Improving Nutrition in the First 1000 Days to Support Childhood Development and Adult Health

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My Own Developmental Trajectory

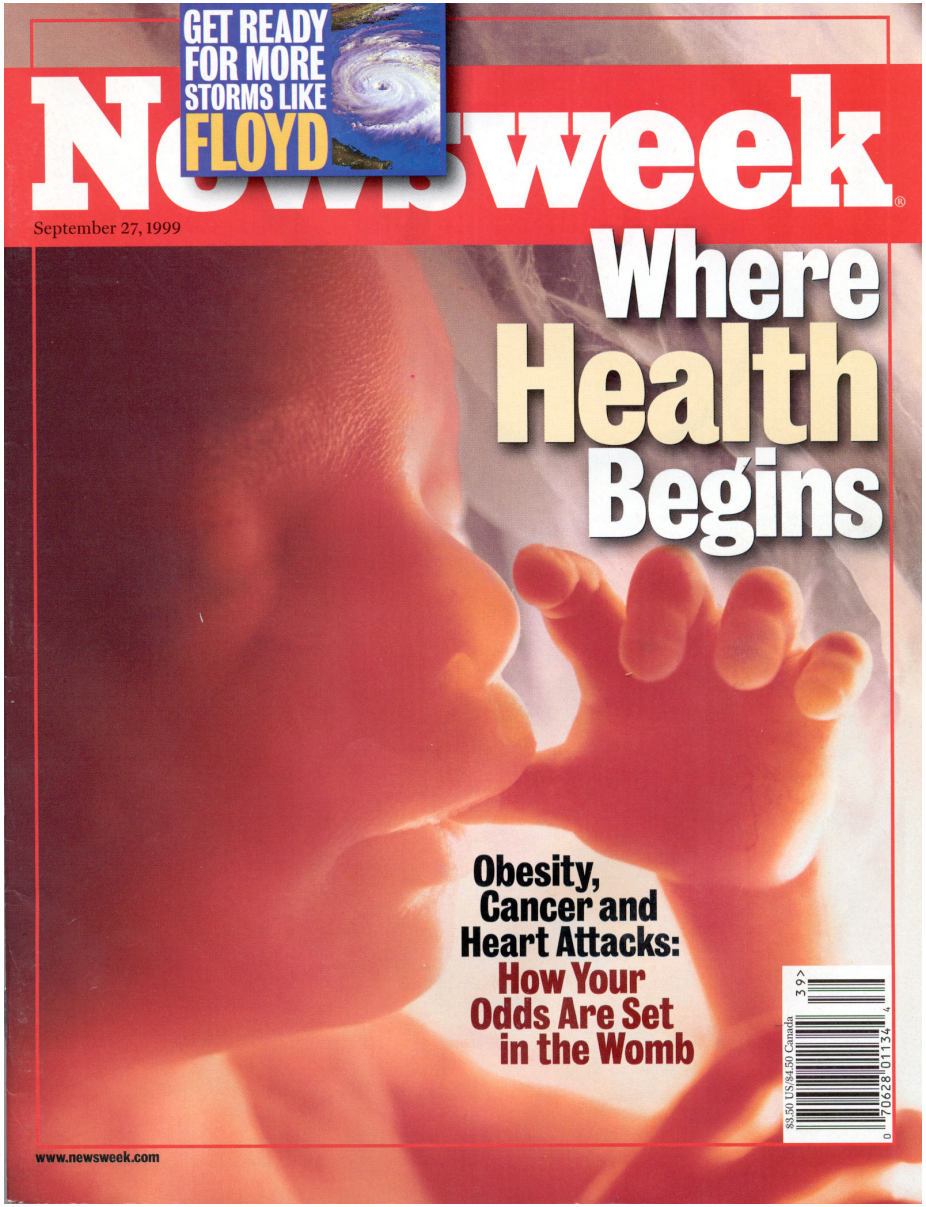
- Undergraduate at Yale: Psychology Major
  - "Biopsychology?"; "Neuropsychology"
    - Brain-behavior relationships
- Medical School at Washington University-St. Louis
  - Great Neuroscience and Pediatric Neurology
    - First exposure to development
- Peds Residency/Neonatology Fellowship at Penn
  - Neonatal Medicine- a route to the developing brain
  - Nutrition-Metabolism training
- Faculty at University of Minnesota
  - "Sorry, we don't do that here"
    - The role of Serendipity (and wives) in scientific careers
  - Collaborative, high-end neuroscience

Life in Academic Medicine

- Protect your time
  - Early career: 80% science/20% practice
  - Later career: 60% science
- Be committed to your science
  - What are the next 5 questions?
  - “Can you live without your science?” (Bruce Blazar, MD)
- Practice medicine like you do your science
  - ”Spirit of curiosity”: Learn from every patient
  - Imagine what research needs to be done to answer the questions you have about your patient
- It takes a team- you can’t know everything
  - Surround yourself with good students and colleagues

The Medical Perspective on Neurodevelopment

- Obstetricians, Family Practitioners and Pediatricians are concerned with the neurodevelopmental outcome of the fetus and child
  - Provide optimal environment
  - Identify risk factors
  - Early diagnosis of problems
  - Early medical intervention
  - Referral and coordination of services for family
- Time frame: (pre)conception=>?



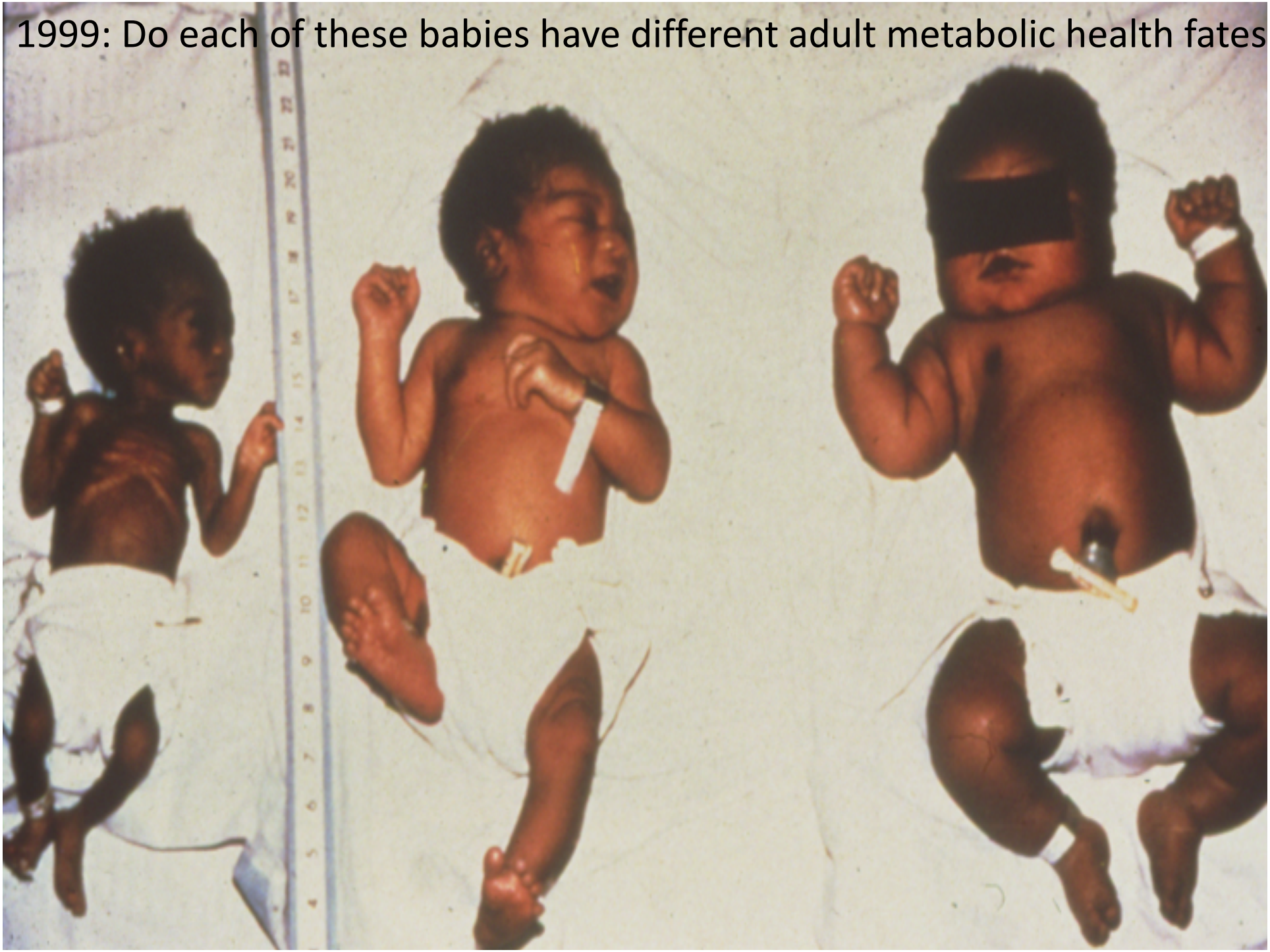
This is 1999
In 2018 we should add:

Mental Health

Why the Interest in Early Events and Brain Development?

