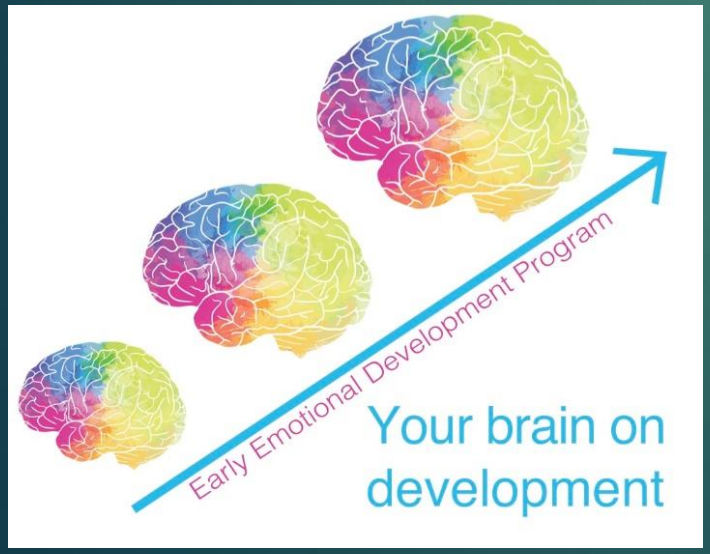
Washington University in St. Louis
School of Medicine

Capitalizing on Sensitive Periods and Neuroplasticity to Enhance Treatment Response



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Disclosure of Interest

Joan L. Luby, M.D.

Nov 2022

- Sources of Research Support
  - 1. NIMH
  - 2. American Foundation for Suicide Prevention
- Consulting Relationships
  - 1. None
- Stock Equity
  - 1. None
- Speaker's Bureau(s)
  - 1. None

Review of Validity of Preschool MDD:

- Data from at least 5 independent samples support the validity of preschool MDD

  (e.g., Luby et al., 2003, Luby et al., 2009, Klein et al., 2012, Egger and Angold, 2006, Wichstrom 2016).

- Biological markers, familial transmission, and observational evidence provided (Luby et al., 2003, Luby et al., 2002, Luby et al., 2006)
- Alterations in neural function and structure (Barch et al., 2012, Gaffrey et al., 2017, Luby et al., 2015, Belden et al., 2016 etc.)
- Evidence of impairment in multiple settings (Luby et al., 2009)
- Preschool MDD detected in epi samples in US and EU with prevalence rate of 1-2%

  (USA: Lavigne et al., 1996, Egger and Angold, 2006, Norway: Wichstrom et al., 2012, Bufferd et al., 2012)

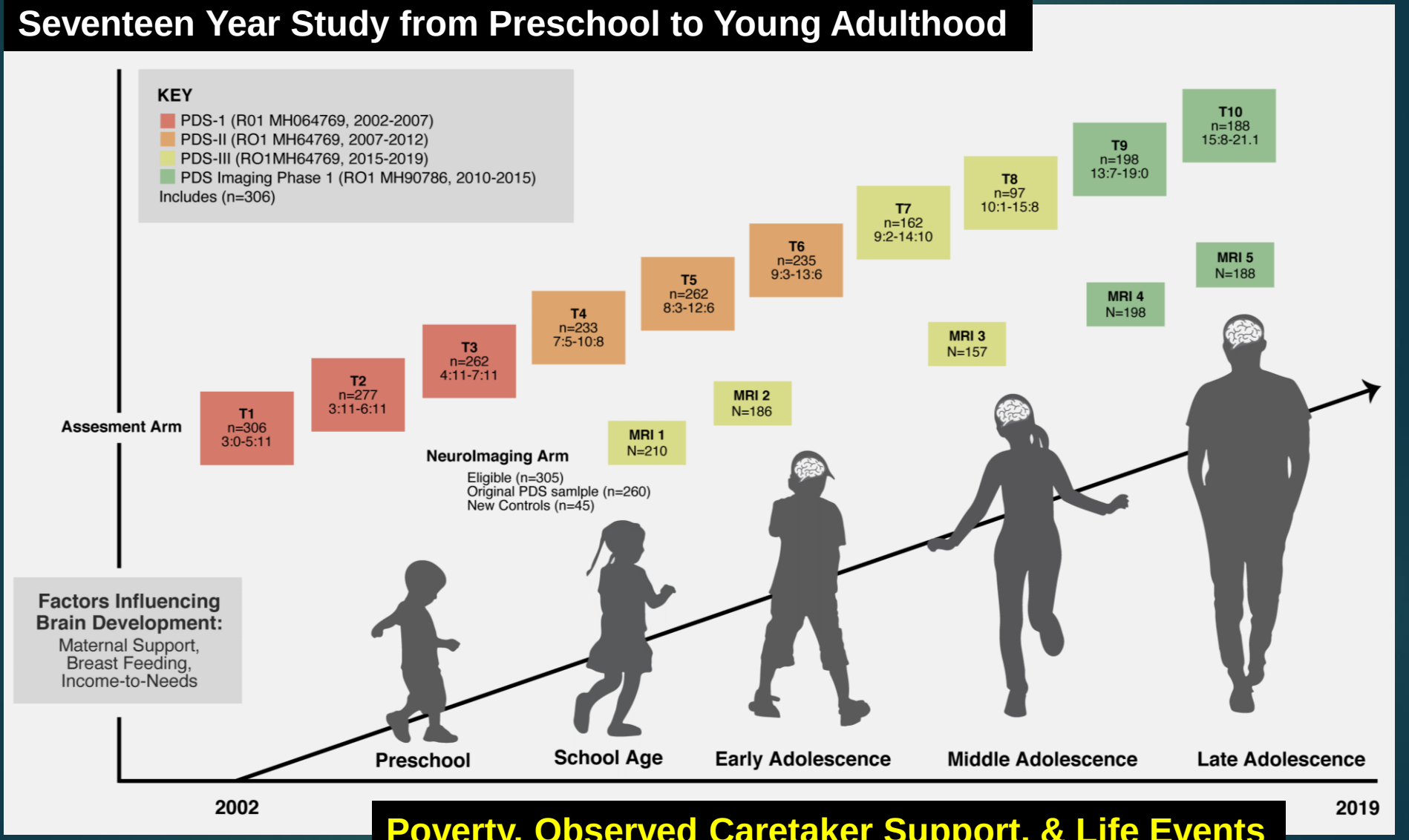
Clinical Characteristics of Preschool Depression:

- Depressed preschoolers display "typical" symptoms and vegetative signs of MDD predominantly.
- Depressed preschoolers show high levels of guilt, anhedonia, fatigue, sad/tearful and preoccupation with death/negative themes in play.
- Depressed preschoolers are functionally and developmentally impaired.
- They have increased rates of suicidality.


No one wants to play with me.
I wish I was never born.
Nothing is fun.
I'm a bad kid.
I feel so bad I broke my sister's toy.

Preschool Depression Study:

Seventeen Year Study from Preschool to Young Adulthood



Sensitive Period Primer:

- Periods of heightened **neuroplasticity** when the effects of experience on brain architecture are enhanced.
- These are neurobiological processes involving the timing and balance of processes at the molecular, cellular, and circuit levels that control sensitive period opening and closing
- Sensitive periods represent closing windows of opportunity or vulnerability (early in development) when the brain is more receptive/able to be informed by experience.

Parent Child Interaction Therapy-Emotion Development (PCIT-ED):

- Child Direction Interaction (CDI)
- Parent Directed Interaction (PDI)
- Emotion Development (ED)
- In vivo coaching through a "bug in the ear"
- Caregiver serves as "arm of the therapist"
- Emotionally evocative events in vivo

PCIT-ED Empirical Support

- Large effects for early childhood depression >1.0 effect sizes (Luby et al., Am J , 2018)
- Effects on parent depression and parenting stress (Luby et al., Am J , 2018)
- Sustained efficacy-effects evident 3 months after treatment ended (Luby et al, EJCP 2019)
- Neural change evidence by change in reward response using ERP (Barch et al., Bio Psych 2019)
- Specific effects of novel ED module (Luby et al., JAACAP 2020)

Emotion Development Treatment Targets:

