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)

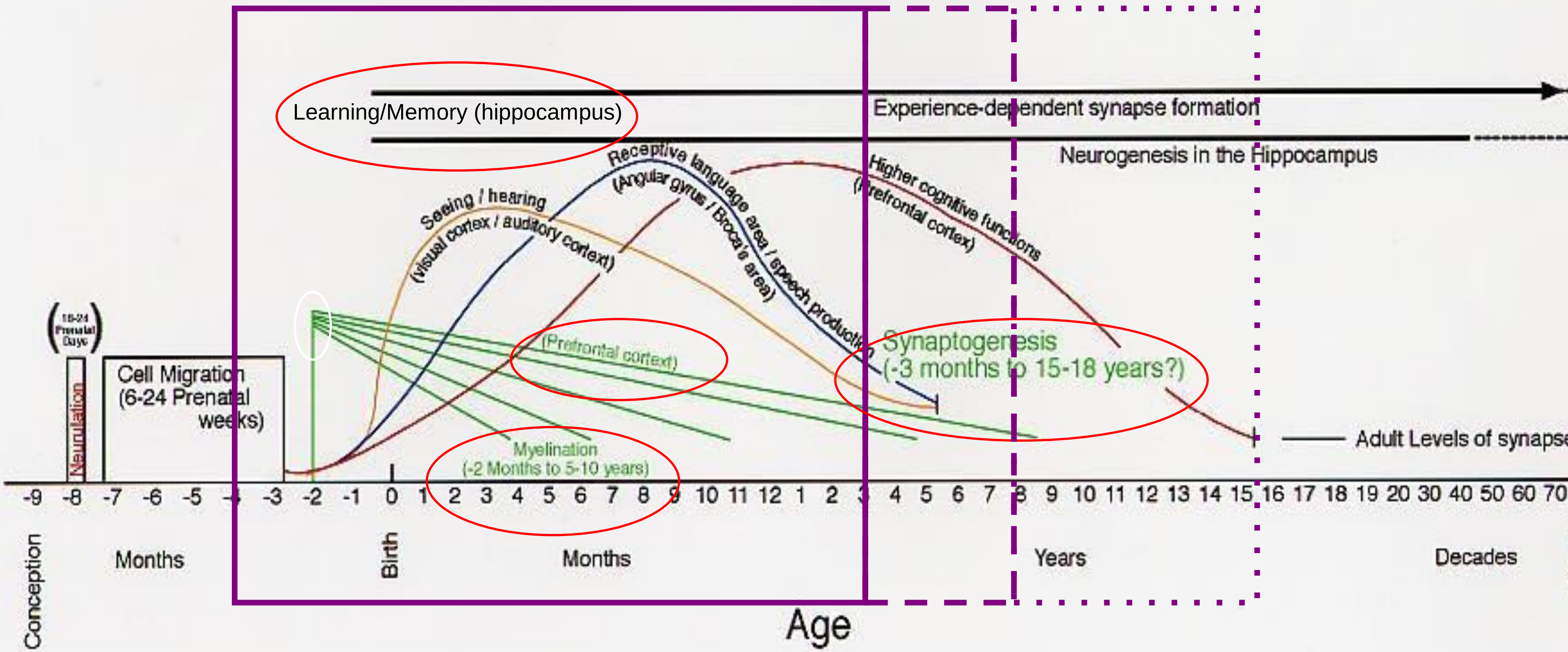
“Environment” in our context:

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

Human Brain Development



Fetus Late Infancy/Toddler Pubertal

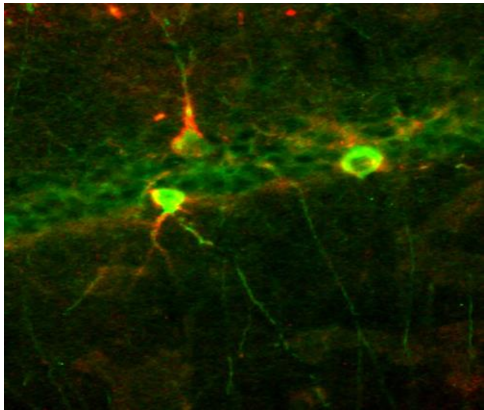
Thompson & Nelson, 200

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 <u>integrated</u> 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

