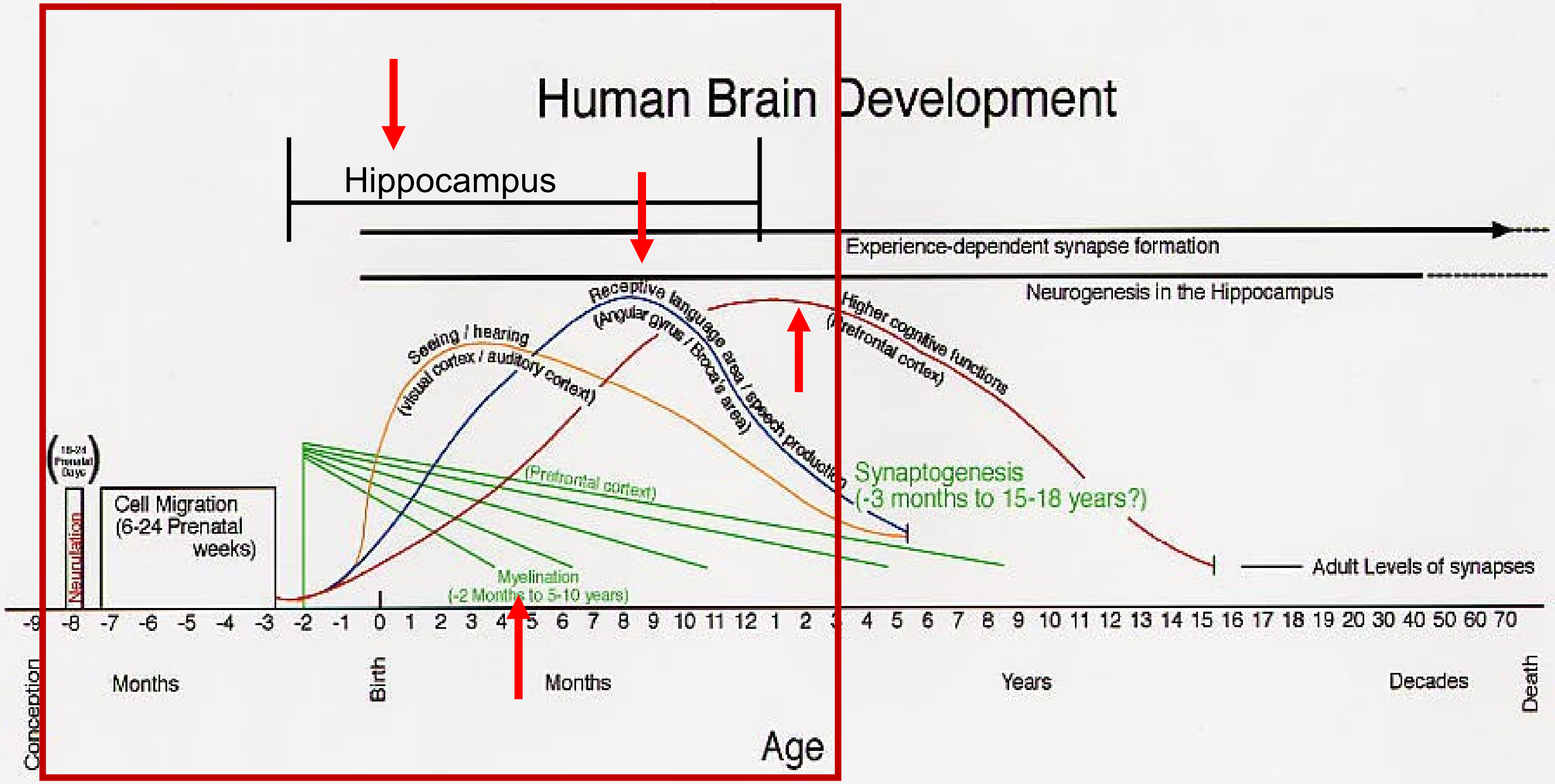
- General principles for nutrient and brain interactions
- Mechanisms of how deficiency can lead to long-term dysfunction
- Macro and micronutrients critical for brain development
- Application of general principles to nutrient/brain literature
- Implications for research and programming

Fetal brain development



Why is the brain at risk for early life changes in nutritional status?

- Brain is rapidly developing in the late fetal and early neonatal period
  - Regions (cortex, hippocampus, striatum, cerebellum)
  - Processes (myelin, neurotransmitters)
- Highly metabolic process
  - 60% of total body O_2 consumption in infancy
  - Reliant on metabolic substrates (nutrients) that support metabolism (e.g., O_2, glucose, amino acids, iron, copper, iodine)



Thompson & Nelson, Am Psychol, 2001

Early neural development is important immediately and later on

- Early years of life (fetal to 3 years): development and sensitivity of early neural systems to extrinsic influences
  - Primary systems
    - Learning and Memory (Hippocampus/Striatum)
    - Speed of Processing (Myelination)
    - Reward (Dopamine/Serotonin)
- Later developing higher order neural systems: rely on fidelity of early developing neural systems
  - Prefrontal Cortex
    - Initial connectivity from hippocampus, striatum

Early nutrition and brain development: General principles

- Nutrients and growth factors regulate brain development during prenatal and postnatal life.
- Rapidly growing brain is more vulnerable to damage and more amenable to repair following nutritional perturbations
  - Vulnerability outweighs Plasticity
- Vulnerability to a nutrient deficit is based on
  - When a nutrient deficit occurs
  - Region's requirement for that nutrient at that time
- Nutrient deficiencies may produce negative or no effect
- Nutrient overabundance may produce positive, negative, or no effect

Critical periods

- As brain ages, it specializes and is less vulnerable to insults, but loses plasticity and ability to recover

•Lower Efficiency
•Higher Plasticity
•More Amenable to Treatment

Critical period of rapid development →

•Higher Efficiency
•Lower Plasticity
•Less Amenable to Treatment

- Developing brain is highly vulnerable but also has greater plasticity
- Cellular basis of critical periods being elucidated in
  - Visual system, cortex, hippocampus, language nuclei (bird)