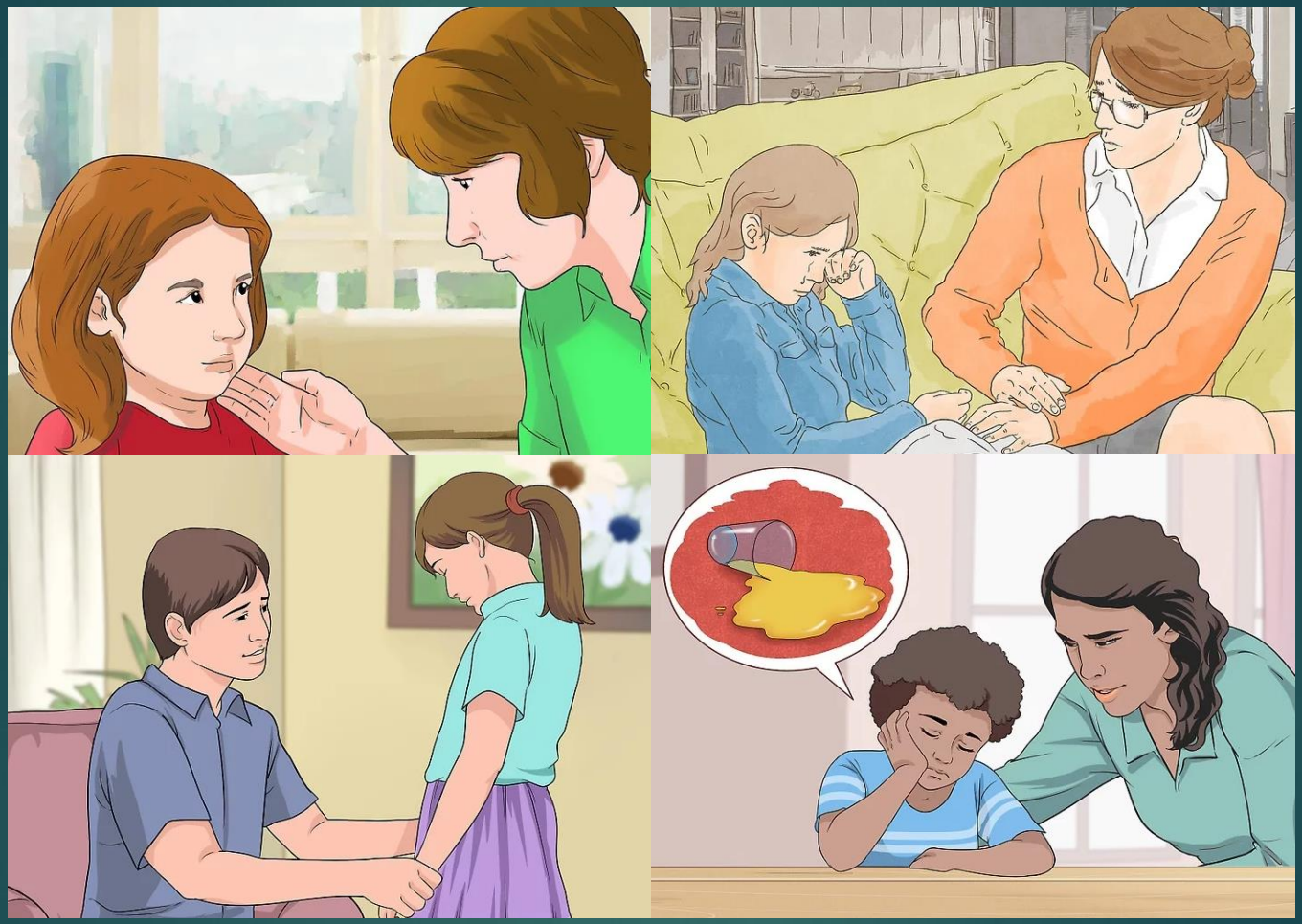
- Learn to accurately identify and label a broad range of emotions in self and others.
- Learn adaptive strategies to deal with guilt and utilize pro-active reparation.
- Learn to regulate intense emotions by utilizing cognitive control strategies and relaxation strategies.
- Learn to focus on positive events and sustain positive emotions.

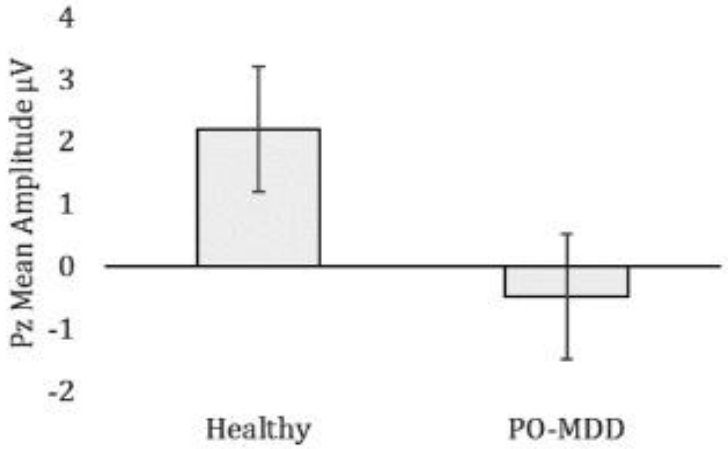
Fundamental Importance of the Caregiver-Child Relationship

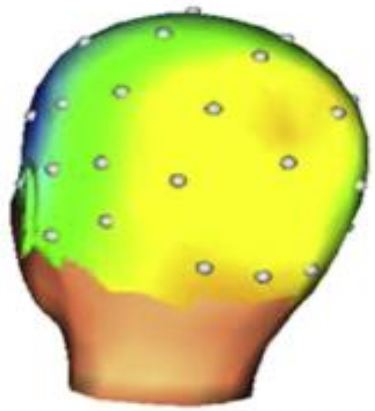
- Meeting basic safety and survival needs
- Validation of developing identity
- Attachment—reliable and stable nurturing presence
- Promoting positive development/stimulation
- Promoting organization, rhythms, regularity and structure

An under-recognized vital sign

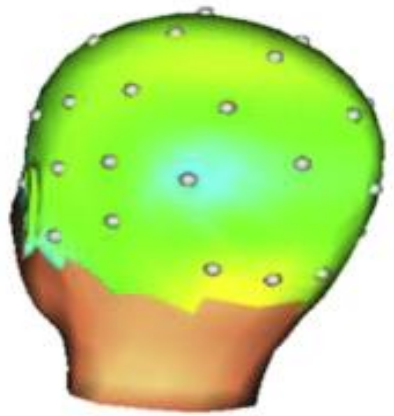
Enhancing Emotion Development







Healthy
(Reward minus Loss)

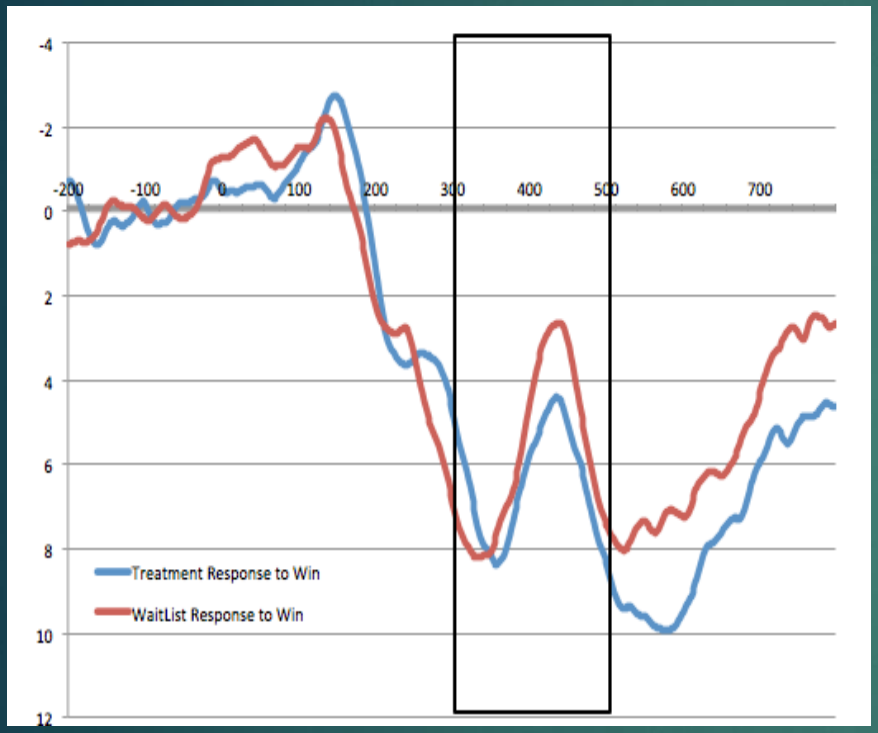


PO-MDD
(Reward minus Loss)

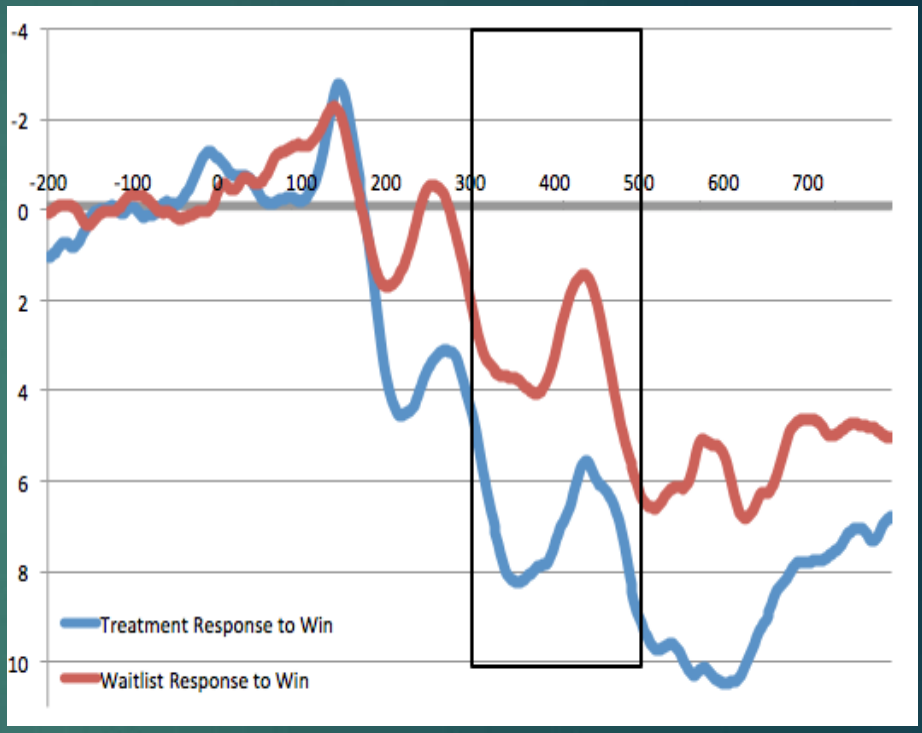
Belden, A, et al. (2016) Neural correlates of reward processing in depressed and healthy young children. *Journal of the American Academy of Child and Adolescent Psychiatry*. .

