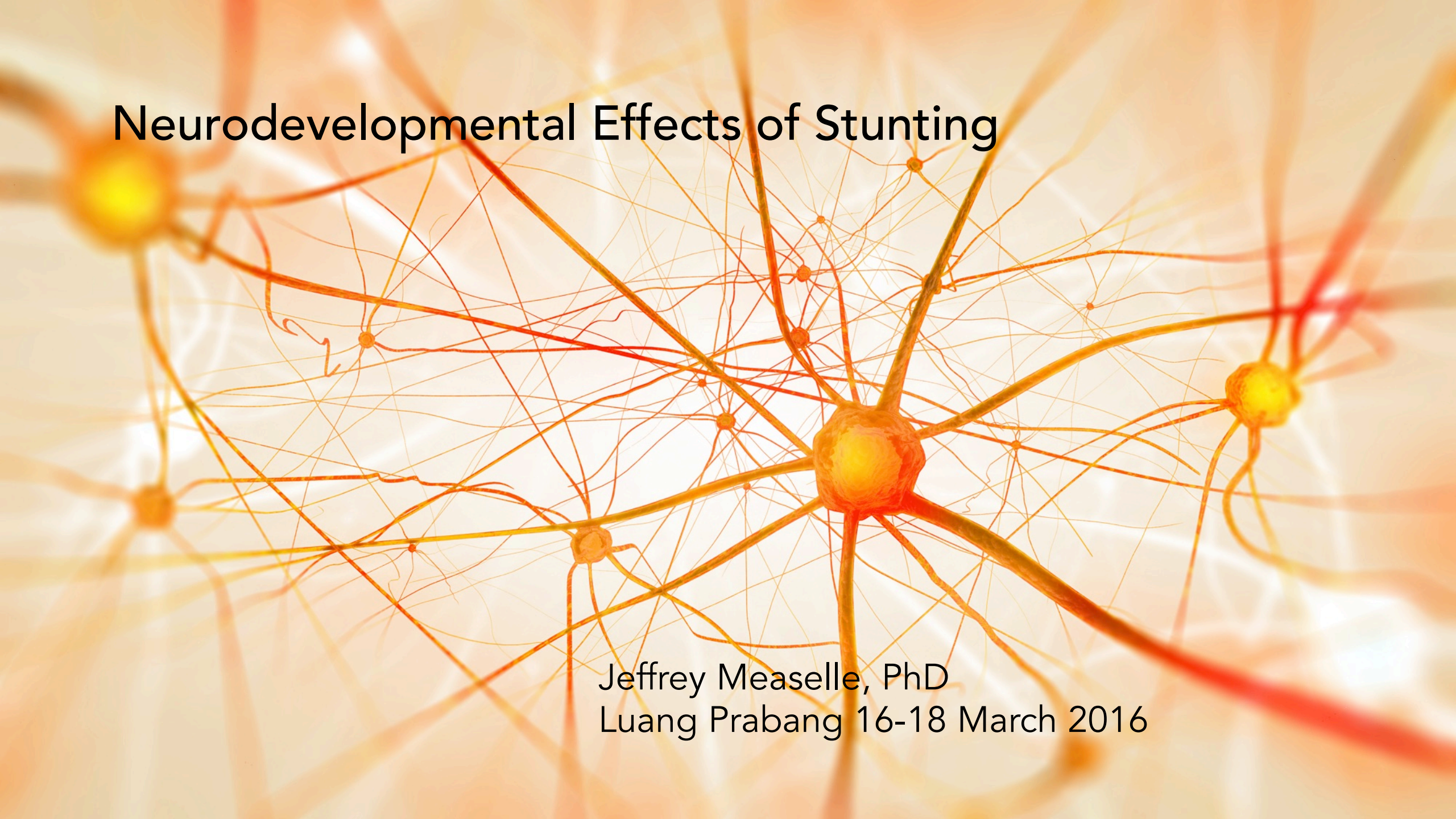
Neurodevelopmental Effects of Stunting



Jeffrey Measelle, PhD
Luang Prabang 16-18 March 2016

Aims

- ABC's of brain development in first 1000 days: Critical role for nutrients
- Measuring effects of stunting on brain & role of neuroscience methodologies
- Examples from Laos

Healthy Brain = Healthy Future

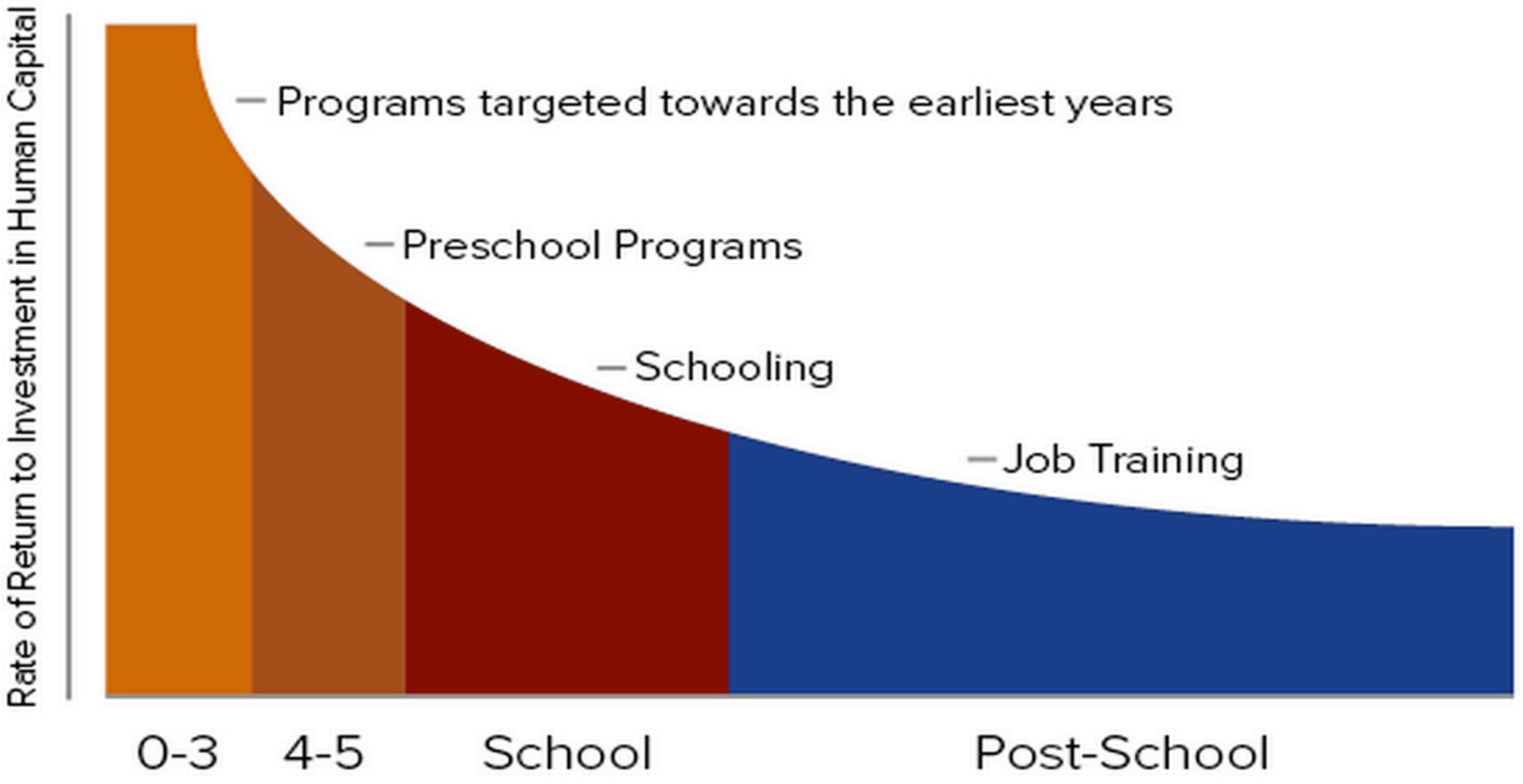
Healthy Child Brain

- Improved health & development
- Academic success
- Social Health
- Mental Health

Healthy Adult Brain

- Improved health
- Higher earnings
- Social Health
- Mental Health

Return on early investment superior



10:1 return**

1:1 return

- 4:1 return

Source: Heckman and LaFontaine (2007)

Brains are built

<u>Prenatally</u>

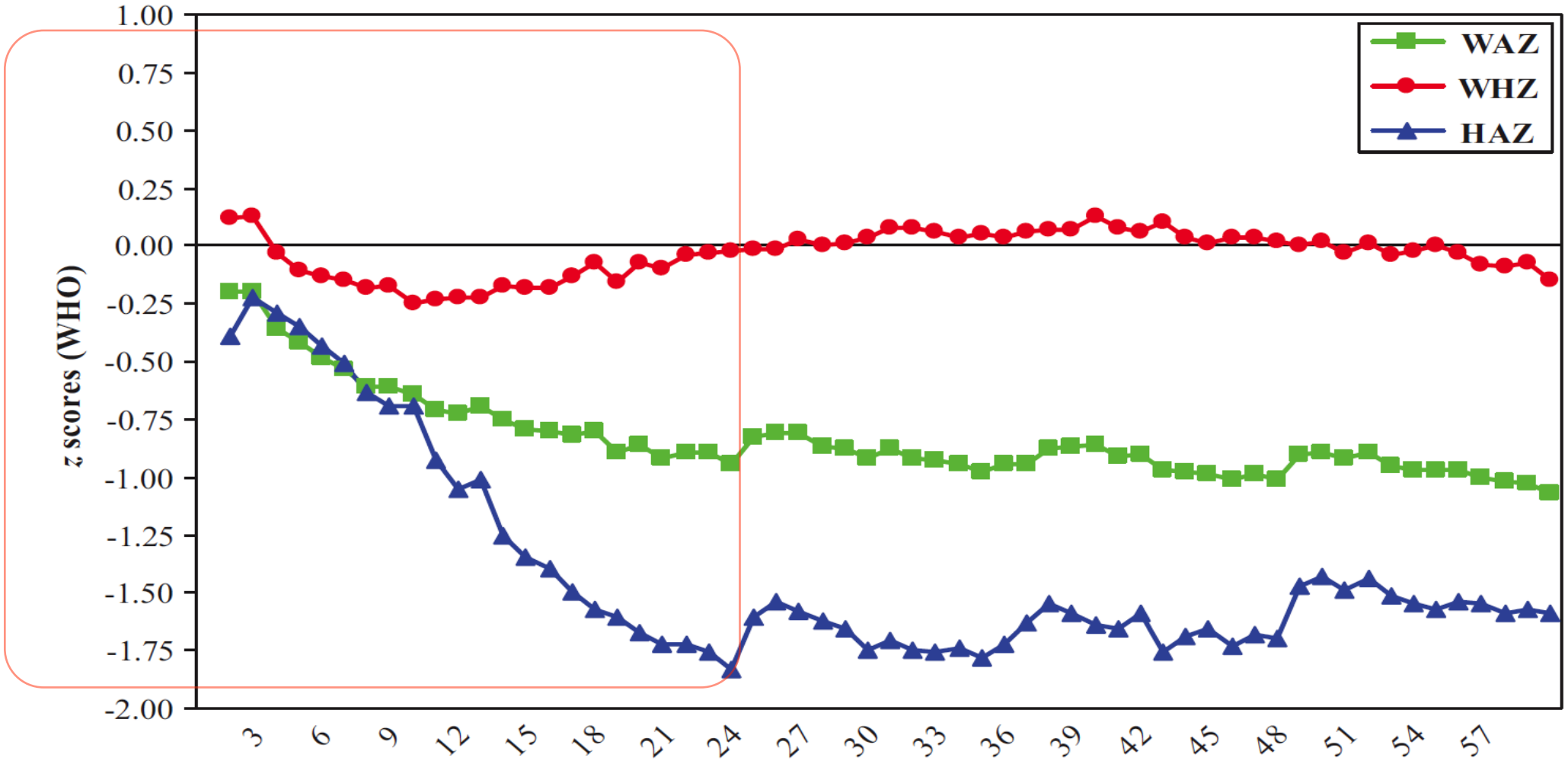
- Genetics
- Nutrition
- Antenatal Care
- Low Stress

<u>Postnatally</u>

- Supportive care
- Nutrition
- Stimulation
- Healthy environ
- Low Stress

Best Building Window: -9 months to 24 months

Mean z scores relative to WHO standards across 54 DHS/MCIS studies, by age (1-59 mo.)