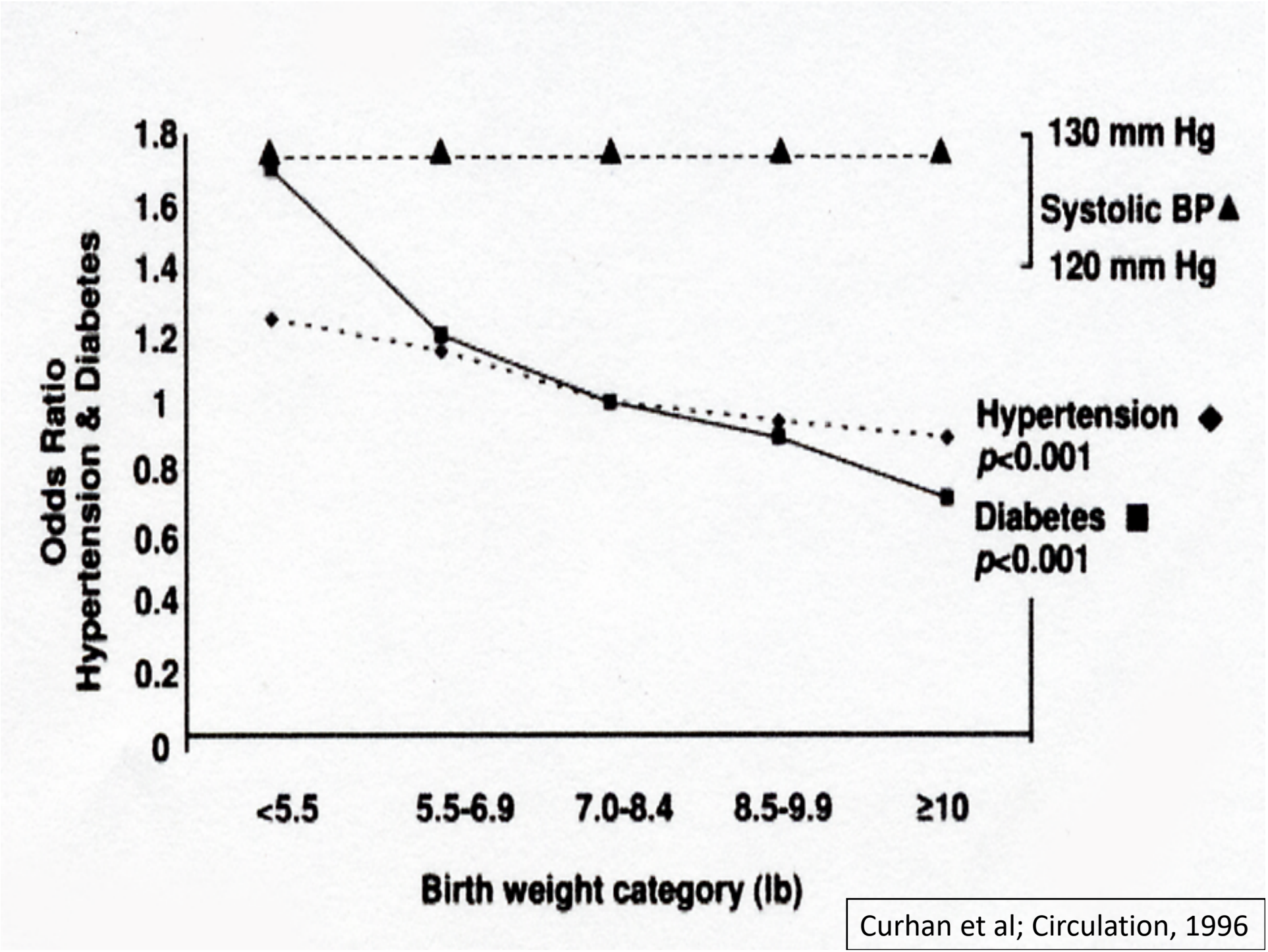
- About 10% of research is about developmental
- Yet, “The Child is the Father of the Man” (Wordsworth)
  - DOHaD and the problem with congress (and the NIH)
- Development is based on
  - Genetics
  - Experience dependent influences => Epigenetics
- The brain is rapidly growing in the late fetal/early neonatal period
  - Is highly vulnerable to insults
  - Demonstrates its greatest plasticity/resilience and response to therapy
  - **Vulnerability outweighs plasticity** (NIH Consensus, 1994)

1999: Do each of these babies have different adult metabolic health fates



“Fetal” “Programming”

- “Programming” refers to process (eg, epigenetic) by which early environmental stimuli (e.g. **nutrition**) alter how genes are expressed throughout the lifetime
- Best described in fetal period with effect of prenatal nutrition=> adult cardiovascular health (D. Barker)
- Current thinking: May also apply to postnatal nutrition in term and preterm infants, adopted orphaned children, foster children, children after severe illness
- Suggests vulnerable period based on post-conceptional age irrespective of *in utero* vs *ex utero* (ie, no longer “fetal”)

