Developmental Programming of Neurobehavioral Development by the Perinatal Environment

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Gaps in Knowledge

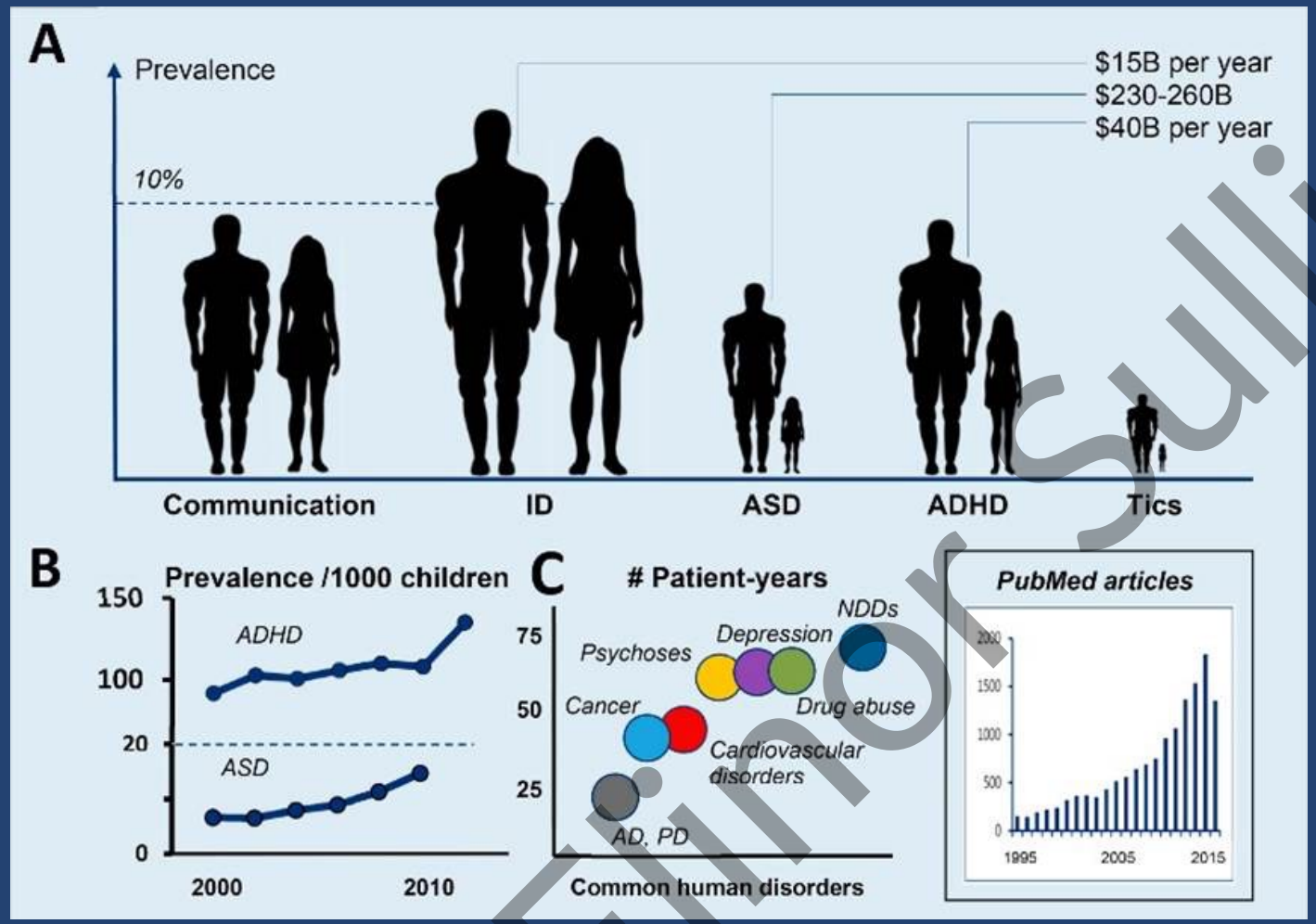
- Which prenatal factors are protective versus risk factors for child neurobehavioral development?
- The identification of critical periods to target prevention and intervention strategies.
- The interaction between prenatal and post-natal risk and protective factors.
- What mechanisms underlie the association between early environmental factors and child outcomes?