Source: CG Victora, M de Onis, PC Hallal, M Blössner and R Shrimpton, "Worldwide timing of growth faltering: revisiting implications for interventions." Pediatrics, 125(3, Mar. 2010):e473-80.

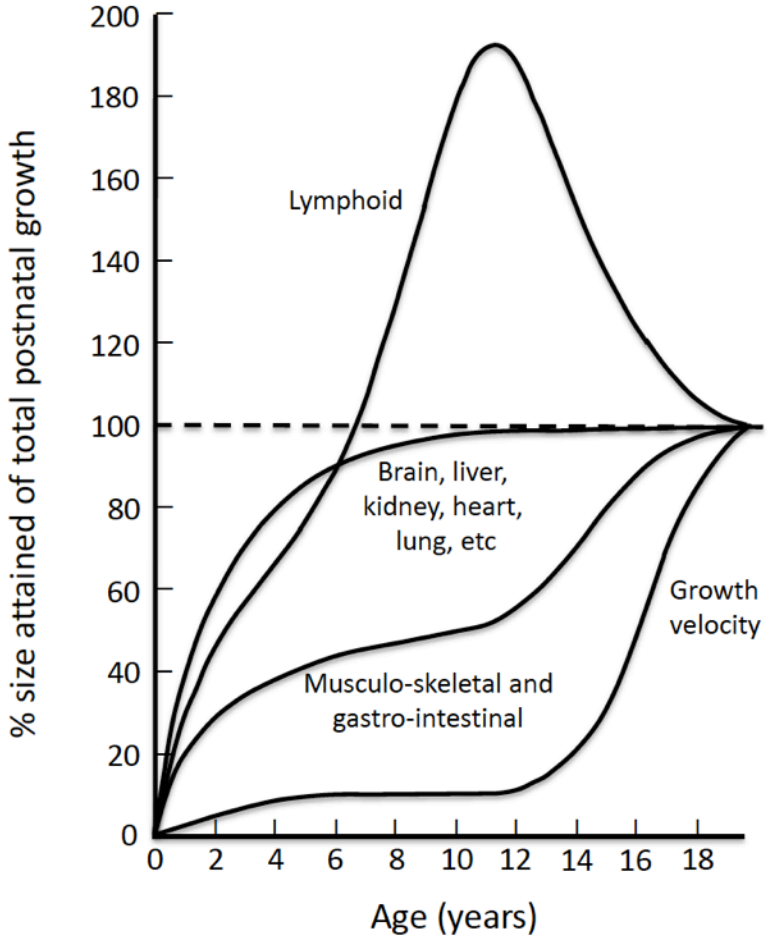
Stunting:

Key indicator
of failure to thrive

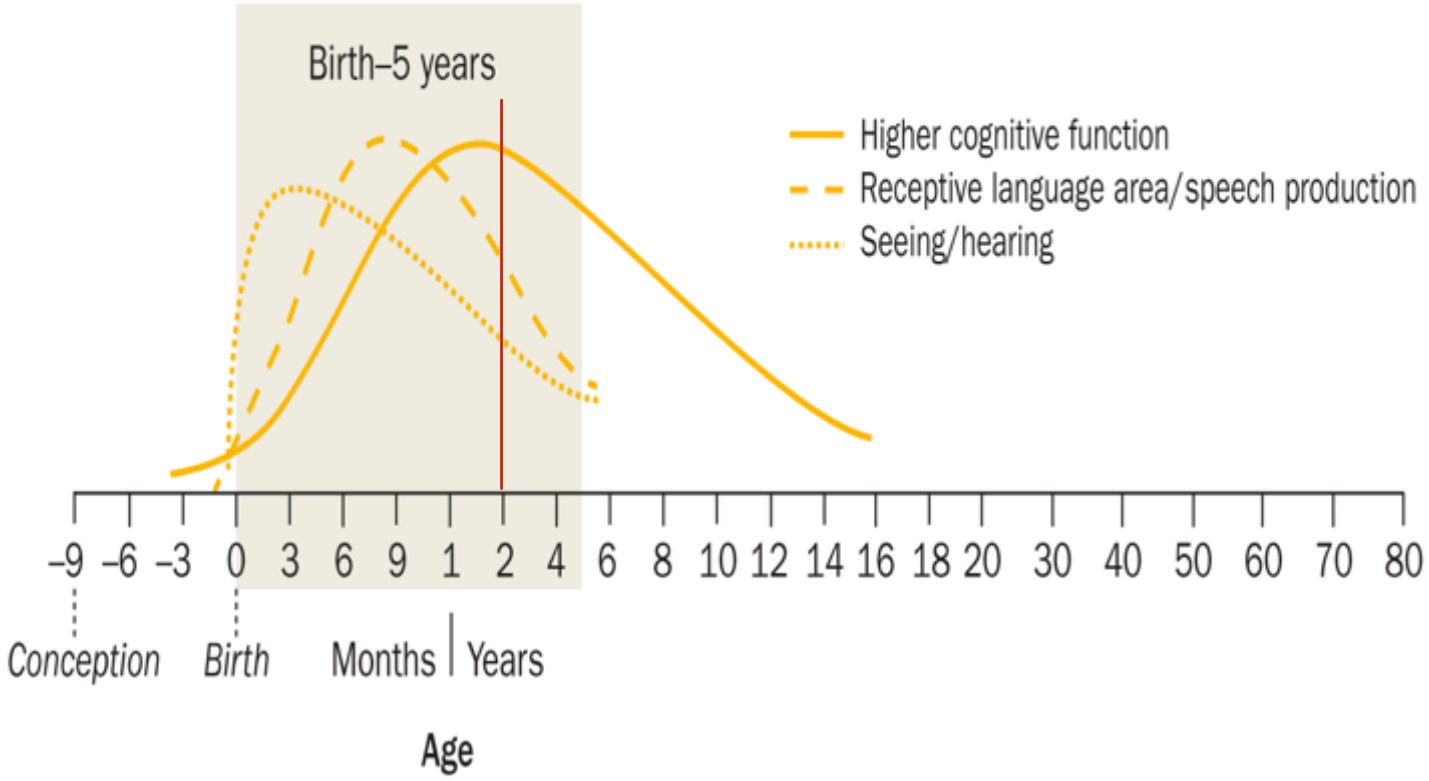
Key indicator of what is not going right for the brain

80% of brain's development occurs during first 1000 days

Absolute Size

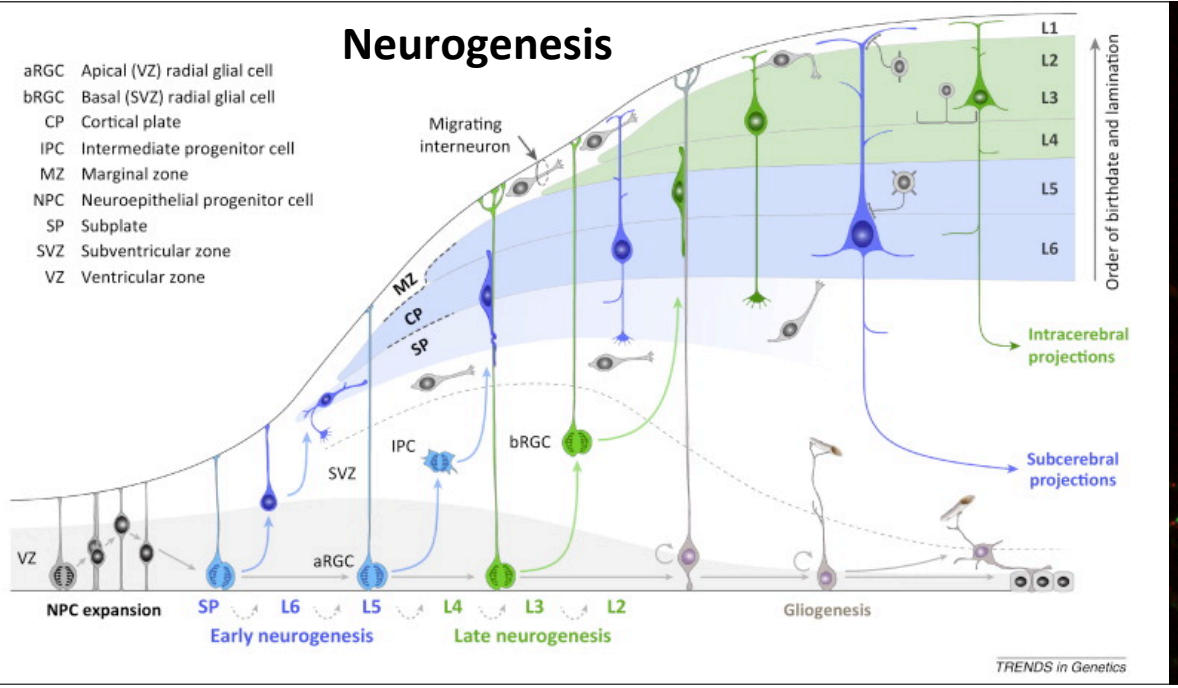


Neural Circuitry

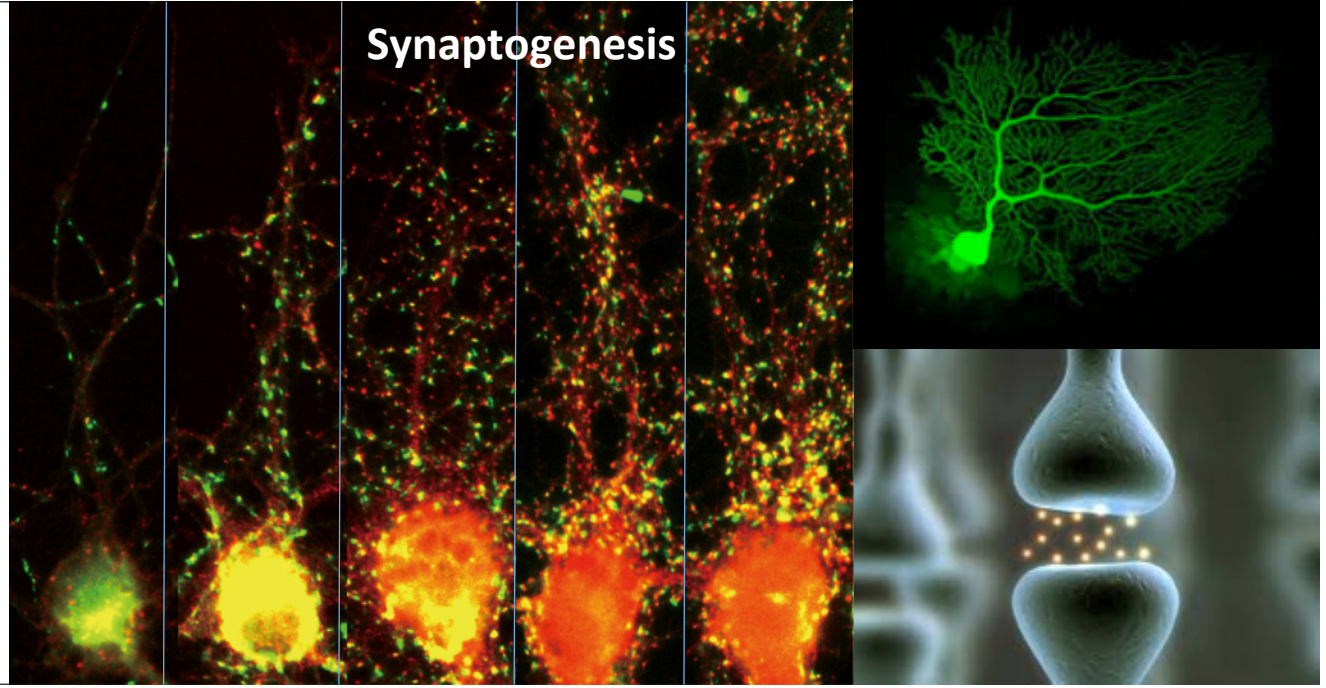


Courtesy: C. Nelson (2016)