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

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

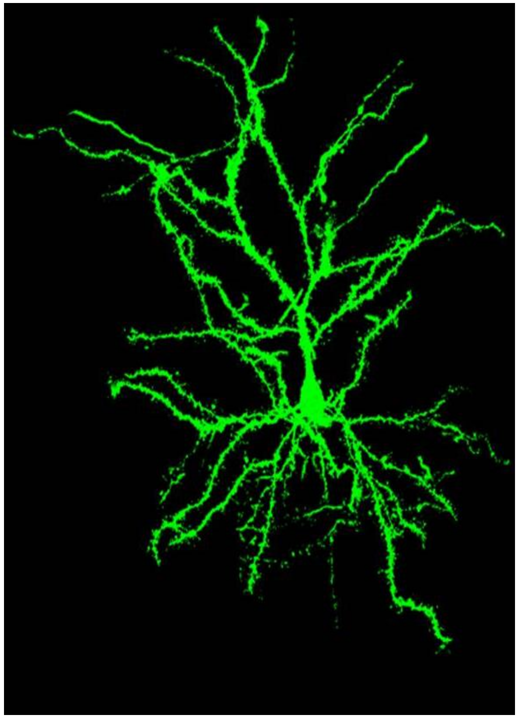
Toxic Stress

- 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



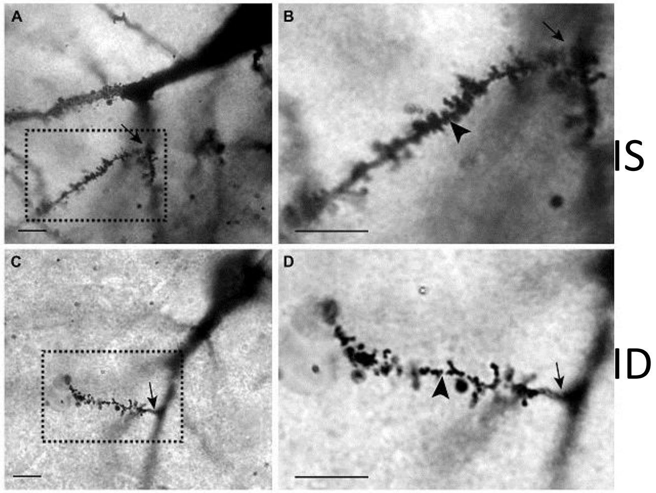
Dendrites

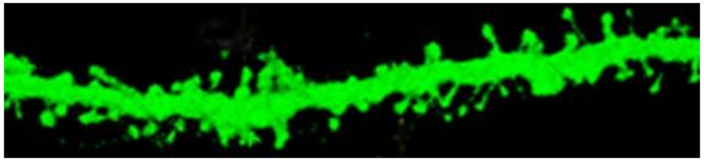
Shrink and expand

Hippocampus *ATROPHIES* in:

- Chronic stress
- Lack of exercise
- Chronic inflammation

Note similarity to iron deficiency effects

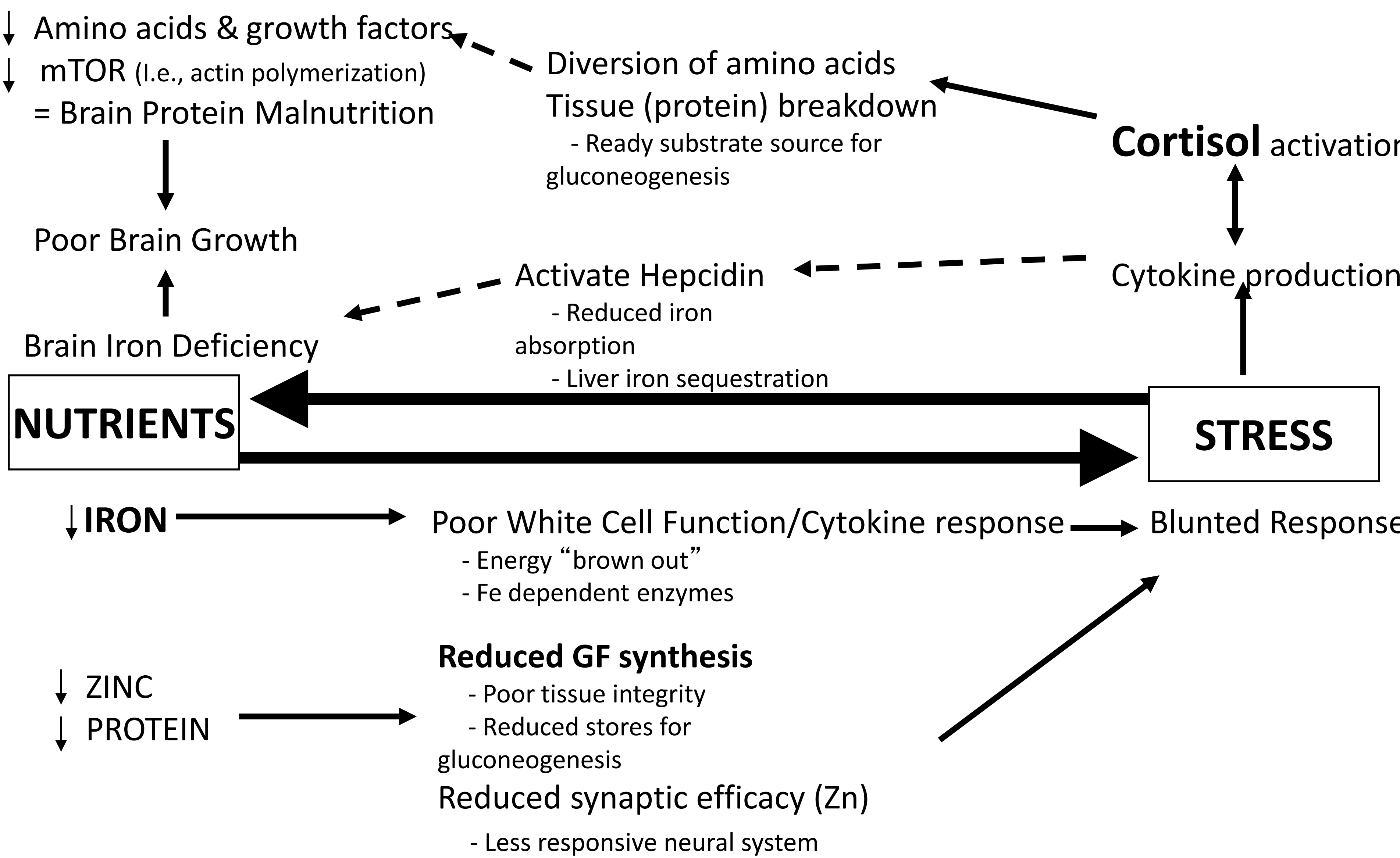




Synapses

Disappear and are replaced

Nutrition and Stress: 2-Way Model



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