Early nutrition and brain development: General principles

Positive or negative nutrient effects on brain development

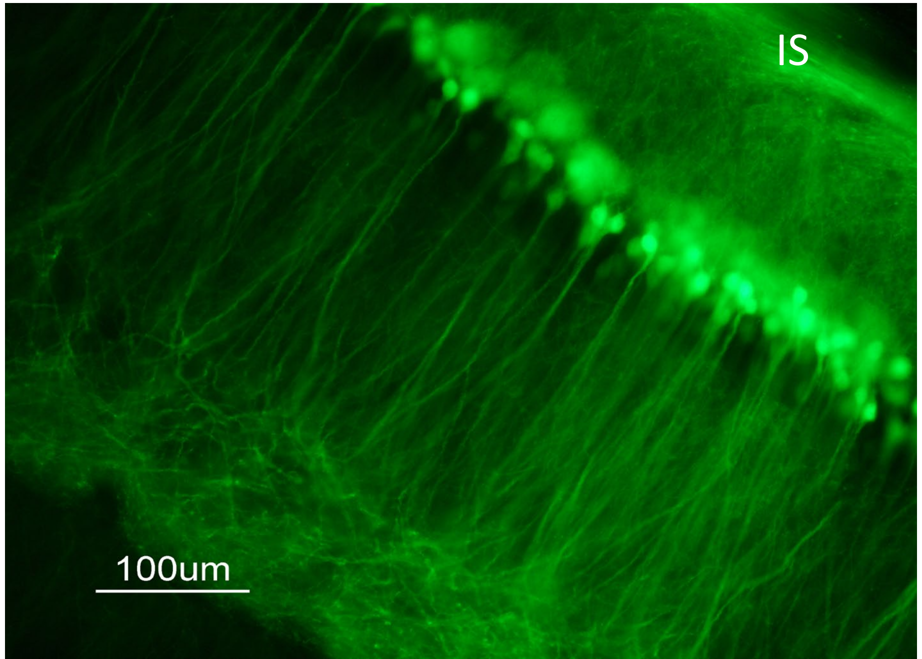
based on…

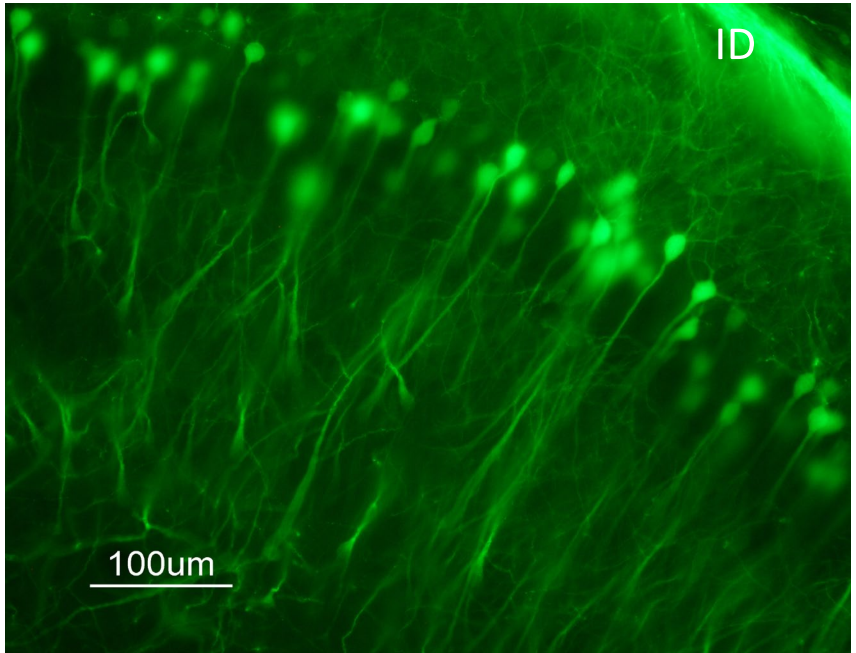
Timing, Dose, and Duration of Exposure

Kretchmer, Beard, Carlson (1996)

2 major theories accounting for long-term loss of synaptic plasticity

1. **Residual structural deficits**
   - Nutrient deficiencies during critical periods of development result in permanent structural change (Hensch, 2004; Carlson et al, 2009; Fretham et al, 2012; Callahan et al, 2013)
   - Neurobehavioral deficits relate to disordered neuronal structure (Jorgenson et al, 2005; Pisansky et al, 2013)





2 major theories accounting for long-term loss of synaptic plasticity

2. **Altered regulation of synaptic plasticity genes** through epigenetic modification of chromatin
   - Gene networks responsible for neurobehavioral performance and risk of psychopathology
   - Specific genes; e.g., Brain Derived Neurotrophic Factor (BDNF)
     - Critical for neuronal differentiation during development
     - Critical for maintenance of adult plasticity
     - Epigenetically modifiable by
       - Fetal and Neonatal Stress
       - Early Life Nutrition
         - (Martinowich et al., 2003; Roth et al, 2009; Tyagi et al, 2015; Cho et al, 2013)

Nutrients that particularly affect early brain development and later adult function

- Macronutrients
  - Protein[1,2]
  - Fats (LC-PUFA)[1,2,3]
  - Glucose[1,2]
- Micronutrients
  - Iron[1,2,3]
  - Zinc[1,2]
  - Copper[1,2]
  - Iodine (Thyroid)[1,2]
- B vitamins (B6, B12[1])
- Vitamin A
- Vitamin K
- Folate[1,2,3]
- Choline[1,2,3]

[1]Exhibits critical/sensitive period for neurodevelopment
[2]Early deficiency results in long-term dysfunction
[3]Evidence for epigenetic mechanism

The cost to the individual and to society

- Altered nutrient status in fetal and neonatal life can affect organ structure and function
  - Only during deficiency=> Acute dysfunction
  - Beyond time of deficiency=> Altered development & adult dysfunction
- The cost to society is from the long-term effects
  - Intrauterine growth restriction reduces IQ by 7 points (Strauss & Dietz, J Pediatrics, 1998)
  - Eradicating the iron, zinc, and iodine deficiency would increase the world's IQ by 10 points (Morris et al, Lancet, 2008)

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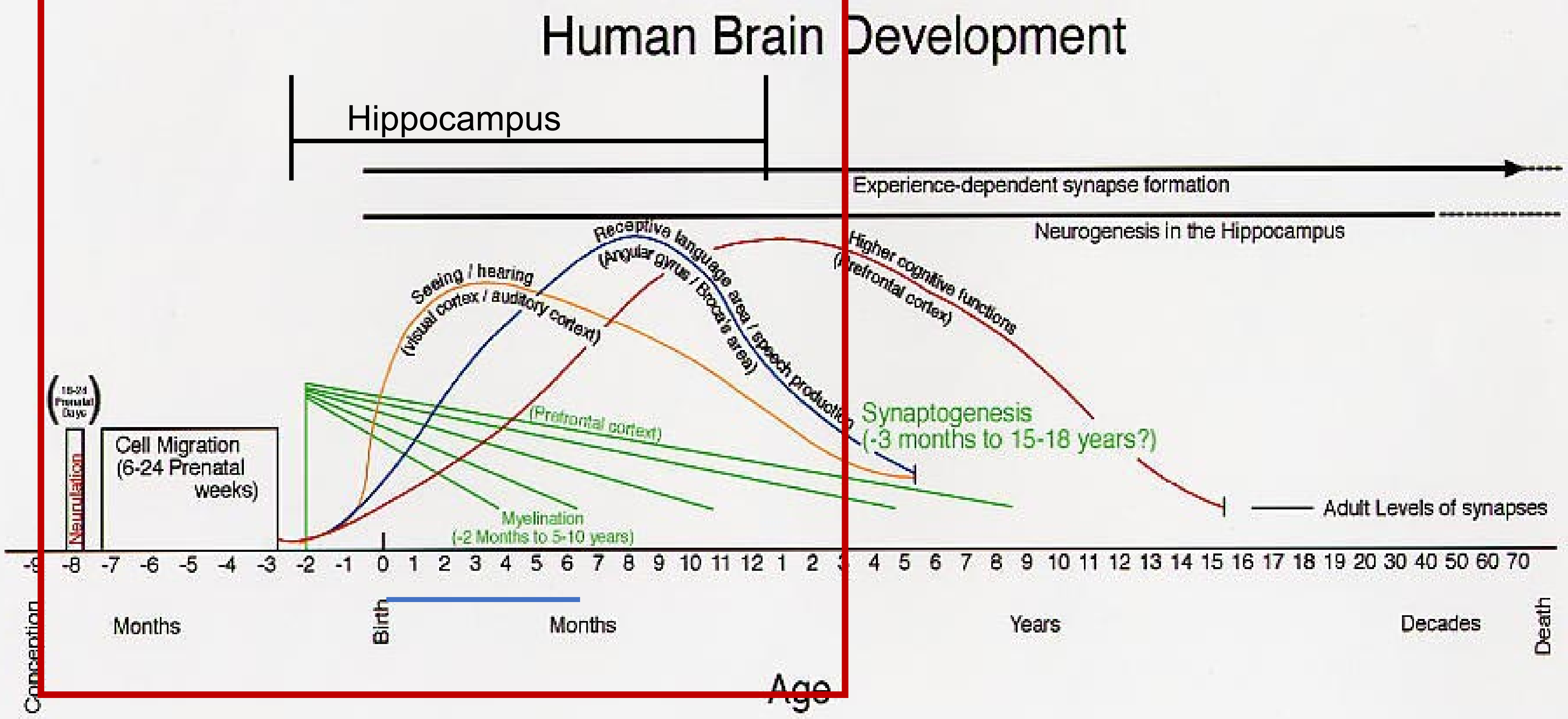
What the brain does with protein

