The Dunning-Kruger Effect-
My predictions for the next decade:
Brain Health in CHD

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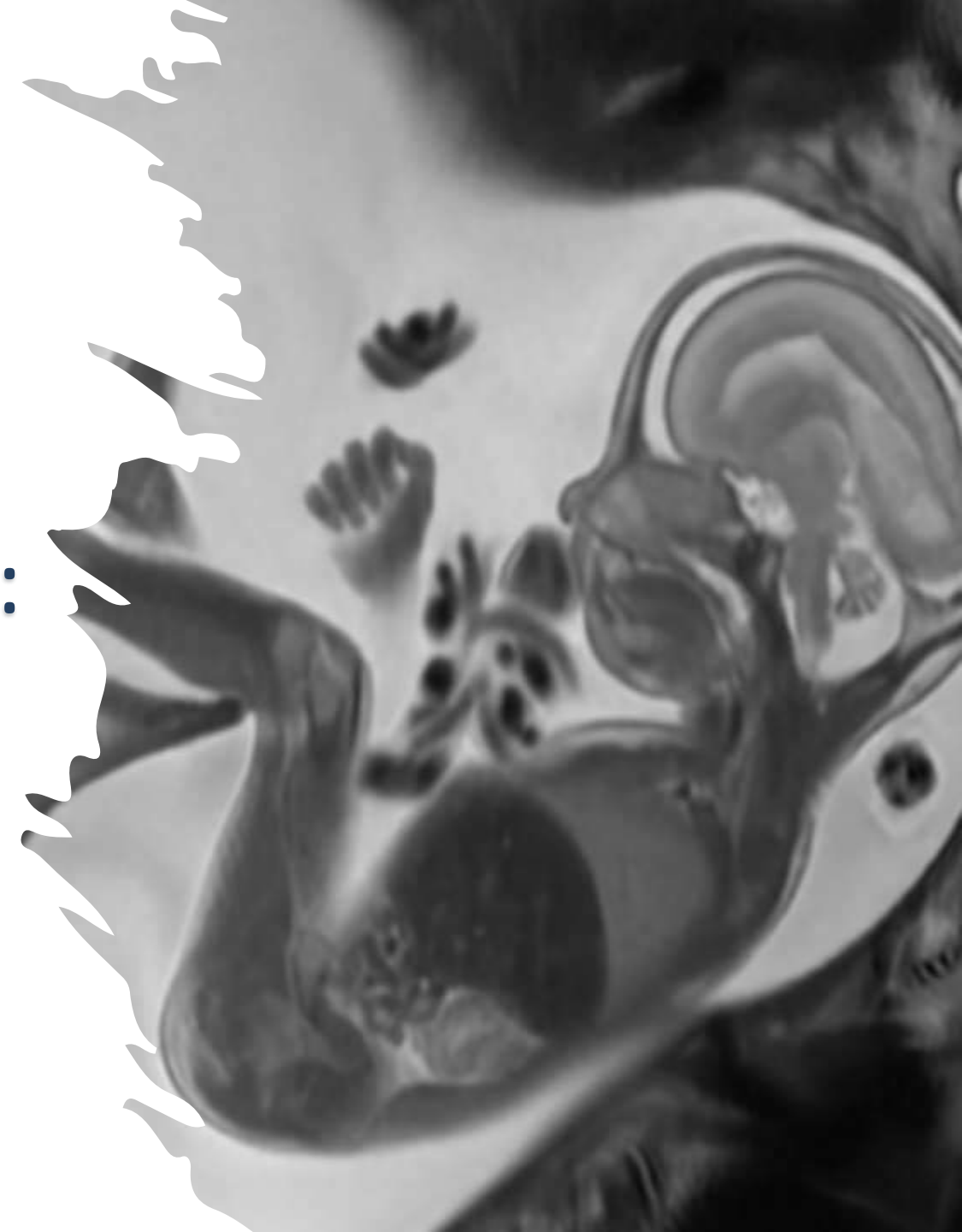
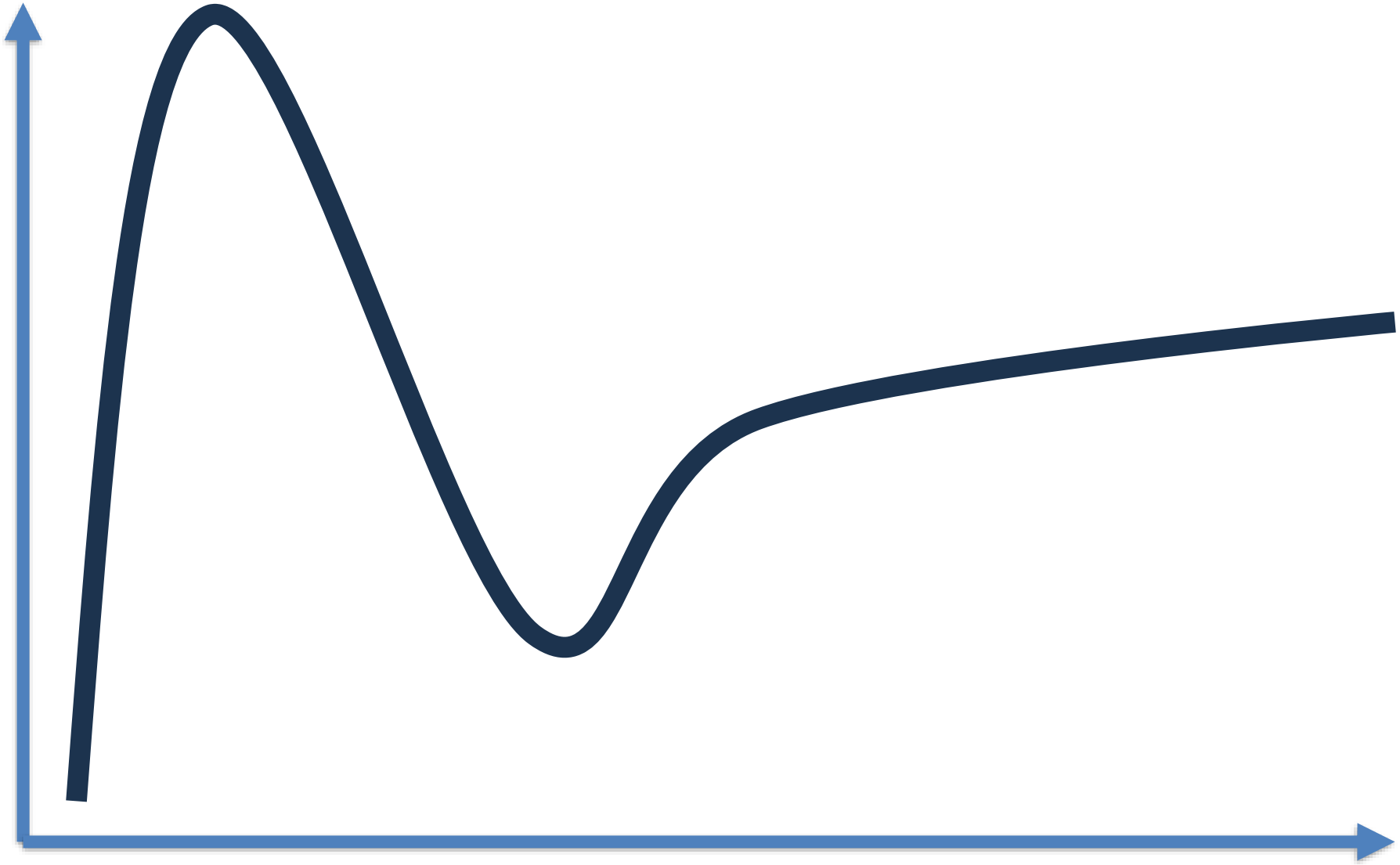