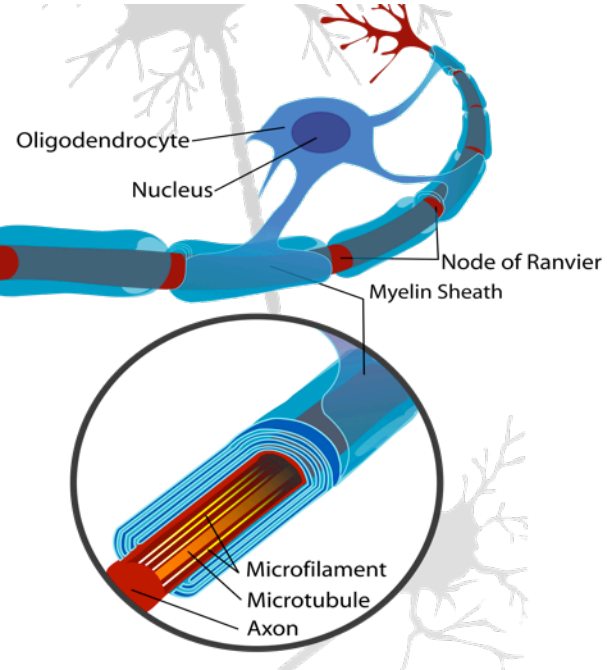
Neurogenesis



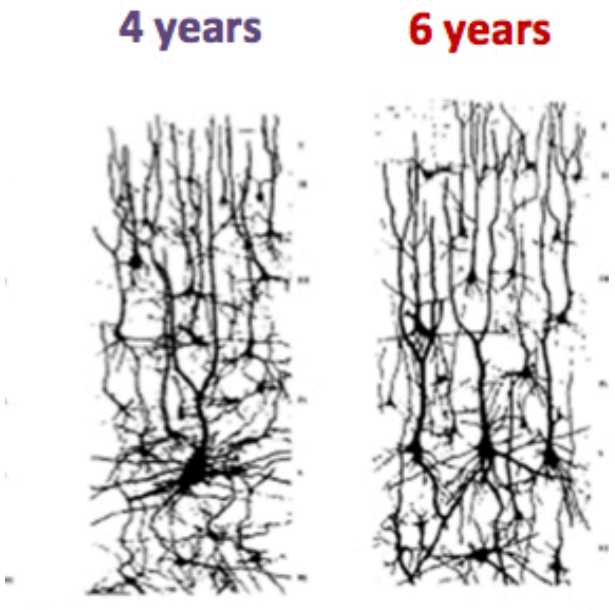
Synaptogenesis



Myelinogenesis



Synaptic Reduction



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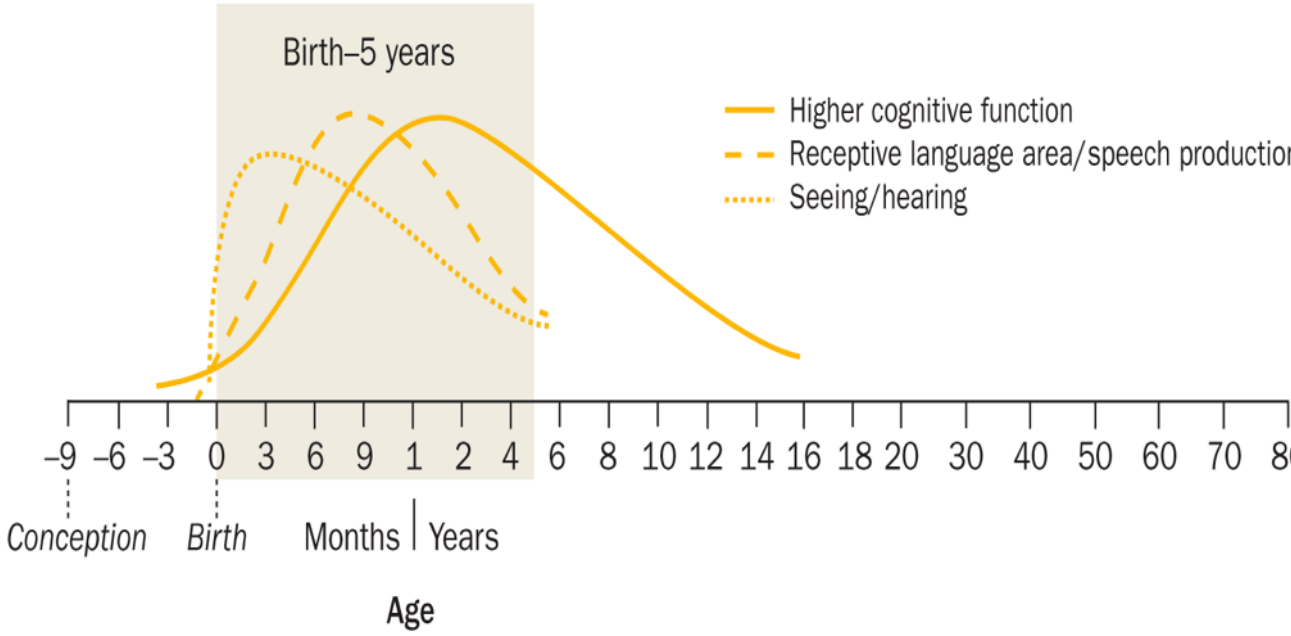


Micronutrients During First 1000 Days

- Specific nutrients needed for specific neural development
  - Deprivation of nutrients supporting basic neuronal/glial metabolic processes most deleterious

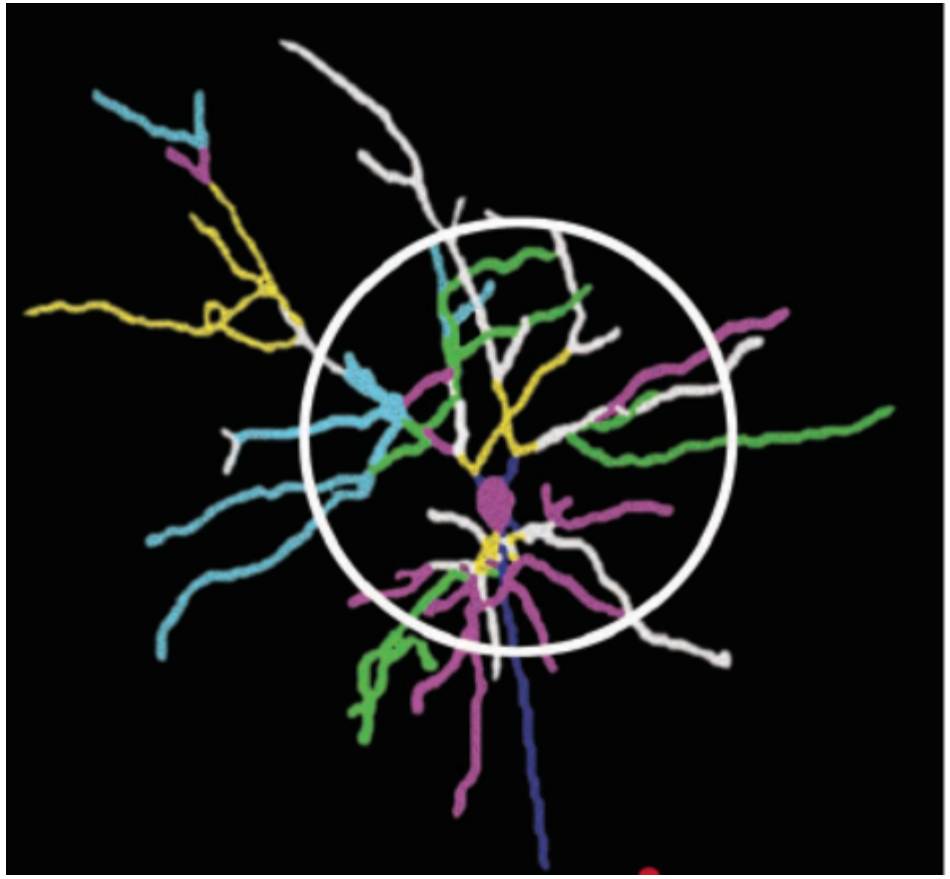
- Effect of nutrient deficiency or overabundance on brain governed by:
  - Timing
  - Dose
  - Duration

Micronutrients During First 1000 Days

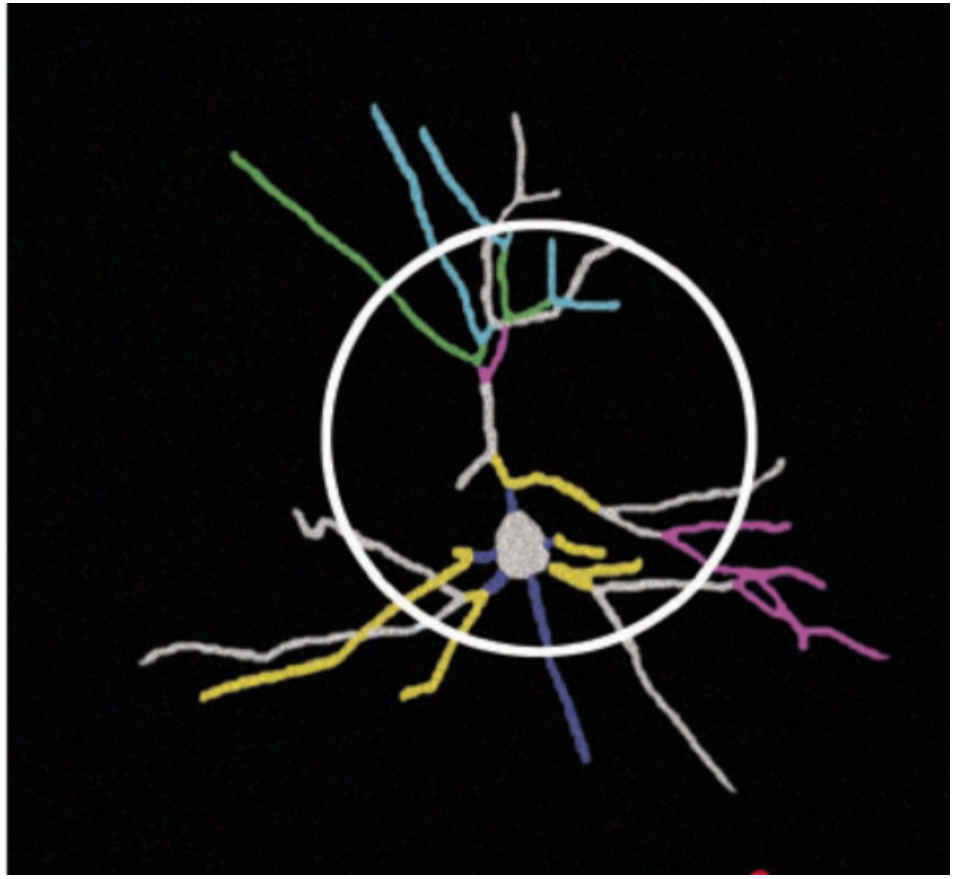
Nutrient	Period(s) of particularly high brain demand for nutrient	Principal brain region or circuitry affected
Protein	(1) Gestation	(1) Global, hippocampus, striatum, myelin, cerebellum
	(2) 4–12 months postnatal	(2) Cortex (especially prefrontal), myelin
LCPUFAs	Last trimester of gestation: 2–3 months postnatal	Global, retina
Iron	(1) Last trimester of gestation	(1) Myelin, striatum, hippocampus
	(2) 6 months–3 years postnatal	(2) Myelin, frontal cortex, basal ganglia (motor)
Zinc	(1) Last four months of gestation	(1) Autonomic nervous system, cerebellum, hippocampus
	(2) 6 months–10 years	(2) Cortex
Iodine	(1) First trimester of gestation	(1) Global
	(2) Last trimester of gestation	(2) Cortex, striatum, cerebellum, hippocampus
	(3) Infancy–12 years	(3) Myelin, prefrontal cortex
Copper	Last trimester of gestation	Occipital and parietal cortex, striatum, cerebellum, hippocampus

Adapted from Wachs et al. (2014) Ann. N.Y. Acad. Sci.

