Early Life Nutrition and Neurodevelopment

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Disclosure

• I have the following financial disclosure
  – I have a grant from Mead Johnson Nutritionals to study Biomarkers of Brain Iron Deficiency

• I will not discuss any off-label use an/or investigational use in my presentation
Objectives

• Define the principles of nutrient brain interactions in the neonate
• Describe the effect of fetal and neonatal growth rates on neurodevelopment
• Define the meaning of the term Developmental Origins of Adult Health and Disease as it relates to the brain
Principles of Nutrient-Brain Interactions

Early Nutrition and Brain Development: General Principles

• Nutrients regulate brain development during prenatal and postnatal life
• Rapidly growing brain in neonate
  – More vulnerable to damage
  – More amenable to repair

“Vulnerability outweighs Plasticity”
  (National Institutes of Health)
Early Nutrition and Brain Development: General Principles

Positive or negative nutrient effects on brain are based on:

**Timing, Dose and Duration of Exposure**

Kretchmer, Beard, Carlson

(Am J Clin Nutr, 1996)

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Nutrients->Brain

- 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
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
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

Nutrients and Brain Development: Processes Affected

• NEUROANATOMY
  – Neurons
    • Division (numbers)
    • Growth (size)
    • Development (complexity)
  – Supporting Cells
    • Oligos=> Myelin
    • Astrocytes=>Nutrient Delivery; Repair
    • Microglia=>Trafficking

Nutrient examples: protein, fats, energy, iron, zinc, choline
Nutrients and Brain Development: Processes Affected

• **NEUROCHEMISTRY (Neurotransmitters)**
  - Concentration
  - Receptors
  - Re-Uptake
  
  Nutrient examples: protein, iron, zinc, choline

• **NEUROPHYSIOLOGY**
  - Neuronal metabolism => Electrical activity of brain

  Nutrient examples: glucose, protein, iron, zinc, choline

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Brain Requirement for Nutrient</th>
<th>Affected Areas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein-Energy</td>
<td>Cell Proliferation, Cell Differentiation, Synaptogenesis, Growth Factors</td>
<td>Global Cortex, Hippocampus</td>
</tr>
<tr>
<td>Iron</td>
<td>Myelin, Dopamine, Energy</td>
<td>White Matter, Striatal-Frontal, Hippocampal-Frontal</td>
</tr>
<tr>
<td>Zinc</td>
<td>DNA, Neurotransmitter release</td>
<td>Autonomic NS, Hippocampus, Cerebellum</td>
</tr>
<tr>
<td>LC-PUFAs</td>
<td>Synaptogenesis, Myelin</td>
<td>Eye, Cortex</td>
</tr>
</tbody>
</table>
Developmental Origins and the Brain

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” neurodevelopmental abnormalities
  - 30% increased risk of schizophrenia (Eide et al, 2013)

- Fetal/postnatal iron deficiency and 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)

The Clear...

- Clear
  - Poorer neonatal growth (OFC, Weight, Length) is associated with poorer neurodevelopment (Georgieff et al, 1985; Ehrenkranz et al, 2005; Ramel et al, 2012)
    - Macronutrient interventional strategies improve growth in premature infants (see work by Rigo, Cooke, Embleton)
  - Similarly, deficiencies of certain micronutrients are known to negatively affect early brain development
    - Micronutrient supplements improve micronutrient status
...and the Unclear

• Unclear
  – Whether interventions/improvements in preterm infant nutrition status affect relevant long-term health outcomes
    • **Neurodevelopment**, metabolic health, bone health, immune health
  • Currently studies use growth & nutrient status as **surrogate markers** for neurodevelopment
    – “If status is better, neurodevelopment will follow”

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**Infant Growth after Preterm Birth and Neurocognitive Abilities in Young Adulthood**

Sara Salmi-Toiviainen, MA1, Vilho Pyhältö, PhD1, Marius Latini, PhD2, Jari Lehtilä, PhD3, Anu-Katriina Pekonen, PhD4, Kari Helsvanen, PhD5, Pentti Kivi, MD, PhD5,6,7, Johanne G. Eriksson, MD, PhD5,6,7, Sonja Stenäng-Wartiovaara, MD, PhD5,6,7, Sven Andersson, MD, PhD5, Anna-Liisa Järvenpää, MD, PhD5, Eero Kajantie, MD, PhD5,6,7, and Katri Iläkkönen, PhD1