- No Disclosures

A brief historical look at neurodevelopment research in CHD

(by way of the Dunning-Kruger Effect)



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Fundamental knowledge: ➡ **"It must be the operation"**

Neurodevelopment is impaired in CHD

Boston Circulatory Arrest Trial

Brain MRI Research

- Abnormal brain development (fetal)
- Perinatal Brain Injury (before operation)

Innovation + Fundamental Knowledge

Neurodevelopmental Outcomes After Cardiac Surgery in Infancy *Gaynor et al, Pediatrics 2015*

1770 patients, 1996-200 (13 years)

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TIME- EXPERIENCE - WISDOM

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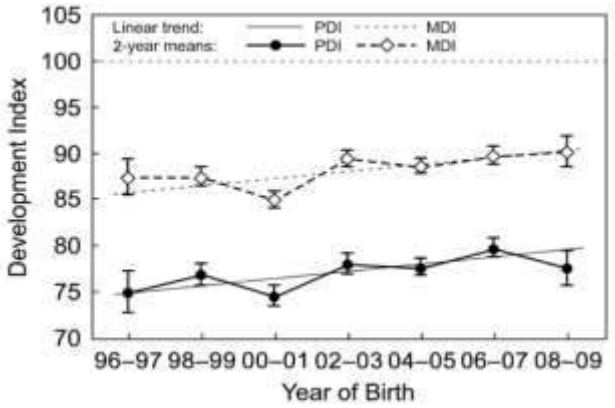
1) Minimal improvement over 13 years



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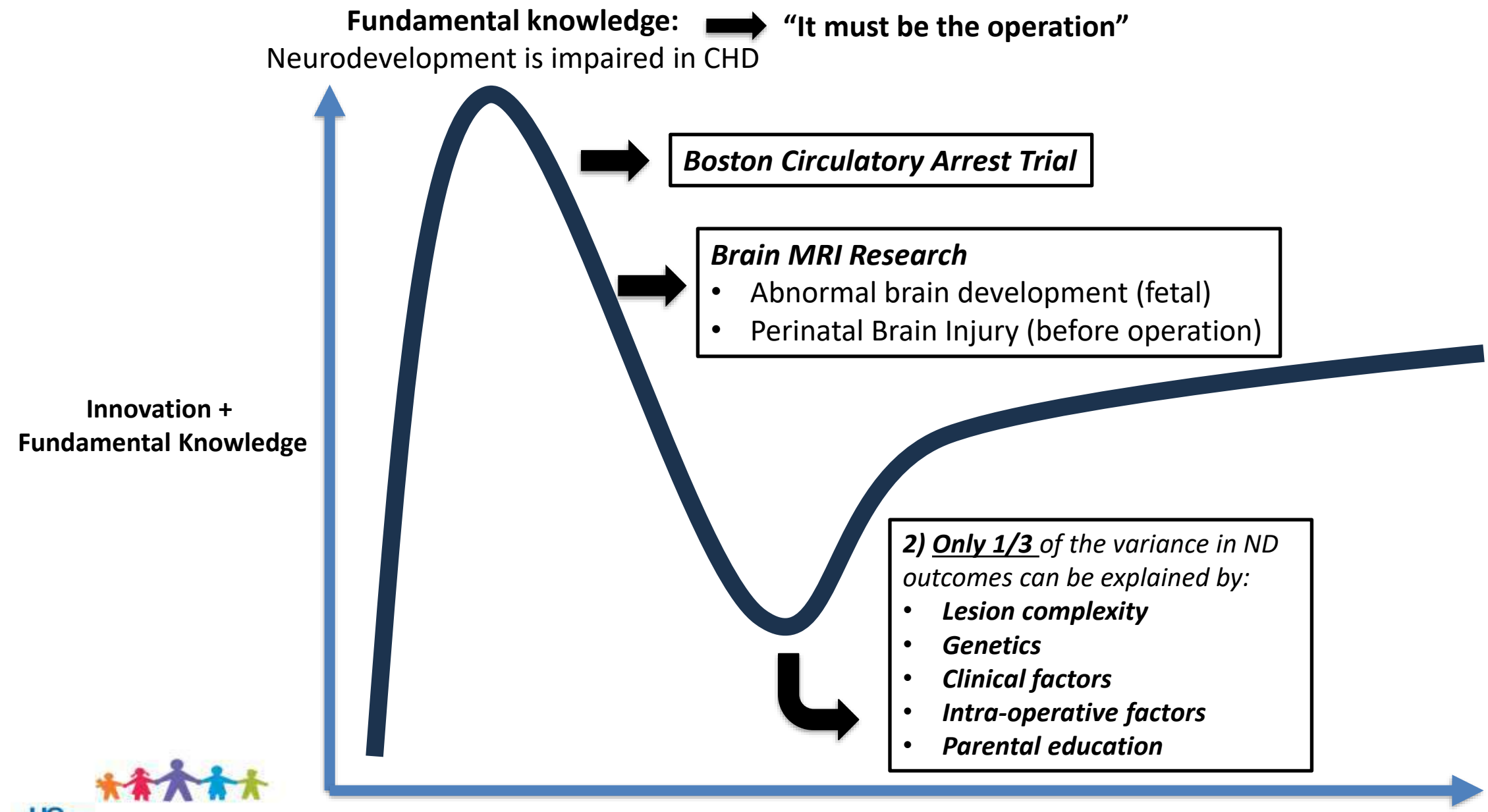
TIME- EXPERIENCE - WISDOM



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Fundamental knowledge: → **"It must be the operation"**

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Innovation + Fundamental Knowledge

"we know nothing"

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TIME- EXPERIENCE - WISDOM

Fundamental knowledge: → **"It must be the operation"**

Neurodevelopment is impaired in CHD

Boston Circulatory Arrest Trial

Brain MRI Research

- Abnormal brain development (fetal)
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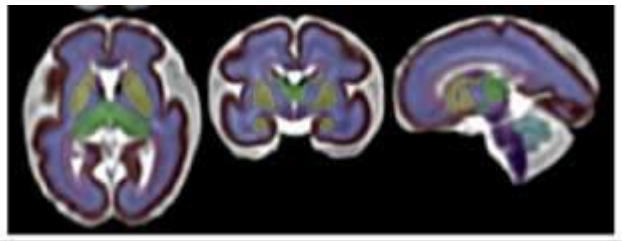
Fetal brain MRI:



Innovation + Fundamental Knowledge

TIME- EXPERIENCE - WISDOM

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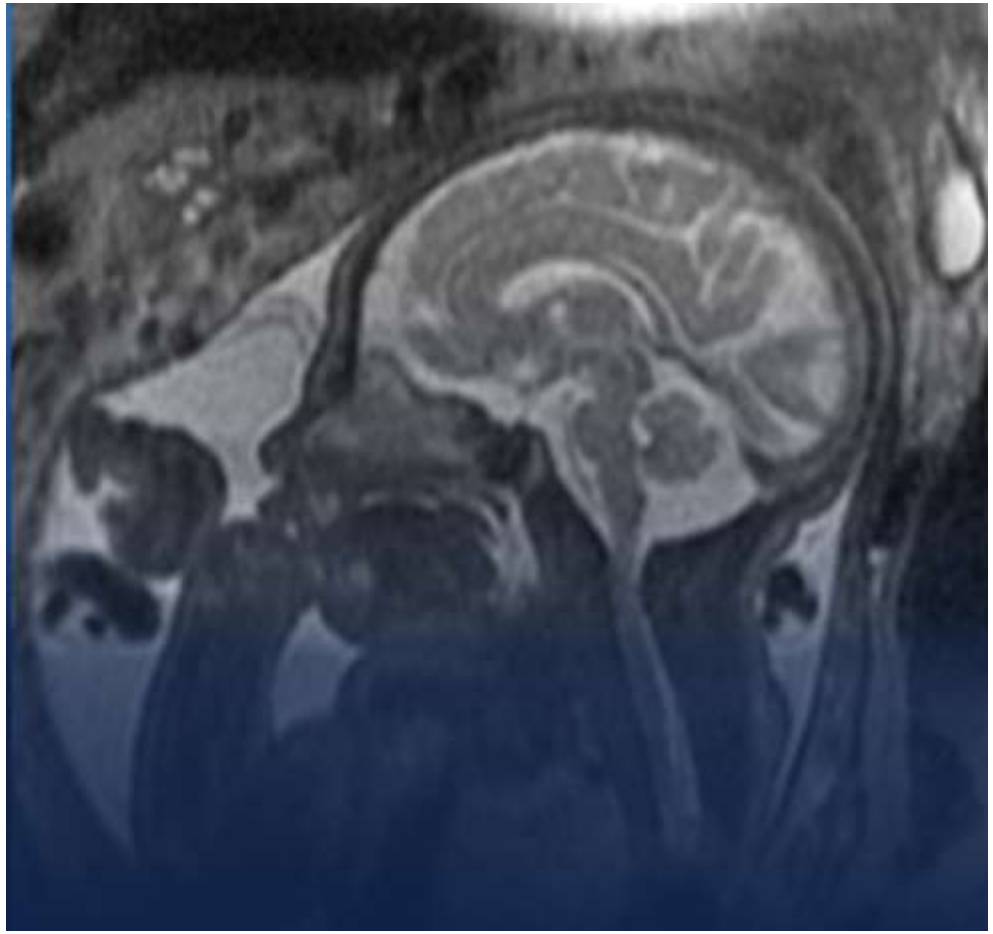


Brain MRI observations-

Late gestation fetus and neonates:

- Smaller brain volumes
- Simplified cortical gyrification
- Less organized connections
- Immature biochemistry
- Immature metabolism

Miller S et al, NEJM, 2001
Licht D et al, JTCVS, 2009
Limperopoulos C et al, Circulation, 2010
Clouchoux C et al, Cerebral cortex, 2012
Rhein MV et al, J Peds, 2015
Peyvandi et al, JAHA, 2021
Rollins C et al, Neuroimage, 2021

Circulation
Volume 145, Issue 15, 12 April 2022; Pages 1108-1119
https://doi.org/10.1161/CIRCULATIONAHA.121.056305

ORIGINAL RESEARCH ARTICLE

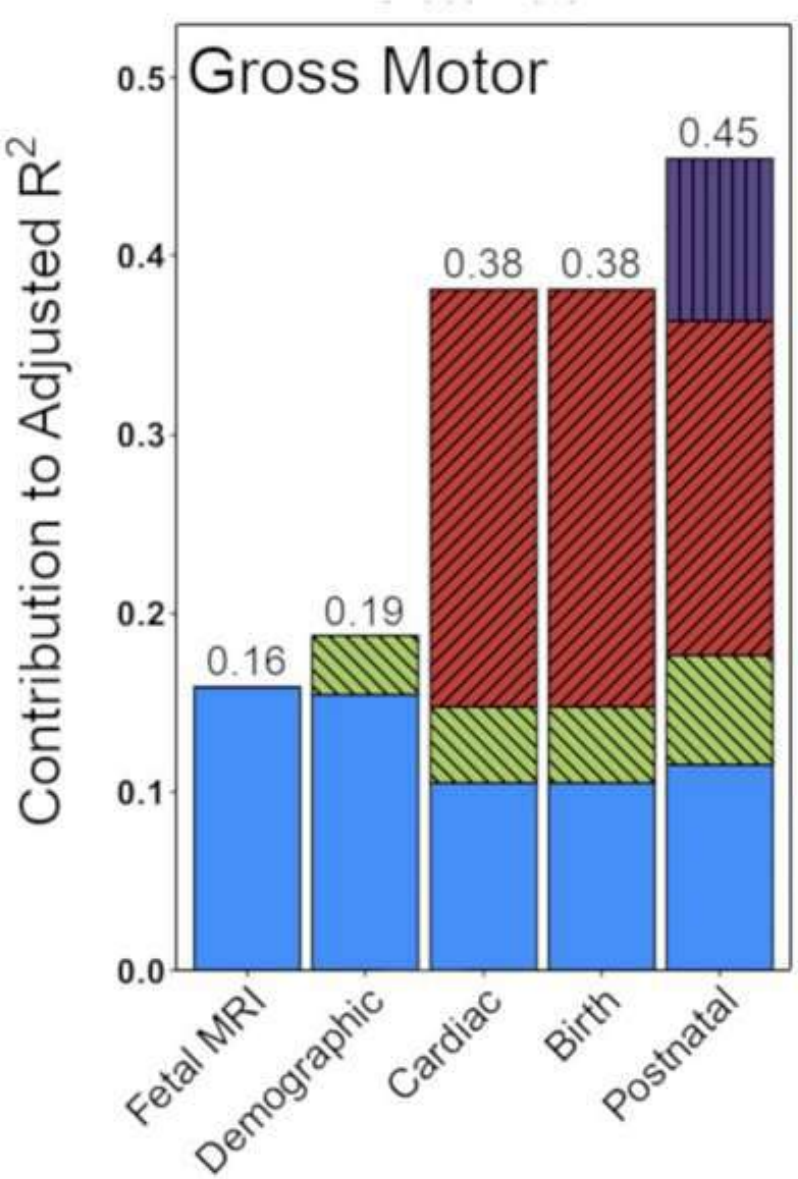
Fetal Brain Volume Predicts Neurodevelopment in Congenital Heart Disease

Editorial, see p 1120

Anjali Sadhwani, PhD, David Wyp[EPUB]D, Valerie Rofeberg, MS, Ali Gholipour, PhD, Maggie Mittleman, BS, Julia Rohde, BA, Clemente Velasco-Annis, BS, Johanna Calderon, PhD, Kevin G. Friedman, MD, Wayne Tworetzky, MD, P. Ellen Grant, MD, Janet S. Soul, MDCM, Simon K. Warfield, PhD, Jane W. Newburger, MD, MPH, Cynthia M. Ortinau, MD*, and Caitlin K. Rollins, MD, SM*

At two years of age **fetal total brain volume**:

- ALONE explains 10-21% of variance in ND outcomes
- In combination with other risk factors models explained up to ***45% of variance*** in ND outcomes
- most consistent predictor across domains and only predictor of adaptive functioning.