Stunting damages brain architecture



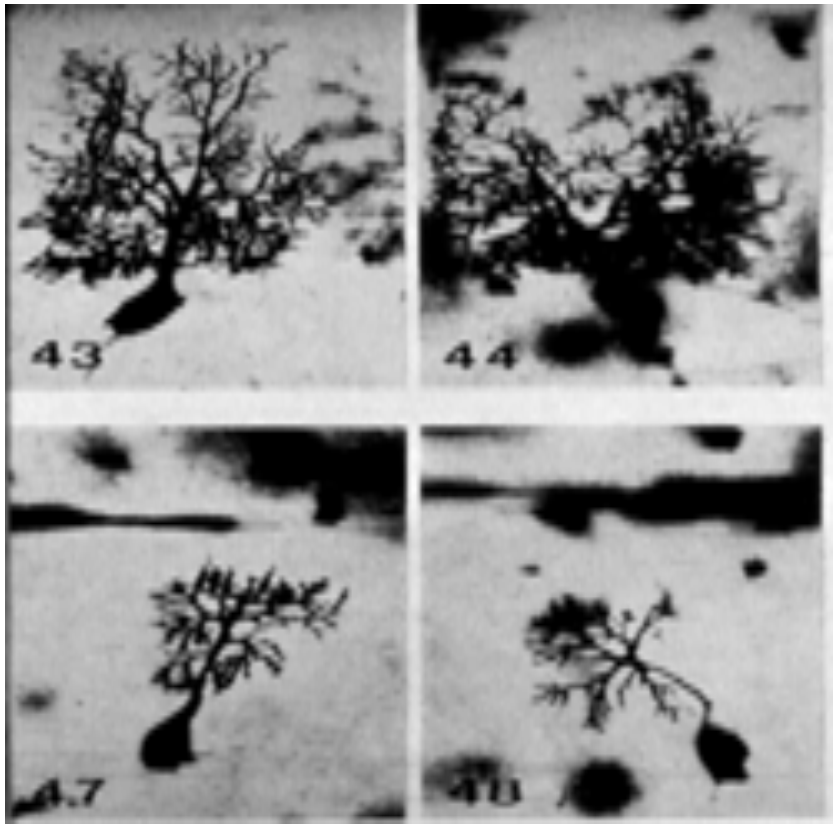
Hippocampal CA1 neuron:
many connections



Chronically malnourished hippocampal CA1 neuron:
fewer connections

Nyaradi et al., (2013) *Front in Human Neuroscience*

Stunting damages brain architecture

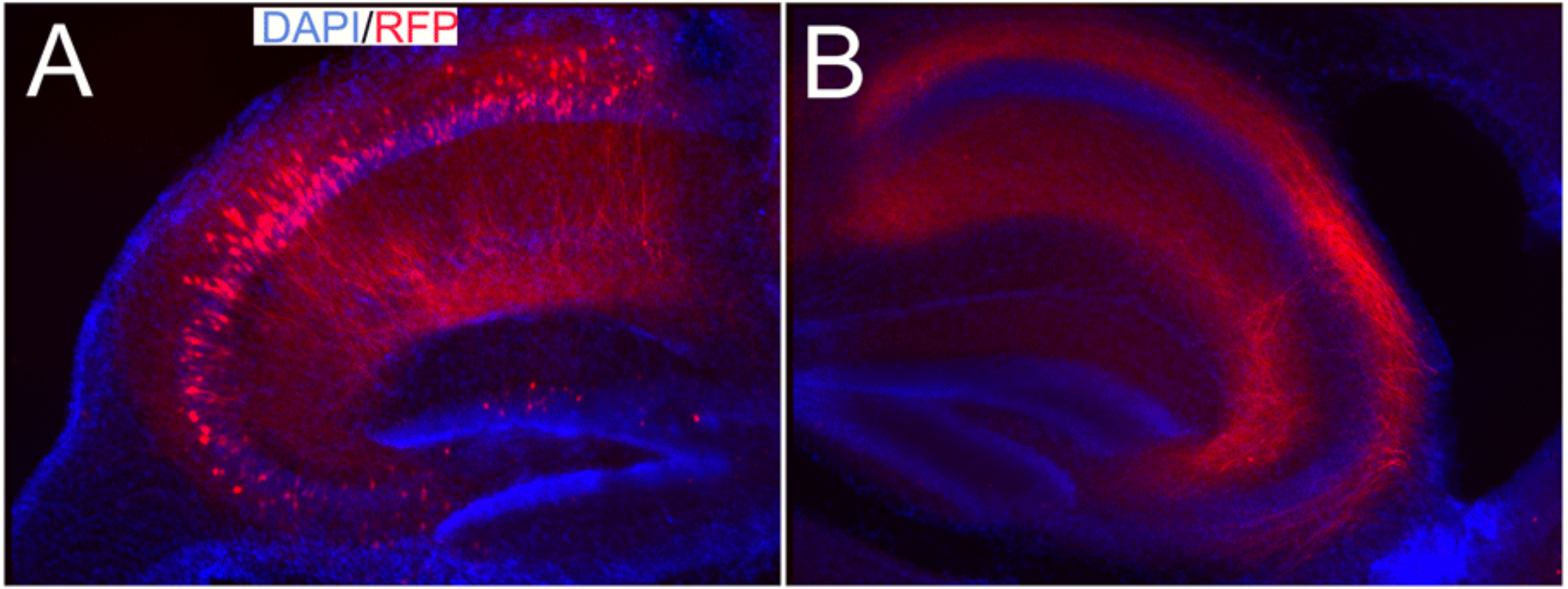


Sufficient Iodine Intake

Insufficient Iodine Intake

Courtesy: Curtis Boren, USAID

Stunting damages brain architecture



Hippocampus CA1, CA3 - Healthy

Hippocampus CA1, CA3 – Prenatal protein deficiency

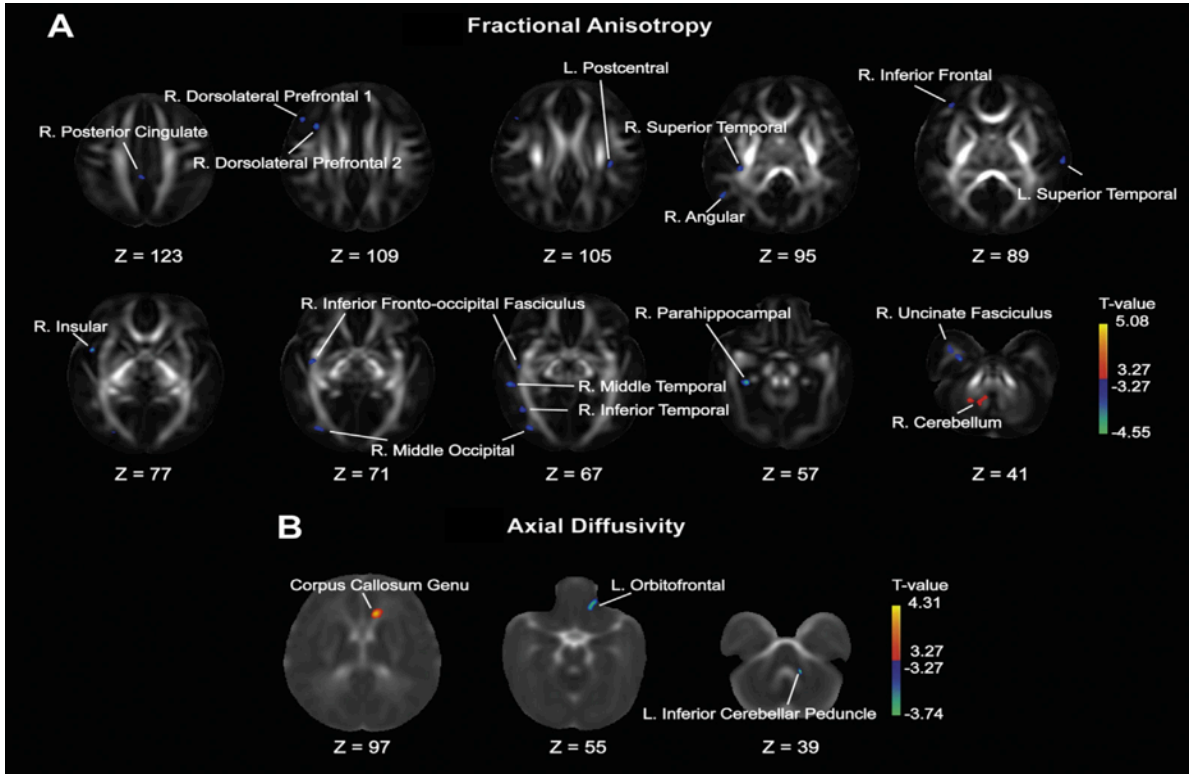
Beard & Connor (2013) Annu Rev Nutr

Prenatal Maternal Protein Deficiency Predicts Gray Matter Deficits in Newborn

Maternal malnutrition predicted variation in **diffuse** regions important to:

- cognitive-emotional responses to stress (e.g., the right insula and dorsolateral prefrontal cortex),
- sensory processing (e.g., right middle occipital),
- socio-emotional function (e.g., the right angular gyrus, uncinate fasciculus, posterior cingulate, and parahippocampus).
- Volume differences in hippocampus.

Structural MRI



Rifkin-Graboi, Meaney et al. (2015)

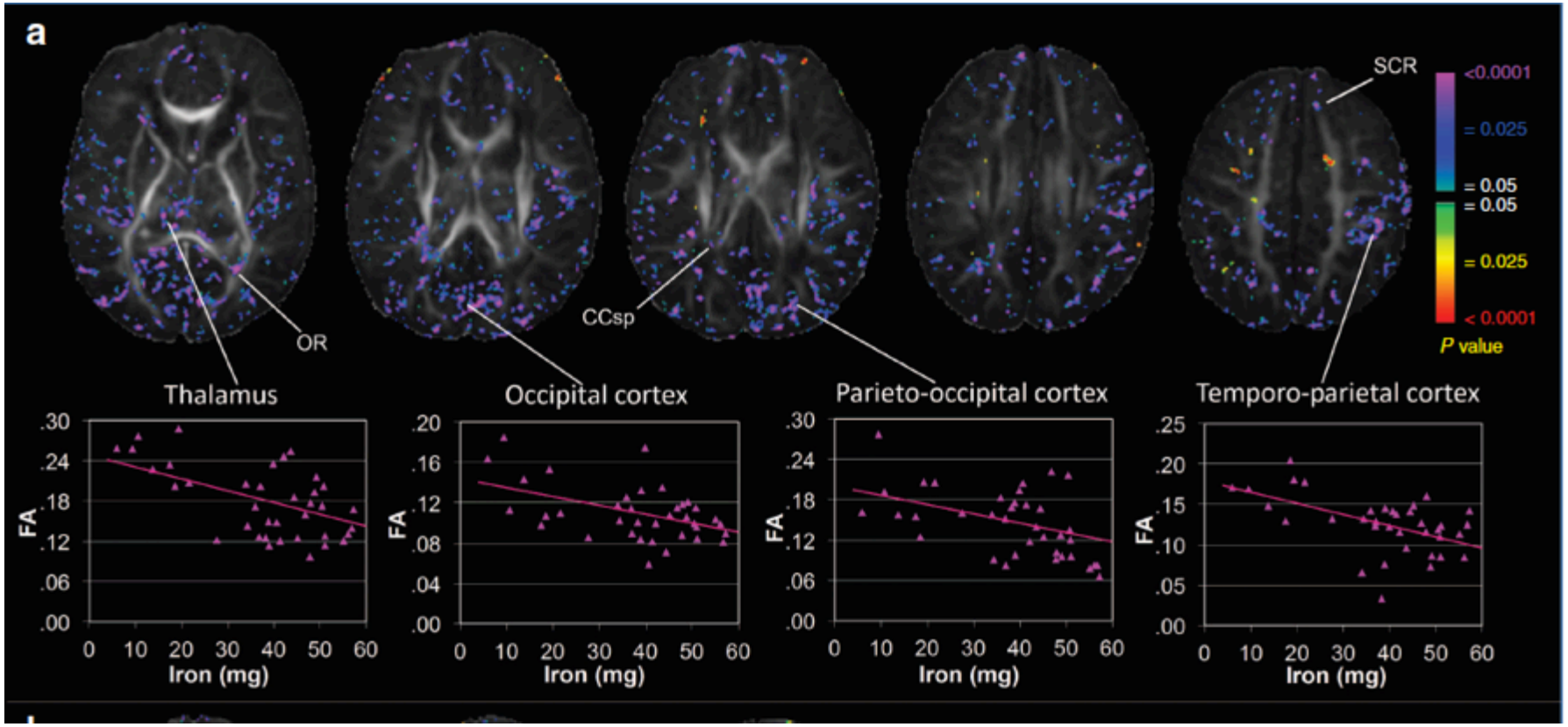
Prenatal Maternal Iron Deficits Predicts Grey & White Matter Deficits in Newborn