Group Differences Response to Win and Loss

Baseline



Post 1

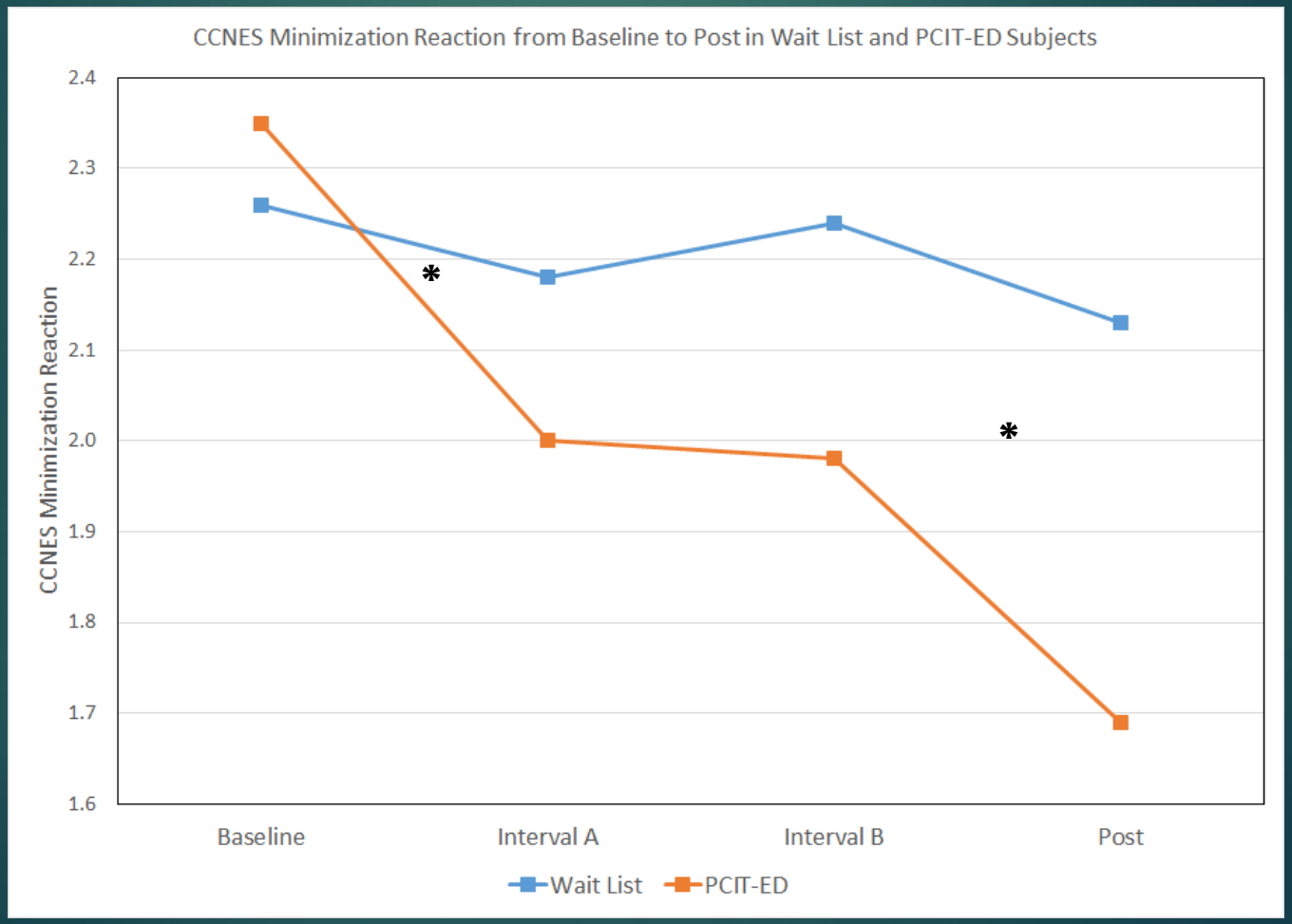


Effects on Parents:

- Decreases in parenting stress
- Changes in parenting approach to addressing child's emotional expression
- Decreases in parental depression

Parental Minimizing

CDI (BL to A) Wait List vs. PCITED			PDI (A to B) Wait List vs. PCITED			ED (B to Post) Wait List vs. PCITED		
t	p	Cohen's d	t	p	Cohen's d	t	p	Cohen's d
2.54	0.0118	0.37	1.17	0.2447	0.18	2.74	0.0069	0.41



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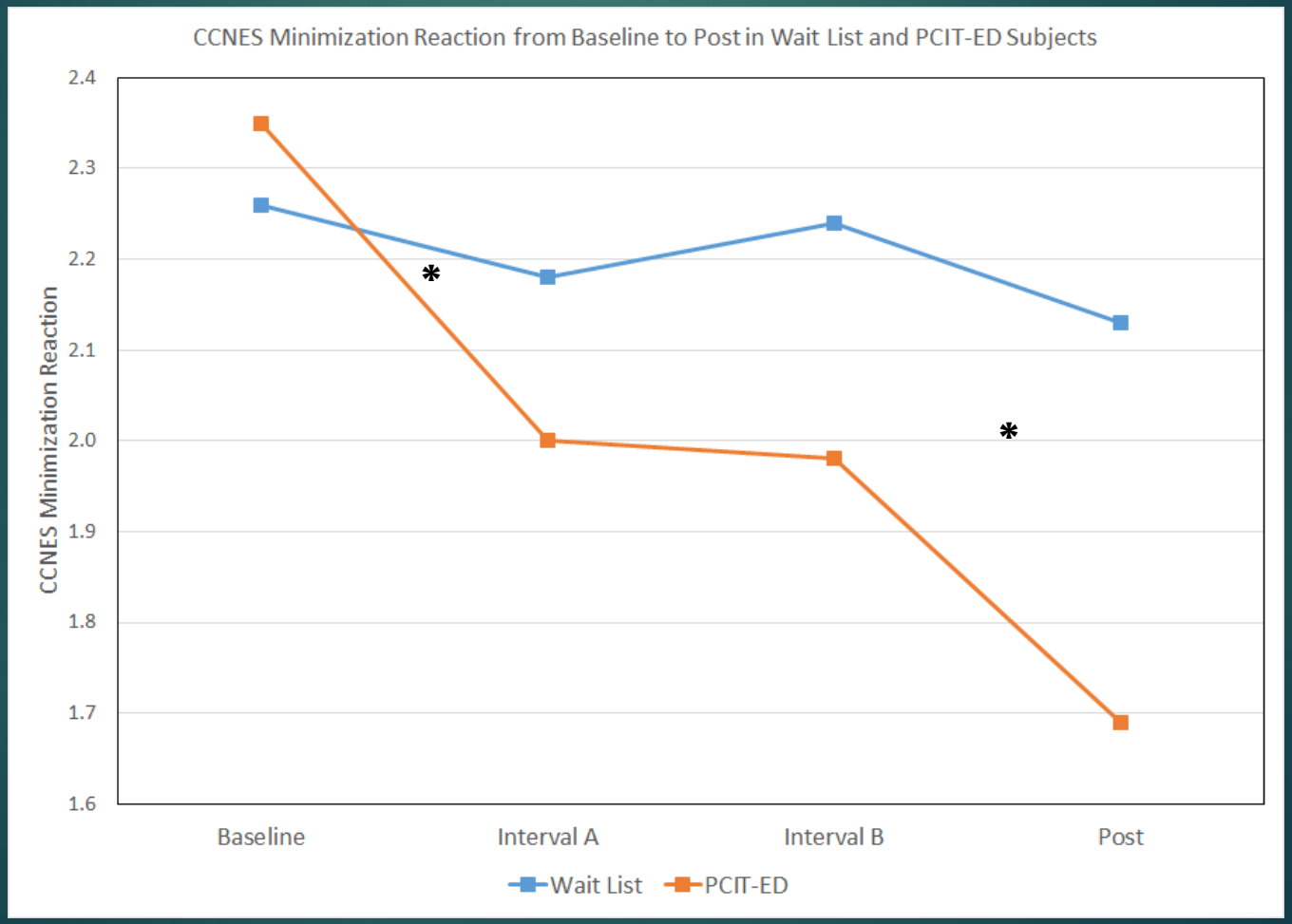
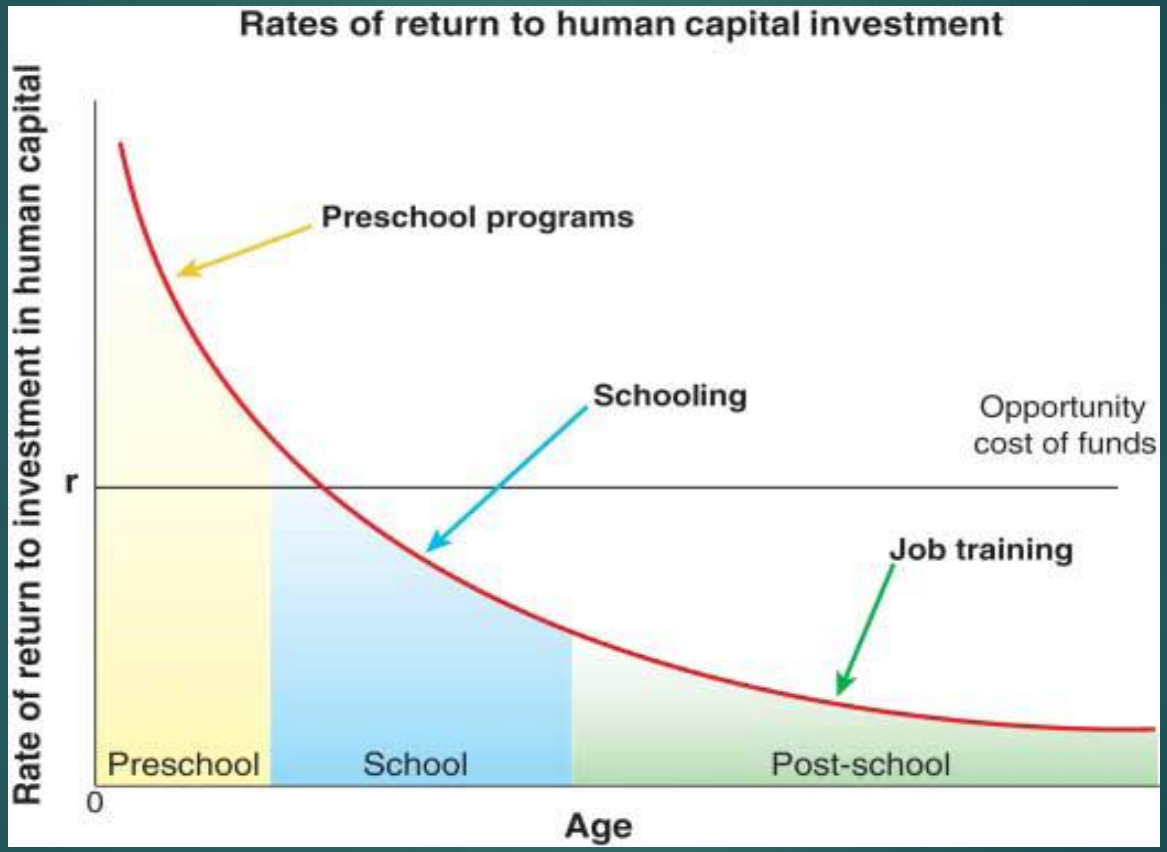
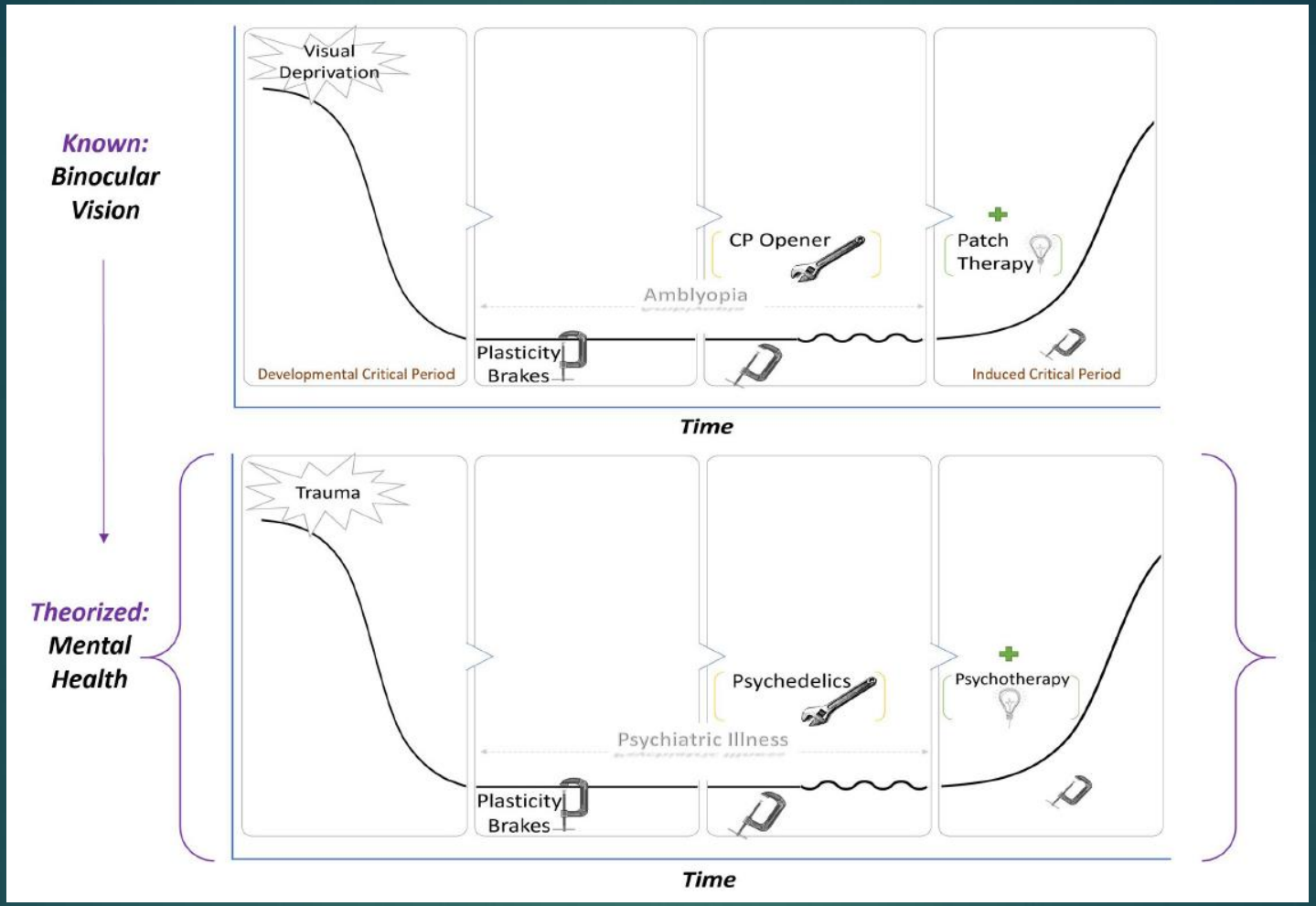