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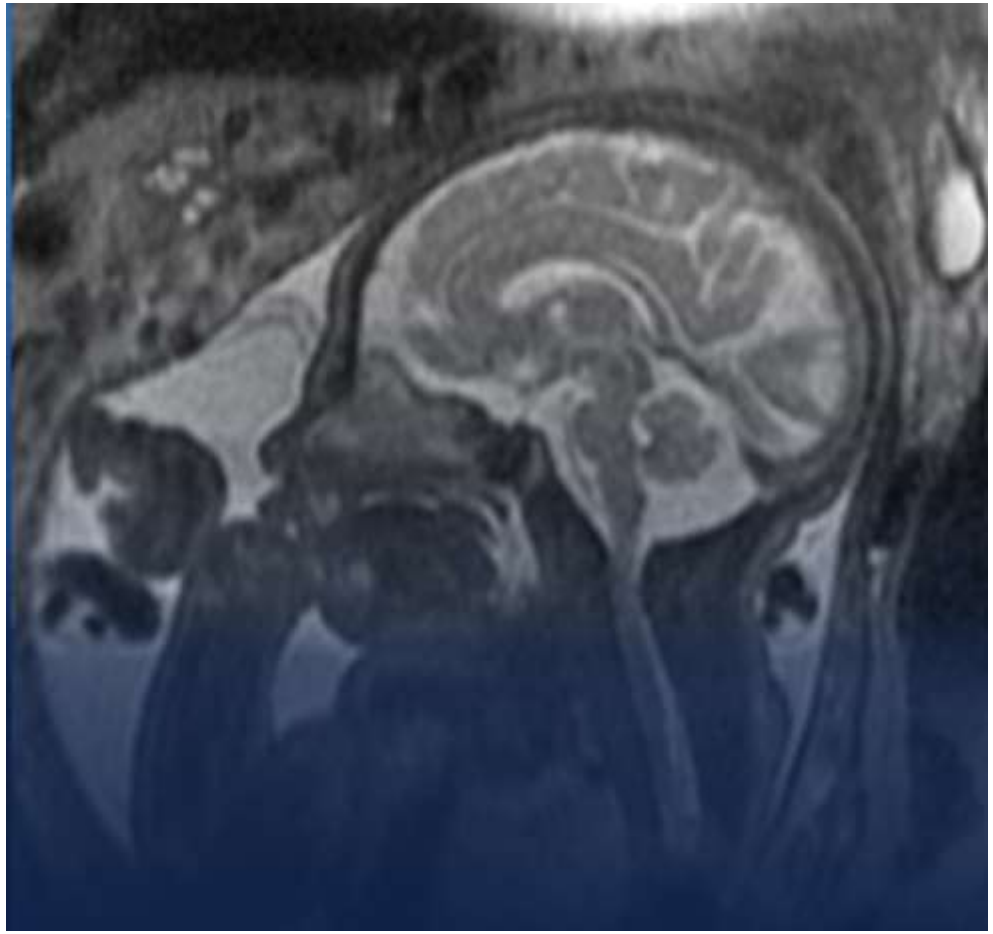

Opportunity:

The ***foundation*** for long-term brain structure begins before birth AND can have a direct impact on long-term brain function

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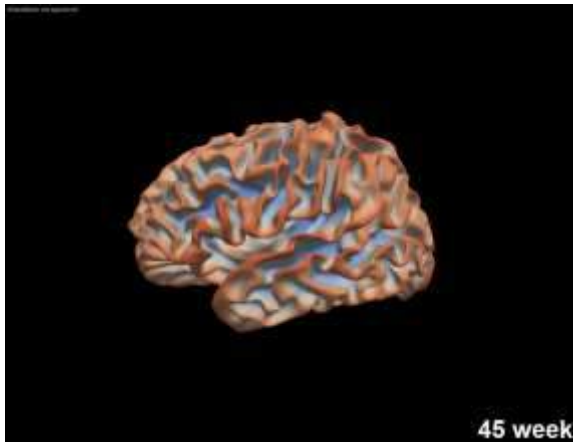
Challenge: Multiple pathways influence brain development in utero → potential targets for neuroprotection

Genetic Underpinnings

Cardiovascular Physiology:
Oxygen and nutrient delivery, perfusion

Maternal Fetal Environment
Maternal health conditions
Exposures
SDOH

Placental Health



Neurodevelopmental Outcomes

SDOH

Clinical/medical factors

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Novel Analytic Approaches

ADDITIONAL VENTURES

- Multi-center study (Boston, Wash U, UCSF)
- Goal: Integrate multiple types of prenatal data to predict ND (53 “predictors”)
  - SDOH
  - CV physiology
  - Genetics
  - Maternal health conditions and medications
  - Maternal exposures
- Primary outcome: BSID-IV by 24 months of age (n= 84)
- **Analysis: Machine learning**

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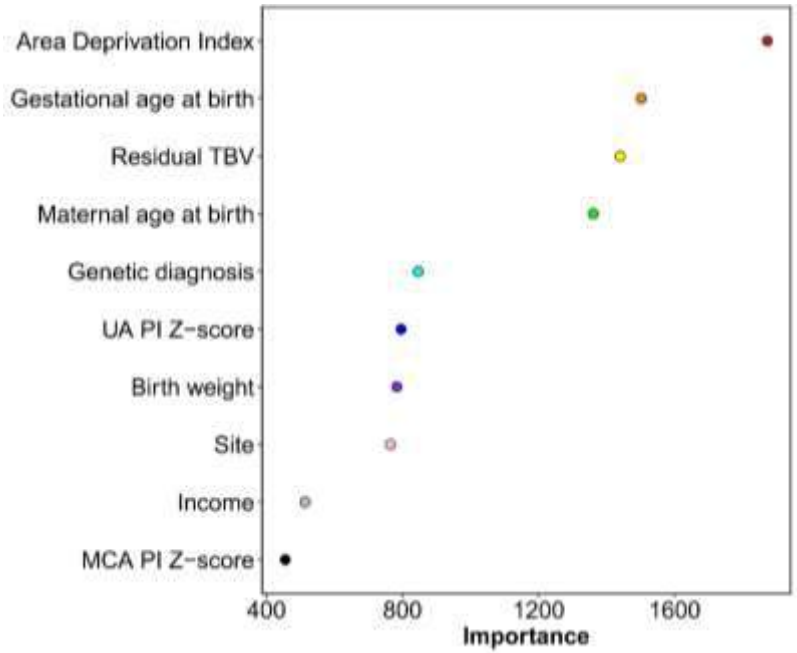
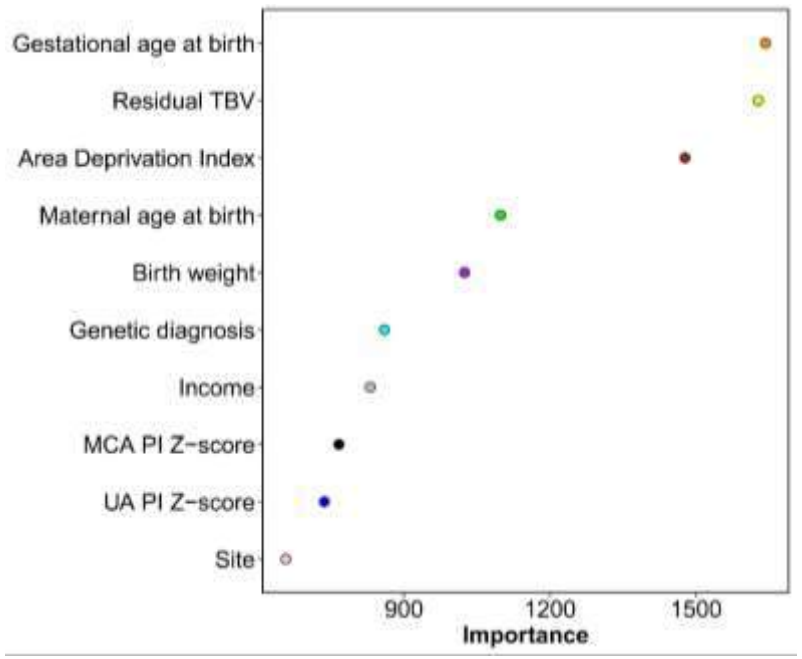
Random Forest Importance Plots:

Ranking top 10 ***prenatal*** variables most likely to predict worse developmental outcome