A. GROWTH FROM BIRTH TO TERM

- Neurocognitive ability
- Weight SDS
- Height SDS
- Length SDS
- Head circumference SDS

<table>
<thead>
<tr>
<th>Neurocognitive outcome and growth phase</th>
<th>Weight SDS</th>
<th>Height SDS</th>
<th>Length SDS</th>
<th>Head circumference SDS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Effect size</td>
<td>95% CI</td>
<td>Effect size</td>
<td>95% CI</td>
</tr>
<tr>
<td>General neurocognitive ability</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IQ</td>
<td>0.221</td>
<td>0.13-0.30</td>
<td>0.22</td>
<td>-0.07-0.51</td>
</tr>
<tr>
<td>Birth</td>
<td>0.302</td>
<td>0.12-0.49</td>
<td>0.28</td>
<td>-0.13-0.69</td>
</tr>
<tr>
<td>12 mo CA</td>
<td>0.277</td>
<td>0.05-0.50</td>
<td>0.18</td>
<td>-0.04-0.38</td>
</tr>
<tr>
<td>WD</td>
<td>0.221</td>
<td>0.00-0.46</td>
<td>0.18</td>
<td>-0.01-0.29</td>
</tr>
<tr>
<td>Birth</td>
<td>0.226</td>
<td>0.05-0.41</td>
<td>0.21</td>
<td>0.03-0.39</td>
</tr>
<tr>
<td>12 mo CA</td>
<td>0.197</td>
<td>-0.03 to 0.41</td>
<td>0.14</td>
<td>-0.08 to 0.34</td>
</tr>
<tr>
<td>PD</td>
<td>0.286</td>
<td>0.11-0.47</td>
<td>0.24</td>
<td>0.10-0.38</td>
</tr>
<tr>
<td>Birth</td>
<td>0.297</td>
<td>0.12-0.48</td>
<td>0.25</td>
<td>0.11-0.38</td>
</tr>
<tr>
<td>12 mo CA</td>
<td>0.304</td>
<td>0.05-0.55</td>
<td>0.14</td>
<td>-0.08 to 0.34</td>
</tr>
</tbody>
</table>

- Executive functioning, attention, and visual memory
- Mental flexibility component
- Birth                                 | 0.258       | 0.14-0.45  | 0.17       | -0.01-0.30             |
| 12 mo CA                              | 0.304       | -0.03 to 0.43 | 0.21   | 0.00-0.42              |

(J Pediatr 2014;165:1109-15)
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. **Altered regulation of synaptic plasticity genes** through epigenetic modification of chromatin
   - 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 GCRC (stress model) (Ke et al, 2010)
         - Stress alters BDNF DNA methylation
     - LC-PUFA status (Tyagi et al, 2015)
       - DNA methylation of BDNF
     - Methyl donors and DNA methylation
       - Choline (Reviewed by Zeisel, 2010, 2012)
       - Folate (Cho et al, 2013; Barua et al, 2014; Langie et al, 2013)
     - Iron deficiency (Blegen et al, 2013; Tran et al, 2015)
       - Iron, anemia (hypoxia), or both
Macronutrients

Why does the brain need protein and energy?

Effects of early protein-energy malnutrition

Macronutrients: Major Roles in the Brain

• Carbohydrate:
  – Neonatal brain utilizes 60% (!) of total body VO2
  – Glucose is the main metabolic fuel for the brain
    • Can use alternate sources (lactate, ketones, amino acids)
  – Oligosaccharides
    • Role(s) being defined

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

• Fats:
  – Membrane composition
  – Myelin
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)
  – dose responsive based on degree of IUGR
  – 15% with mild neurodevelopmental abnormalities

• Compounded by postnatal growth failure (prenatal + postnatal malnutrition) (Casey et al, 2006)

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

IQ at 7y


Weight gain at 16 weeks of age (grams)
Long Chain Polyunsaturated Fatty Acids

Aka “Fish oils”