Evidence of Sensitive Periods for the Effects of Interventions:



Heckman, J. (2006). Skill Formation and the Economics of Investing in Disadvantaged Children. *Science*. 312(5782); 1900-1902.

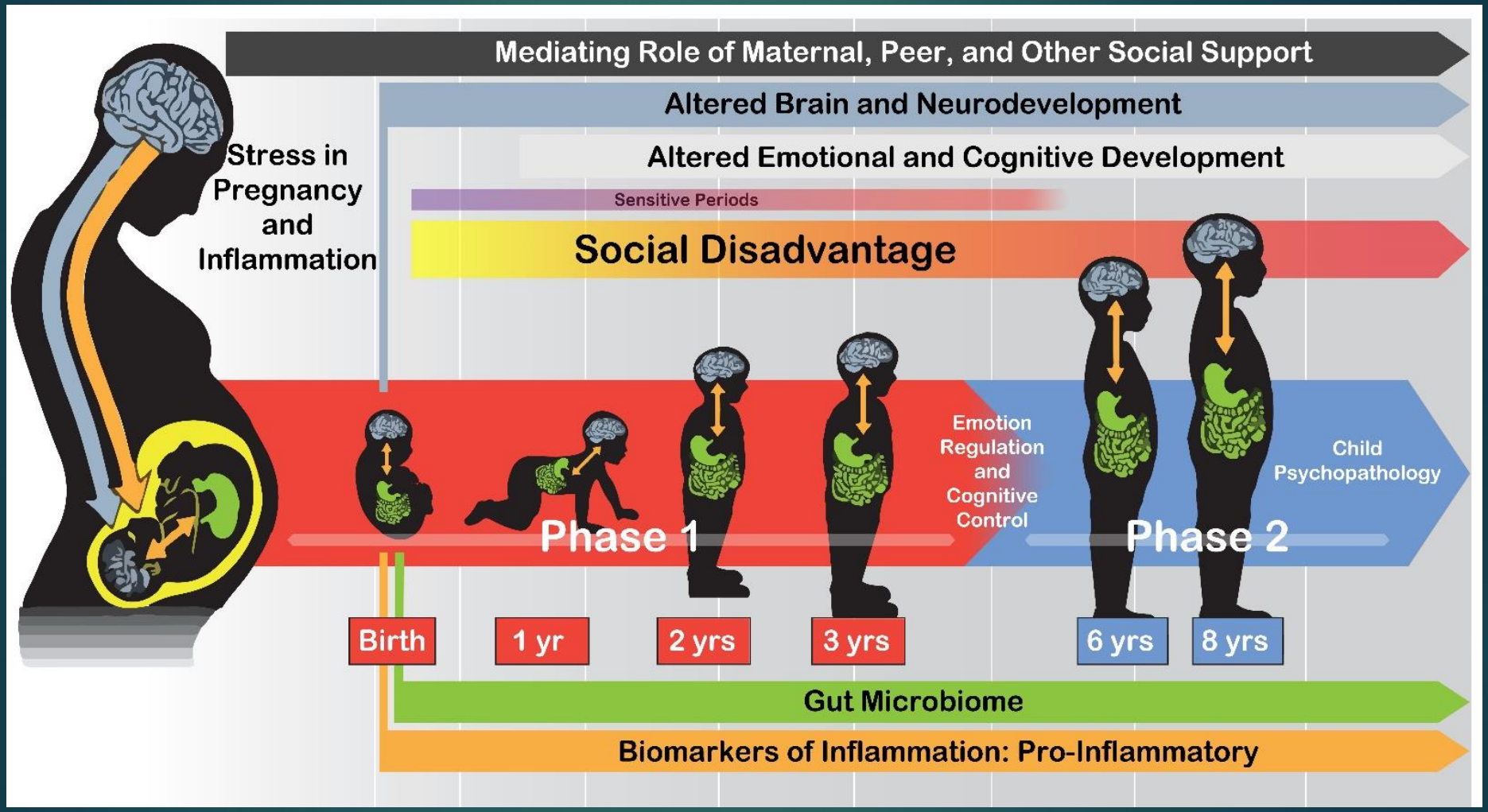


Lepow, L., Morishita, H., & Yehuda, R. (2021). Critical period plasticity as a framework for psychedelic-assisted psychotherapy. *Frontiers in neuroscience*, 1165.