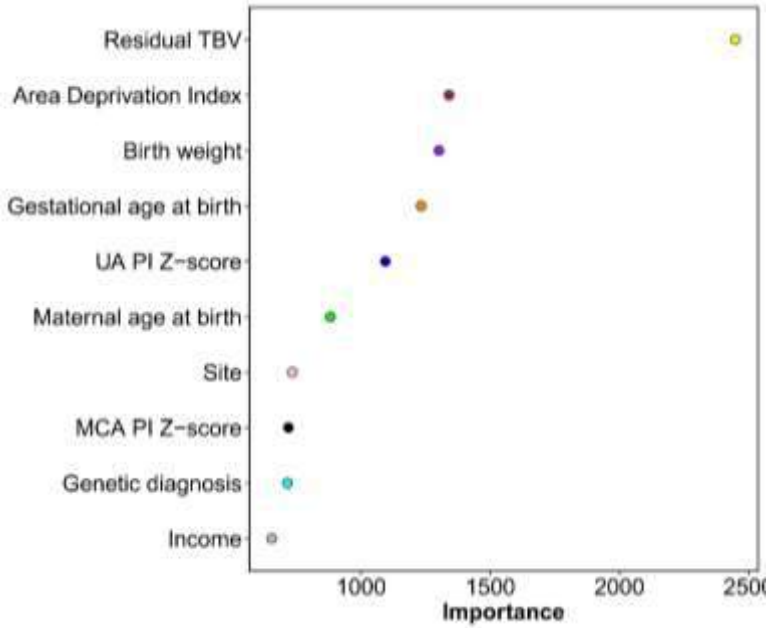
Cognition



Language



Motor



➢ ***Social determinants of health in top 3 for all domains***

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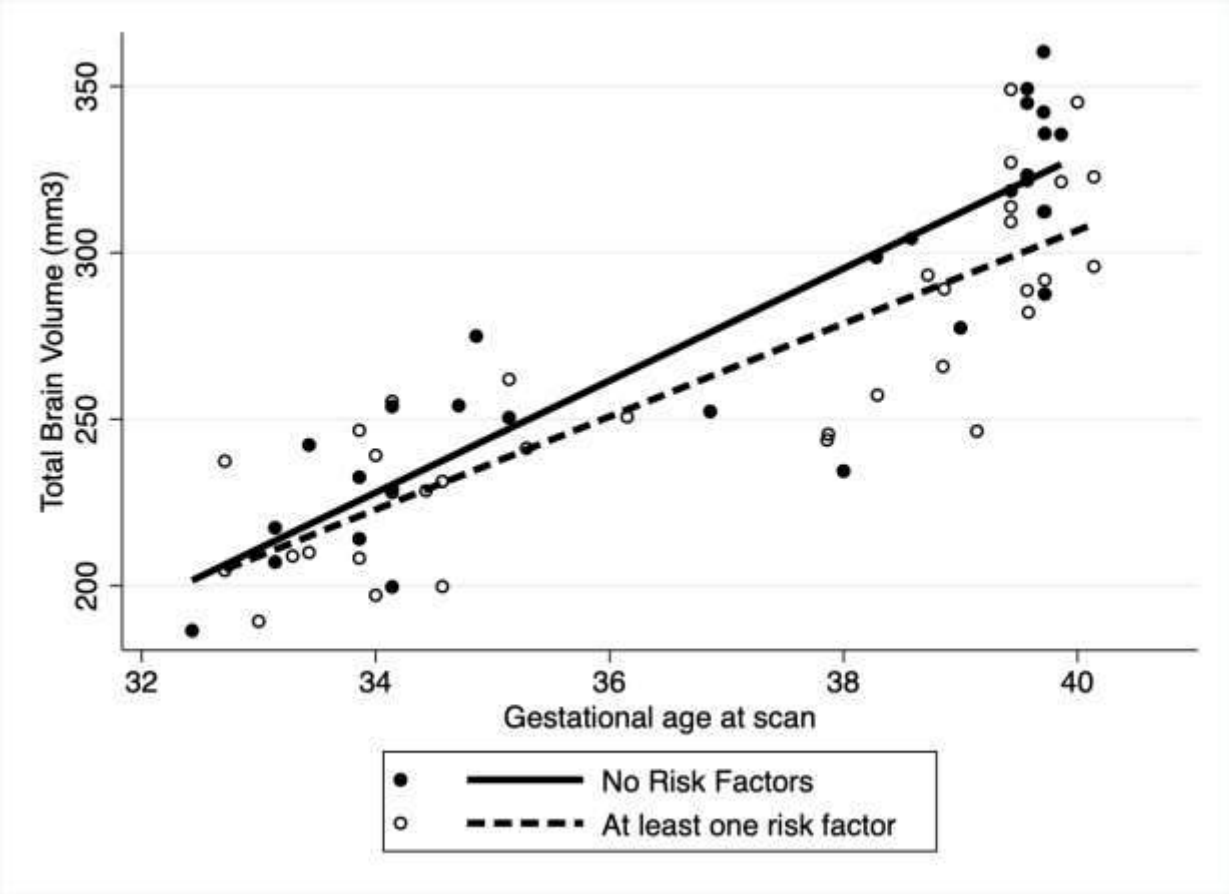
Unpublished data: Rollins, Ortinau Peyvandi, Versoulis, Rofeberg, Wypij

Which SDOH impact neurodevelopment?



Exposure to smoking

Poverty

Nutritional Assistance Program

Slower fetal brain growth

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DeRose L et al, AHA 2024

Baby's First Years Study

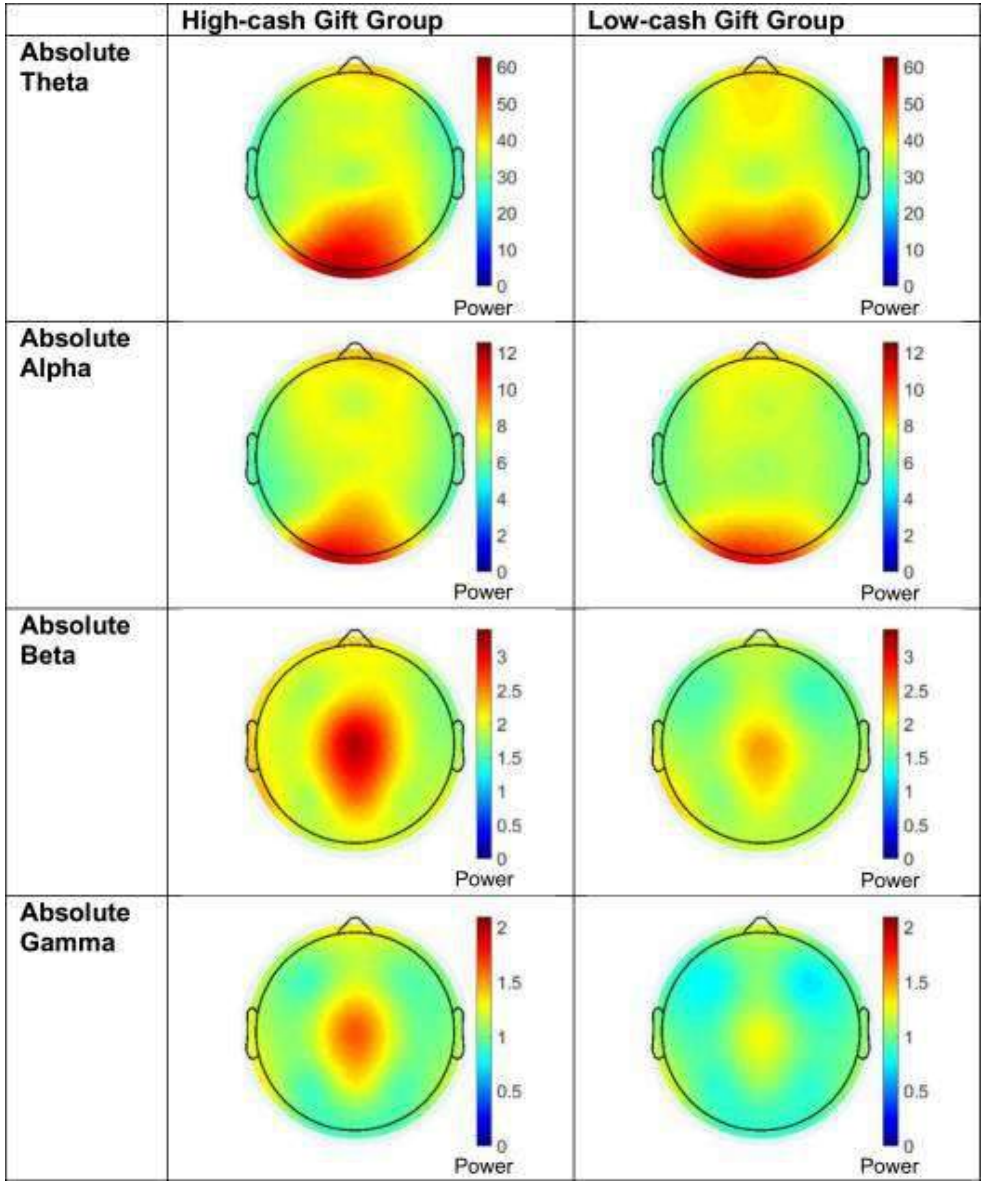
(Kim Noble)