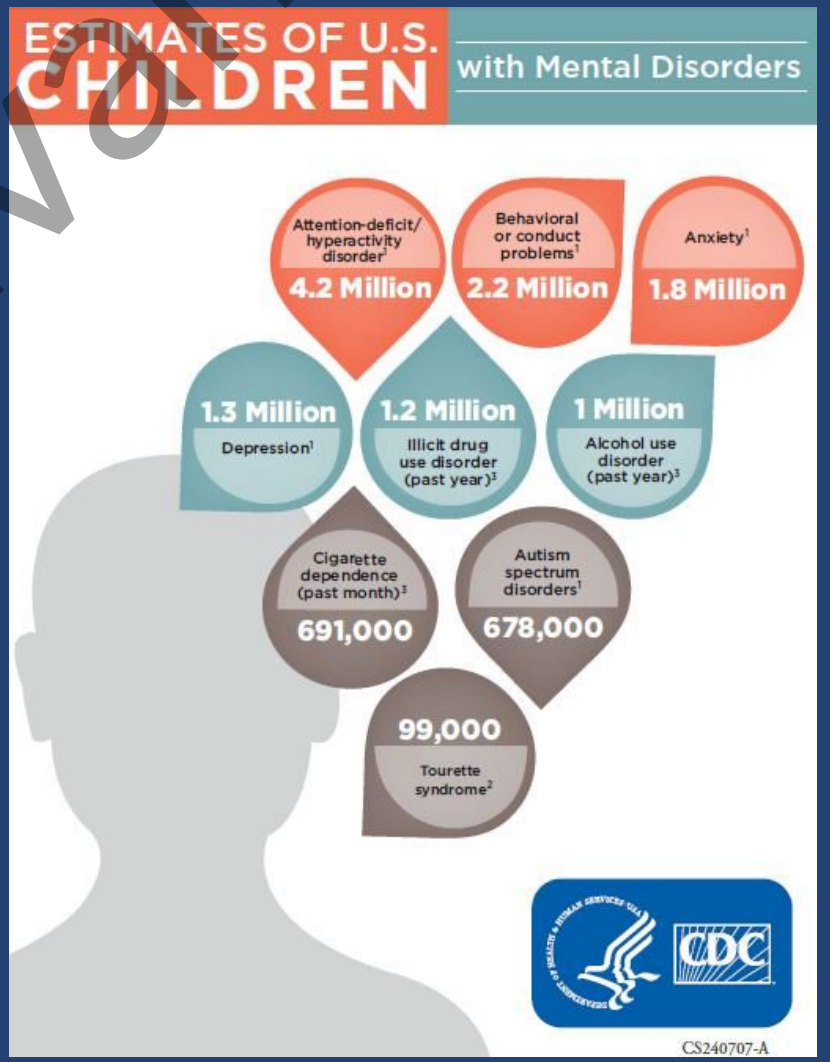
Outline

1. Childhood Mental Health Disorders are Highly Prevalent
2. The Influence of Prenatal Nutrition and Metabolic State During Pregnancy on Offspring Neurobehavioral Development
    1. NHP Data
    2. Validation in human cohorts

1. CHILDHOOD MENTAL HEALTH DISORDERS ARE HIGHLY PREVALENT

Prevalence of Neuropsychiatric Disorders



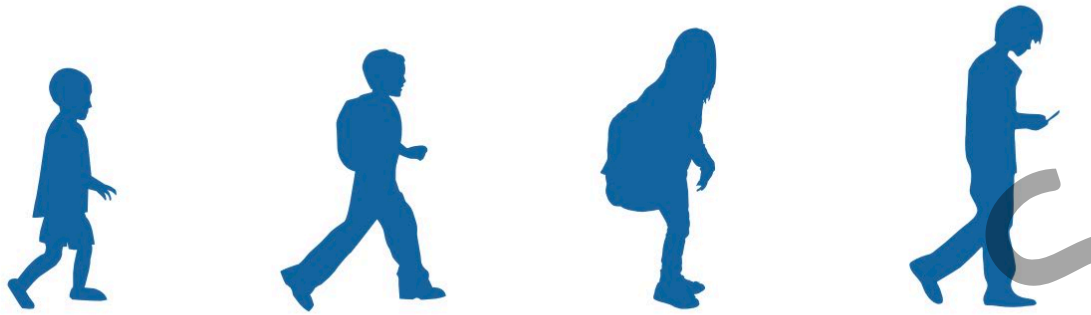


J.R. Homberg et al. / Neuroscience and Biobehavioral Reviews 65 (2016) 292–312

ASD—autism spectrum disorder, ID—intellectual disabilities, ADHD—attention deficit hyperactivity disorder