Prenatal Programming:

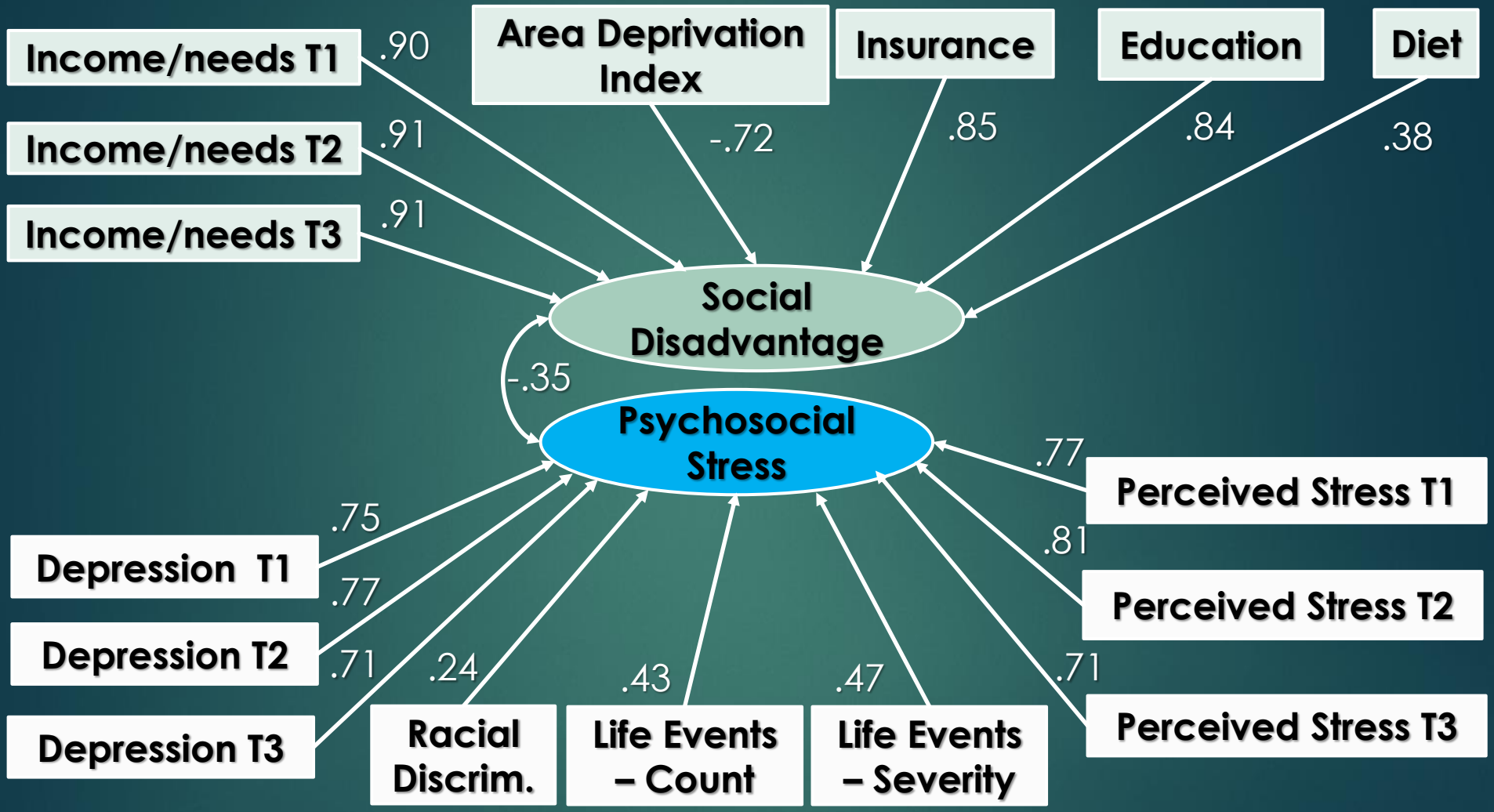
- Experiences in utero prepare the fetus for the expected post-natal environment.
  - Maternal Stress/Adversity
  - History of childhood maltreatment (epigenetic mechanisms)
  - Maternal mental health

Early Life Adversity, Gut Microbiome, Inflammation, and Brain Development



P.I.'s: Luby, Warner and Smyser
Co-I's: Barch and Rogers

eLABE – Prenatal Disadvantage & Baby Outcomes



N = 399 pregnant mom recruited and followed through pregnancy, offspring imaged at birth or shortly after.

Luby et al. (in press)

Washington University in St. Louis

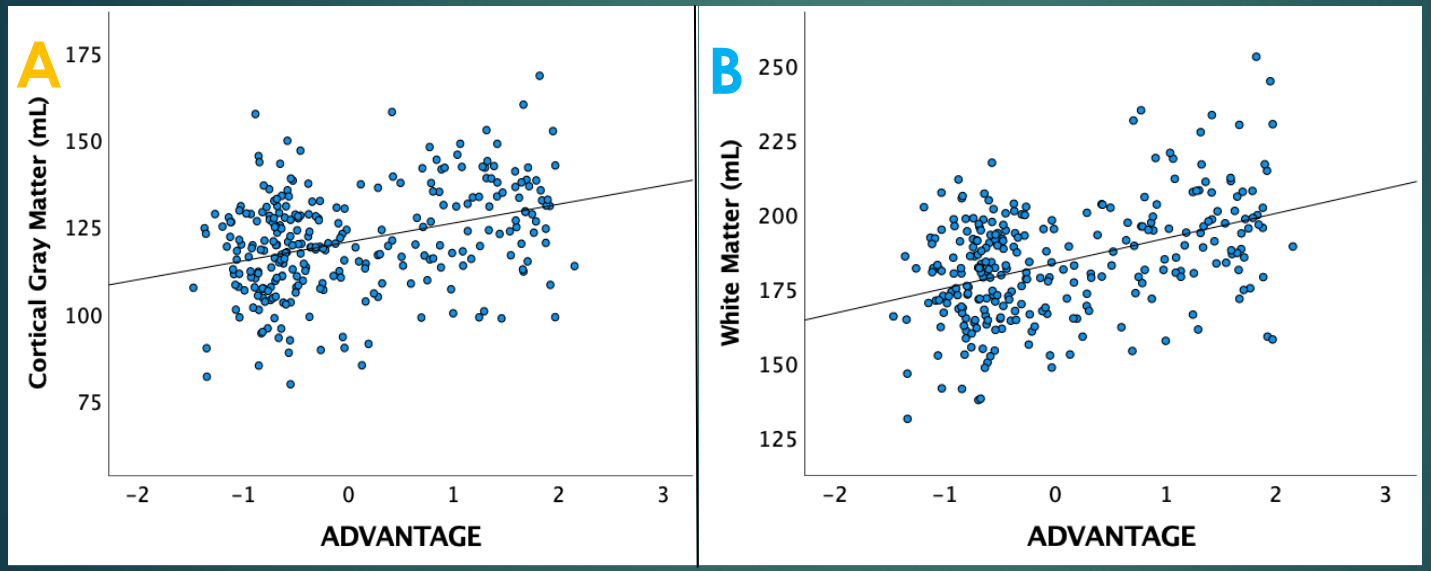
Mothers with Lower Socioeconomic Advantage Have Infants with Smaller Brain Volumes

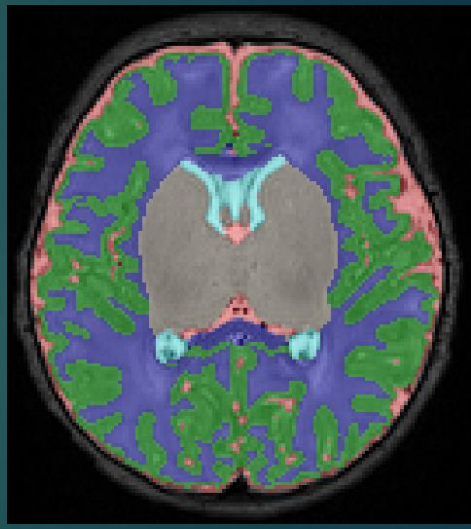
Regina Triplett, M.D.

JAMA Open, 2022

N = 280 healthy, full term infants

Stepwise Linear Regression controlled for infant sex, PMA at scan, birthweight, maternal PSYCH.