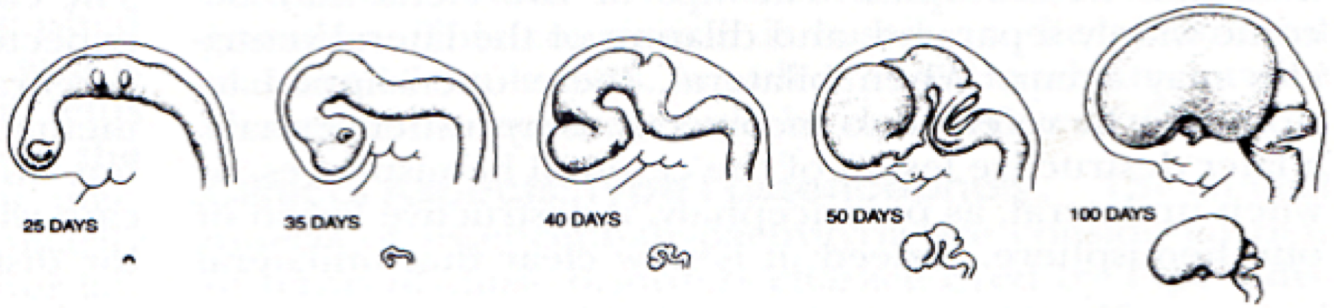


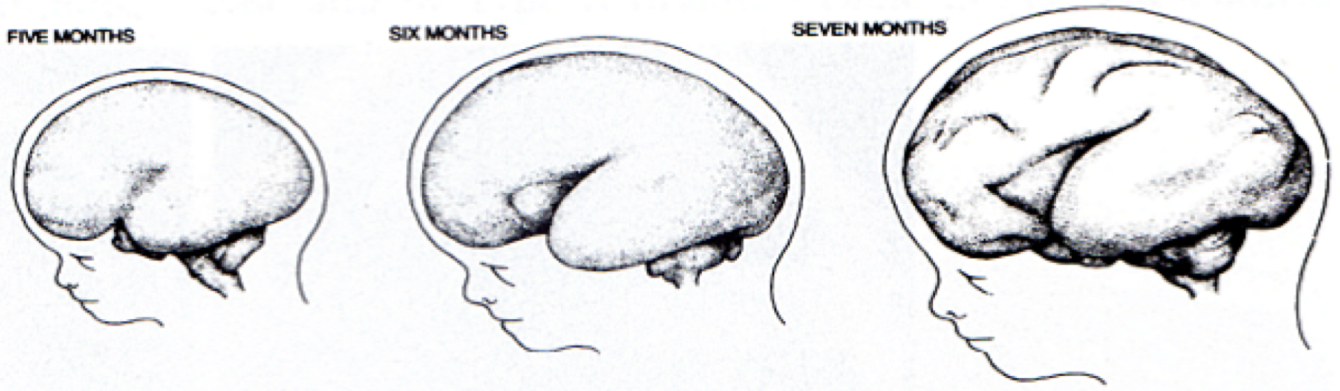
Curhan et al; Circulation, 1996

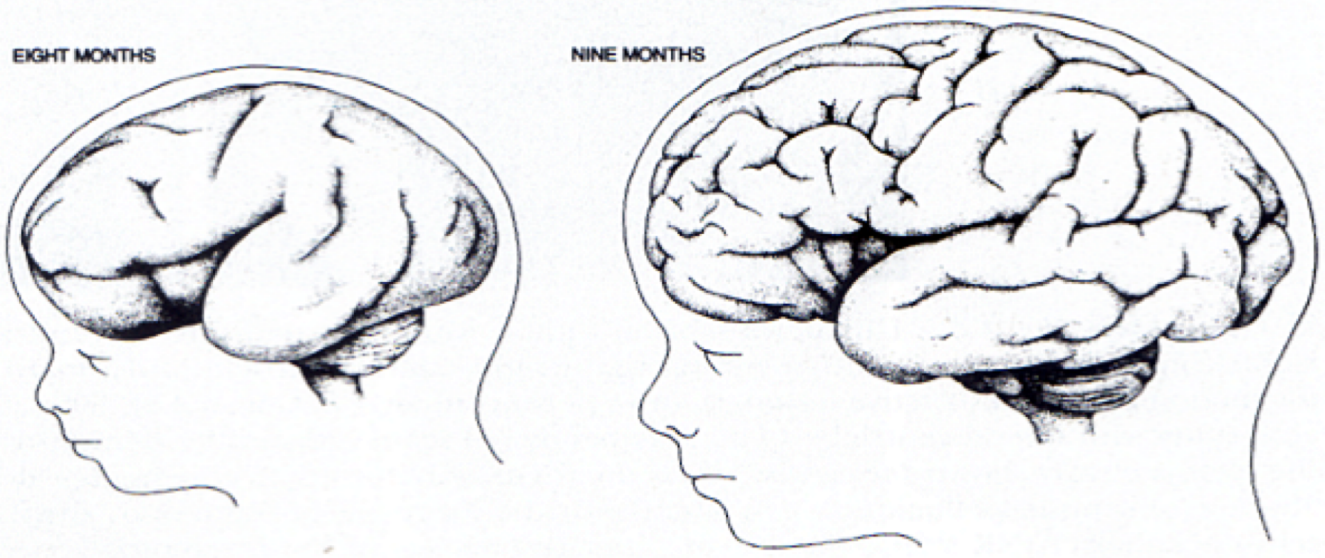
Developmental Origins and the Brain

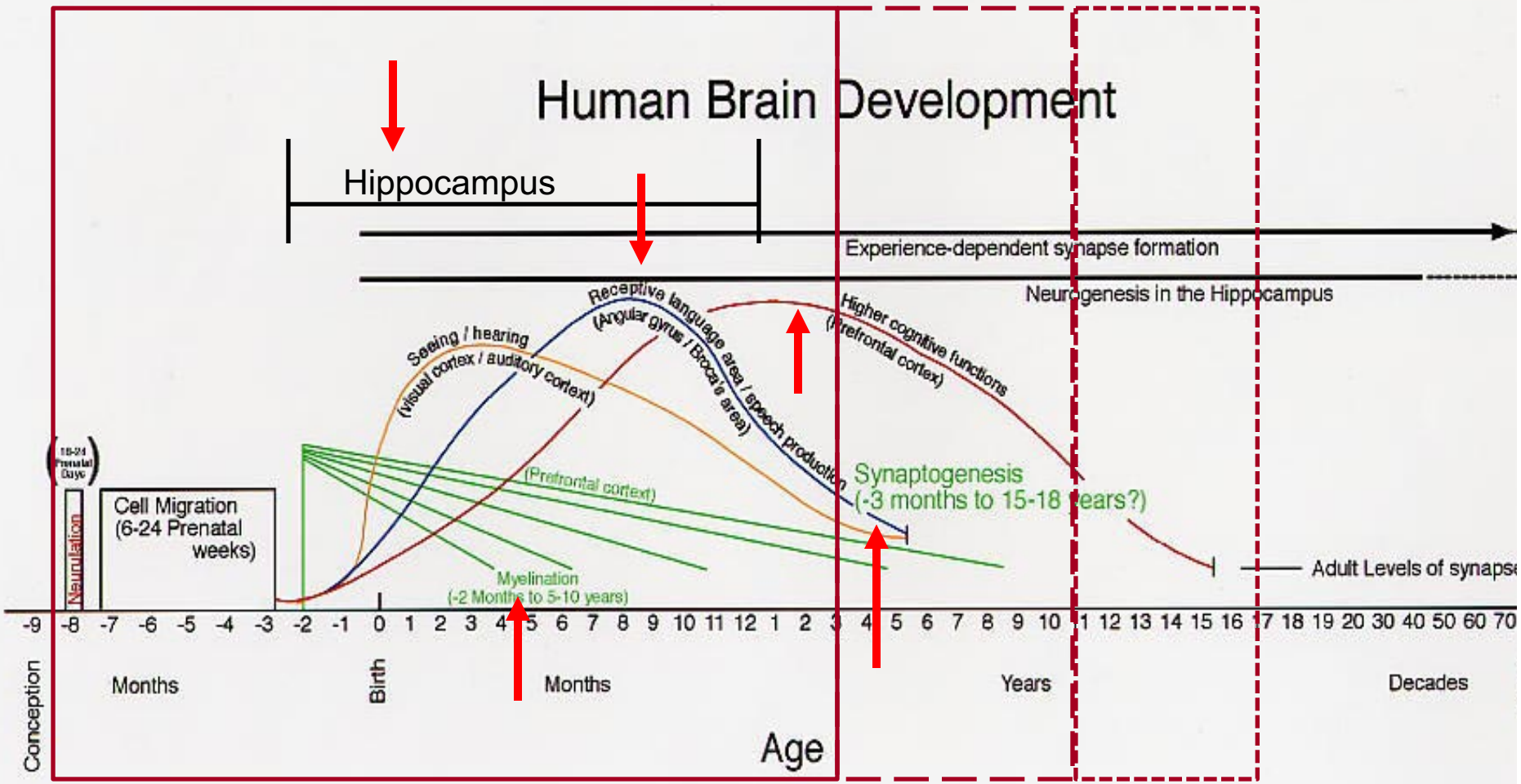
Early Neural Development is Important Immediately and Later

- 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 HC, Striatum (early in life)
      - Examples: Prematurity, Intrauterine growth restriction, newborn ID
    - Maintenance (throughout development)
      - Example: preschool development programs


25 DAYS
35 DAYS
40 DAYS
50 DAYS
100 DAYS


FIVE MONTHS
SIX MONTHS
SEVEN MONTHS


EIGHT MONTHS
NINE MONTHS



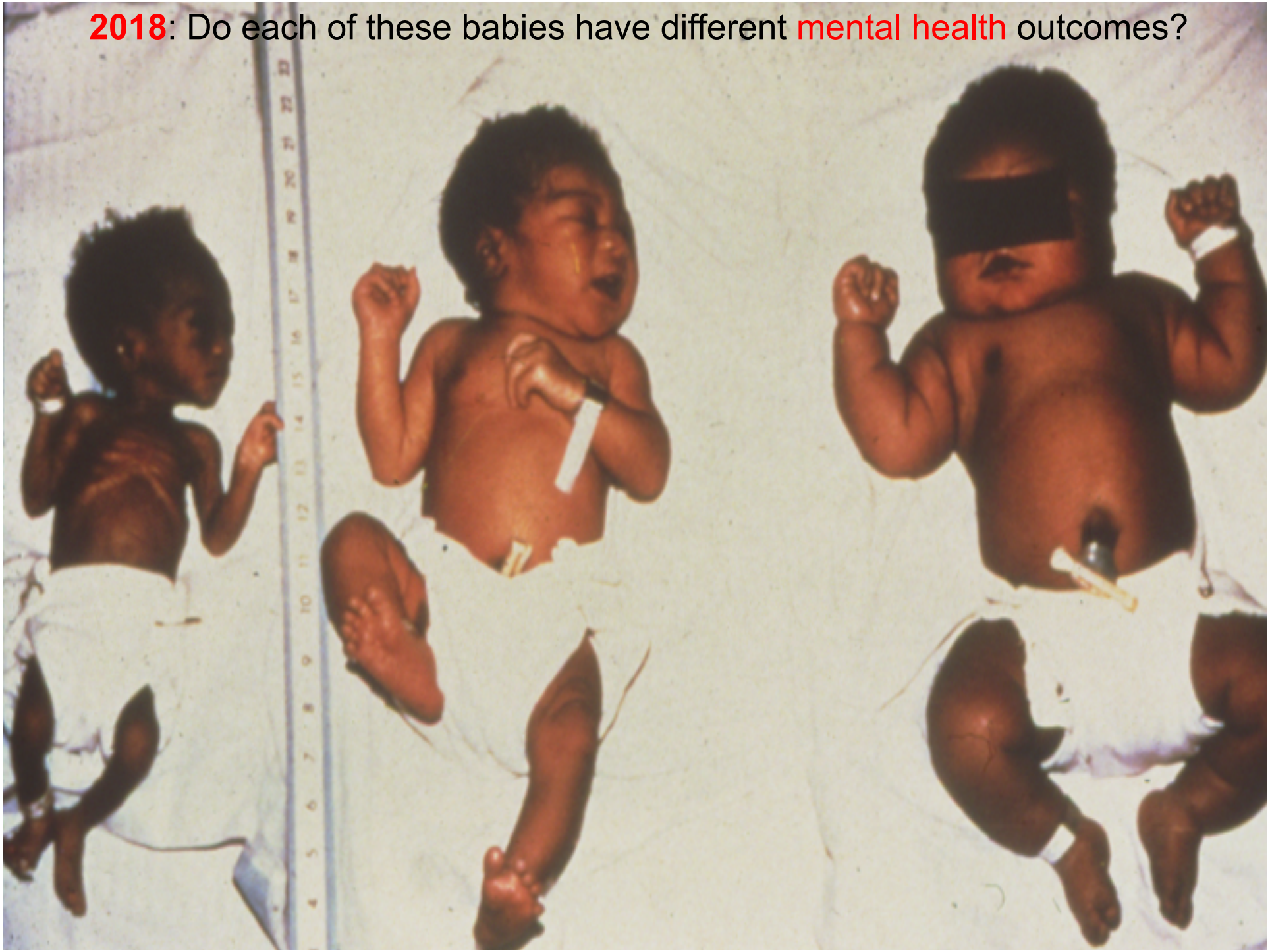
Thompson & Nelson, Am Psychol, 2001

Risks to the Developing Brain

- Fetal
  - Nutrient deficiencies (glucose,folate, iron, oxygen, amino acids; fatty acids)
  - Premature birth
  - Genetic disorders
  - Alcohol (Fetal Alcohol Syndrome)
  - Lead (environmental toxins)
  - Infectious diseases (CMV, Herpes, Toxoplasmosis)
  - Maternal Stress
  - Diabetes in Pregnancy
- Postnatal
  - Lack of oxygen at birth
  - Nutrient deficiencies
  - Bleeding/Stroke
    - Esp prematures
  - Infection (meningitis)
  - Stress
  - Obesity (probably)

Role of Nutrition in Brain Development

2018: Do each of these babies have different mental health outcomes?



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
  - Regionalized process
    - At risk: Hippocampus, myelination, neurotransmitters
- Highly metabolic process
  - 60% of total body O2 consumption
  - Reliant on metabolic substrates (nutrients) that support metabolism (eg, O2, glucose, amino acids, iron, copper, iodine)

Nutrients & Brain: Importance of Timing

- Brain is not a homogenous organ
  - Regions (cortex, hippocampus, striatum, cerebellum)
  - Processes (myelin, neurotransmitters)
- All have different developmental trajectories
- Vulnerability to a nutrient deficit is based on
  - When a nutrient deficit occurs
  - Region's requirement for that nutrient at that time

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]
- Vitamins/Cofactors
  - 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

Examples of Nutrients and Regional vs Global Perinatal Brain Effects

Nutrient	Brain Requirement for Nutrient	Affected Areas
Protein-Energy	**Cell Proliferation, Cell Differentiation Synaptogenesis, Growth Factors**	**Global Cortex Hippocampus**
Iron	**Myelin Dopamine Energy**	**White Matter Striatal-Frontal Hippocampal-Frontal**
Zinc	**DNA Neurotransmitter release**	**Autonomic NS Hippocampus Cerebellum**
LC-PUFAs	**Synaptogenesis Myelin**	**Eye Cortex**