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



Thompson & Nelson, Am Psychol, 2001

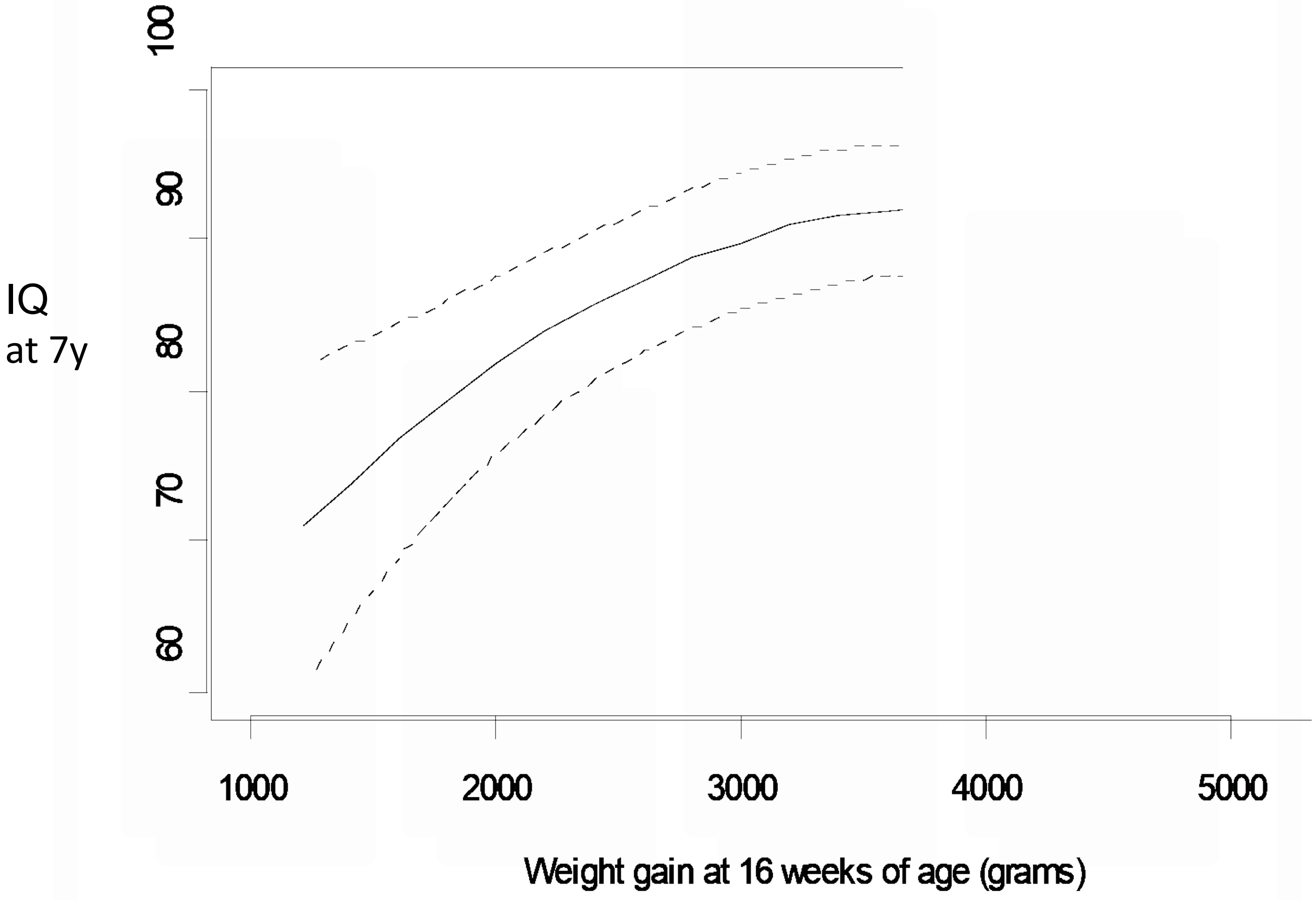
Protein undernutrition

- Protein-energy undernutrition >>> growth failure
- Intrauterine Growth Restriction (IUGR): < 10^{th} percentile for sex-specific weight-for-gestational age (> 30 million children worldwide)
  - Maternal undernutrition
  - Maternal hypertension
  - Gestational diabetes
  - Drugs/smoking
- Poor postnatal growth, e.g., stunting (1 in 4 children worldwide)
  - Poor food access during childhood
  - Chronic illness, e.g., chronic renal, hepatic, cardiac, pulmonary, infectious illness (HIV, TB, malaria)

Evidence for long-lasting effects of IUGR and early nutritional status on brain in humans

- Outcomes of IUGRs (Strauss and Dietz, 1998)
  - Lower IQ
  - Poorer verbal ability
  - Worse visual recognition memory
  - 15% with "mild" neurodevelopmental abnormalities
  - 30% increased risk of schizophrenia (Eide et al, 2013)
- Studies in Guatemala show lasting effects 25 years after protein supplementation in childhood (Pollitt et al, J Nutr, 1995)
- Compounded by postnatal growth failure (prenatal + postnatal malnutrition) (Casey et al, 2006; Pylipow et al., 2009)