The impact of a poverty reduction intervention on infant brain activity

Sonya V. Troller-Renfree[a], Molly A. Costanzo[b], Greg J. Duncan[c,1], Katherine Magnuson[b,d], Lisa A. Gennetian[e], Hirokazu Yoshikawa[f], Sarah Halpern-Meekin[g], Nathan A. Fox[h], and Kimberly G. Noble[a,i,1]

- 1000 low-income mothers and babies enrolled
- Randomized to high vs. low cash gift (ongoing)
- Brain activity measured at 12 months via EEG

➢ ***Greater positive brain activity in high cash gift group***



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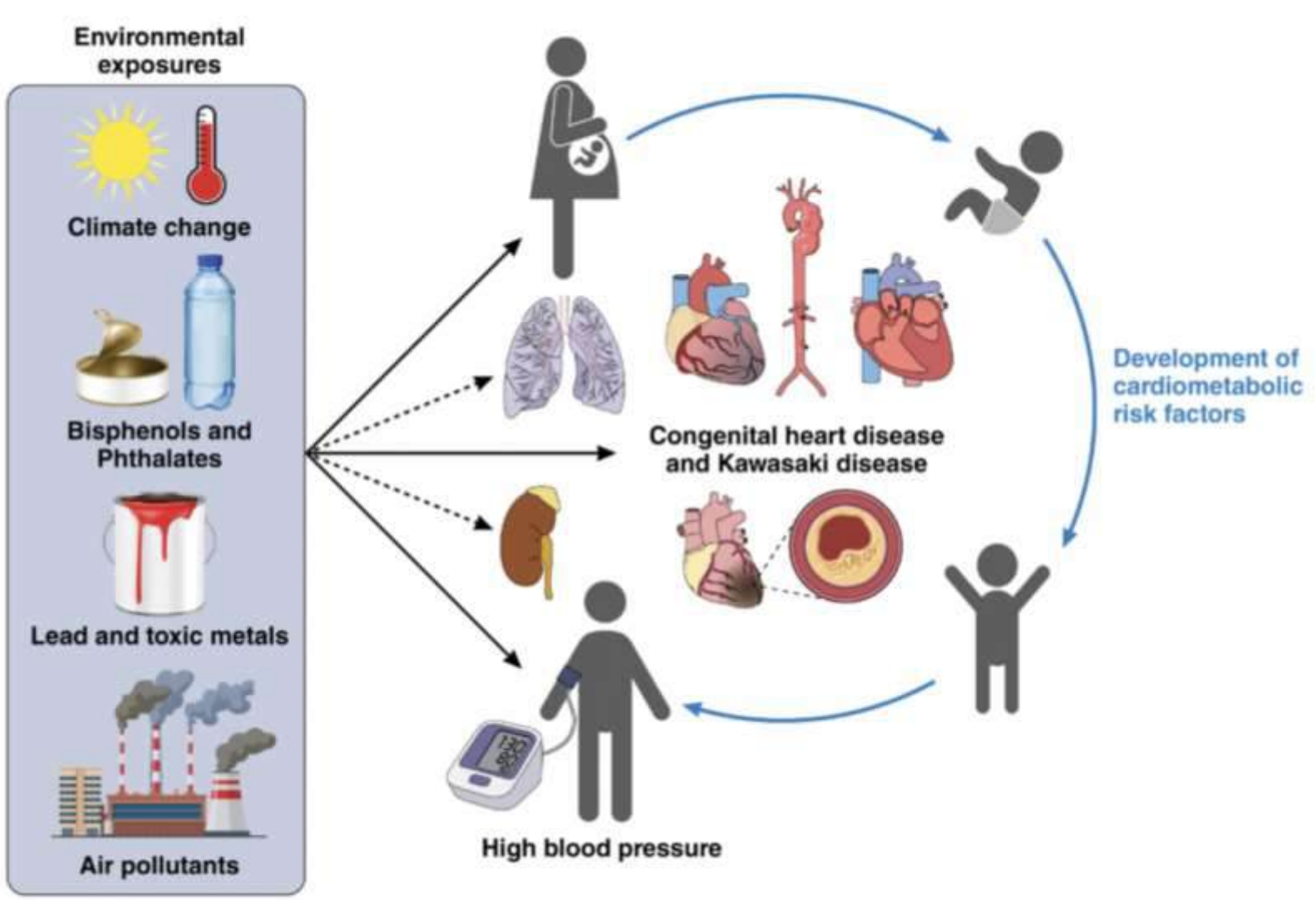
Fetal Environment