DTI measures diffusion of water in brain, which is quantified as fractional anisotropy (FA)

FA decreases across 3rd T and neonatal period as structures, barriers, and myelin form

Result: Lower prenatal iron associated with higher FA throughout newborn brain and axonal pathways

DTI MRI



Monk, Georgieff et al. (2015) J of *Pediatric Research*

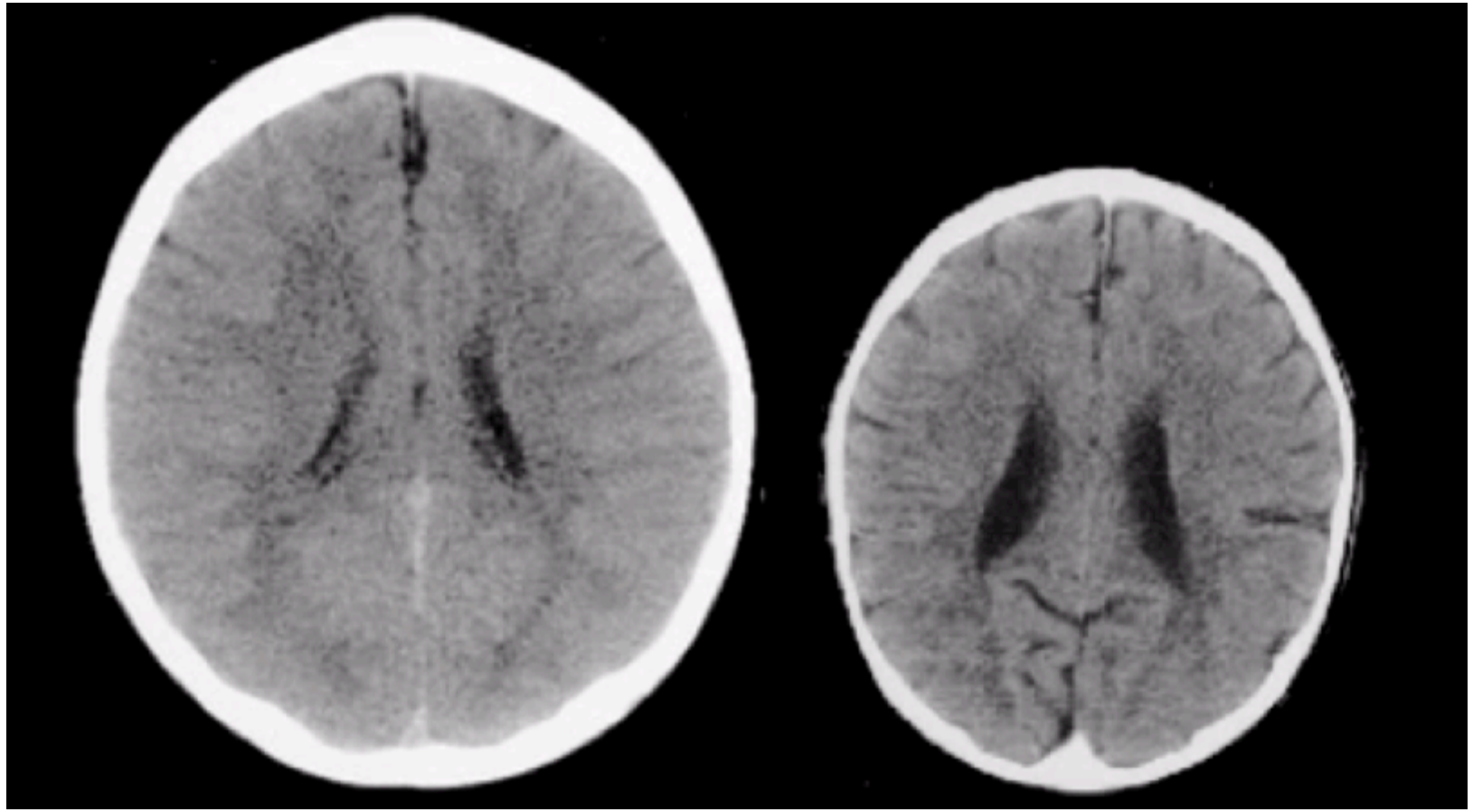
First 1000 Days

- Period also defined by greatest brain “plasticity”
    - vulnerability
    - recovery
- As brain regions become more specialized, plasticity lost

- Vulnerability to nutritional insult > potential for repair

- Beyond critical window, little evidence of brain repair, despite some physical gains due to dietary intervention.

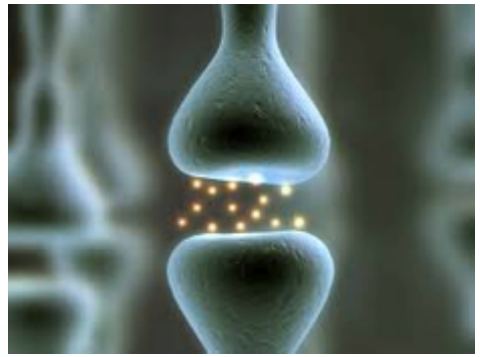
Little Recovery if Dietary Rehabilitation Beyond Critical Period



Healthy diet thru 24 months (*Z*= +0.8 SD)

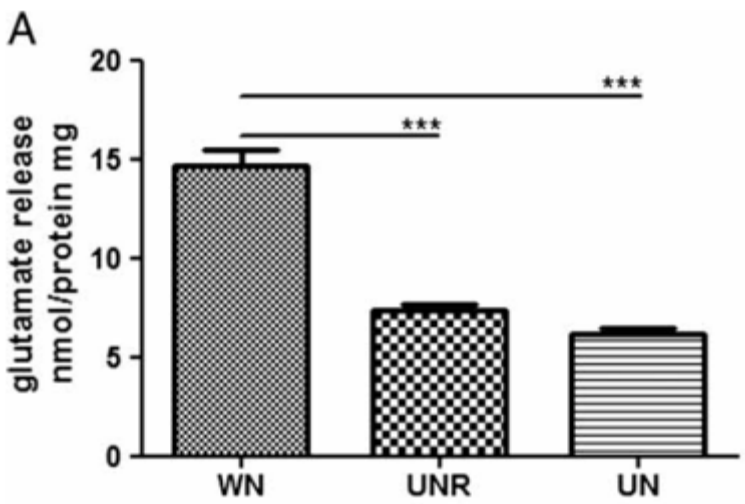
Low Birth Weight/
Stunted at 24 months
Supplementation after 12 months
(*Z* = -3.28 SD)

Little Recovery if Dietary Rehabilitation Beyond Critical Period

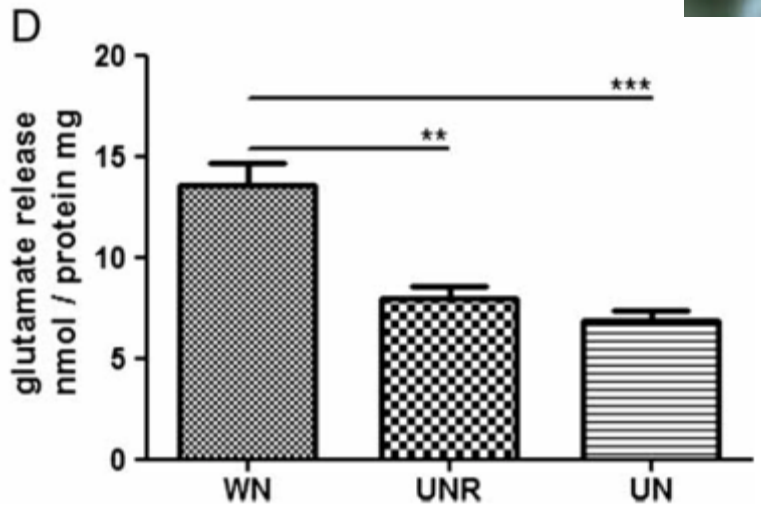


Glutamate Neurotransmission in Auditory Cortex

Hippocampus at ~ 24 months



Hippocampus at ~ 36 months



WM = Well nourished
UN = Undernourished (60% of WM diet beginning at 28 days)
UNR = Dietary rehabilitation (Like UN until 42 days; then WN to 370 days)

Batista Penido et al. (2012) Nutritional Nuroscience

Interim Summary:

- Brain's early vulnerability to nutritional insults outweighs plasticity
- Supplementation ***after*** critical/sensitive windows of development result in incomplete correction of brain dysfunction
- Nutrient may promote development and one time point or at one concentration, but may be toxic at another time point or concentration (e.g. iron)
- Micronutrient deficits confer long-term abnormalities on brain structures
- How should be measure function?

Johnson (2005) Dev Psychobio; Knudsen (2004) J. Cog. NeuroSci

Neurodevelopmental Battery to Assess Malnutrition

- Low-cost
- Easily transferred
- Reliable
- Portable
- Cross-cultural
- Sensitive to development

Physical

Biomarkers

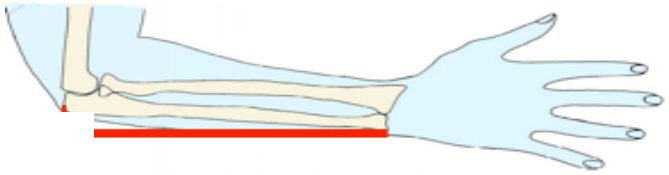
Behavioral

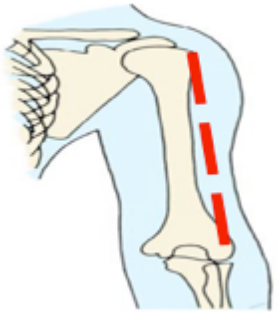
Neuroimaging

Physical

Anthropometrics

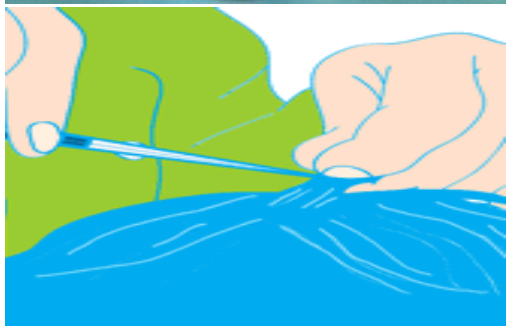
- Weight
- Length/height
- Head circumference
- Mid-arm circumference
- Humorous length
- Ulna length
- Femur & tibia length





Biomarkers

235
7:45 1/28
Hemoglobin Test
235
Control Range
16.8–19.
12.5–14.
6.8–7.8
27130141
20150412