Effect of postnatal failure to gain weight after IUGR on 7 year IQ

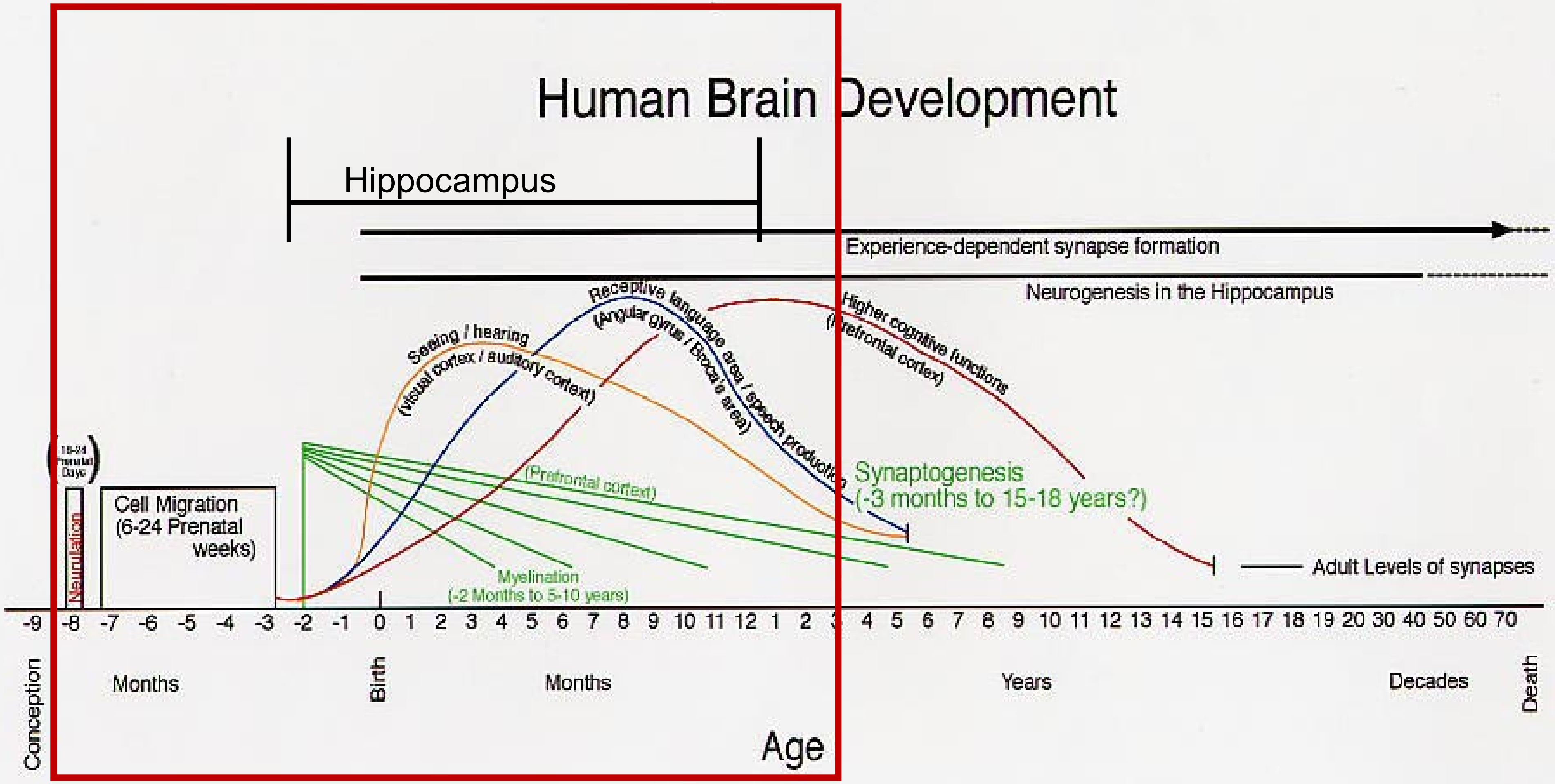


Pylipow et al, J Pediatr 2009

Early life growth and 9-year-old IQ

- Effect of size at birth, growth in early (birth to 4 mo) and late (4 -12 mo) infancy, and late postnatal (1 -9 years) growth on intellectual functioning
- Weschler Intelligence Scale for Children
- Length at birth, early, and late infancy; early infancy weight gain predicted higher IQ
- Late postnatal growth was not related to any outcome

(Pongcharoen et al., Arch Pediatr Adolesc Med, 2012)



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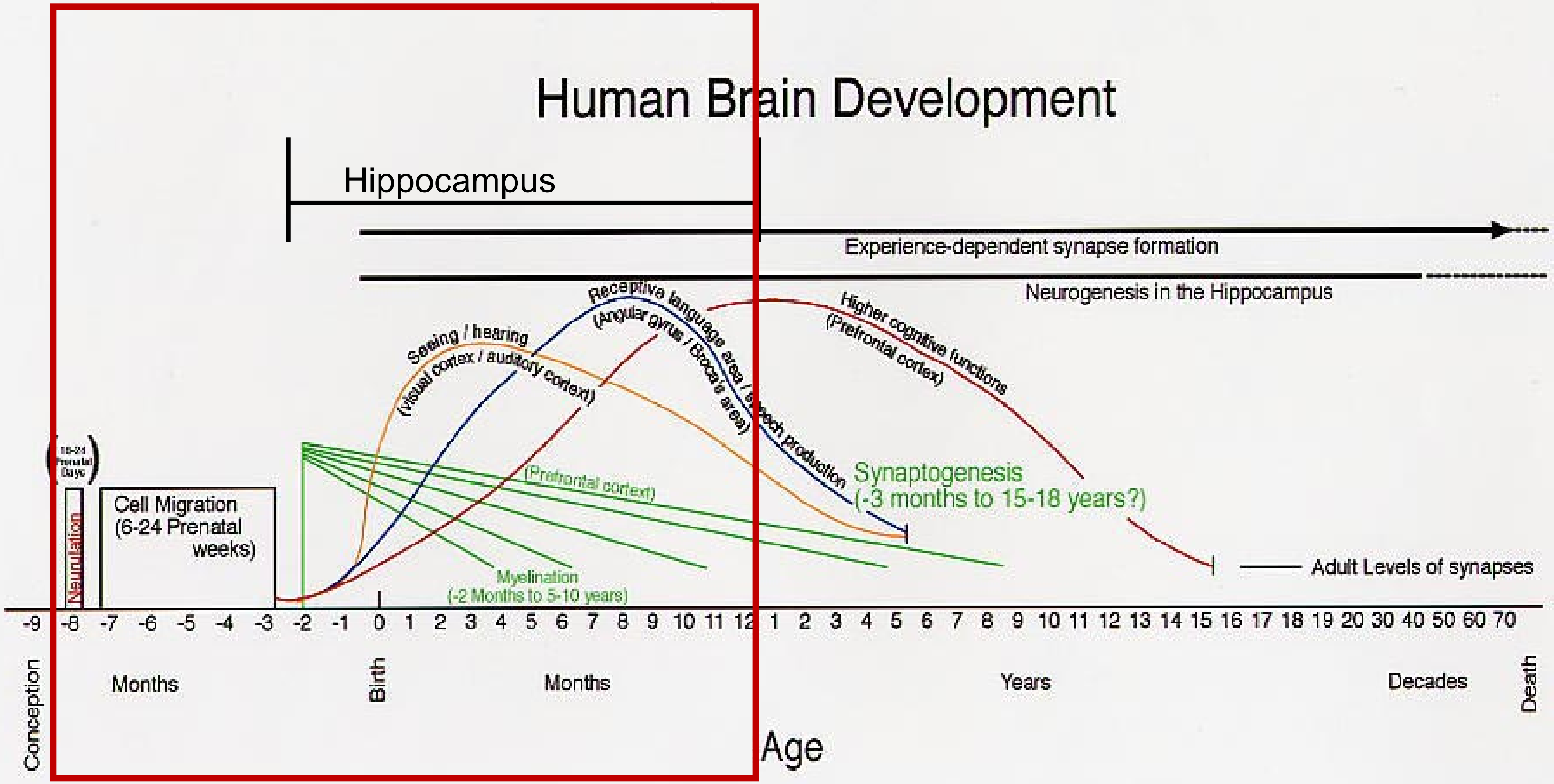