Early Onset of Mental Health Disorders

Age of onset of types of disorders in children

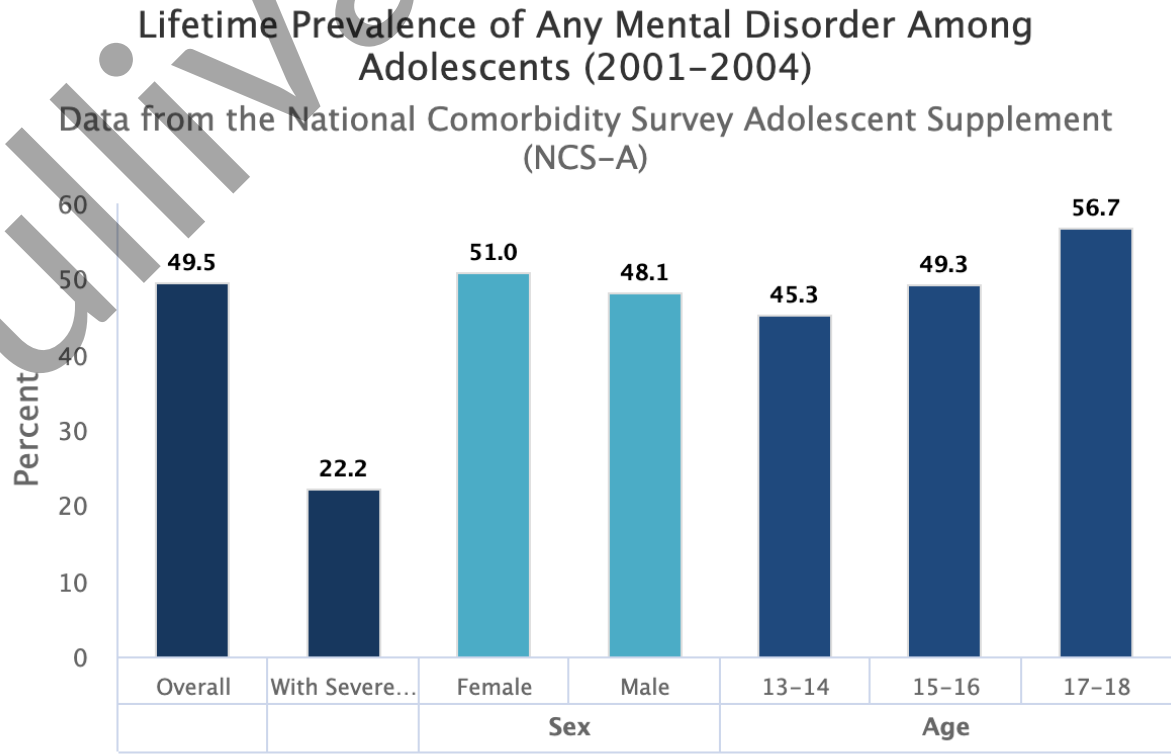


Age 6
median age of onset
Anxiety Disorders

Age 11
median age of onset
ADHD and Behavior Disorders

Age 13
median age of onset
Mood Disorders

Age 15
median age of onset
Substance Use



Merikangas et al. Lifetime prevalence of mental disorders in U.S. adolescents: results from the National Comorbidity Survey Replication--Adolescent Supplement (NCS-A). *J Am Acad Child Adolesc Psychiatry.* 2010 Oct;49(10):980-9.

How Do Prenatal Factors Influence the Developing Child?

Alterations to In Utero Environment

Placental Function & Fetal Brain Development

Lasting Effects on Child Brain & Behavior

2. THE INFLUENCE OF PRENATAL NUTRITION AND METABOLIC STATE DURING PREGNANCY ON OFFSPRING NEUROBEHAVIORAL DEVELOPMENT

Maternal Metabolic State Influences Risk for Child Mental Health Disorders

Child outcome	Maternal factor	References	Study design
↑ ADHD symptomology/Risk	↑ Pre-pregnancy BMI	Rodriguez et al., 2008	Cohort
		Rodriguez, 2010	Cohort
		Chen et al., 2014	Cohort
		Buss et al., 2012	Cohort
	↑ GWG	Rodriguez et al., 2008	Cohort
	Gestational diabetes & SES	Nomura et al., 2012	Cohort
		Schmitt and Romanos, 2012	Survey; Cohort
	↓ Dietary intake of omega-3 fatty acids	Field, 2014	Case-control
↑ ASD risk/Severity of symptoms	↑ Pre-pregnancy BMI	Krakowiak et al., 2012	Case-control
		Reynolds et al., 2014	Cohort
		Moss and Chugani, 2014	Cohort
		Dodds et al., 2011	Cohort
		Bilder et al., 2013	Case-control; Cohort
	↑ GWG	Dodds et al., 2011	Cohort
		Bilder et al., 2013	Case-control; Cohort
	Diabetes, hypertension, or pre-eclampsia	Krakowiak et al., 2012	Case-control
		Dodds et al., 2011	Cohort
		Lyall et al., 2012	Cohort
		Wallace et al., 2008	Cohort
↑ Anxiety/depression risk	↑ Pre-pregnancy BMI	Rodriguez, 2010	Cohort
		Van Lieshout et al., 2013	Cohort
		Colman et al., 2012	Cohort
↑ Schizophrenia risk	↑ Pre-pregnancy BMI	Jones et al., 1998	Cohort
		Schaefer et al., 2000	Cohort
	↑ GWG	Kawai et al., 2004	Case-control
	Pre-eclampsia/hypertension and diuretic treatment	Dalman et al., 1999	Cohort
		Eide et al., 2013	Cohort
		Sorensen et al., 2003	Cohort

Rivera et al., 2015

Best Current Methods to Address Identified Gaps

- Design animal models and human studies to be complementary in order to facilitate translation from bench to bedside.
- Use of methods that can be used across model systems
  - MRI (structural, functional)
  - Behavioral assessments
- Rigorous analysis of biological markers that can be collected noninvasively in humans.