R2 = 0.56

ADVANTAGE β = 0.14, p = 0.004

R2 = 0.36

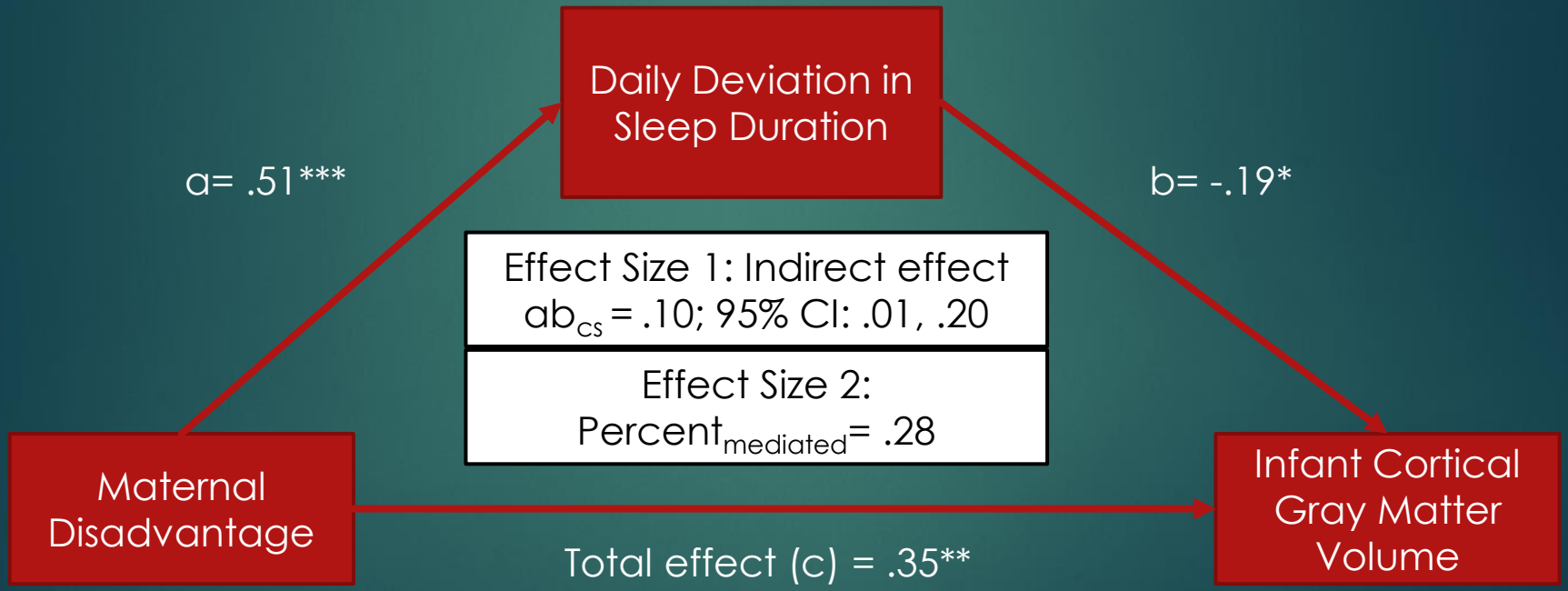
ADVANTAGE β = 0.30, p < 0.001

Triplett RL, Lean RE, Parikh A, Miller JP, Alexopoulos D, Kaplan S, Meyer D, Adamson C, Smyser TA, Rogers CE, Barch DM, Warner BB, Luby, JL, Smyser, CD. JAMA Open (2022). Prenatal Exposure to Early Life Adversity and Neonatal Brain Volumes at Birth.

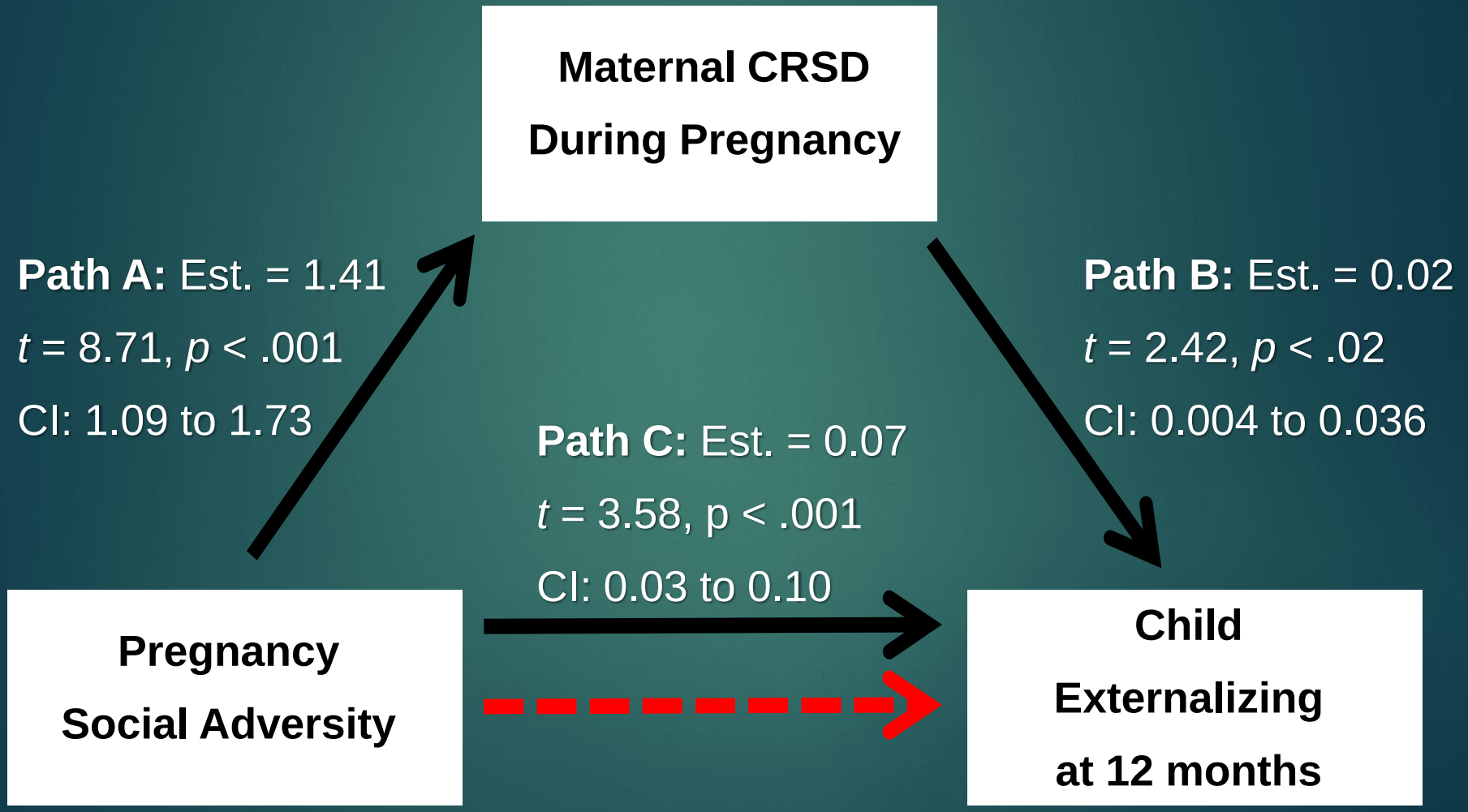
The Effect of Maternal Disadvantage on Neonatal Cortical Gray Matter Volume is Mediated through Chronodisruption:

Caroline Hoyniak, Ph.D

Diana Whalen, Ph.D



Maternal CRSD Mediates Relationship of Adversity to Child Behavioral Outcome



Sleep, Circadian Rhythms and Neurodevelopment

- A significant gap in the literature—especially pertaining to effects on socioemotional correlates.
- Sleep has very important effects on synaptic function and homeostatic processes which are rapidly developing/organizing in the first 3 years of life (clearing of synaptic residue).
- Emerging evidence that sleep duration, timing and stages are very important for healthy brain development in early childhood (high sleep to wake ratios).
- Sleep staging changes markedly during early development.

Conte Center Application Collaborators:

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Joan Luby, M.D.

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Trends in Neurosciences

CellPress
REVIEWS

Opinion

Neurodevelopmental Optimization after Early-Life Adversity: Cross-Species Studies to Elucidate Sensitive Periods and Brain Mechanisms to Inform Early Intervention

Joan L. Luby,[1,*] Tallie Z. Baram,[2] Cynthia E. Rogers,[1] and Deanna M. Barch[1,3,4]

Human brain development is influenced by early-life experiences, particularly during sensitive periods, with impact on cognitive and emotional outcomes. Understanding how the timing and nature of such experiences (including adversity, trauma, and enrichment) govern their influence on brain organization is crucial for harnessing key environmental factors early in life to enhance brain development. Here we synthesize findings from human and animal studies focusing on sensitive periods and their regional and circuit specificity and highlight the challenge and power of such cross-species approaches in informing the 'next steps' to optimize cognitive and emotional health in developing children. We propose designs for neurodevelopmental optimization research programs utilizing randomized enhancement trials in early childhood to inform public health strategies on prevention and early intervention.