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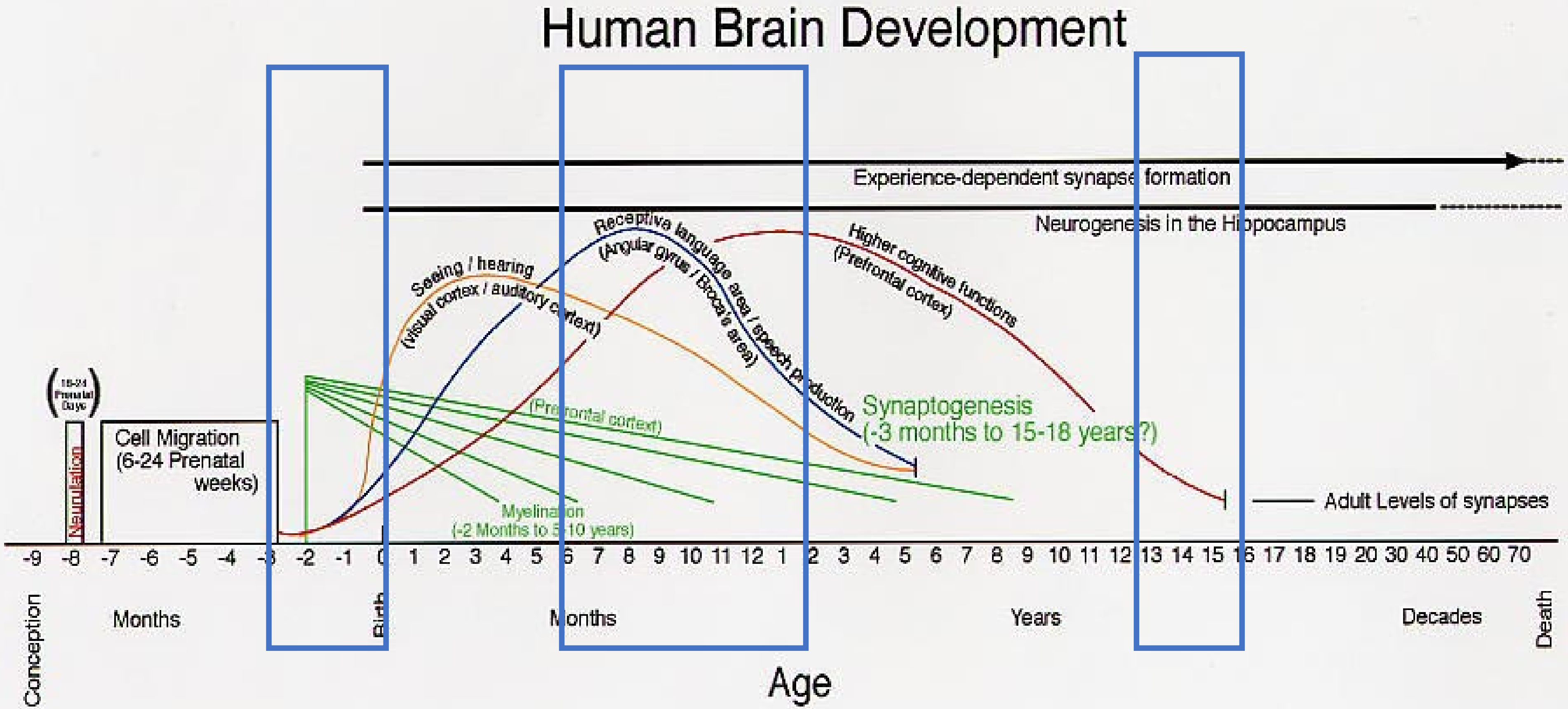
Iron: a critical nutrient for the developing brain

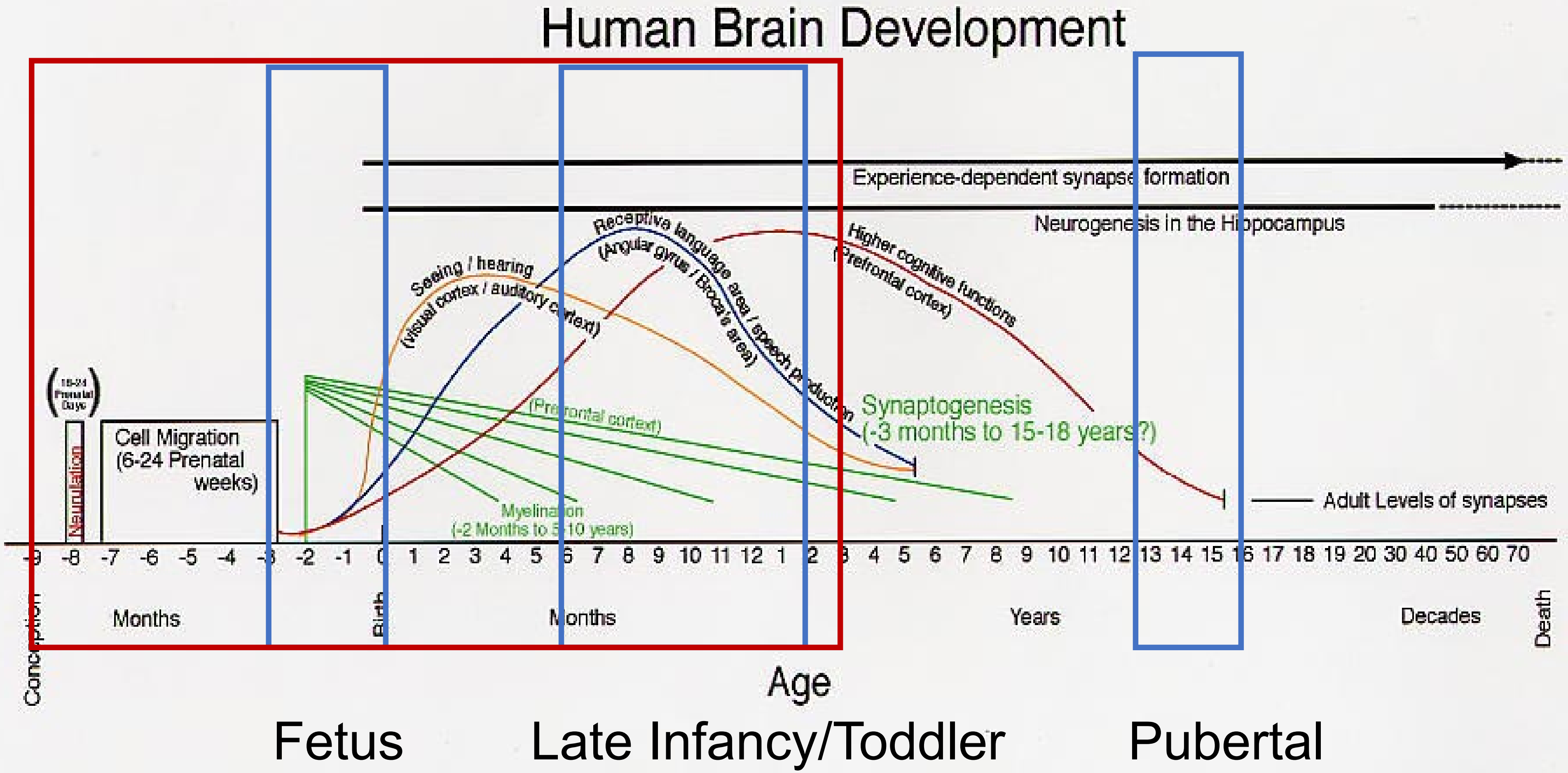
- Delta 9-desaturase, glial cytochromes control oligodendrocyte production of myelin
  - Iron Deficiency=> Hypomyelination
- Cytochromes mediate oxidative phosphorylation and determine neuronal and glial energy status
  - Iron Deficiency=> Impaired neuronal growth, differentiation, electrophysiology
- Tyrosine Hydroxylase involved in monamine neurotransmitter and receptor synthesis (dopamine, serotonin, norepi)
  - Iron Deficiency=> Altered neurotransmitter regulation