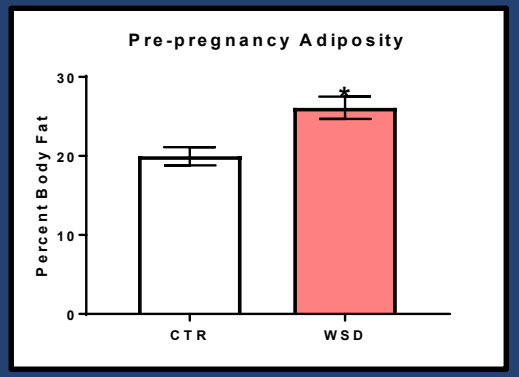
Nonhuman Primate Model:

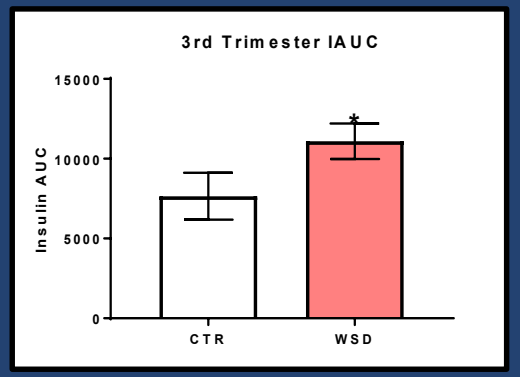
How does Maternal Obesity & Western-Style Diet Impact Mental Health Related Behaviors?

Non-human Primate (NHP) Model

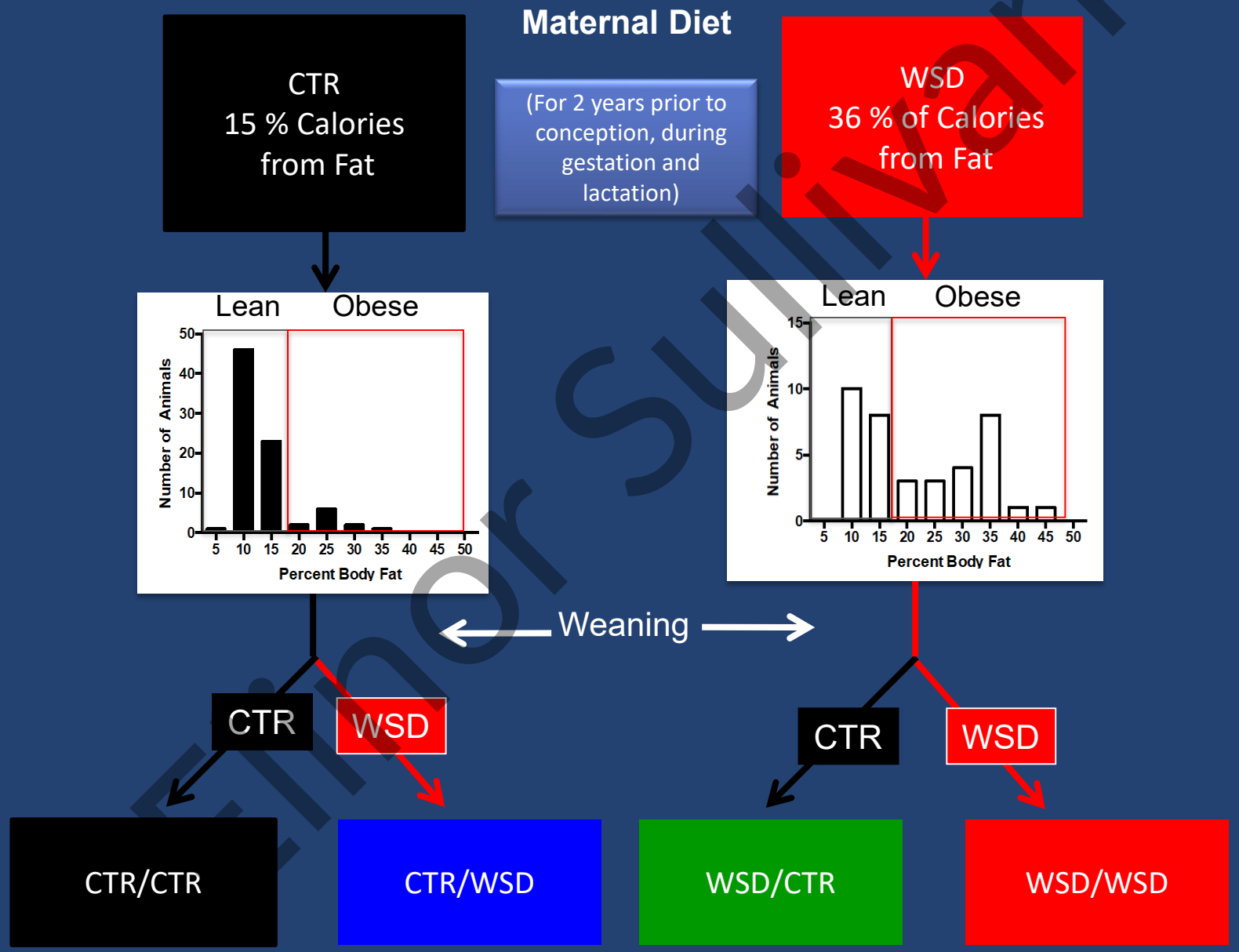
- Control (CTR) vs high-fat, Western- style diet (WSD)
- Adult breeding groups
  - Japanese macaques
- Maternal metabolic state
  - Non-pregnant and third trimester
  - Adiposity
  - Glucose metabolism and insulin response