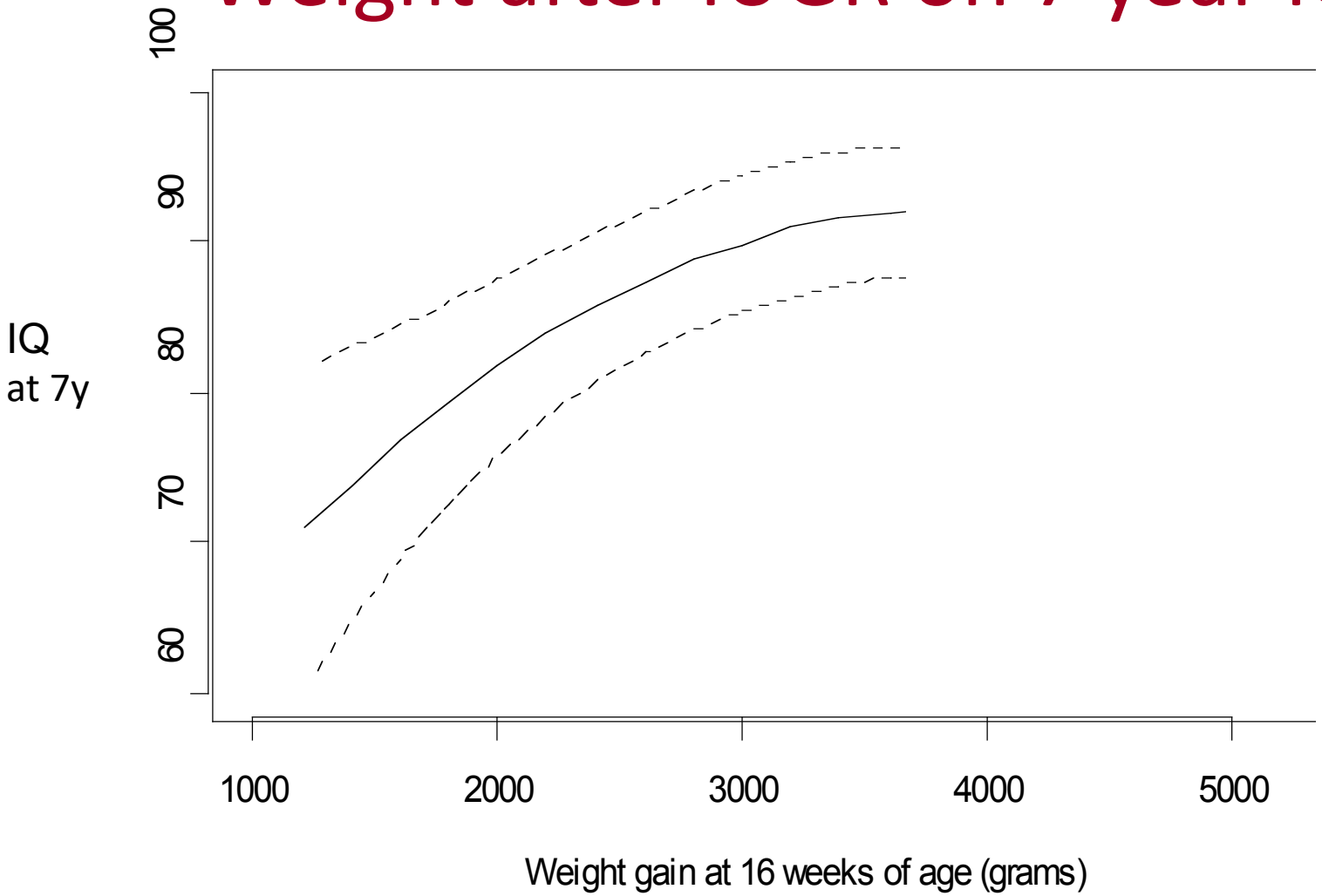
The Cost to Society

- 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 increases adult cardiovascular risk by 25% and reduces IQ by 7 points (Curhan et al., Circulation, 1996; 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)

Evidence for Long-Lasting Effects of Early Nutritional Status on Brain in Humans

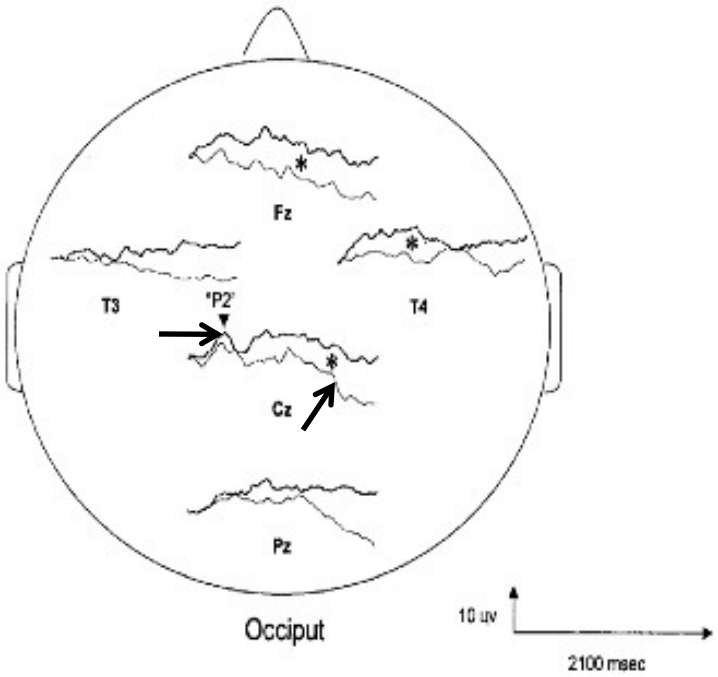
- Outcomes of IUGRs (Strauss and Dietz, 1998)
  - Lower IQ
  - Poorer verbal ability
  - Worse visual recognition memory
  - 15% with “mild” nuerodevelopmental abnormalities
  - 30% increased risk of schizophrenia (Eide et al, 2013)
- Studies in Guatemala show lasting effects 25 years after protein supplementation in childhood (Pollitt et al)
- Fetal iron deficiency increases the risk of
  - Schizophrenia (Insel et al, 2008)
  - Autism (Schmidt et al, 2014)
  - Depression/Anxiety (Lozoff et al, 2000)
  - Poorer executive function (Lukowski et al, 2010)

Effect of Postnatal Failure to Gain Weight after IUGR on 7 year IQ

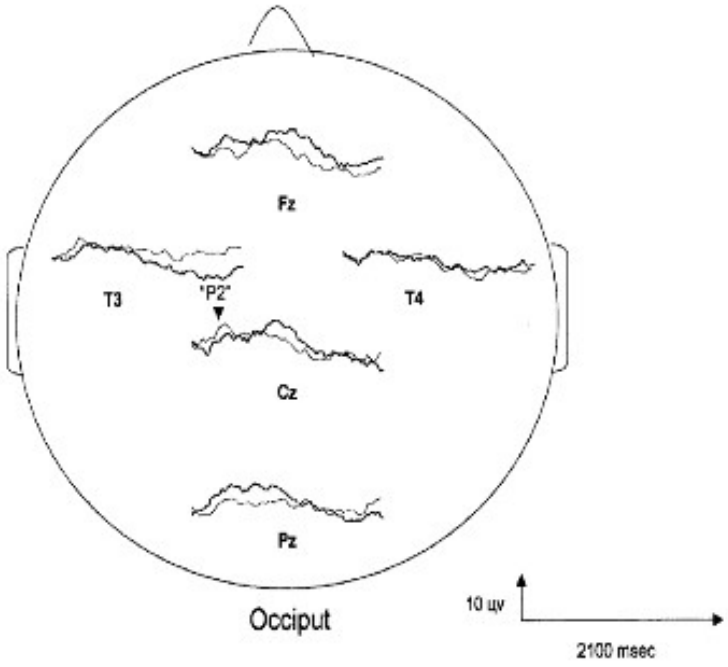


Pylipow et al, J Pediatr. 2009

Fetal ID Disrupts Neonatal Learning & Memory



Iron Sufficient

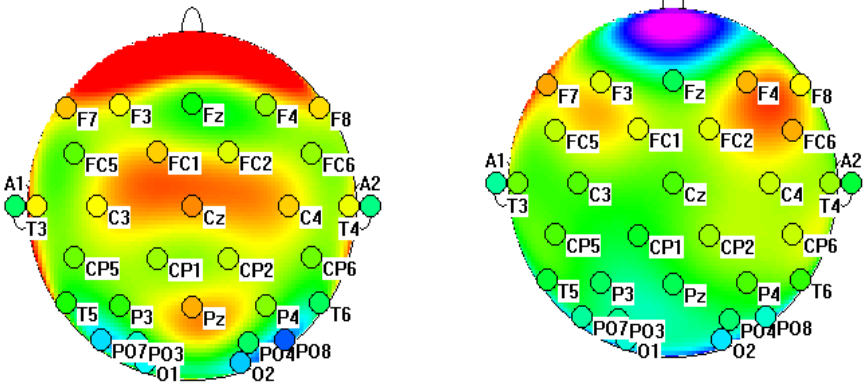


Iron Deficient

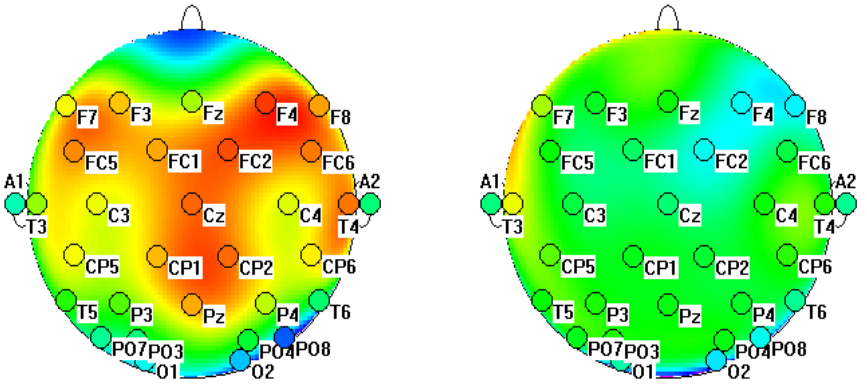
Long Term Effects of Newborn ID at 3.5 years