Docosohexaenoic Acid (DHA)
Neurobiological Effects of LC-PUFAs

• Severe essential fatty acid deficiency
  – Hypomyelination & altered fatty acid profile
  – Abnormal behavior including visual speed of processing
  – Findings in mice, rats, non-human primates

• Suspected effects on
  – Myelin production
  – Neuronal membrane fatty acid composition
  – Synaptogenesis
  – Cell signaling

LC-PUFAs and Mental Development

• More consistent effect seen in preterms compared to terms
• Outcome measurements are short-term, general (MDI), and not generally predictive of later function
• Long term studies - early acceleration may result in
  – No long term advantage
  – Permanent advantage
• Studies are ongoing but are underpowered to draw conclusions about long-term efficacy
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)
IQ at 7 yrs

Effect of Postnatal Excess Weight Gain after IUGR on 7 year IQ

Optimal growth

IQ lost due to excess weight gain (4-5 points)

Weight gain at 16 weeks of age (grams)

Pylipow et al, 2009

Differential Effects of Rapid Postnatal Growth after IUGR on BMI and IQ at 7 Years
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  - 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

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 **gene expression** while ID and long after ID is treated
Neurodevelopmental Sequelae of Perinatal ID

• **Term infants**
  - GENERAL: Low neonatal iron stores (<76 mcg/L) => poorer school age neurodevelopment (Tamura et al, 2002)
  - HIPPOCAMPUS: Cord ferritin <40 mcg/L => impaired recognition memory (Siddappa et al, 2004)
  - DOPAMINE: Iron deficient infants born to IDA mothers => altered temperament (Wachs et al, 2005)

• **Preterm infants**
  - GENERAL: Early iron supplementation => higher mental processing composite score at 5.3 years (Steinmacher et al, 2007)
  - MYELIN; SYNAPTOGENESIS: Ferritin <76 mcg/L at discharge => abnormal reflexes (Armony-Sivan et al, 2004)
  - MYELIN: Cord ferritin <76 mcg/L => slower central nerve conduction speeds (Amin et al, 2010)

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**Behavioral Problems at 3 Years in Late Preterm Infants**

Achenbach Child Behaviour Checklist. Clinical/borderline total score

Subscales
- Emotionally reactive
- Attention problems

Zinc Deficiency: Neurobehavioral Effects

- 3rd trimester fetuses of zinc deficient mothers demonstrate
  - Decreased movement
  - Decreased heart rate variability
  - Altered Autonomic Nervous System stability

- Postnatally, fetal zinc deficiency causes
  - Decreased preferential looking behavior behavior (more random looks and equal looking times)

Suggests fetal ANS, cerebellar and hippocampal effects

Monitoring: not routine, but Zn level <70 is concerning

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Iodine Deficiency and Brain Biology

- Iodine’s primary role is in thyroid hormone
- Low iodine levels lead to hypothyroidism
  - No direct role of I in brain development
- Lower brain weight and brain DNA
- Thyroid sensitive promoter regions
- Reduced dendritic arborization
- Reduced myelination (fatty acid synthesis effect)
- Reduced synaptic counts
Iodine Deficiency: Behavioral Effects

• Timing of deficiency is critical
• Fetal effects are much more profound
  – Greatest effect is I deficiency during first 12 weeks
  – Reduced head size
  – Global mental deficits/not reversible
• Mostly during childhood due to lack of iodine in diet
  – Reduced verbal IQ=> global effect on cell division?
  – Decreased reaction time (motor effect)=> due to delayed myelination or reduced synaptogenesis?

Dose: 30 mcg/day

Non-Nutritional Factors that Affect Nutritional Status
Linear Growth and Neurodevelopment
Ramel et al, Neonatology, 2012

- Weight Z-score at discharge or during follow-up not associated with 24 month outcome
- Linear growth (controlling for weight)
  - Each 1SD greater linear growth at discharge, 4 mos or 12 mos of age improved Cognitive (4.5 points) and Speech (7.9 points) Bayley Index at 24 months

Non-Nutritional Factors that Affect Linear Growth (Ramel et al, 2012)

- Linear growth suppression at 2 years as a function of non-nutritional factors in the NICU
  - Days on antibiotics (p<0.01)
    - Infections/Inflammation
    - Microbiome
  - Days on steroids (p<0.02)
    - Protein breakdown
  - Chronic lung disease (days of O2) (p<0.005)
    - Inflammation
- Potential roles for pro-inflammatory cytokines and glucocorticoids
Stress Physiology