Typical time periods of iron deficiency

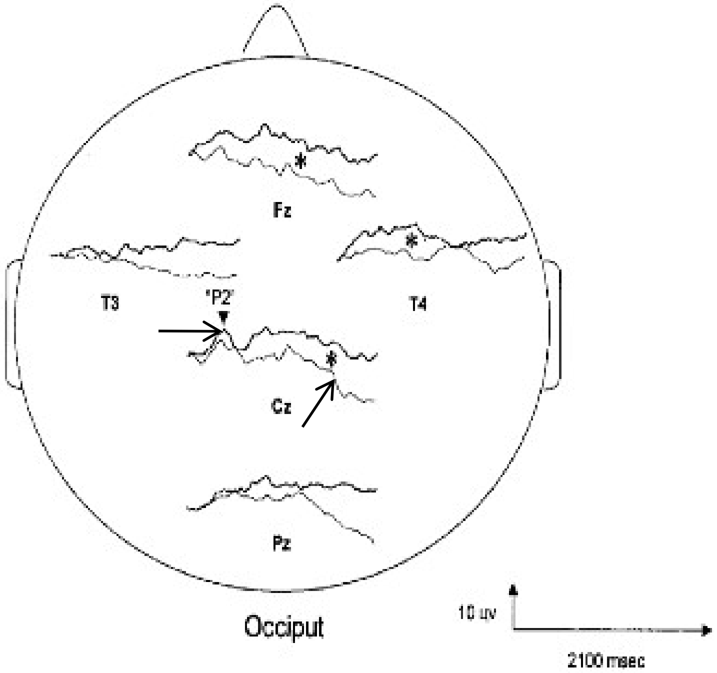


Fetus | Late Infancy/Toddler | Pubertal

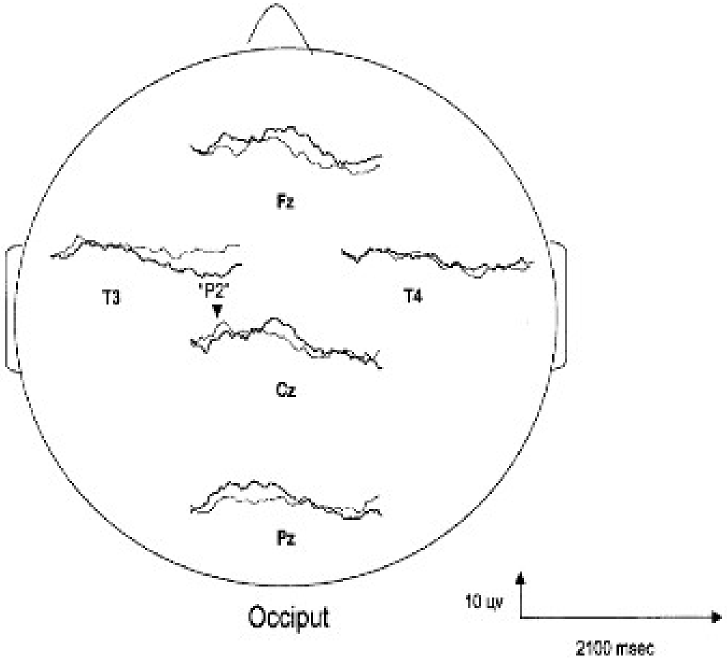
Typical time periods of iron deficiency



Fetal iron deficiency disrupts learning & memory

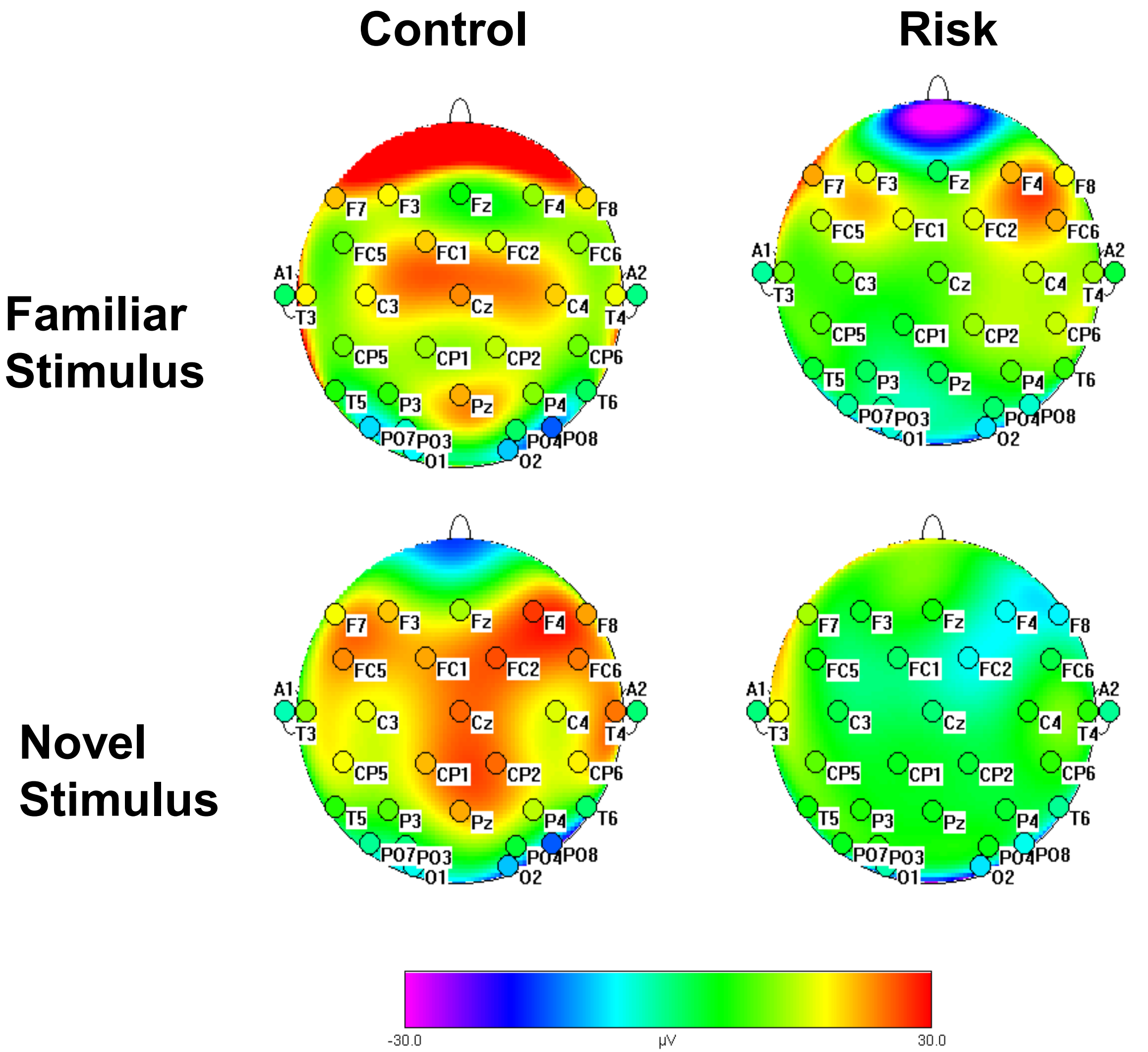


Iron Sufficient



Iron Deficient

Long term effects of newborn iron deficiency at 3.5 years



Conclusion: Infants who were iron deficient as newborns have a differently wired brain and process memory events differently *__even after iron repletion__*