	CTR	WSD
Protein	**20.6**	**17.0**
Fat	**5.0**	**15.0**
Saturated	0.89	5.42
Monounsaturated	1.1	6.2
Polyunsaturated	3.3	2.8
Carbohydrates	**44.8**	**41.5**
Fructose/Sucrose	3.0	14.3
Lactose	0.0	4.6
Glucose	0.02	0.04
Starch	26.0	20.5

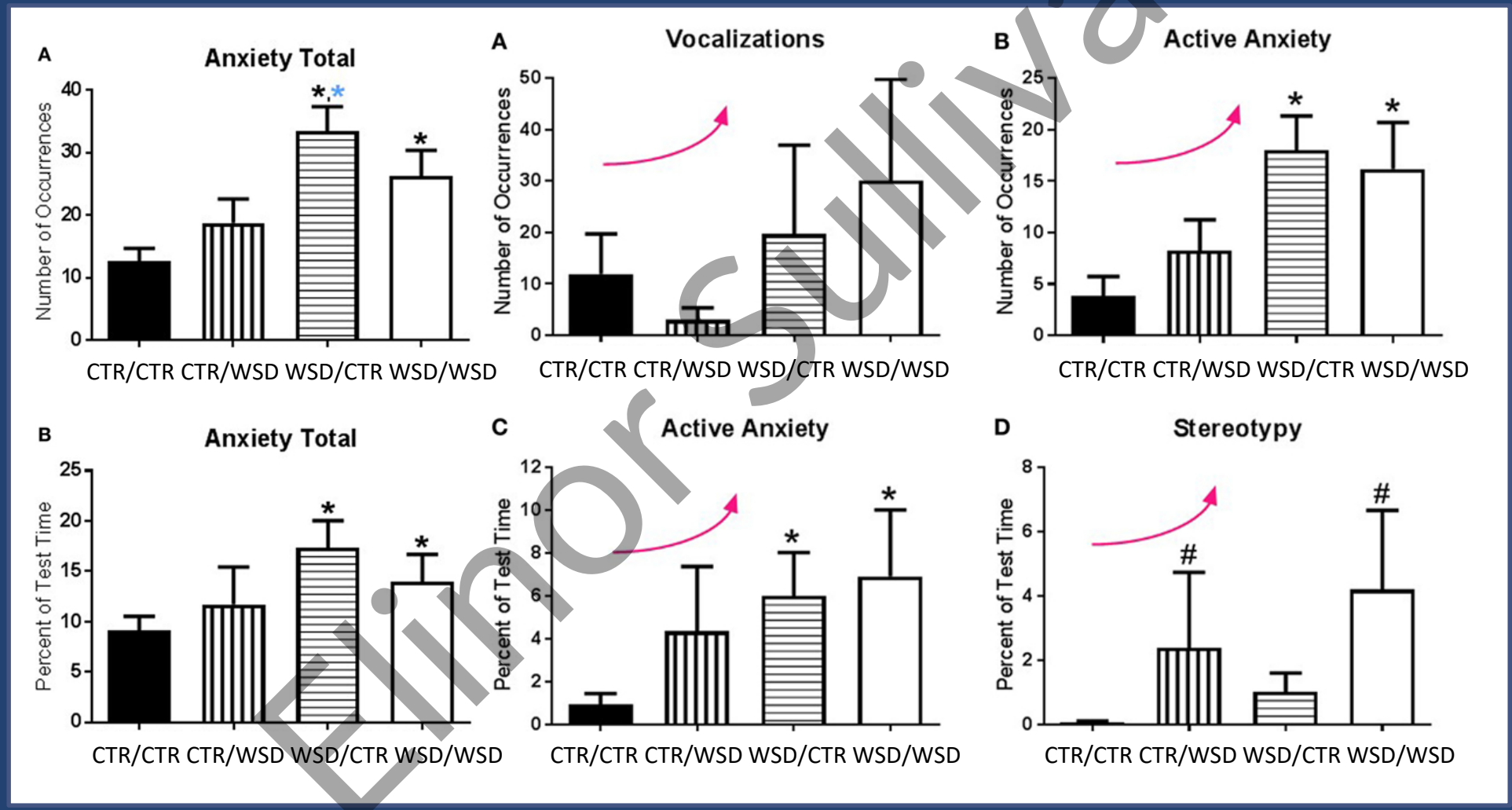




Experimental Groups

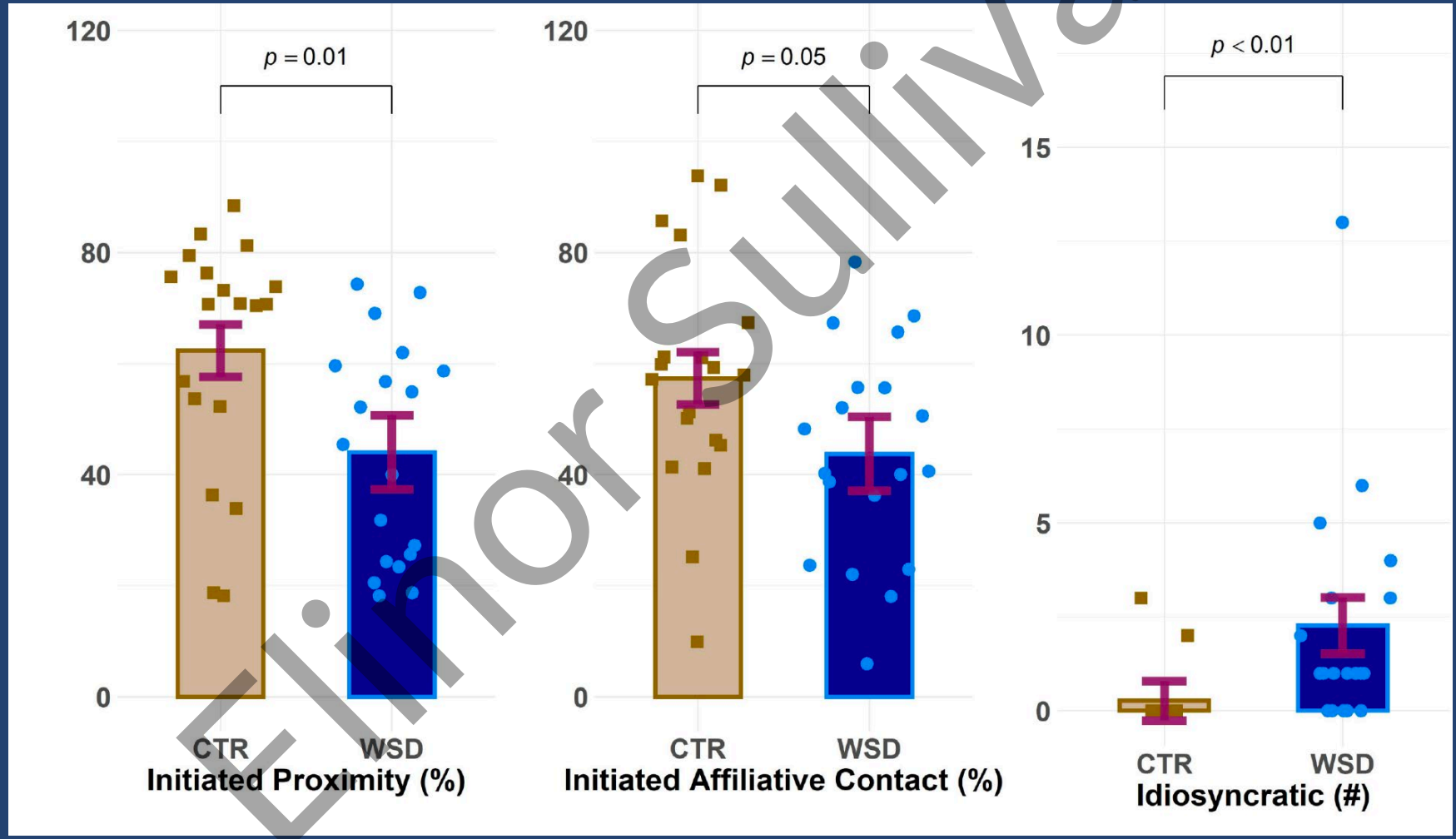