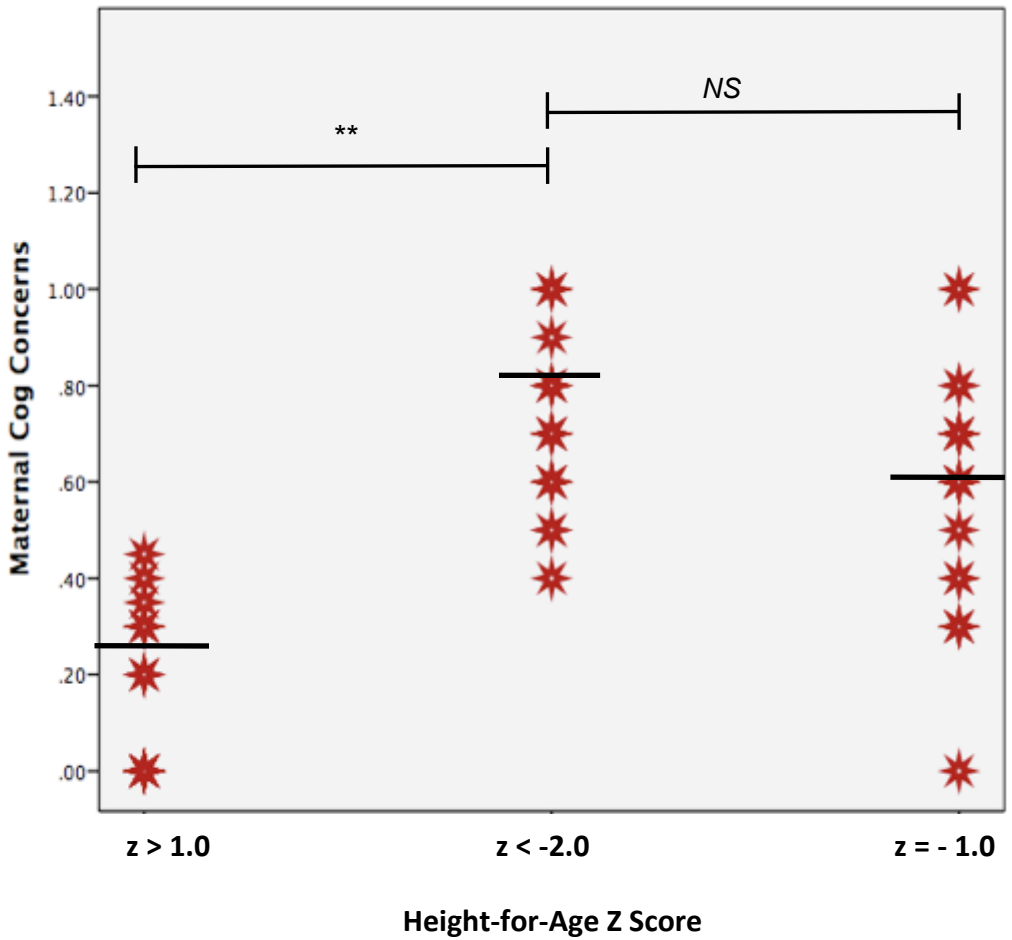


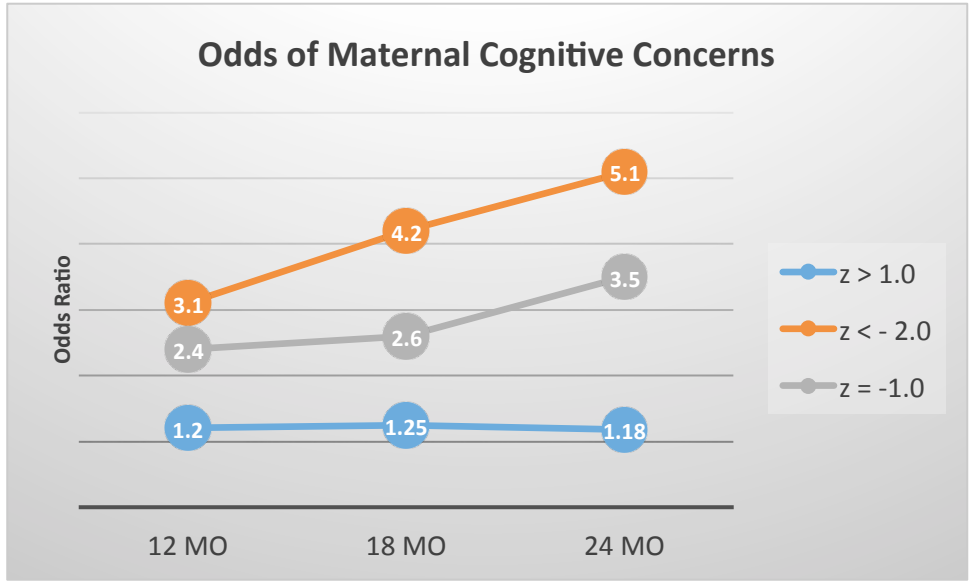
Neurobehavioral

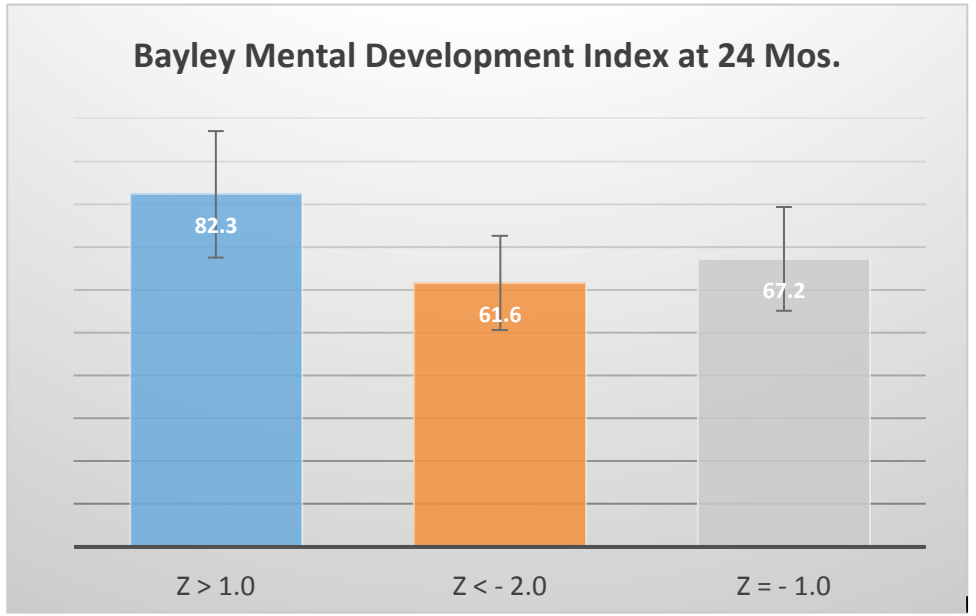
Old Fashion Way: Ask!

Maternal concerns about child's development at 12 months:

- Attention
- Learning
- Memory







Neonatal Facial Imitation

- Neonates ability to mimic simple gestures within the first hours of life
- Linked to newborn myelination and cortical differentiation of brain structures
- Performance predicts later social functioning; sensory/ memory and attention.

Neonatal Facial Imitation

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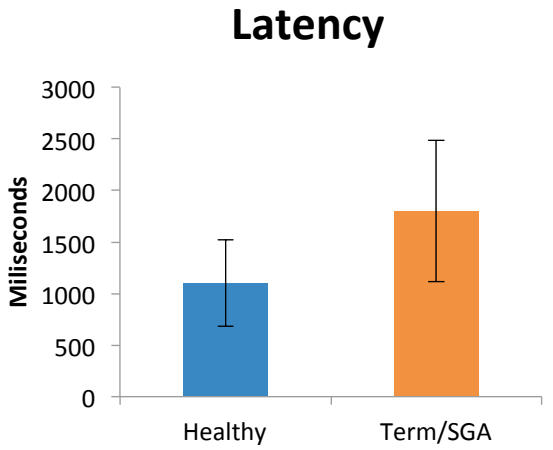
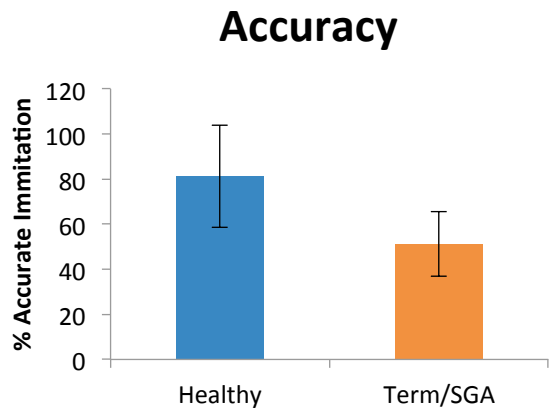
Age: < 2 days old





***Latency predicts rate of growth faltering between 6 to 12 months in full term babies *(Meaney et al., 2016, in press)*

Deferred Imitation

- Memory test to determine whether infants and young children can repeat actions demonstrated to them with novel toys.
- Linked to hippocampal and anterior cingulate
- Predicts learning, working memory, executive functioning

Ages: 6, 12, 24, and 36 months

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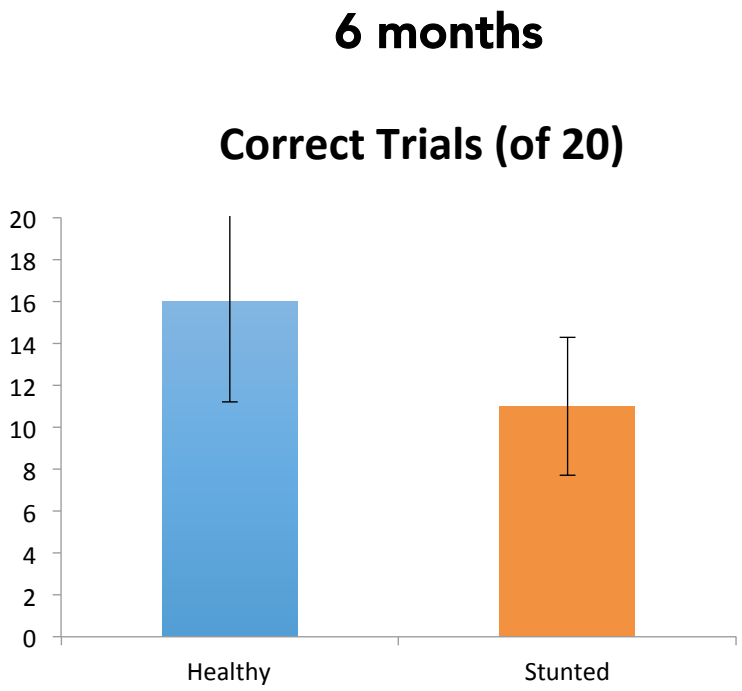
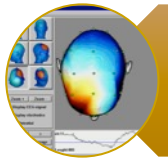


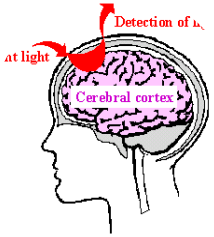
Ages: 6, 12, 24, and 36 months

Neuroimaging

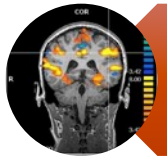
Ultrasound



EEG/ERP



fNIRS



MRI/fMRI

Rational for Neuroscience Approach to Malnutrition

- Often more sensitive to developmental deviations than behavior (e.g., Autism; HIV)
- Can tell us about the brain circuits (component processes) that support healthy development as well as language, cognition, and emotion
- Language and cognition very primitive before 1 yr, however, functional circuits that will support behavior already forming/ predictive