Neurobehavioral sequelae of early iron deficiency

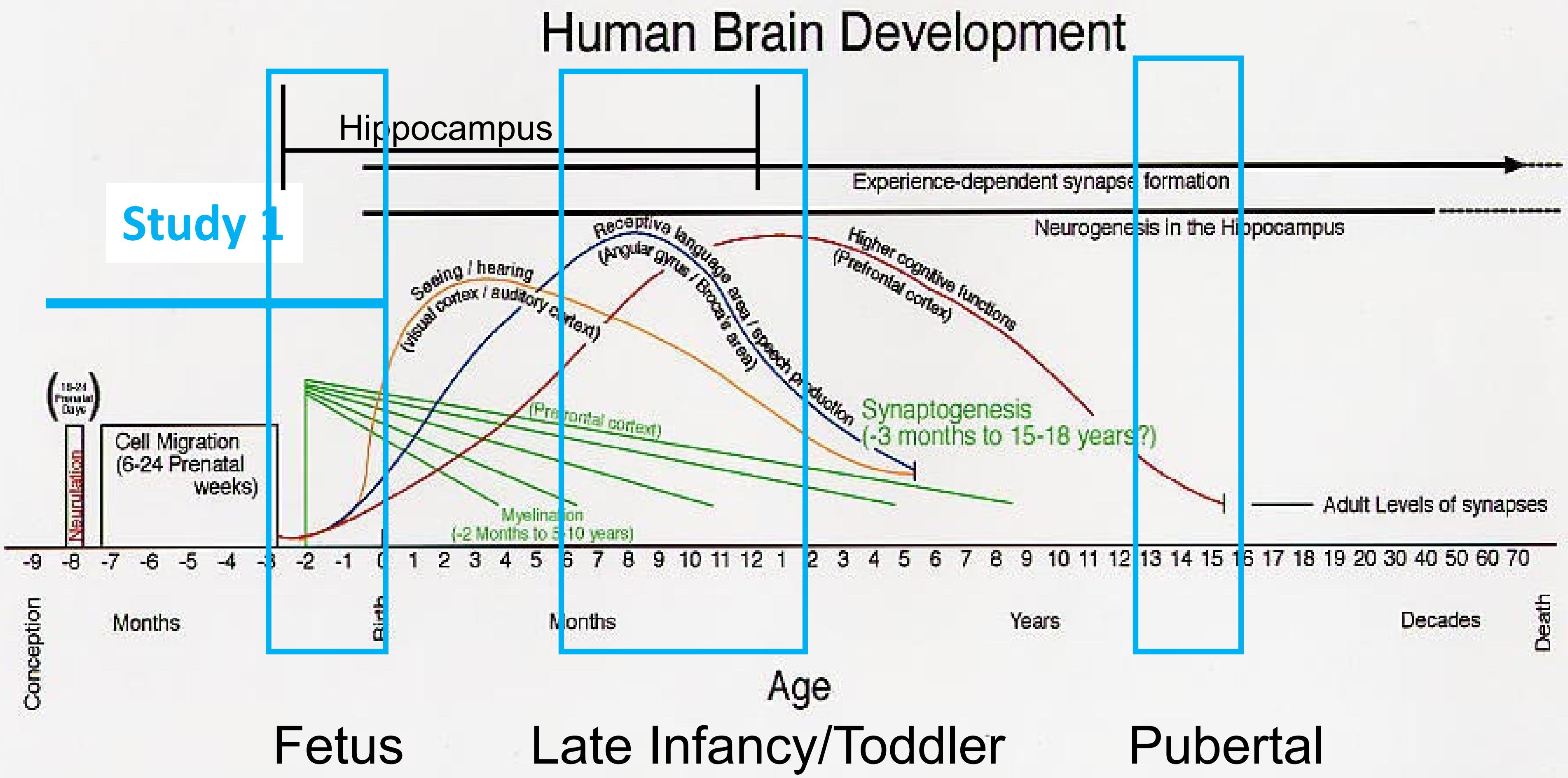
Over 40 studies demonstrate dietary iron deficiency between 6 and 24 months leads to:

- Behavioral abnormalities (Lozoff et al., 2000)
  - Motor and cognitive delays while iron-deficient
  - Profound affective symptoms
  - Cognitive delays 19-23 years after iron repletion
    - Arithmetic, writing, school progress, anxiety/depression, social problems and inattention (Lozoff et al., 2000)
- Electrophysiologic abnormalities (delayed EP latencies)
  - At 6 months while iron-deficient (Roncagliolo et al, 1998)
  - At 2 month if born ID (Geng et al., J Pediat 2015)
  - At 2-4 years after iron repletion (Algarin et al, 2003)
  - Characteristic of impaired myelination, poorer recognition memory (hippocampus)

Pinpointing the optimal timing of intervention: Nepal studies

- Tests of intellectual, executive, and motor functioning administered to ~700 children 7-9 years of age whose mothers had been in an RCT of prenatal iron supplementation
- Children themselves in an RCT of iron from 12-36 months of age
- Study 1: Children whose mothers received iron in pregnancy scored significantly better on working memory, inhibitory control, fine motor (Christian et al. JAMA, 2010)
- Study 2: Iron administered when children were 12-36 months conferred no additional benefit (Christian et al. J Nutr, 2011)
- Study 3: Among children whose mothers did not receive iron in pregnancy, iron from 12-36 months had no effect (Murray-Kolb et al., Arch Pediatr Adolesc Med, 2012)

Pinpointing the optimal timing of iron intervention



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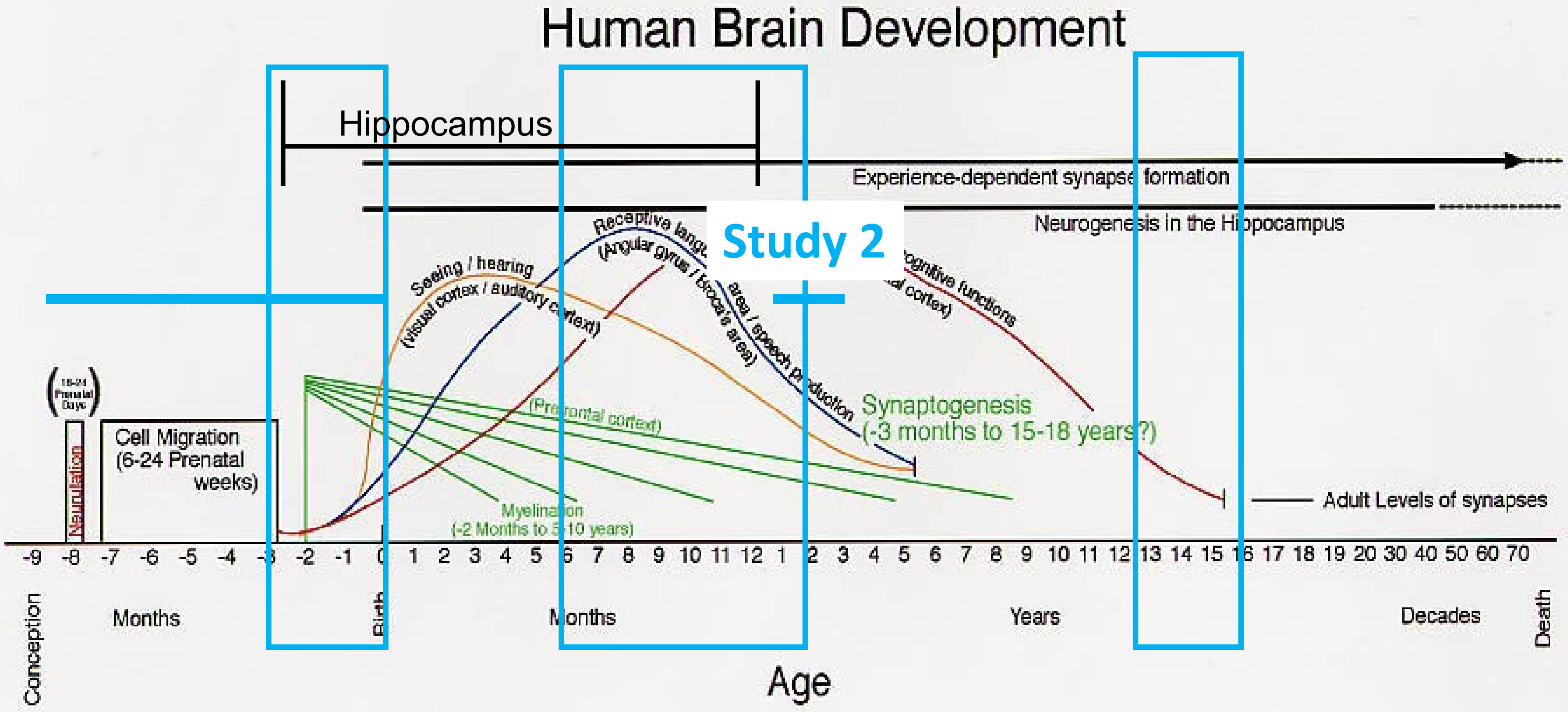