Maternal WSD Exposure Increased Offspring Anxiety (11 mo of age)



Thompson et al. 2017

WSD Juveniles Display Impaired Social Contact in Novel Peer Introduction

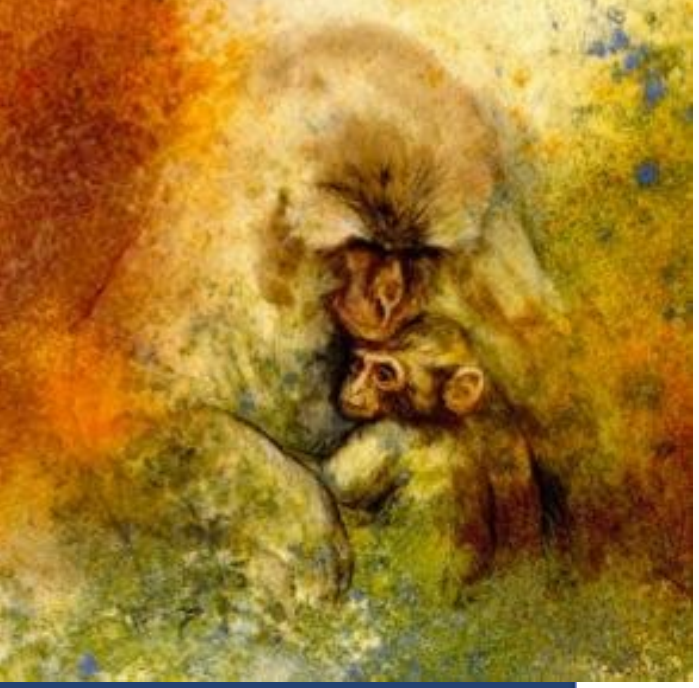


Mitchell et al. 2022

Summary: Offspring From WSD Mothers Are At Increased Risk For Developing Behavioral Disorders