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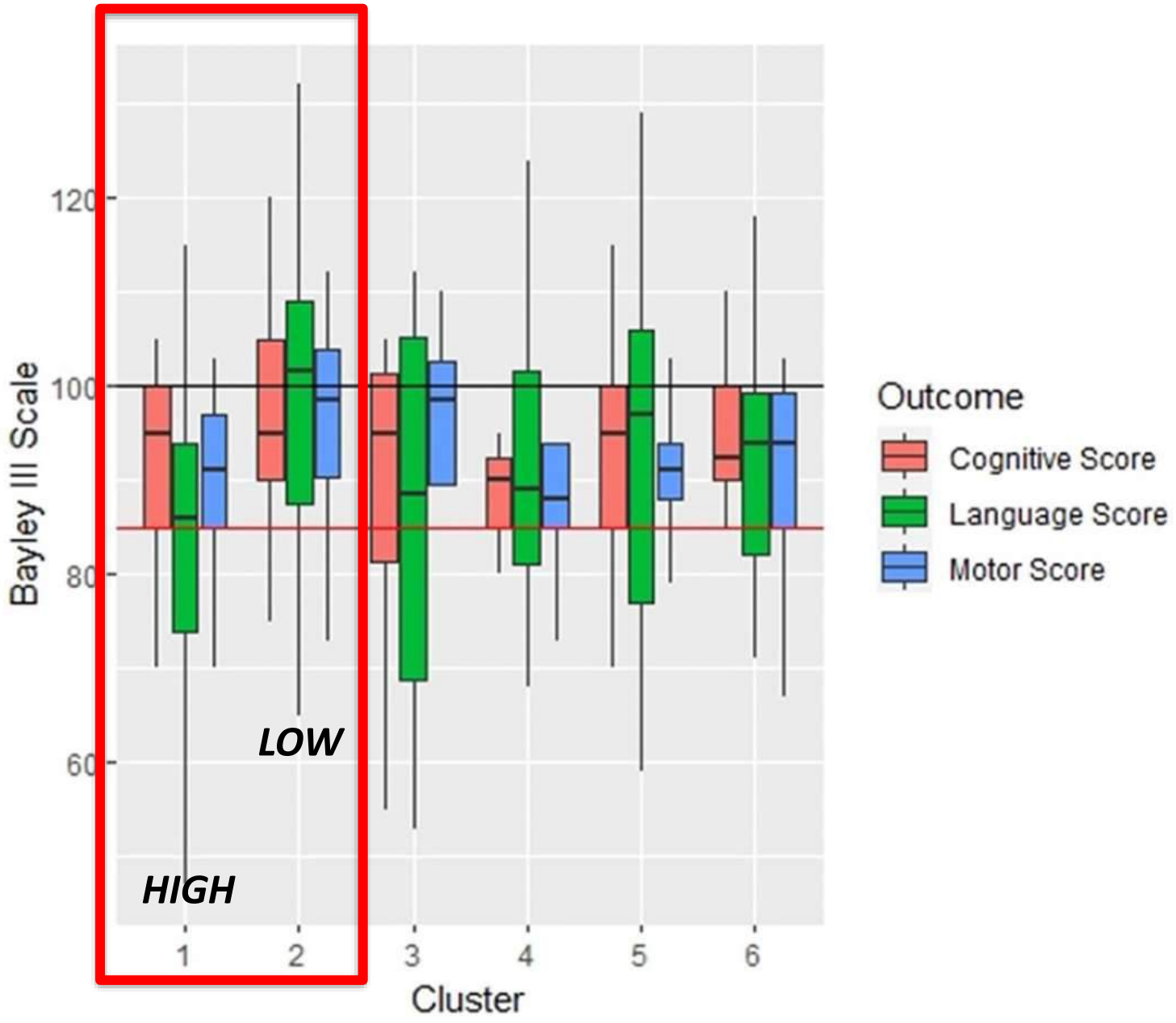
Zacharia JP et al, Circulation 2024

Fetal Environment

- **Environmental Toxins**: Impacts on the brain



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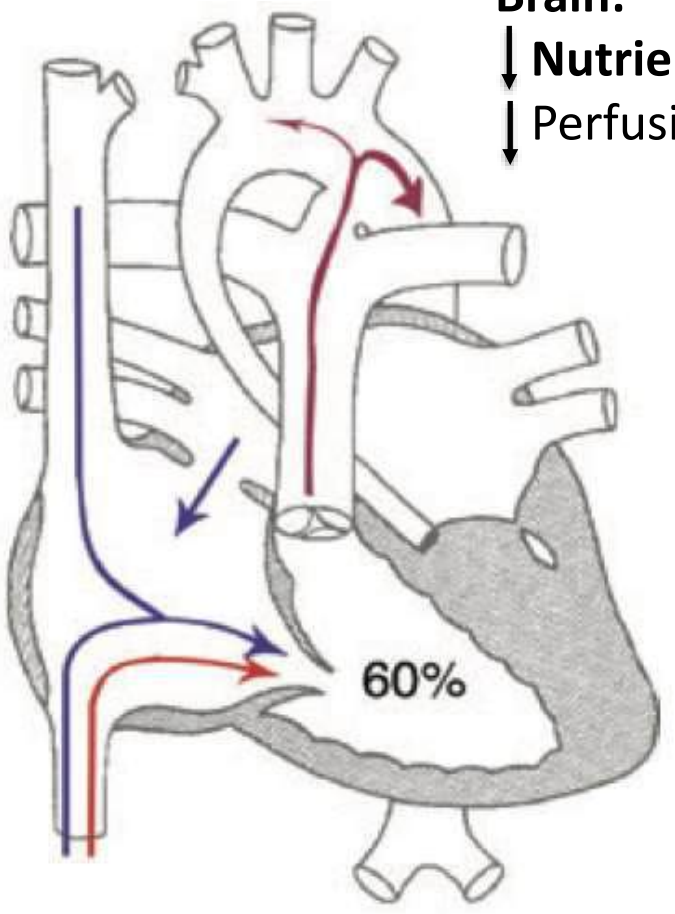
Gaynor JW et al, Plos One 2022

Fetal Nutrition: Relevant to CHD and the brain

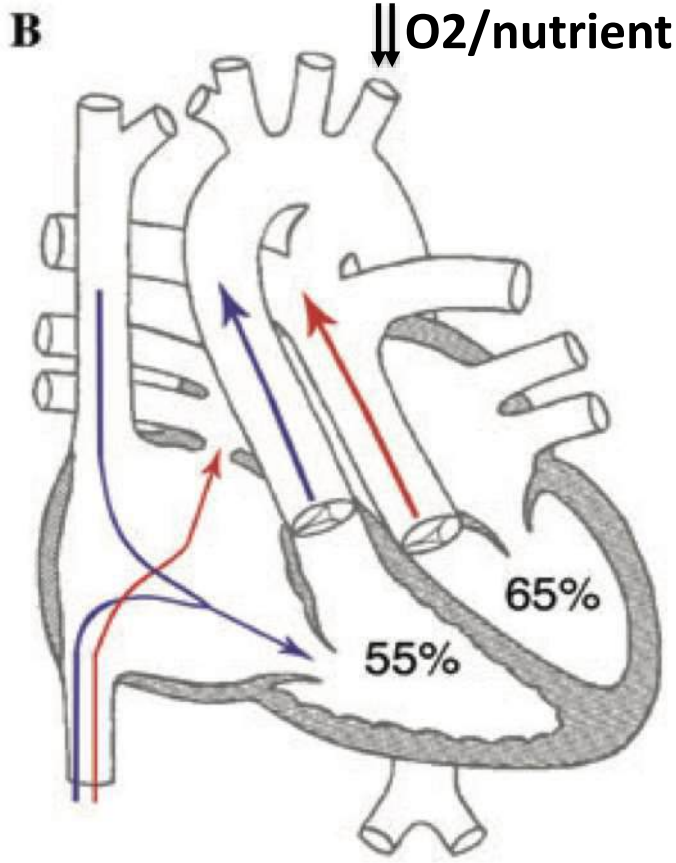
Brain:
↓ **Nutrient**/O2 delivery
↓ Perfusion



HLHS

- Glucose: predominant source of energy for the brain
- Cerebral glucose utilization increases with brain maturation

Brain:
⇓ **O2/nutrient delivery**



d-TGA

Treatment of Growth-Restricted Human Fetuses with Amino Acids and Glucose Supplementation through a Chronic Fetal Intravascular Perinatal Port System

The effect of intraumbilical fetal nutrition via a subcutaneously implanted port system on amino acid concentration by sev

Original Investigation | Pediatrics

August 22, 2023

Effect of a Mediterranean Diet or Mindfulness-Based Stress Reduction During Pregnancy on Child Neurodevelopment