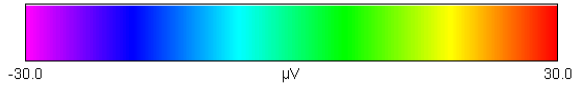
Control **Risk**

Familiar Stimulus



Novel Stimulus

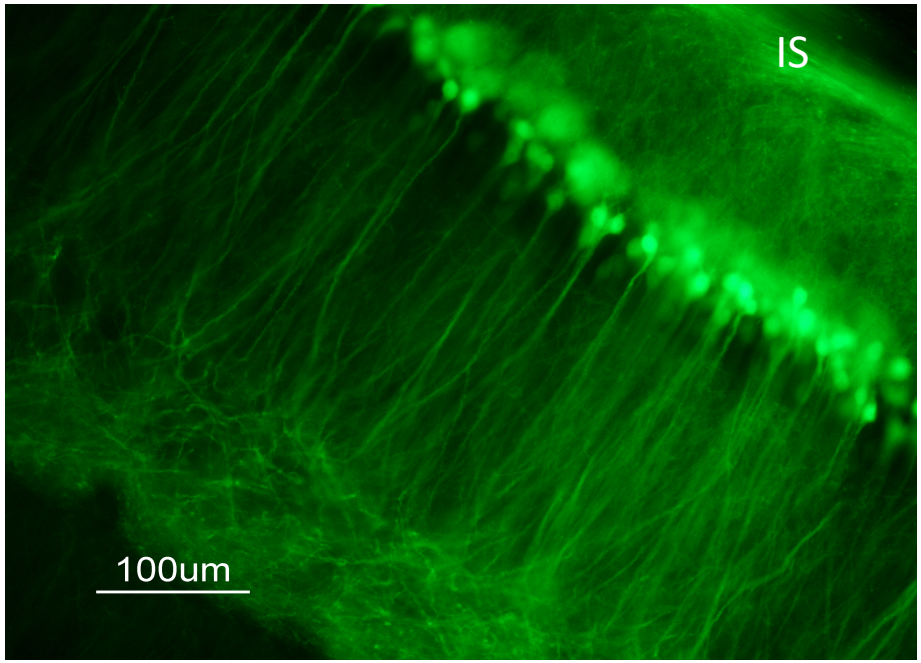


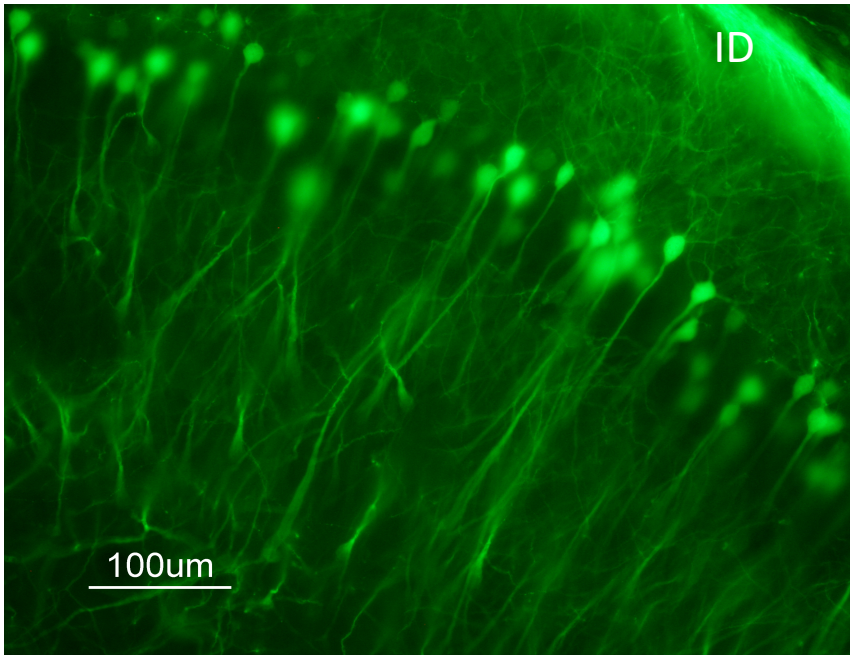


Conclusion: Infants who were iron deficient as newborns have a differently wired brain and process memory events differently *even after iron repletion*

2 Major Theories Accounting for Long-Term Loss of Synaptic Plasticity

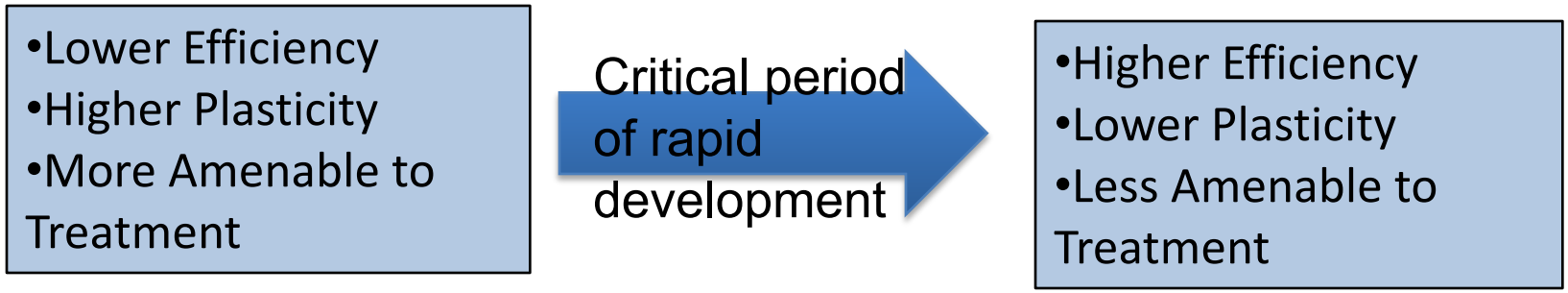
1. **Residual structural deficits**
   - Nutrient deficiencies during critical periods of development result in permanent structural change (Hensch, 2004; Carlson et al, 2009; Fretham et al, 2012; Callahan et al, 2013)
   - Neurobehavioral deficits relate to disordered neuronal structure (Jorgenson et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





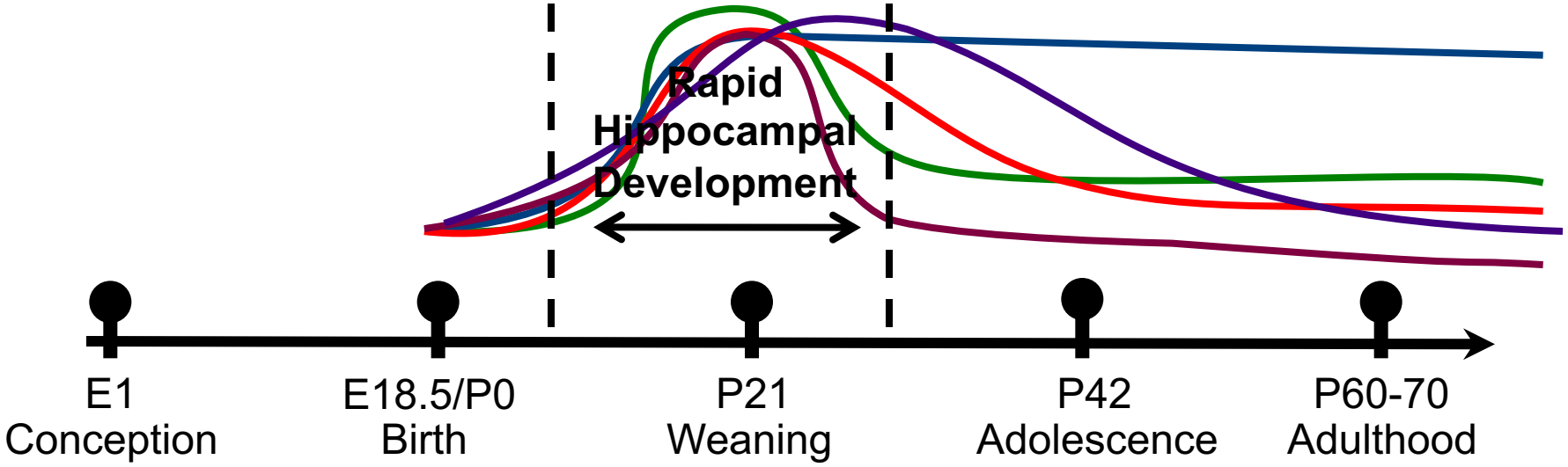
Critical Periods

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



- 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)

Is There a Critical Period for Iron in Hippocampal Development?



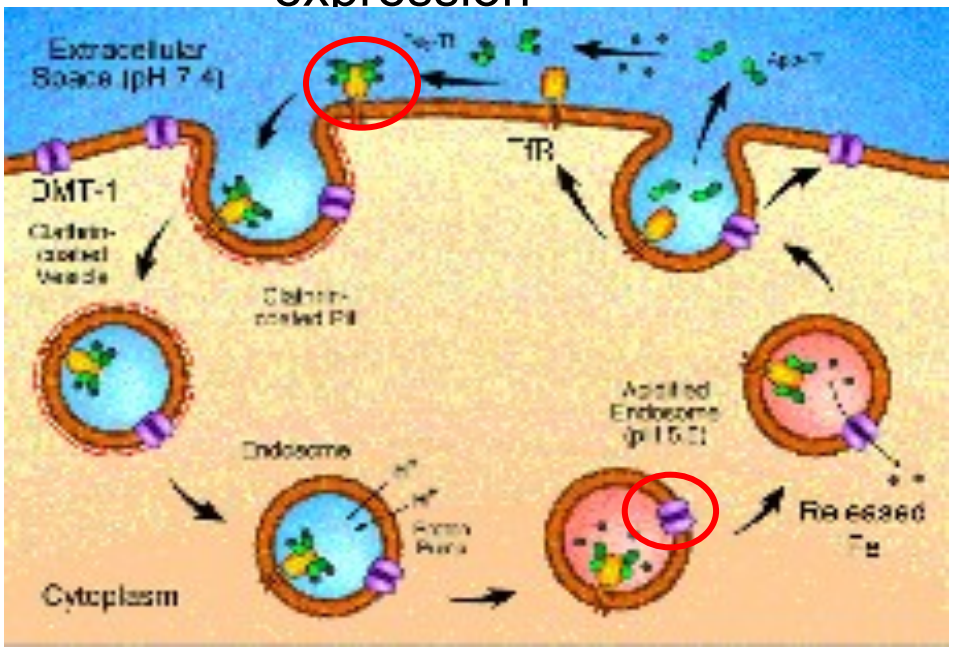
- **Dendritogenesis and Synaptogenesis** *(Pokorny and Yamamato, 1981)*
- **Electrophysiology** *(Bekenstein and Lothman, 1991)*
- **Energy Production/Use** *(Dallman and Schwartz, 1964; Tkac et al., 2005; Erecinska et al., 2004)*
- **Iron Uptake/Utilization** *(Siddappa et al., 2002; Dallman and Sprito, 1977; Moos and Morgan, 2000; Taylor and Morgan, 1990)*
- **Growth Factor Stimulation** *(Tran et al., 2008 and 2009)*

Genetic Models to Define Iron-Specific Hippocampal Neuronal Effects

Conditional DMT-1 KO

(Carlson et al, J Nutr 2009)

- *slc11a2* KO (exons 6-8)
- E18.5
- Hippocampus-specific
  - CaMKIIa driven Cre expression