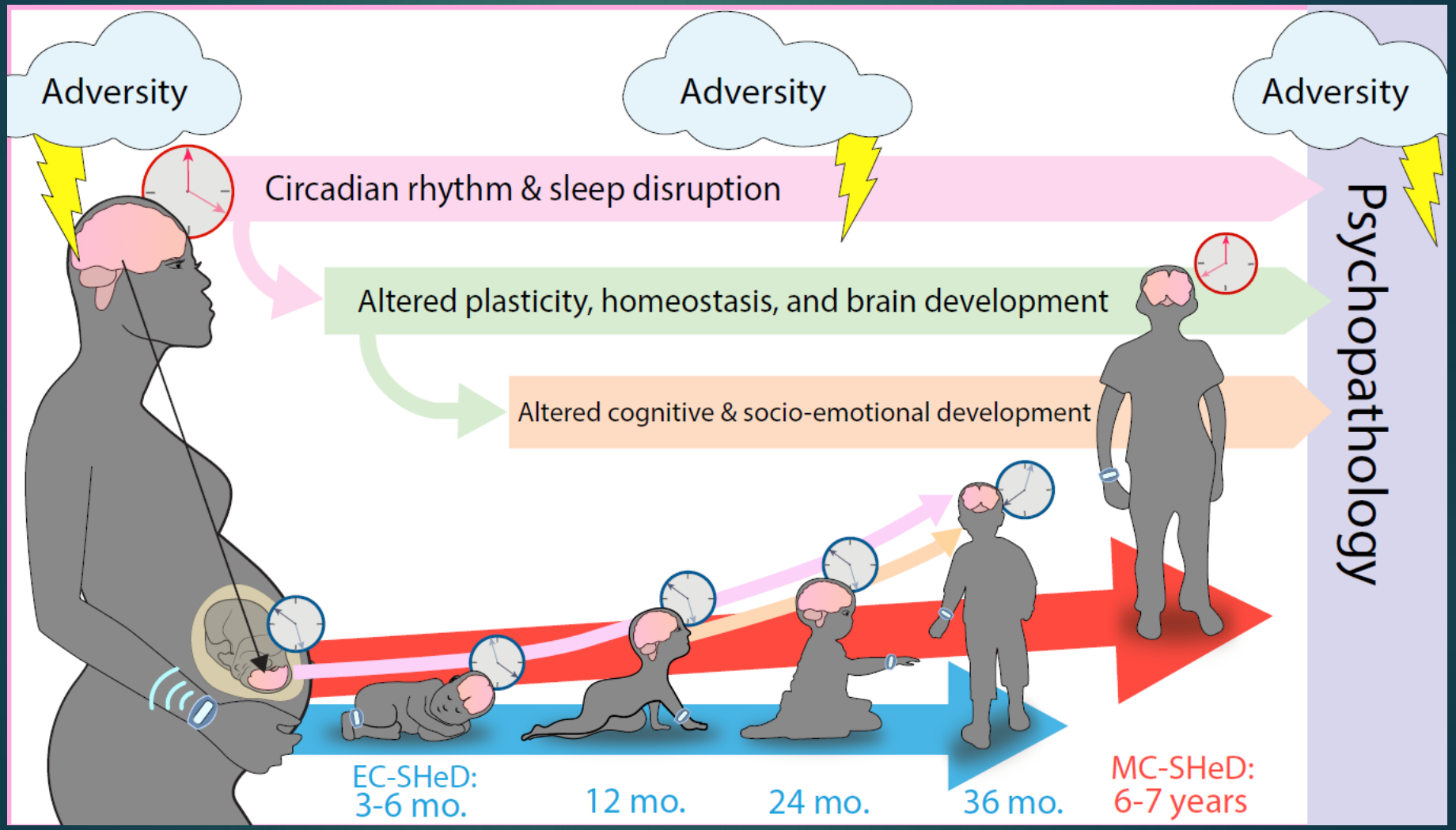
Highlights

Human brain development is influenced by exposure to early-life experiences, including enrichment and adversity, with cognitive and emotional consequences including vulnerability to or protection from mental illness.

The timing of the exposure is critical, because there are sensitive periods when vulnerability is augmented; sensitive periods may pertain also to the timing of enrichment or mitigation efforts.

Animal studies indicate that sensitive

Effects of Circadian Rhythms and Sleep Disruptions on Neurodevelopment and Risk for Psychopathology



Neuroplasticity

- Two broad categories :
  - **Associative plasticity**, such as long-term potentiation and depression (LTP/LTD), are mechanisms of positive feedback that strengthen or weaken synapses as a function of experience.
  - **Homeostatic plasticity** is a form of negative feedback that globally adjust neuronal properties to maintain set-points in activity.
  - Both processes are necessary to maintain optimal neural function. Associative plasticity requires homeostatic plasticity due to dangerous instability introduced by associative mechanisms without homeostatic constraint.

- Sleep is critical to maintain homeostatic plasticity and to achieve "criticality" or optimal neural functioning.

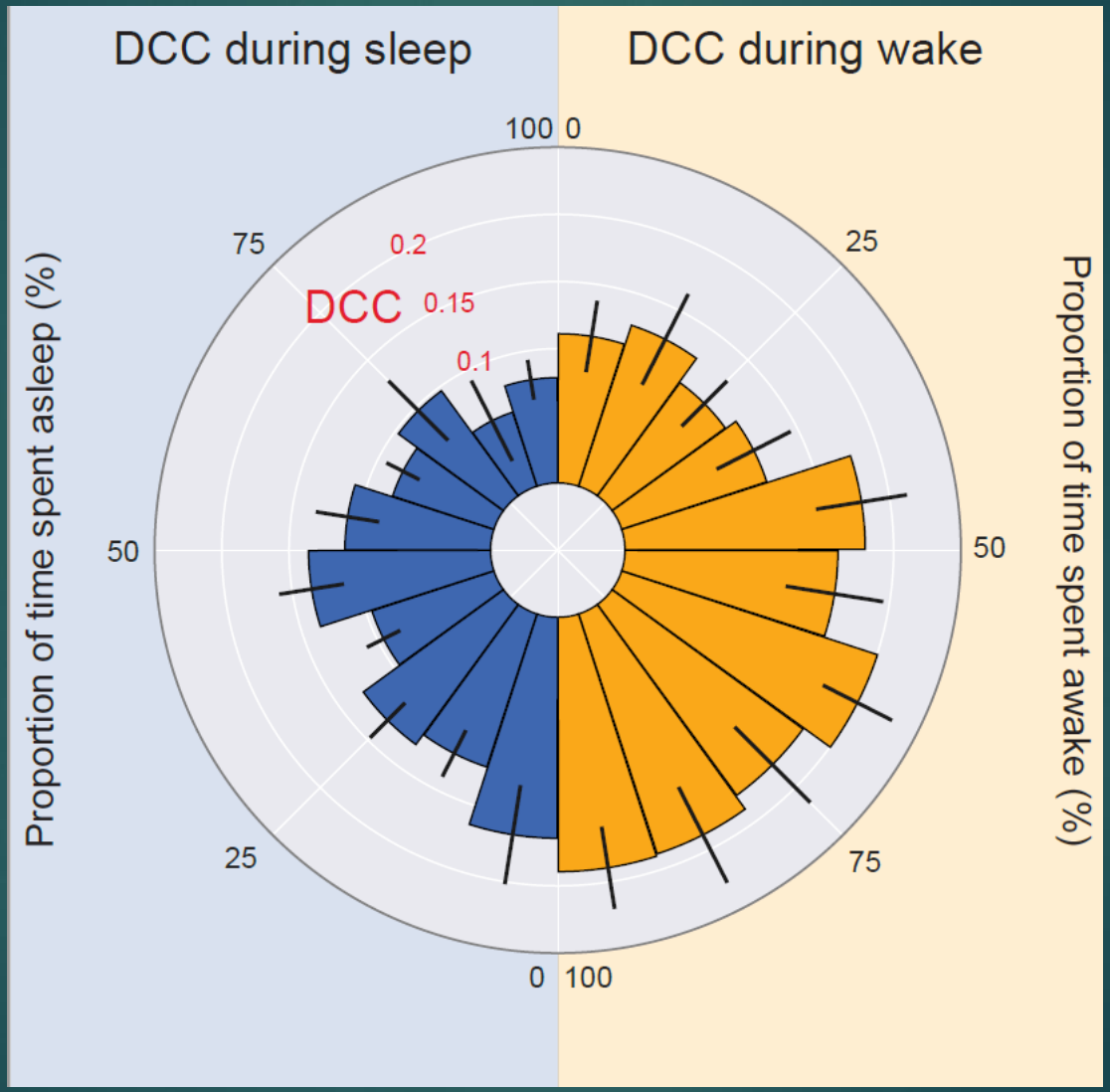
CRSD early in development, alterations in sensitive periods/plasticity and criticality: Implications for Psychopathology

- Stemming from data in rodents, we hypothesize that social adversity related to environmental disruptions of daily rhythms and sleep during sensitive periods impairs the mechanisms of homeostatic plasticity necessary for the emergence and maintenance of effective cortical computation "criticality".
- Alterations in this neurodevelopmental process may underlie increased risk for psychopathology.
- CRSD in mother and child are modifiable risk factors in pregnancy and early childhood.

Criticality: Definition and Application to Sleep and Neurodevelopment

- Neural networks at criticality exhibit optimal processing and computing (e.g. information transmission, computational power) properties (Beggs, 2008; Shew and Plenz, 2013).
- In early life there is a temporal window during which cortical network undergo extensive experience dependent plasticity towards optimization.
- Acute sleep deprivation can prevent these experience dependent refinement of networks.
- CRSD during early development may be detrimental to this refinement of circuits and related function.

Criticality (DCC) across wake and sleep



Xu, et al., in preparation (Hengen Lab)

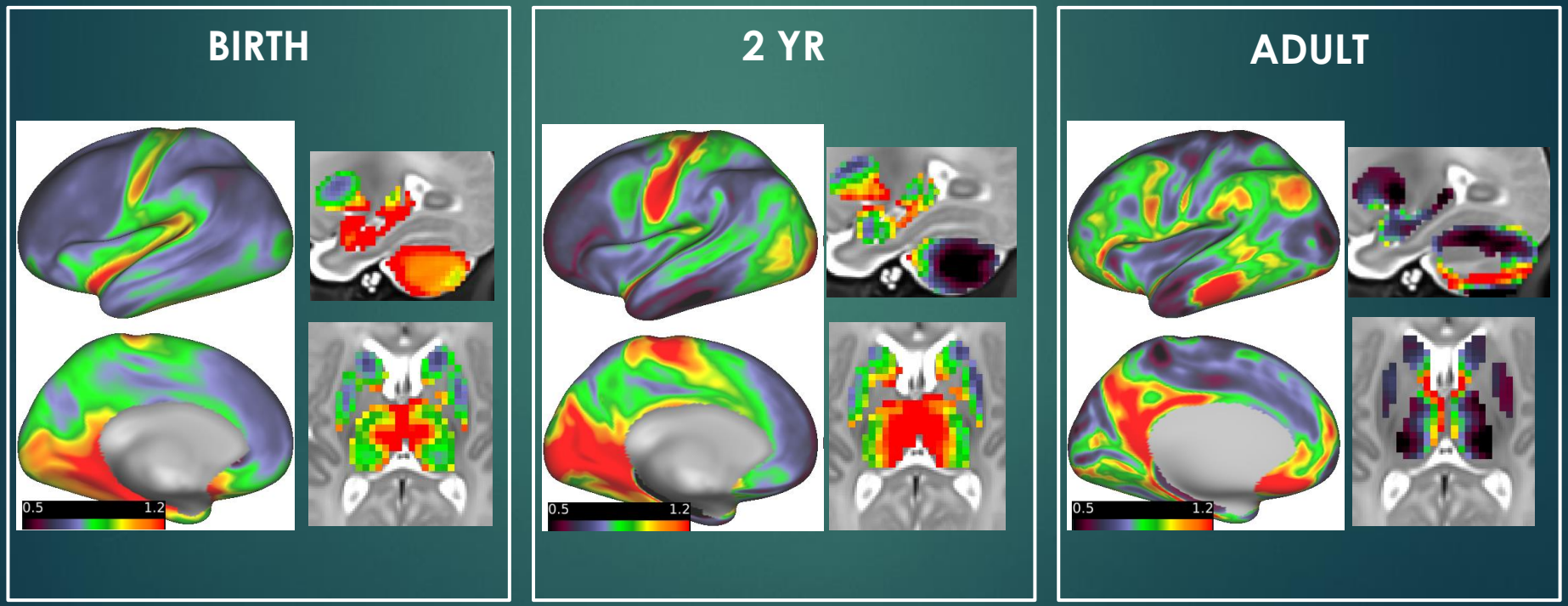
Putative Neural Markers of Plasticity in Humans:

1. **fMRI Marker of Plasticity-Amplitude of Low Frequency Fluctuations (ALFF):** In animal models plasticity is associated with high amplitude synchronized intrinsic activity which becomes more diffuse with maturation and waning plasticity. This can be measured using BOLD signal.