WSD Offspring display:

- Increased anxiety
- Increased repetitive/idiosyncratic behaviors
- Social withdrawal and impairments in social behavior

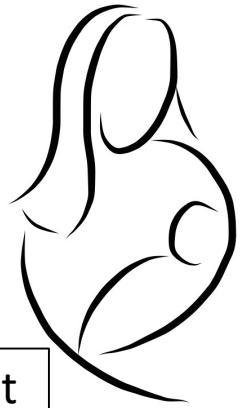


Maternal Diet (Western-Style Diet)
Maternal Metabolic State (Obesity, Metabolic Disease)
Maternal Mental Health (Anxiety, Depression, Stress)

Intrauterine Development ↔ Early Post-natal Development

Placental Dysfunction

Inflammation
Sex Hormones
Metabolic Hormones
Nutrients

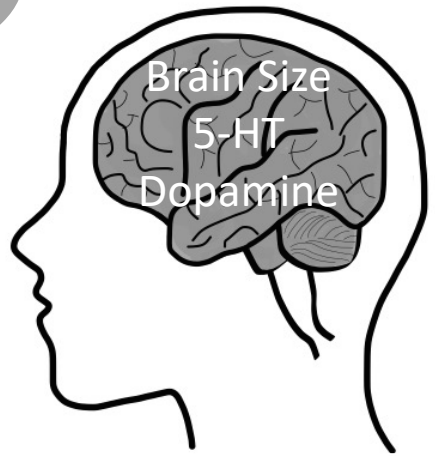


Alterations in Maternal Behavior

↓

Impaired Brain Development

↑ Cortisol



↑ Anxiety (females)
↑ Aggression (males)
↑ Repetitive/Idiosyncratic Behavior
Impaired Social Behavior

↑ Obesity Risk

↑ Risk of Mental Health & Neurodevelopmental Disorders

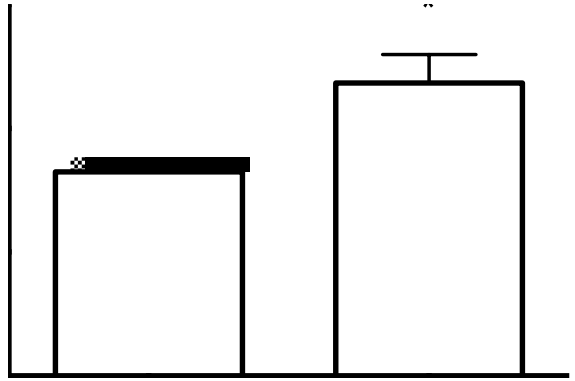
Adapted from Rivera HM, Christiansen KJ and Sullivan EL 2015, Front Neurosci. 2015 Jun 18;9:194

Prenatal Environment and Child Health (**PEACH**) Study

Impact of Maternal Diet and Obesity on Offspring risk for Neurodevelopmental Disorders

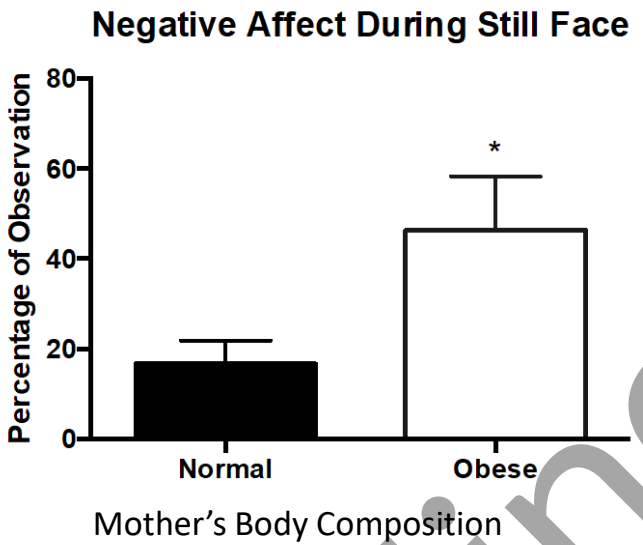
- PEACH Study -cohort of 310 women and children (from prenatal to 5 years of age)
- Study Goals:
  - Validate findings from NHP model.
  - Characterize changes in the *in-utero* environment associated with maternal obesity and poor nutrition.
- Investigate the mechanisms for maternal nutritional induced behavioral programming
  - ***Serotonin and Kynurenine Signaling Pathways***
  - Epigenetics
  - Microbiome
  - Neuroimaging
  - Mesenchymal stem cell isolation and stimulation studies
- Determine which factors are the strongest predictors of alterations in infant and toddler behavior associated with neuropsychiatric disorders.

