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

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The first 1000 days

Right Start. Bright Future.

The right nutrition in the 1000 days between a woman’s pregnancy and her child’s second birthday builds the foundation for a child’s ability to grow, learn and thrive.

Pregnancy: The pregnancy to a baby’s first 1000 days

Babies developing in the womb derive all of their nutrients from their mother. If mom lacks key nutrients, putting the child at risk for future health and development at risk.

Infancy: Birth to 1 year

Breast milk is superfood for babies. Not only is it the best nutrition an infant can get, but it also serves as the first immunization against illness and disease.

Toddlerhood: 1 year to 3 years

Human nutrition from a variety of healthy foods is an essential complement to breast milk to ensure healthy growth and brain development.

The impact of good nutrition early in life can reach far into the future. Children who get right nutrition in their first 1000 days:

- Are 10x more likely to overcome the most life-threatening childhood illnesses
- Complete 4.6 more grades of school
- Go on to earn 21% more as adults

The 1000 Days movement is working to ensure all women and children in the United States have access to healthy food, safe spaces, and hope for the future.

SOURCES
1. United States, National Institute of Child Health and Human Development (2017)
3. Noval
4. Noval

www.1000days.org
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 O2 consumption in infancy
  • Reliant on metabolic substrates (nutrients) that support metabolism (e.g., O2, glucose, amino acids, iron, copper, iodine)
Hippocampus

Human Brain Development

Experience-dependent synapse formation

Neurogenesis in the Hippocampus

Cell Migration (6-24 Prenatal weeks)

Formation 

Synaptogenesis (-3 months to 15-18 years?)

Adult Levels of synapses

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

• 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\(^1,2,3\)

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\(^1\) 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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  • Fats (LC-PUFA)\textsuperscript{1,2,3}
  • Glucose\textsuperscript{1,2}

• Micronutrients
  • Iron\textsuperscript{1,2,3}
  • Zinc\textsuperscript{1,2}
  • Copper\textsuperscript{1,2}
  • Iodine (Thyroid)\textsuperscript{1,2}

• B vitamins (B6, B12\textsuperscript{1})
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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)
Protein undernutrition

• Protein-energy undernutrition >>> growth failure
• Intrauterine Growth Restriction (IUGR): < 10\textsuperscript{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)
Human Brain Development

Hippocampus

Experience-dependent synapse formation

Neurogenesis in the Hippocampus

- Cell Migration (6-24 Prenatal weeks)
- Synaptogenesis (~3 months to 15-18 years?)
- Myelination (~2 months to 5-10 years)
- Myelination (Prefrontal cortex)
- Myelination (Mesial cortex)
- Myelination (Caudate)
- Myelination (Nucleus accumbens)
- Myelination (Putamen)
- Myelination (Basal ganglia)
- Myelination (Cerebellum)
- Myelination (Pons)
- Myelination (Medulla oblongata)
- Myelination (Spinal cord)

Adult Levels of synapses

Thompson & Nelson, Am Psychol, 2001
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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
Typical time periods of iron deficiency

Human Brain Development

- Experience-dependent synapse formation
- Neurogenesis in the Hippocampus
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- Adult Levels of synapses

Cell Migration (6-24 prenatal weeks)

Months

Fetus  Late Infancy/Toddler  Pubertal
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
Pinpointing the optimal timing of iron intervention

Human Brain Development

Study 2

Hippocampus

Experience-dependent synapse formation

Neurogenesis in the Hippocampus

Synaptogenesis (<3 months to 15-18 years?)

Adult Levels of synapses

Cell Migration (E-24 prenatal weeks)

Receptive fields (Angular gyrus; inferior temporal cortex, superior parietal lobule, occipital pole)

Myelination (<2 months to 3-10 years)

Fetus  Late Infancy/Toddler  Pubertal

Months

Years

Decades

Death
Pinpointing the optimal timing of iron intervention

Human Brain Development

Study 3

Hippocampus

Neurogenesis in the Hippocampus

Synaptogenesis (-3 months to 15-18 years?)

Adult Levels of synapses

Fetus Late Infancy/Toddler Pubertal

Cell Migration (6-24 Fetal weeks)

Receptive field/auditory cortex

Myelination (-2 Months to 3-10 years)

Prefrontal cortex

Higher cognitive functions

Memory

Sensing / hearing

Birth

Months

Age

Years

Decades

Death
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 receive 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