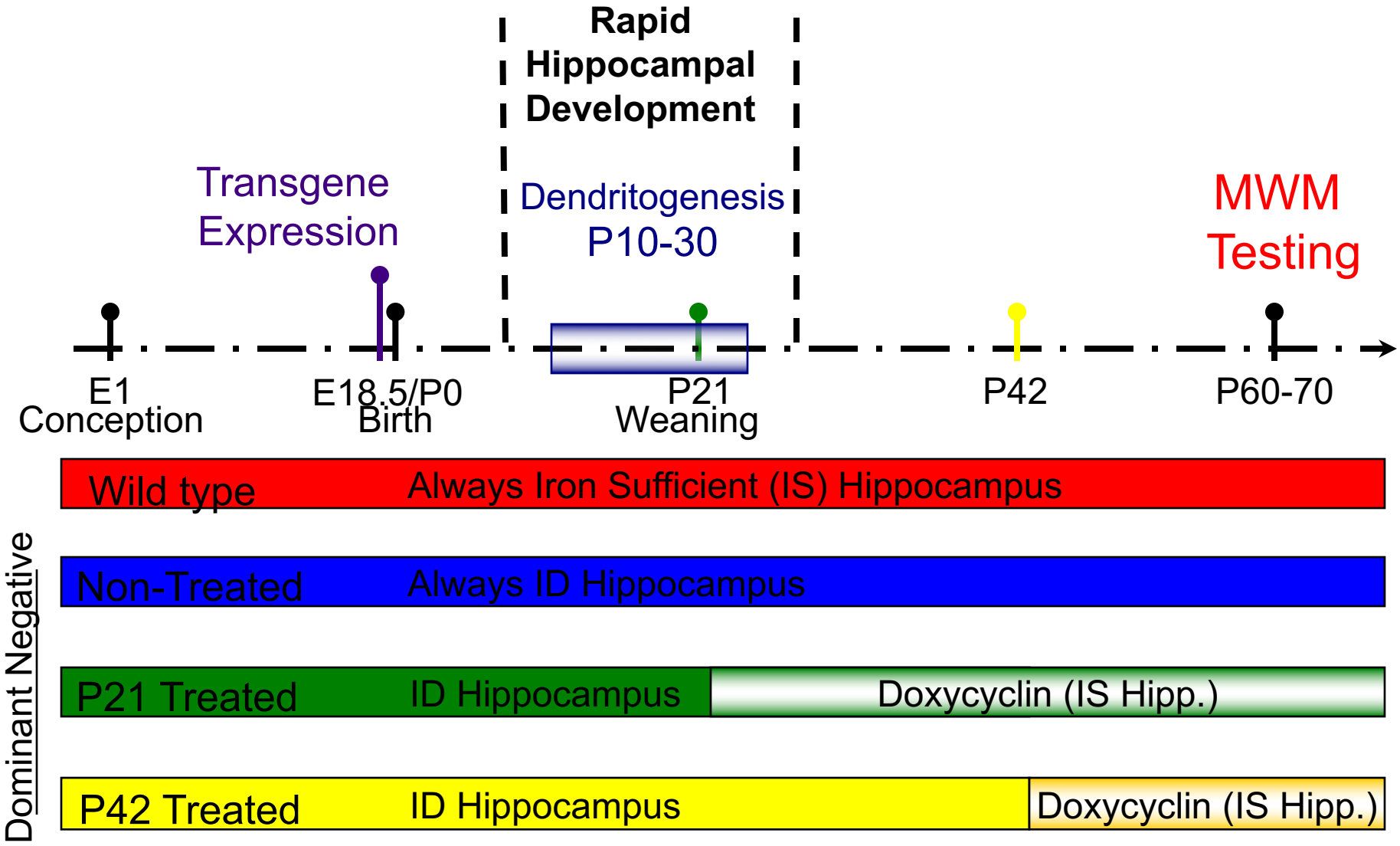


Conditional D/N TfR1

(Fretham et al, Hippocampus, 2012)

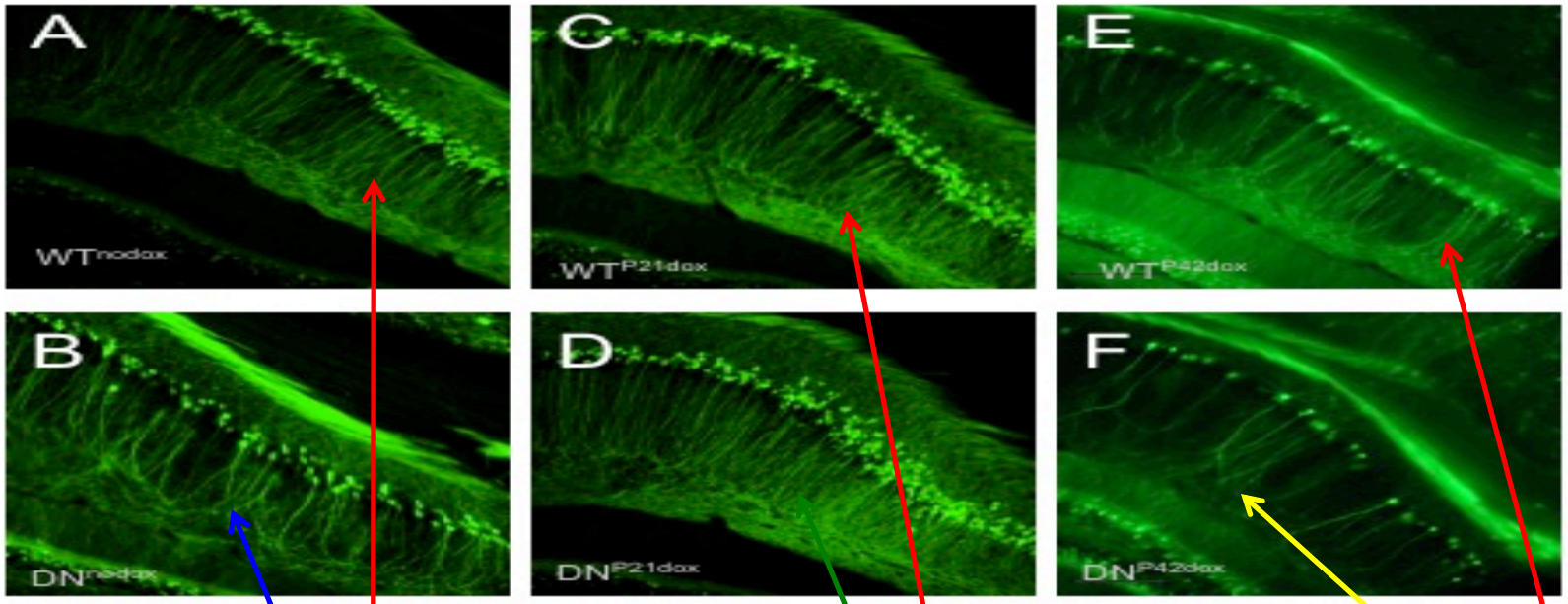
- Nonfunctional dominant-negative TfR-1
- E18.5
- Hippocampus-specific
- "Tet-OFF" doxycycline control
- Fast iron reversibility
  - 6 days
- Critical periods

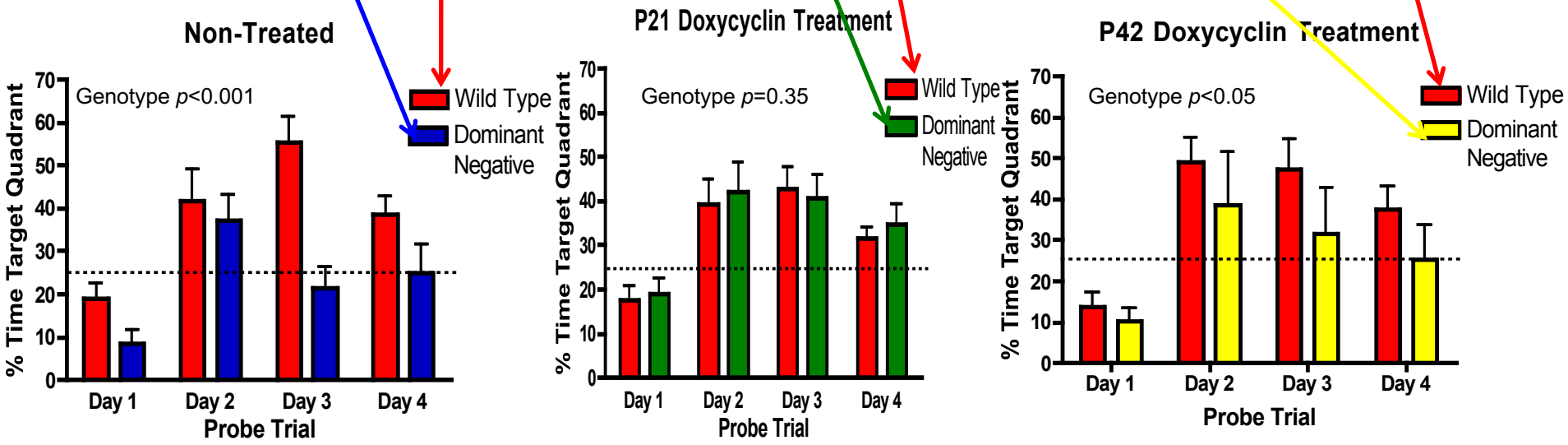
Is There a Critical Period for Iron in Hippocampal Development?