0 mins

26 mins

35 mins

47 mins

52 mins

60 mins

EEG Resting State

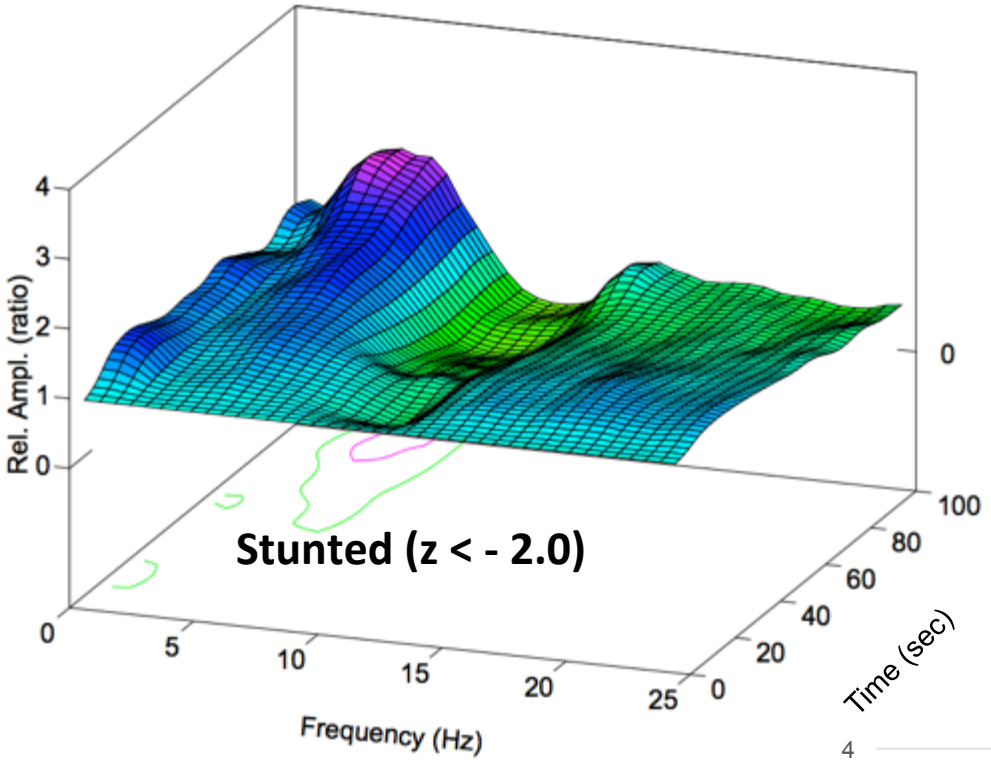
Optimal baseline for ERP tasks

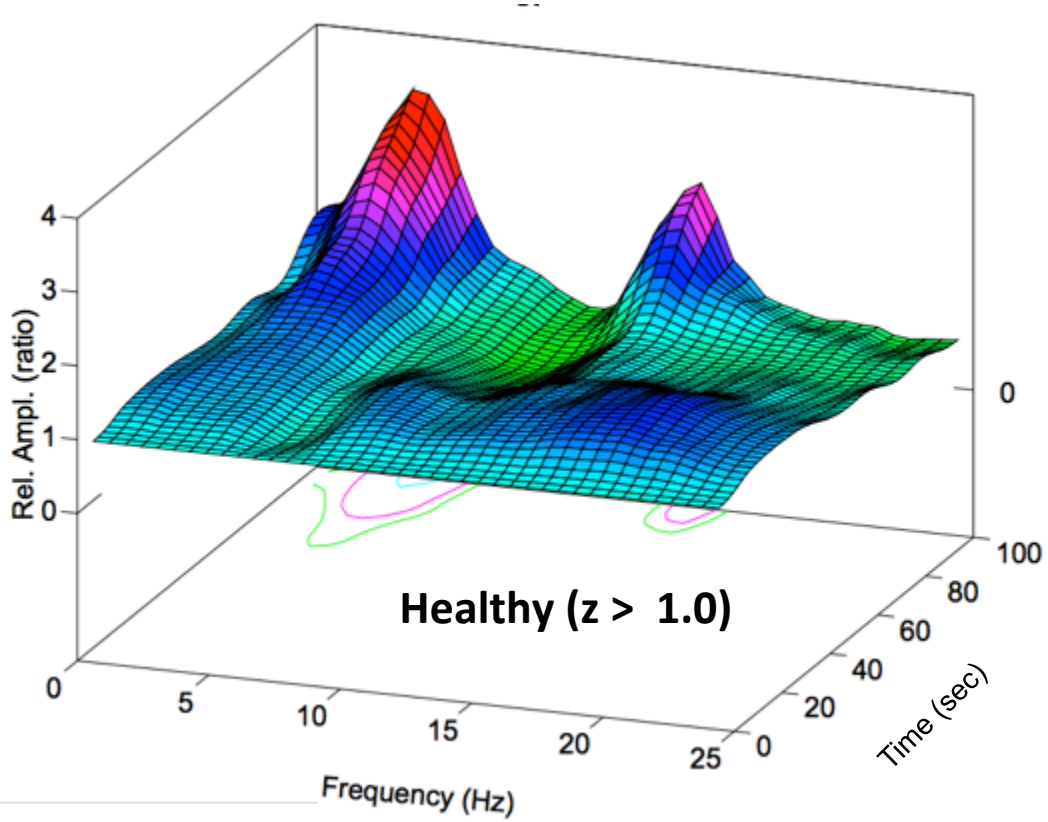
Resting state waveform oscillations that have particular properties (frequency, amplitude, phase) that reveal information on underlying neural processes

Sensitive measure to trait levels of cortical activity – less a measure of "rest"; better measure of alertness

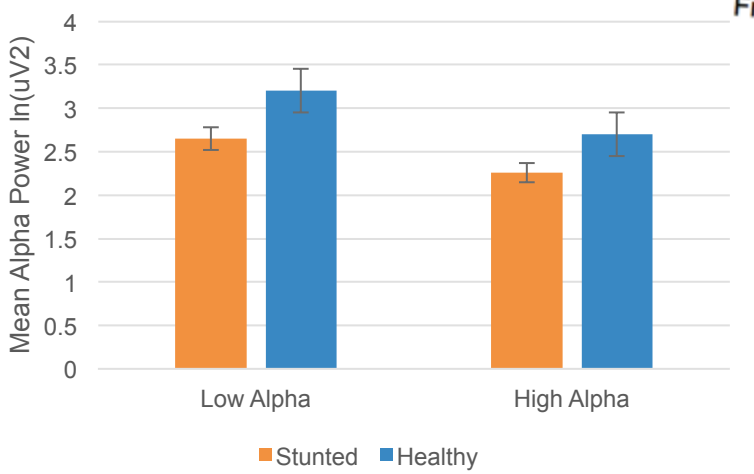
Peek-a-boo variation useful for detecting face-processing capacity and later level of social engagement/attunement, Attachment at 18 months

EEG Power Spectrum Analysis of 3 month old children at rest-to-Peek-a-Boo transition





Inferior temporal cortex
(T4, T6, T5, T7)