2. **EEG markers of plasticity (FOOF):** Synaptic E:I balance can be inferred from EEG field potentials. In simulations and in vivo recordings in animal models, a measure of 1/f explains a significant amount of the variance in E:I balance. Data in humans suggests that 1/f may have potential as a neurobiological marker of plasticity.

ALFF: a putative marker of plasticity

Ashley Nielsen, Ph.D

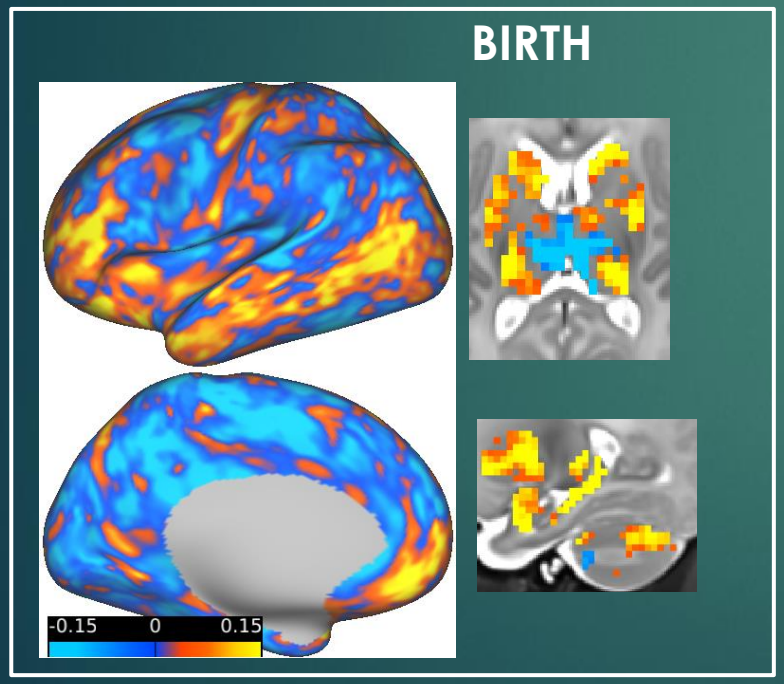


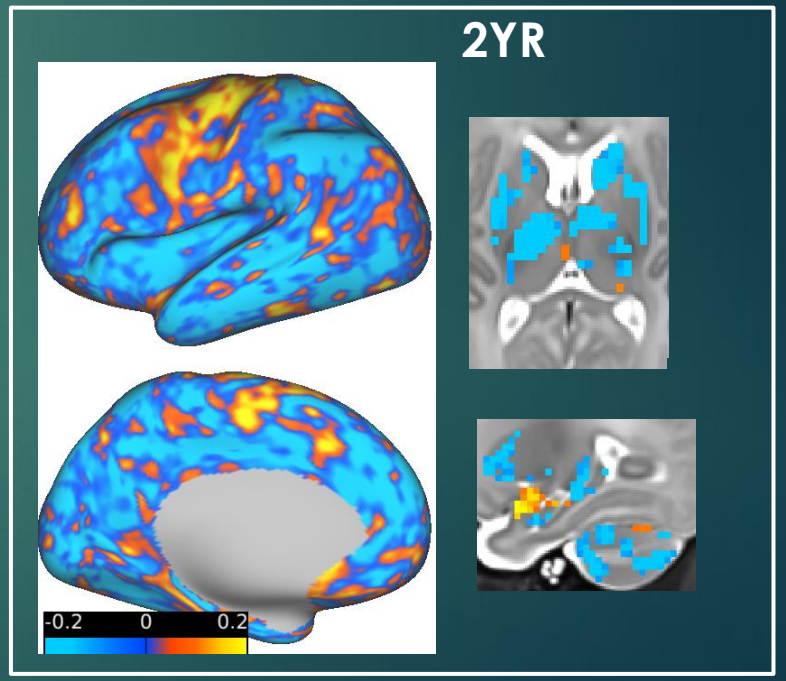
Impacts of Prenatal Social Disadvantage on ALFF at Birth & 2 YRs

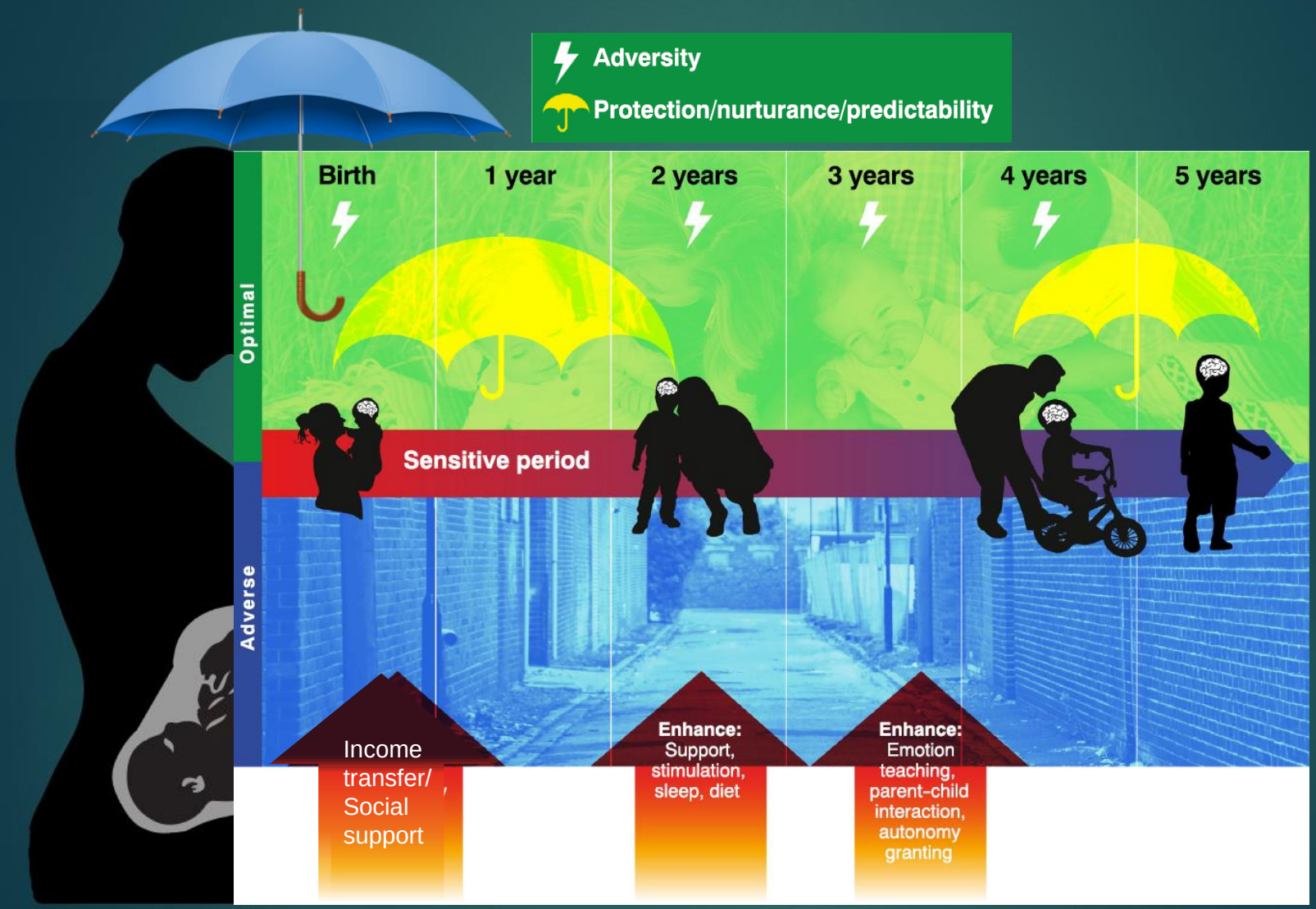
Ashley Nielsen, Ph.D

↑ Increased ALFF w/ Greater Social Disadvantage

↓ Decreased ALFF w/ Greater Social Disadvantage






Adversity
Protection/nurturance/predictability
Birth
1 year
2 years
3 years
4 years
5 years
Optimal
Adverse
Sensitive period
Income transfer/ Social support
Enhance: Support, stimulation, sleep, diet
Enhance: Emotion teaching, parent-child interaction, autonomy granting

Conclusions:

- Humans are born with inherent positivity and potential to thrive.
- The psychosocial environment can and should be used to support and facilitate those developmental skills.
- Developing children need key basic resources and protections from adversity to support this natural drive to thrive.
- Essential biological processes depend/vary based upon the presence or absence of basic resources to function adaptively
- Timing of these variables are key---based on sensitive periods.

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