Fretham et al., Hippocampus 2012

Restoring Neuronal Fe at P21, But Not P42, Rescues Structure, Behavior and BDNF Gene Expression





Fretham et al., Hippocampus 2012

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; eg, 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)

Epigenetic Modifications of Chromatin

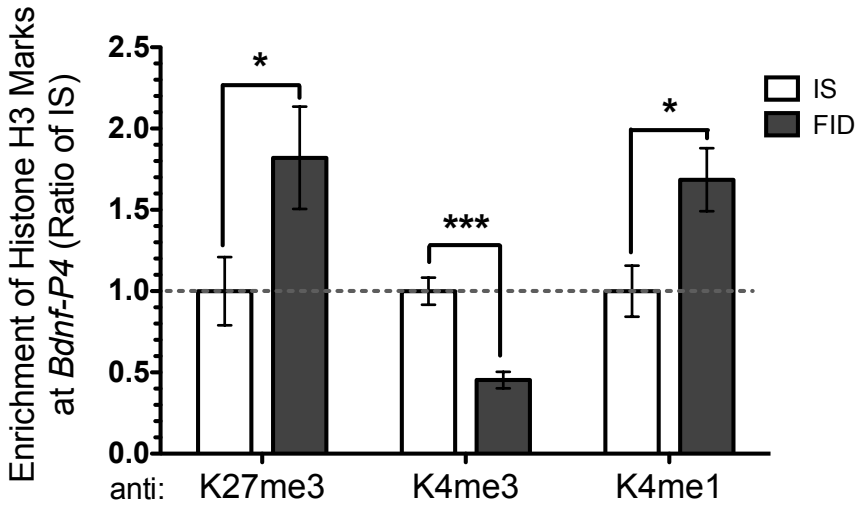
- Methylation of CpG Islands
  - Methyl (CH3) groups attach to “islands” of DNA where C (Cytosine) and G (Guanine) nucleotides are next to each other
    - More methylation; less DNA transcription -> less protein
- Histone Acetylation and Methylation
  - Histones found outside of DNA nucleotides and wind around them
  - Histone status can “open up” gene to more transcription or “close it off” leading to less transcription
- Overall effects depend on whether genes are active or repressive
  - Difficult to make predictions on effect without mapping pathways

Nutrients, Epigenetics and the Developing Brain

- Several fetal/neonatal nutritional conditions associated with brain epigenetic modifications in rodents
  - **IUGR** (Ke et al, 2014; reviewed by Grissom & Reyes, 2013; Ke et al,, 2010)
    - Generalized fetal malnutrition
      - Specific nutrients that are responsible have not been isolated
      - Disruption of hippocampal H4K20 me(1) (Ke et al, 2014)
    - Activation of glucocorticoids (Ke et al, 2010)
      - Stress alters BDNF DNA methylation
  - **LC-PUFA** (Tyagi et al, 2015)
    - DNA methylation of BDNF
  - Methyl donors and DNA methylation
    - **Choline** (Reviewed by Zeisel, 2010, 2012)
    - **Folate** (Ly et al, 2016; Cho et al, 2013; Barua et al, 2014; Langie et al, 2013)
  - **Iron** (Blegen et al, 2013; Tran et al, 2015)
    - Iron deficiency, anemia (hypoxia), or both
  - **Vitamin A**- DNA methylation of POMC in hypothalamus
    - Vitamin A supplementation reduces DNA methylation
  - **Riboflavin**- co-factor for small family of lysine histone demethylases
  - No current evidence for zinc, copper, iodine, selenium, B12, thiamine, other B vitamins, vitamin E, vitamin D

Long-Term Differential Effects on Histone Marks at the BDNF-IV Promoter Following Early-life ID (P65)

A



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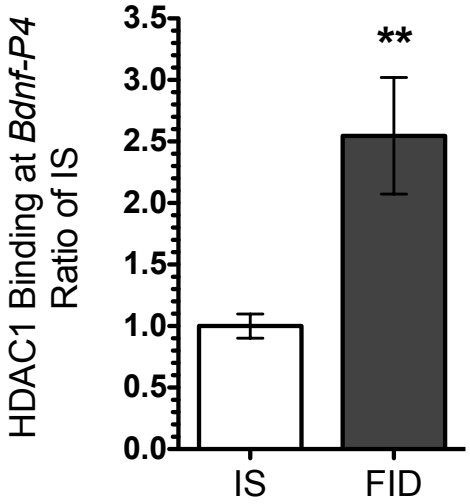

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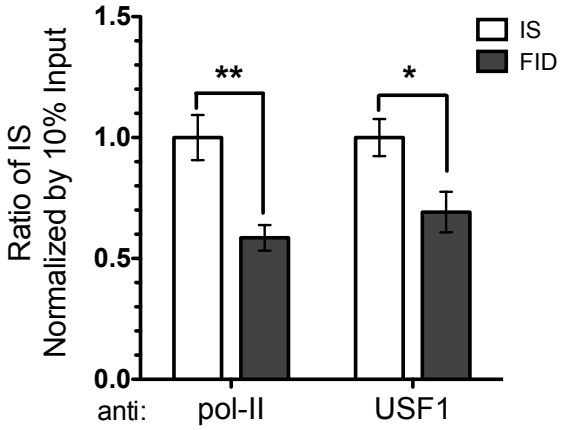
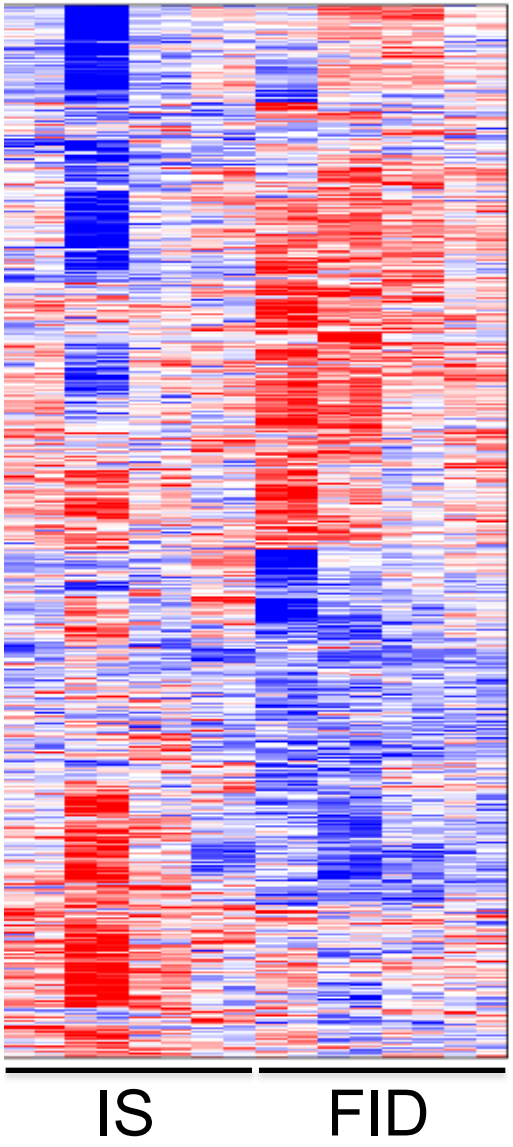
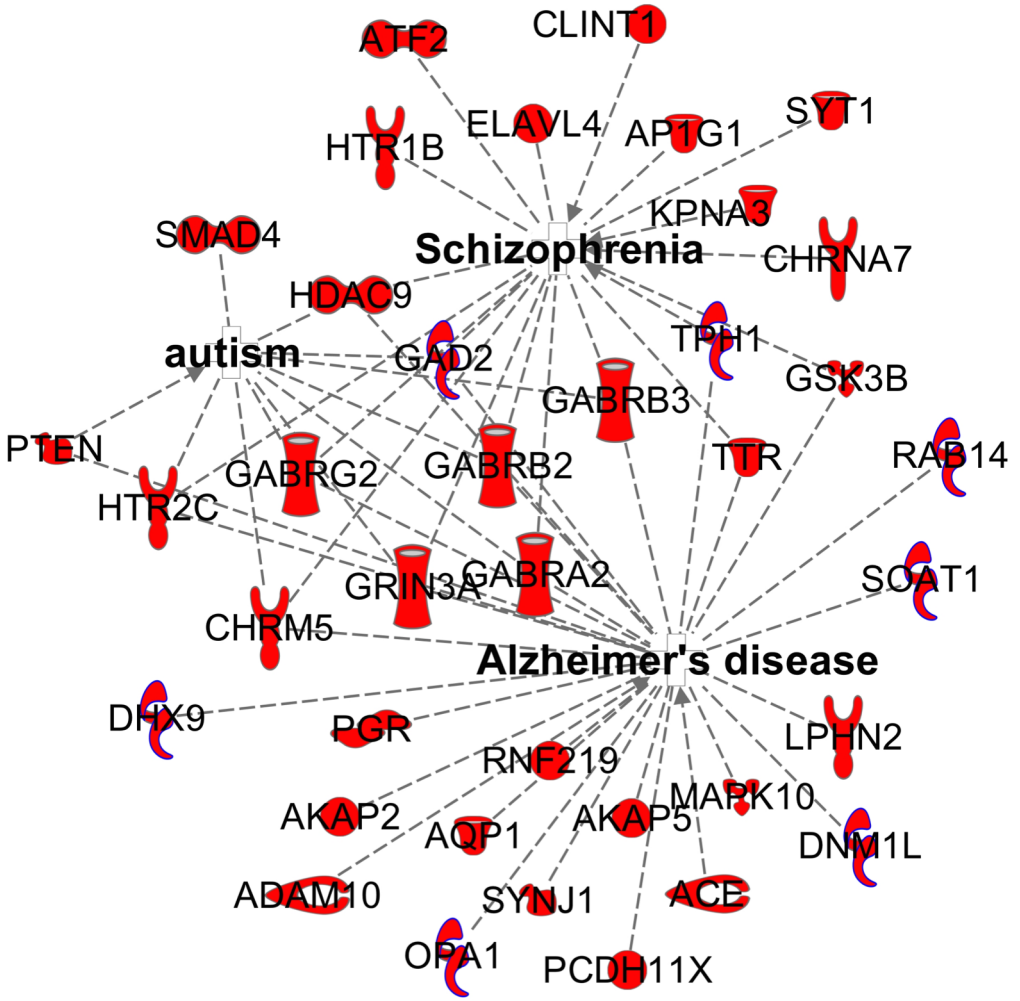


Tran et al, AJP, 2014

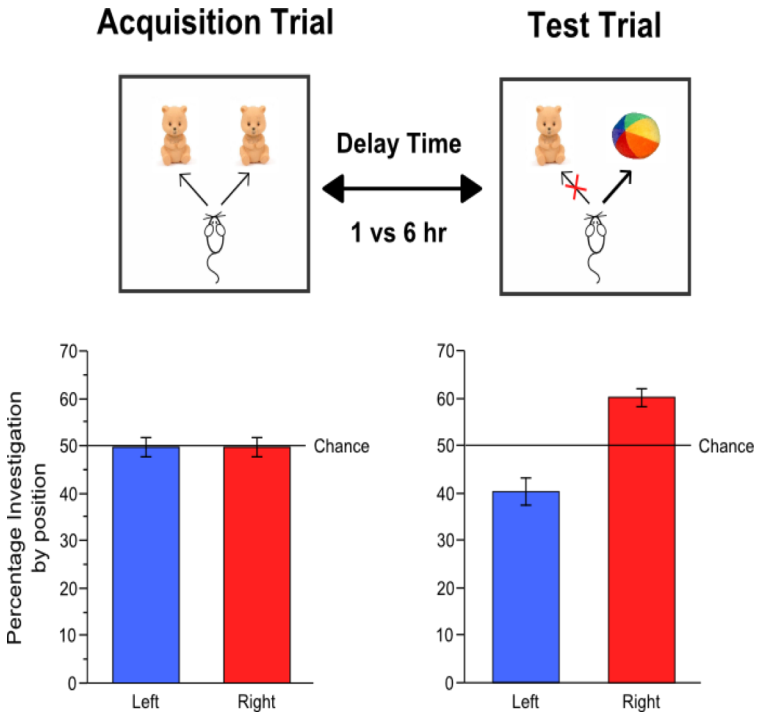
Adult Hippocampus Gene Expression and Activated Pathways Following Fetal/Neonatal IDA