1 month

2 months

3 months

4 months

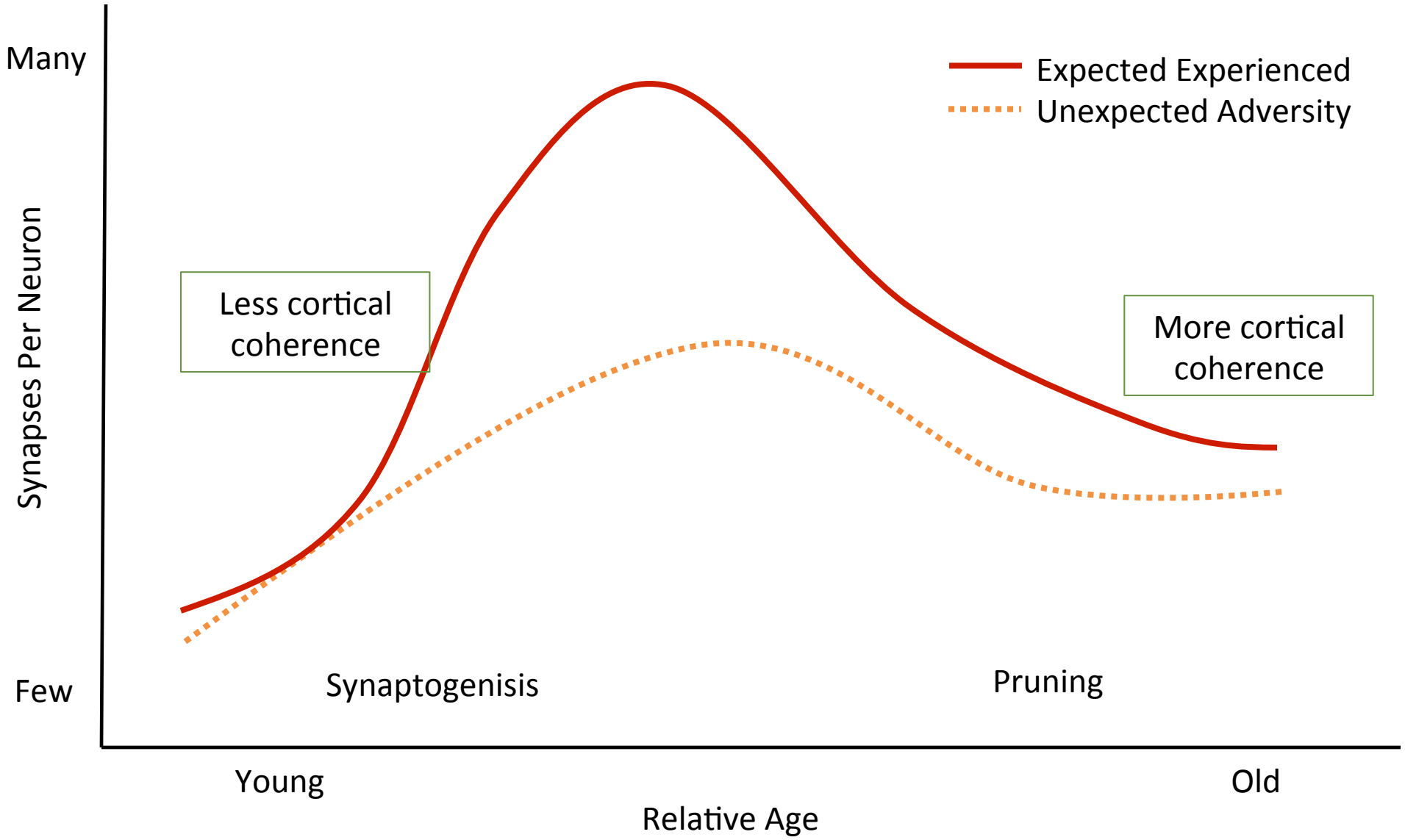
5 months

6 months

7 months

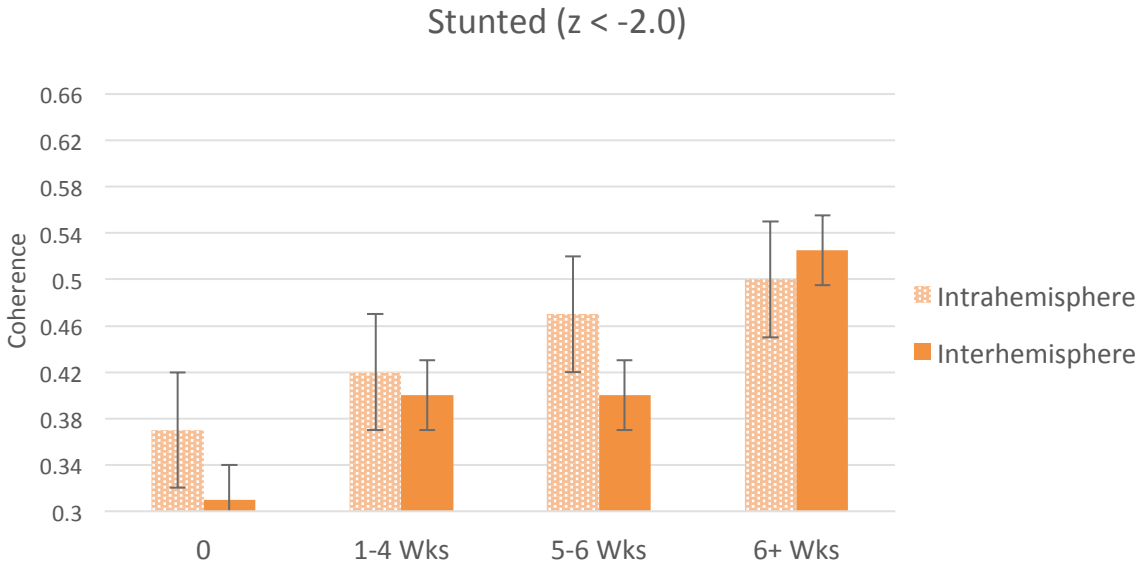
8 months

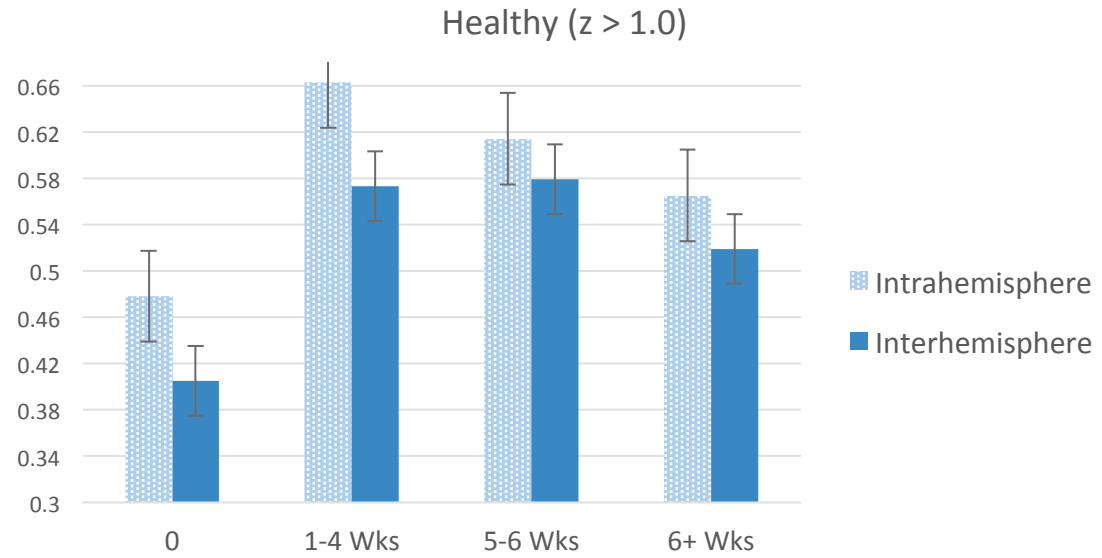
Plasticity & Coherence

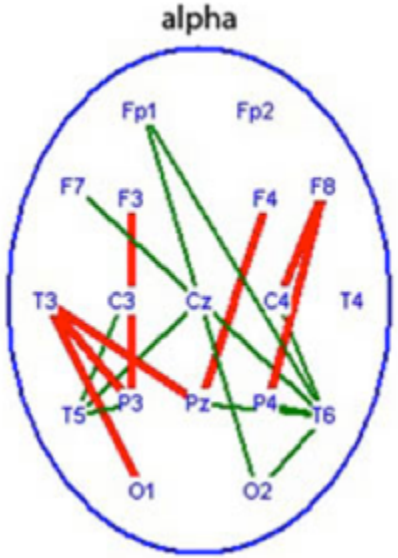


Black & Greenough (1986)

EEG Estimates of Cortical Coherence at 8 months







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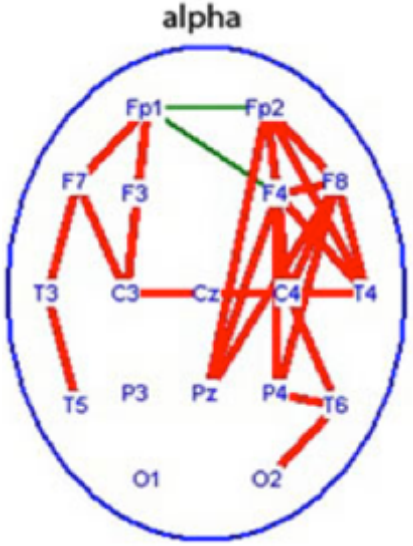
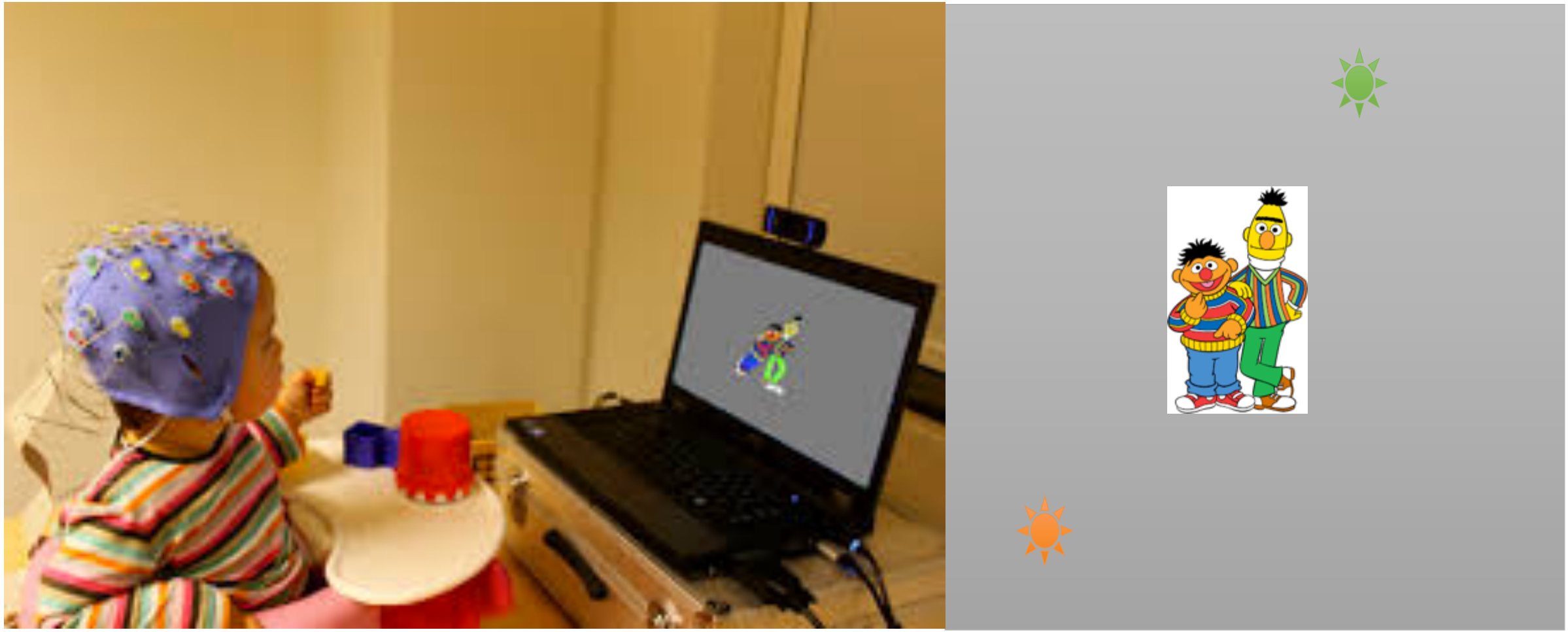


n= 15

Selective Visual Attention

12 months



Ages: (0), 6, 12 18, and 40-42 months; 5 years

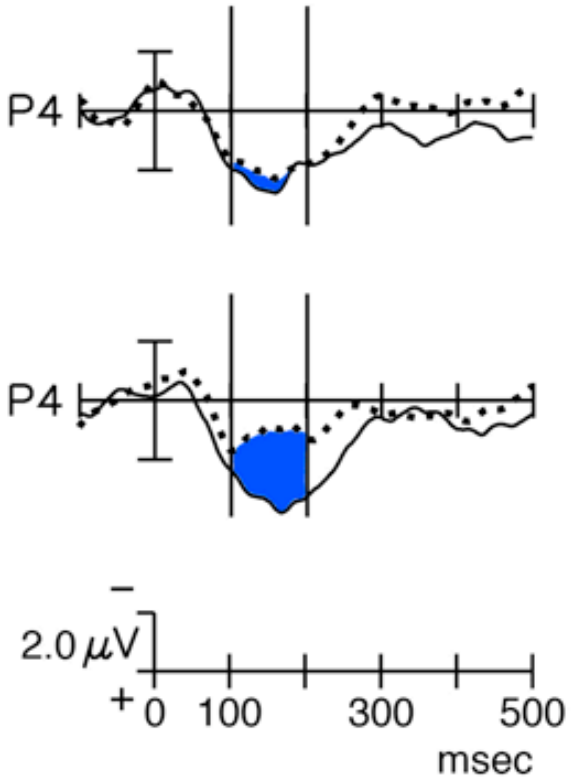
Measelle et al., (2015) SRCD

Selective Visual Attention

12 months

Stunted
(< Z= -2.0)

Normal
(> Z = 1.0)



When you account for stunting:

- Healthy kids utilize attention boost to ignore distraction
- Stunted kids do not show this attention boost

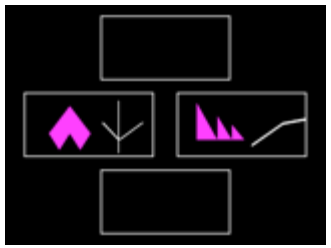
Ages: (0), 6, 12 18, and 40-42 months; 5 years

Measelle et al., (2015) SRCD

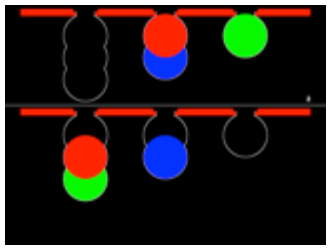
Cognitive Development to be Assessed by Cambridge Neuropsychological Test Automated Battery (CANTAB)

Children is to complete a series of computerized cognitive tasks that assess their:

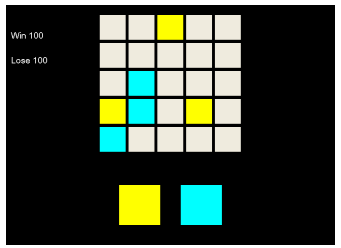
- **Executive Function**
  - Intra-Extra Dimensional Set Shift (IED)
    - Assesses executive function by testing rule acquisition & reversal
  - Stocking of Cambridge (SOC)
    - Spatial planning test which measures frontal lobe function
- **Decision Making & Response Control**
  - Information Sampling Test (IST)
    - Assesses impulsivity and decision making
  - Stop Signal Task (SST)
    - Assesses one's response control
  - Affective Go / No-Go (AGN)
    - Assesses information processing biases for positive & negative stimuli
- **Visual Memory**
  - Spatial Recognition Memory (SRM)
    - A test of visual spatial recognition memory



IED



SOC



IST

CANTAB performed during visits at 4, 6 & 8 years old.

Validation of Lao School Readiness Battery *Underway!!*

48 Month School Readiness Battery

Peabody Picture Vocabulary Test

This is a test of receptive vocabulary which assesses the child's vocabulary acquisition.

Lollipop Test

This test assesses the child's ability to identify colors, shapes, numbers and letters.

Number Knowledge Test

This test assesses the child's intuitive knowledge of numbers.

Visually Cued Recall Test

This test evaluates the child's working memory through visual images and verbal information.

Random Object Span Test

This test assesses the child's visual working memory.

Comprehensive Test of Phonological Processing- 2

This test evaluates the child's phonological processing as a prerequisite to reading fluency.

\+ **Panamath**

This test measures the child's number sense and approximate number system (ANS) which underlies the ability to produce abstract number representation.

\+ **Child Behavior Checklist**

This checklist measures the child's behavioral and socio-emotional functioning as reported by parents.

These tasks carried at 48 Months to assess the child's 'school readiness.

Measelle et al., (2016) ICIS

Thank you

ຂອບ ໃຈ

Cảm ơn bạn

ကျေးဇူးတင်ပါတယ်

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