A Prespecified Analysis of the IMPACT BCN Randomized Clinical Trial

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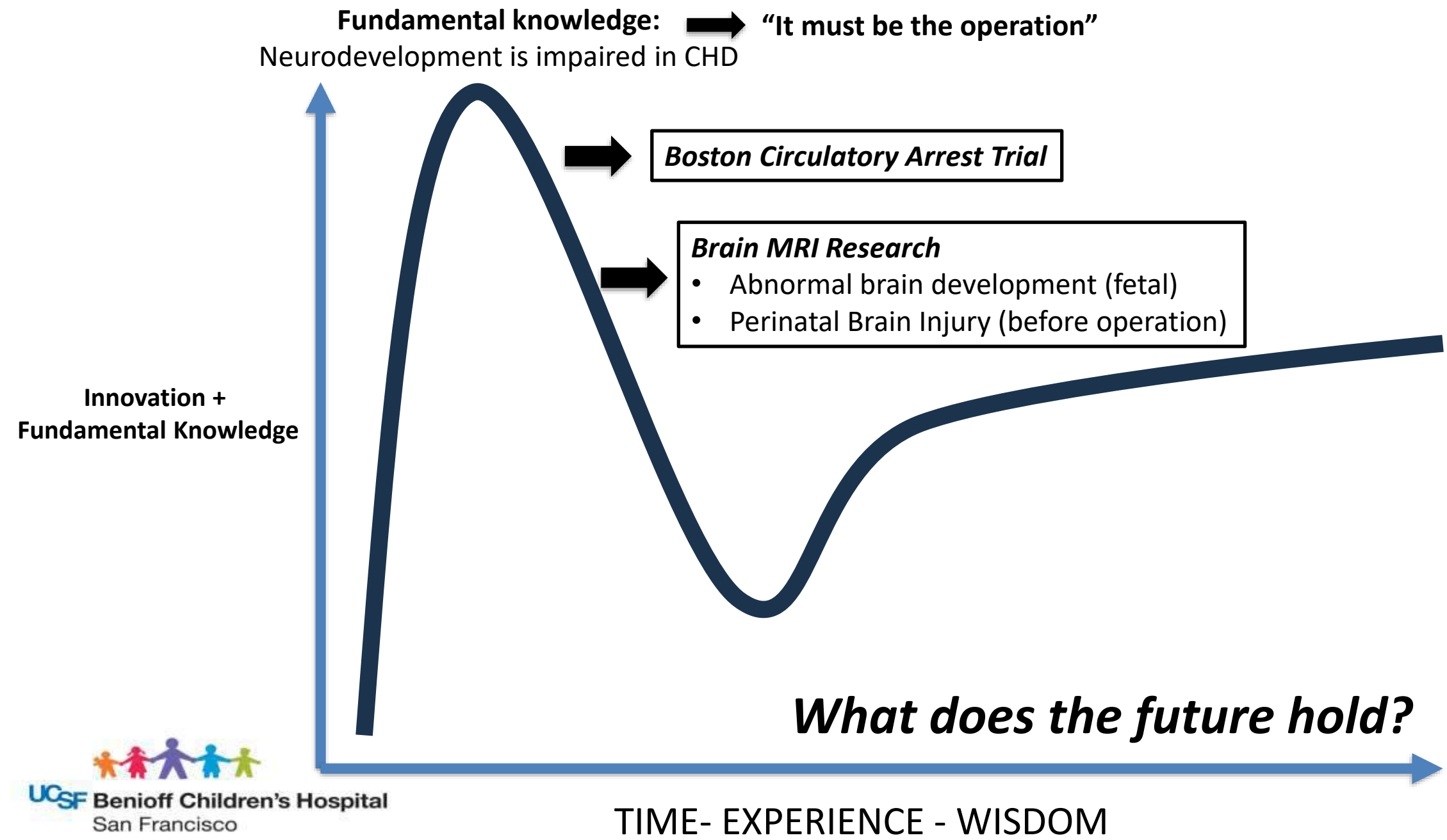

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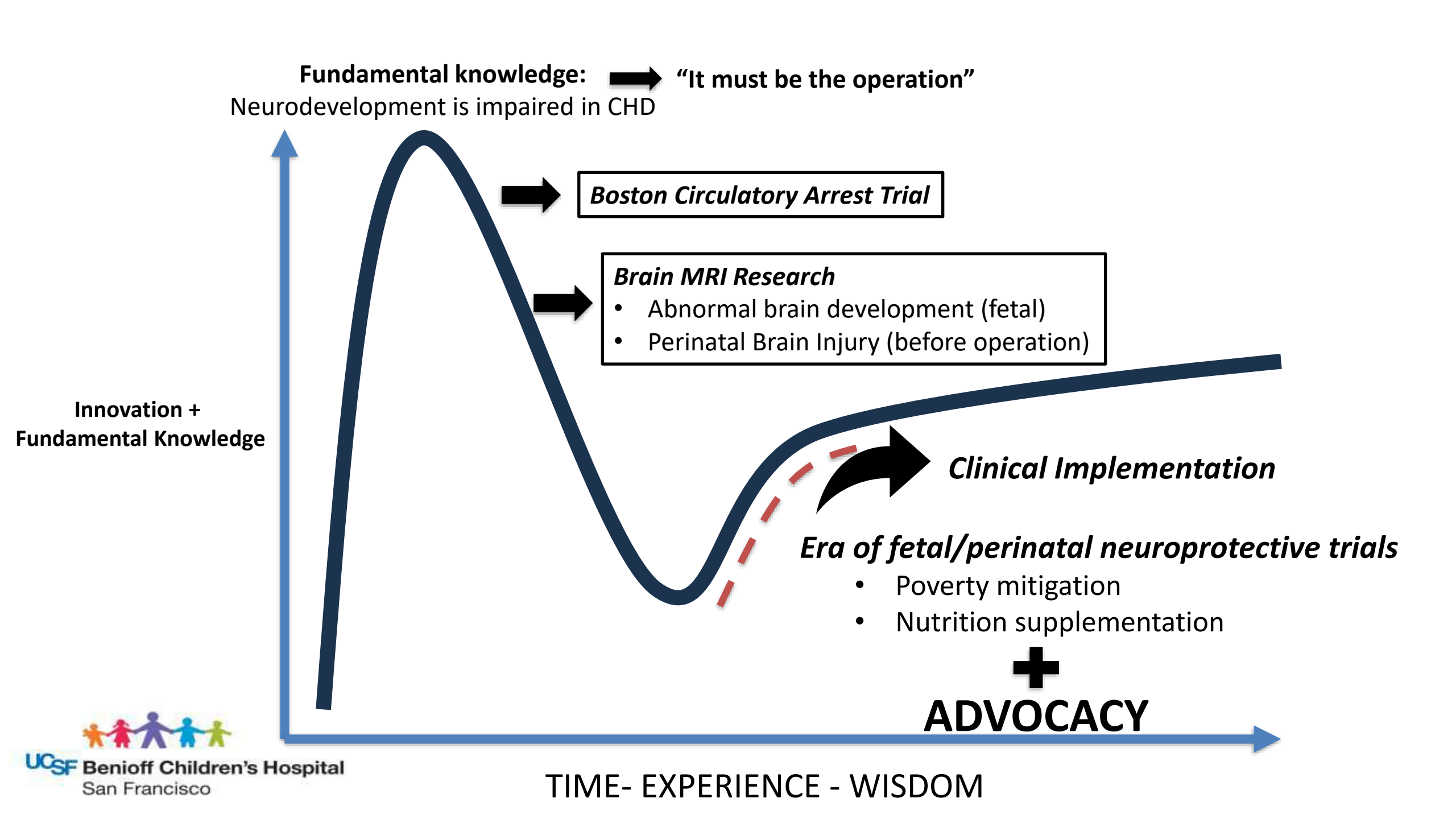

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Thank You

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