Fetus Late Infancy/Toddler Pubertal

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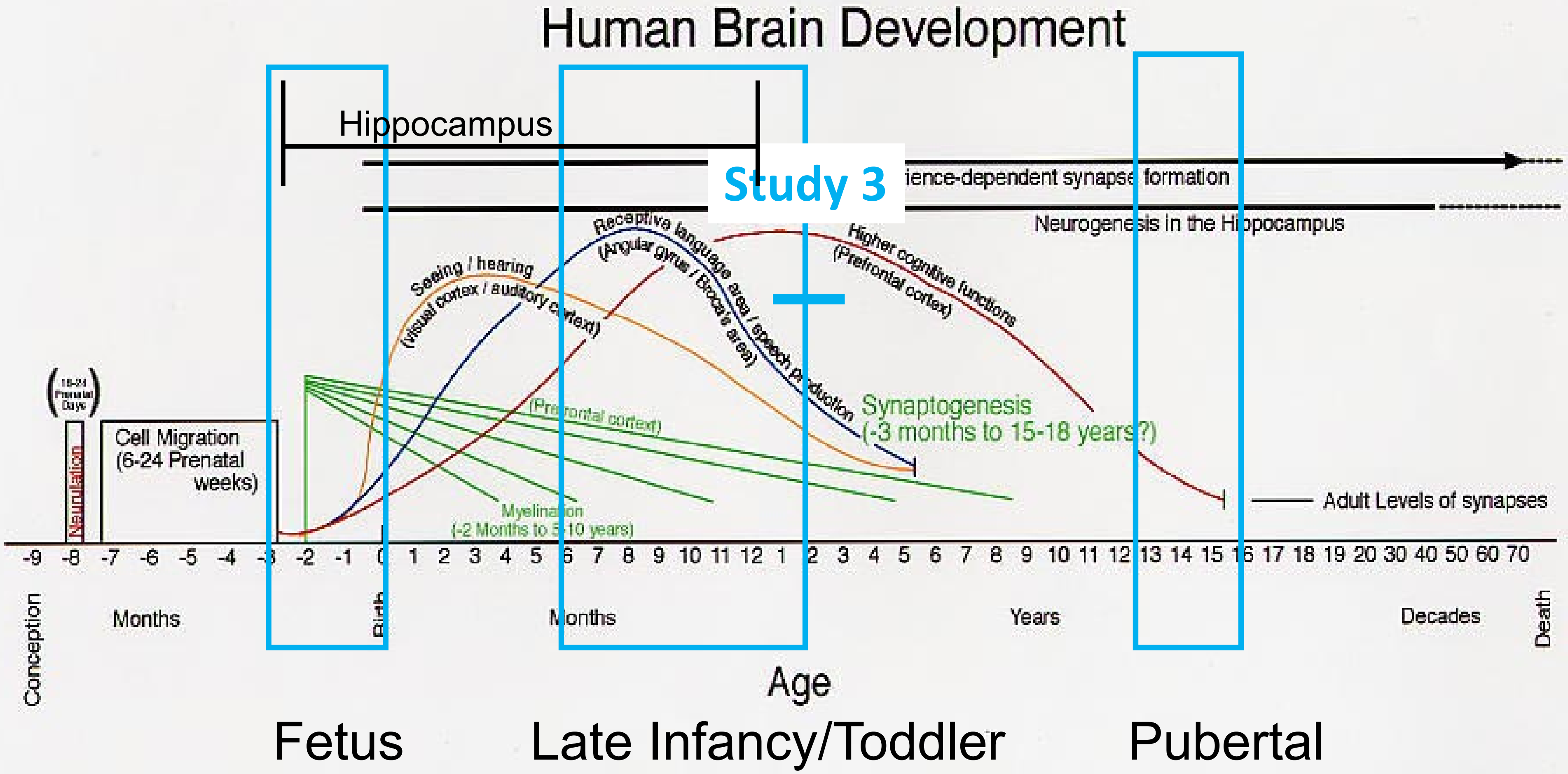

Pinpointing the optimal timing of intervention: China studies

- Children who received iron between 6 weeks and 9 months of age had better gross motor scores at 9 months than children who did not received iron in infancy regardless of whether their mothers received iron in pregnancy (Angula-Barroso et al., Pediatrics 2016)
- Motor development starts after hippocampal and striatal development that underlies cognition
- Motor control by infants shifts from primitive reflexes driven by brain stem and midbrain to more coordinated movements by motor cortex at 3-4 months of age
- Myelination 36wks through first 2 postnatal years

Implications for programming and research design/interpretation

- Time of intervention must match time of brain need for nutrient
  - Supplementation outside of window may have no effect.
  - Extra supplementation may have no additional benefit.
- Age at follow-up assessment and circuits affected must be considered.
  - Impaired socioemotional behavior a hallmark of iron deficiency, secondary to disruptions in monoaminergic signaling
  - May occur throughout life if iron is insufficient
  - May have seen a benefit if socioemotional behavior measured in Nepal?

Programming points: Pre-conceptional period

- Ensure optimal nutrition in women of childbearing age
  - Pre-conceptional status for many nutrients critical
- Encourage healthy weight for women of childbearing age

Programming points: Pregnancy

- Provide prenatal multivitamin, nutritional counseling
- Manage non-nutritional factors that affect nutrient handling/status
  - Maternal high blood pressure>>75% of IUGR in U.S.
  - Gestational diabetes mellitus>>fetal iron deficiency (Georgieff MK et al., J Pediatr, 1990)
  - Maternal stress

Programming points: Postnatal period

- Optimal breastfeeding practices
- Nutritional counseling of mother during breastfeeding
- Complementary feeding beginning at 6 months of age
  - Emphasis on minerals>>iron and zinc
  - Screening for iron deficiency

Programming points: Postnatal period

- Growth monitoring
- Reduction of non-nutritional factors that affect nutritional status
  - Stress
  - Inflammation/infection