The Timing of Integrated Early Interventions: Nutrition, Stress and Environmental Enrichment

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Early Environment and Brain Development: General Principles

Positive or negative effects on brain development

Based on...
Timing, Dose & Duration of Exposure
Kretchmer, Beard, Carlson (1996)

“Environment” in our context:
1) Nutrition
2) Stress
3) Nurturing events
4) Combinations of 1-3
Environment->Brain->Behavior Relationships: “Timing is Key”

• Brain is not a homogeneous organ

• Different brain regions have different developmental trajectories

• Vulnerability of a brain region to environmental stimuli is based on
  – Timing of deficits/enrichment programs during the lifespan
  – Brain region requirement for a nutrient, vulnerability to stress, and receptivity to enrichment at that time
Environment->Brain->Behavior: Ascribing Cause and Effect

- Behavioral changes map onto those brain structures/circuits altered by the environmental experience
  - Transient => acutely alters brain function
  - Long-term => permanent changes anatomy
    - Residual Structural Deficits (critical period hypothesis)
    - Epigenetic Modification of Synaptic/Structural Genes
      - Stress (Meaney et al), Iron deficiency (Tran et al)
  - Biological plausibility
    - Helps design targeted interventions
Vulnerability & Plasticity During Rapid Brain Development

• A period of rapid regional brain growth and differentiation is characterized by
  – High vulnerability to insult
  – Greater plasticity
    • Greater effect of positive influences
    • Greater chance for recovery from negative influences
• NIH: “Vulnerability outweighs plasticity” (1994)
• Periods of less rapid regional brain growth doesn’t mean immutability
  – “Sensitive” periods vs “critical” periods
  – Biologic basis for true critical periods (Hensch, 2004)
    • Parv+ GABA interneurons & perineuronal nets
    • Can critical periods be re-opened?
Early Neurodevelopment is Important Immediately and Later

• Early years of life: development and sensitivity of early neural systems to extrinsic influences
  – Primary systems (fetal to 3 years)
    • 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 (through teenage years)
    • Initial connectivity from HC, Striatum (early in life)
      – Examples: Prematurity, Intrauterine growth restriction, newborn ID
    • Maintenance (throughout development)
      – Example: IHDP, Head Start
Coordinating the Timing of Interventions Based on the Biology

• The possibility of different sensitive periods & integrated interventions across domains
  – Nutrition- early?
  – Reduction of toxic stress- all times?
  – Environmental enrichment- later?

• Primary question: are there sensitive time window(s) within which to provide integrated biological and psychosocial interventions to promote the development of children
  – If so, when is this?
Nutrition
Nutrients with Large Effects on Early Brain Development and Behavior That Demonstrate Sensitive or Critical Periods in Clinical Studies or Animal Models

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Period(s) of particularly high brain demand for nutrient</th>
<th>Principal brain region or circuitry affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein</td>
<td>Gestation-4 – 12 months postnatal</td>
<td>Global, hippocampus, striatum, myelin, cerebellum, Cortex (esp prefrontal), myelin</td>
</tr>
<tr>
<td>LCPUFAS</td>
<td>Last trimester &amp; 2-3 months postnatal</td>
<td>Global, retina</td>
</tr>
<tr>
<td>Iron</td>
<td>Last trimester-6 months-3 years postnatal</td>
<td>Myelin, striatum, hippocampus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Myelin, frontal cortex, basal ganglia (motor)</td>
</tr>
<tr>
<td>Zinc</td>
<td>Last four months of gestation-6 months – 10 years-</td>
<td>Autonomic nervous system, cerebellum, hippocampus, Cortex</td>
</tr>
<tr>
<td>Iodine</td>
<td>First trimester of gestation-Last trimester-</td>
<td>Global, Cortex, striatum, cerebellum, hippocampus</td>
</tr>
<tr>
<td></td>
<td>Infancy-12 years-</td>
<td>Myelin, prefrontal cortex</td>
</tr>
<tr>
<td>Copper</td>
<td>Last trimester</td>
<td>Occipital-parietal cortex, striatum, cerebellum, hippocampus</td>
</tr>
</tbody>
</table>
Sensitive Periods for Nutrient Supplementation

• Growth velocity prior to 1 year (but not afterwards) predicts IQ at 9 years (Pongcharoen et al., 2012)
  – Linear growth at birth and in the first year has stronger association than weight
  – Growth between 1 and 9 years => no effect on IQ

• Fetal supplementation of iron/folic acid improves working memory, inhibitory control, fine motor at 7-9 years (P Christian et al, 2010)
  – But... late infancy/toddler supplementation of iron/folic acid (12-36 months) has no effect (Murray-Kolb et al., 2012)
Stress
Types of Stress

Positive Stress
• Exhilaration from a challenge that has a satisfying outcome
• Sense of mastery and control
• Good self esteem

Toxic Stress
• Exacerbated by chaos, abuse, neglect
• Poor social and emotional support
• Unhealthy brain architecture
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

Note similarity to iron deficiency effects

**Dendrites**
Shrink and expand

**Synapses**
Disappear and are replaced
Nutrition and Stress: 2-Way Model

- **Iron**
  - Poor White Cell Function/Cytokine response
    - Energy "brown out"
    - Fe dependent enzymes
  - Blunted Response
- **Zinc**
  - Reduced GF synthesis
    - Poor tissue integrity
    - Reduced stores for gluconeogenesis
    - Reduced synaptic efficacy (Zn)
    - Less responsive neural system
- **Protein**
  - Poor Brain Growth
  - Brain Iron Deficiency
- **Cortisol**
  - Activation
  - Cytokine production
  - Diversion of amino acids
    - Tissue (protein) breakdown
    - Ready substrate source for gluconeogenesis
  - Activate Hepcidin
    - Reduced iron absorption
    - Liver iron sequestration
  - Amino acids & growth factors
    - mTOR (i.e., actin polymerization)
    = Brain Protein Malnutrition
Early Enrichment
Long-term Impact of Early Environmental Interventions

• 6-12 months is a sensitive period for promoting secure attachment (van IJzendoorn & Juffer, 2006)

• The early years of life are a salient time period for interventions to improve quality of parenting (Bakermans-Kranenburg et al., 2003)

• Intervention during early years in high (Barnett, 2011) & LAMI countries (Engle, et al., 2011) have long-term cognitive-academic benefits
Follow-up/Follow-on Interventions Maintain Impacts of Early Interventions

• Follow-up interventions during primary school stabilize initial cognitive gains from short duration early intervention programs – (Reynolds et al., 2001).

• Follow-up interventions beyond the first 5 particularly critical for children at high cumulative developmental risk – (Reynolds & Robertson, 2003).
The Process Doesn’t End at 5 Years

• Experience dependent brain development in **adolescence** mediates:
  – Social-emotional communication skills
  – Executive function
  – Abstract thought
  – Ability to evaluate the comparative value of risks and rewards

(Baird, 2010; Steinberg, 2005)
Integrated Conclusions

• Early environment (prenatal to 3-5 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
    • Higher cognitive functions

• Early events confer a lifetime of risk through epigenetic modification of critical genes

• The early years are not the sole sensitive time period,
  – But the task is harder in later years

• Follow-up/follow-on interventions are crucial for children with multiple cumulative high risk events

• Integrated interventions are essential because neural, nutritional/metabolic, physiological and behavioral biology form a linked multi-dimensional system