- Physiologic adaptation to stress is to produce adequate fuel (glucose) and to promote survival
  - Starts in fetal life (IUGR as adaptive response)
- The most common stressor threatening species survival is infection
  - Psychological stress co-opts many of the same pathways (eg, cortisol, pro-inflammatory cytokines) as the more primitive response to infection
Hippocampus Under Stress:

Hippocampus **INCREASES** in size with:
- Regular exercise
- Intense learning
- Anti-depressant treatment
- Mediated by +BDNF

Hippocampus **ATROPHIES** in:
- Chronic stress
- Lack of exercise
- Chronic inflammation

Dendrites
Shrink and expand

Synapses
Disappear and are replaced

Courtesy of Bruce McEwan

Note similarity to iron deficiency effects

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Stress and Nutrition: a 2-Way Model

- Amino acids & growth factors
- mTOR (i.e., actin polymerization)
  - = Brain Protein Malnutrition

- Diversion of amino acids
  - Tissue (protein) breakdown
    - Ready substrate source for gluconeogenesis

- Poor Brain Growth
- Brain Iron Deficiency

Cortisol activation

- Cortisol activation
  - Cytokine production
  - Diversion of amino acids
    - Tissue (protein) breakdown
      - Ready substrate source for gluconeogenesis

- Activate Hepcidin
  - Reduced iron absorption
  - Liver iron sequestration

- Iron
  - Poor White Cell Function/Cytokine response
    - Energy “brown out”
    - Fe dependent enzymes

- Zinc
  - Reduced GF synthesis
    - Poor tissue integrity
    - Reduced stores for gluconeogenesis
    - Reduced synaptic efficacy (Zn)
      - Less responsive neural system

- Protein

- Stress
  - Poor White Cell Function/Cytokine response
    - Blunted Response
Nutritional and Non-Nutritional Modulation of mTOR

Strategies to Protect the Developing Brain

- Pre-conception
  - Nutrient sufficiency
    - Not just macronutrients, but micronutrients
    - 25-40% of women of CBA are iron deficient
      - Not just a developing world problem
  - Weight management in women of child-bearing age
    - Reduction of obesity

Wullschleger et al, 2006

• Pre-conception
  – Nutrient sufficiency
    • Not just macronutrients, but micronutrients
    • 25-40% of women of CBA are iron deficient
      – Not just a developing world problem
  – Weight management in women of child-bearing age
    • Reduction of obesity
Strategies to Protect the Developing Brain

- Gestation
  - Blood pressure control
    - IUGR due to maternal hypertension or preeclampsia during pregnancy
    - 10% of population suffered IUGR
      - 50% are iron deficient at birth; all have protein malnutrition
  - Blood sugar control
    - 10% of pregnancies complicated by maternal diabetes (pregestational or gestational)
    - 65% of infants of diabetic mothers are iron deficient at birth
  - Stress reduction
    - Maternal stress -> fetal stress -> abnormal fetal brain development (and iron deficiency)
  - Weight management
    - Reduction of obesity
  - Nutrient sufficiency
    - Prenatal vitamins including iron
    - LC-PUFA (DHA) supplementation

- Postnatal (especially 0-3 years)
  - Nutrition
    - BREAST MILK
      - Breastfed babies are smarter, have less obesity, less infections
    - LC-PUFA (DHA) supplementation of formula fed babies
    - Maintain iron and zinc sufficiency
    - Screen for thyroid status
      - In China, this means iodine and selenium nutritional status
  - Avoidance/reduction of toxic stress
    - Toxic stress alters brain development
    - Toxic stress alters how critical nutrients are accreted
  - Reduce infectious burden
    - Infection and inflammation alter brain development during critical periods of growth
Summary

• Non-nutritional factors influence nutritional status
  – Stress physiology
  – Inflammation
  – Steroid use
  – Infections
• Sometimes the best nutritional therapy is non-nutritional

Summary

• 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
• Certain nutrients have high impact on early brain development
  – Effects can be global or circuit specific
• Nutrition is something that affects the young child’s brain that we can control