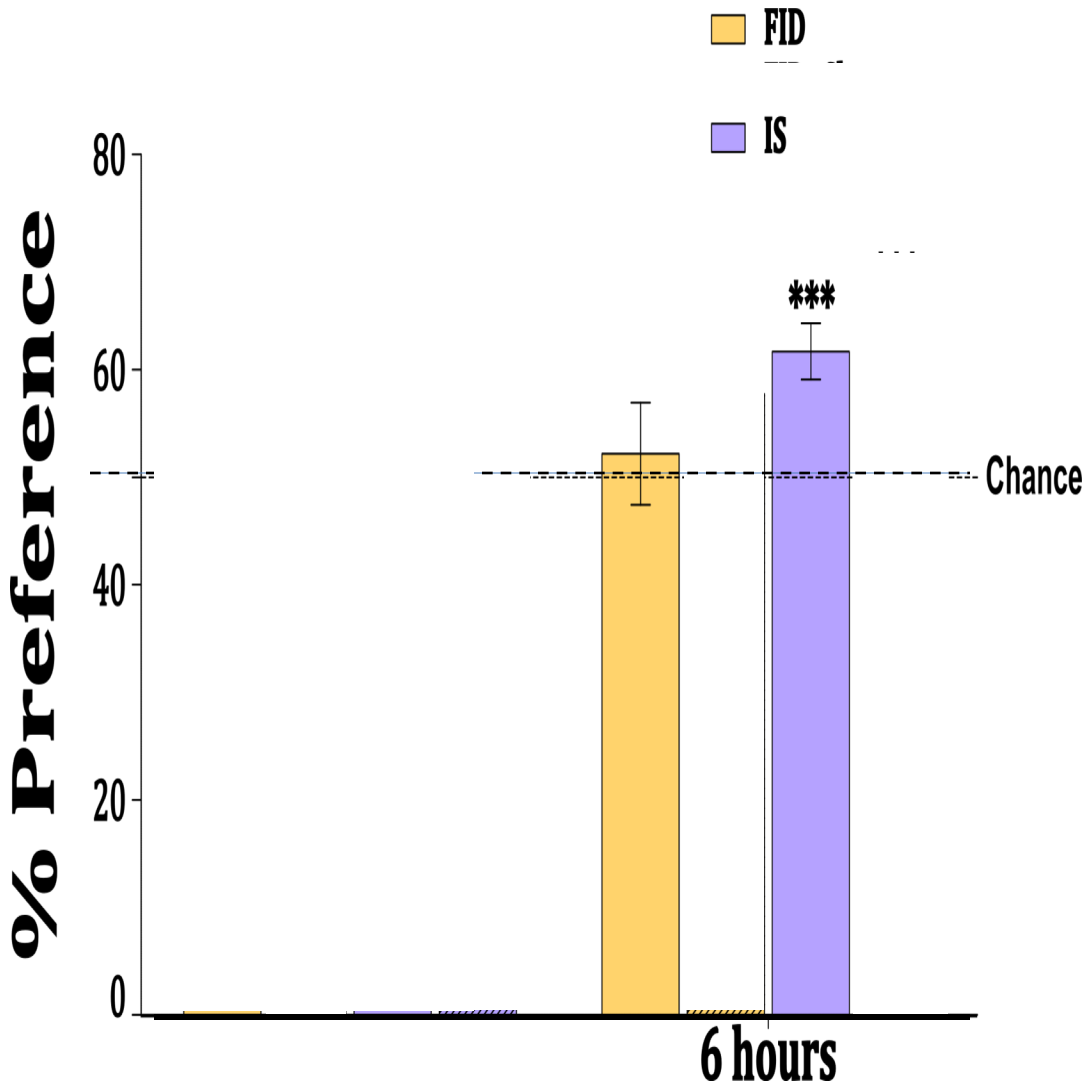




PV Tran et al, J Nutr 2016

Novel Object Recognition
Memory Performance in Adulthood





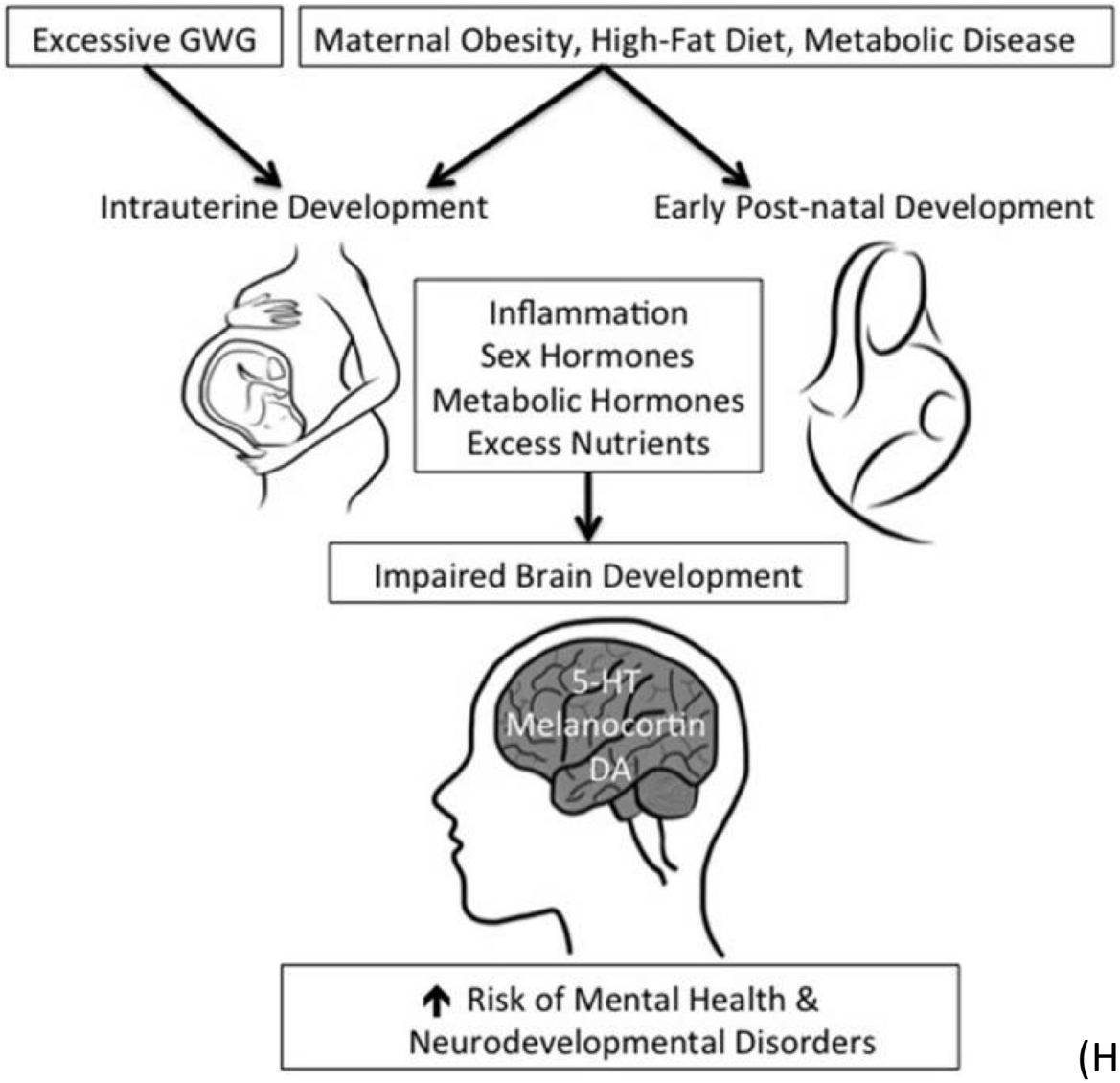
B Kennedy et al, J Nutr; 2014

*<0.05, **<0.01, ***<0.001 compared to chance preference

What About Too Rapid Growth?

Is that a risk to the brain?

Effect of Maternal Obesity on Offspring Mental Health



(HM Rivera et al, 2015)

Summary

- Early life nutrient effects depend on timing, dose and duration
  - Timing in terms of early brain development process
- Certain nutrients have high impact on early brain development
  - Effects can be global or circuit specific
  - Long-term risk is mediated through critical periods and epigenetics
- Nutrition is something that affects the young brain that we can influence

National Policy and Funding Implications

NIH/NICHD

- Traditionally one of the lowest funded major research institute within NIH
  - Covers ALL topics in pediatrics including mental health, neurologic diseases, obesity, kidney disease, diabetes, prematurity, pregnancy health, cancer risk

- Budget of $1.3 billion in 2017
  - 3.6% of total NIH budget ($36.1 billion)
  - Contrast to NHLBI (8.5%) or NCI (15%)
  - Contrast to NHLBI + NIDDK + NIMH + NINDS + NCI (40%)

- Less than 10% of grants are funded

- And, of course, children don't vote!
  - So, who will be their advocate?

Summary

- Optimizing brain development in childhood is an investment in society
- Early nutrition (prenatal to 3 years) profoundly affects developing primary brain structures necessary for:
  - Fundamental brain functions
    - Learning and memory, speed of processing, emotional reward
  - Neural scaffolding for later developing complex circuits subserving higher cognitive functions
- The early years are not the **sole** sensitive time period to influence brain development, but…the task is harder in later years if:
  - Improper early development (poor scaffolding)
  - New stressors are introduced in later years
  - Follow-up of initial gains are not maintained (regression to the mean)