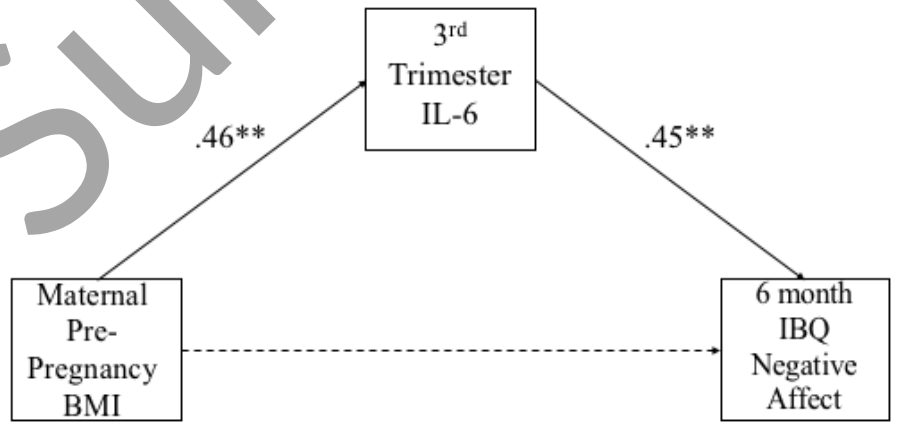
Obesity was Associated with Increased Inflammation During Pregnancy (Humans)



Gustafsson et al. 2019, Front Neurosci. 2019 Oct 1;13:1035

Maternal Pre-Pregnancy BMI and Inflammatory Profile Increase Infant's Negative Emotionality (6 months of Age)

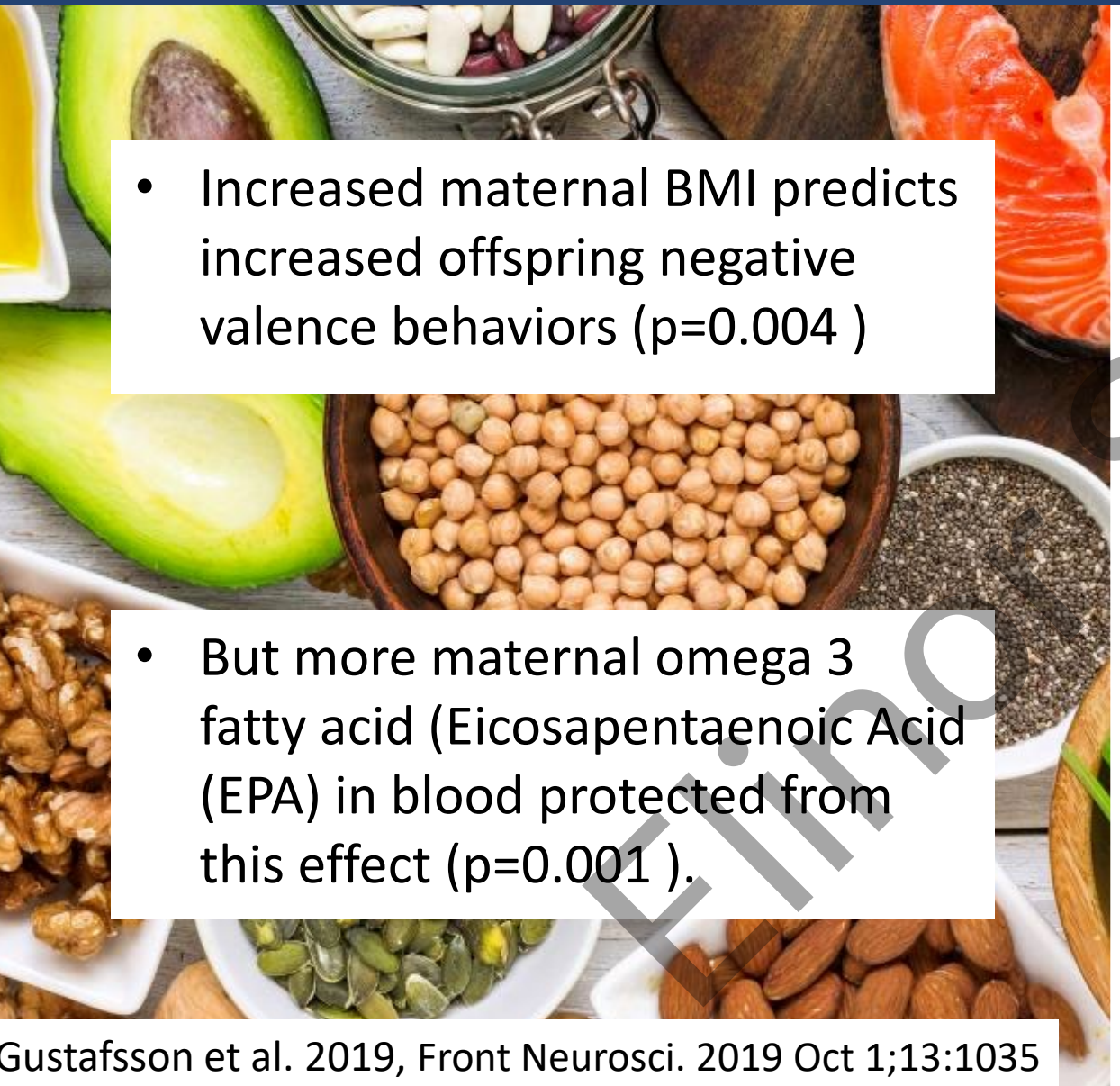




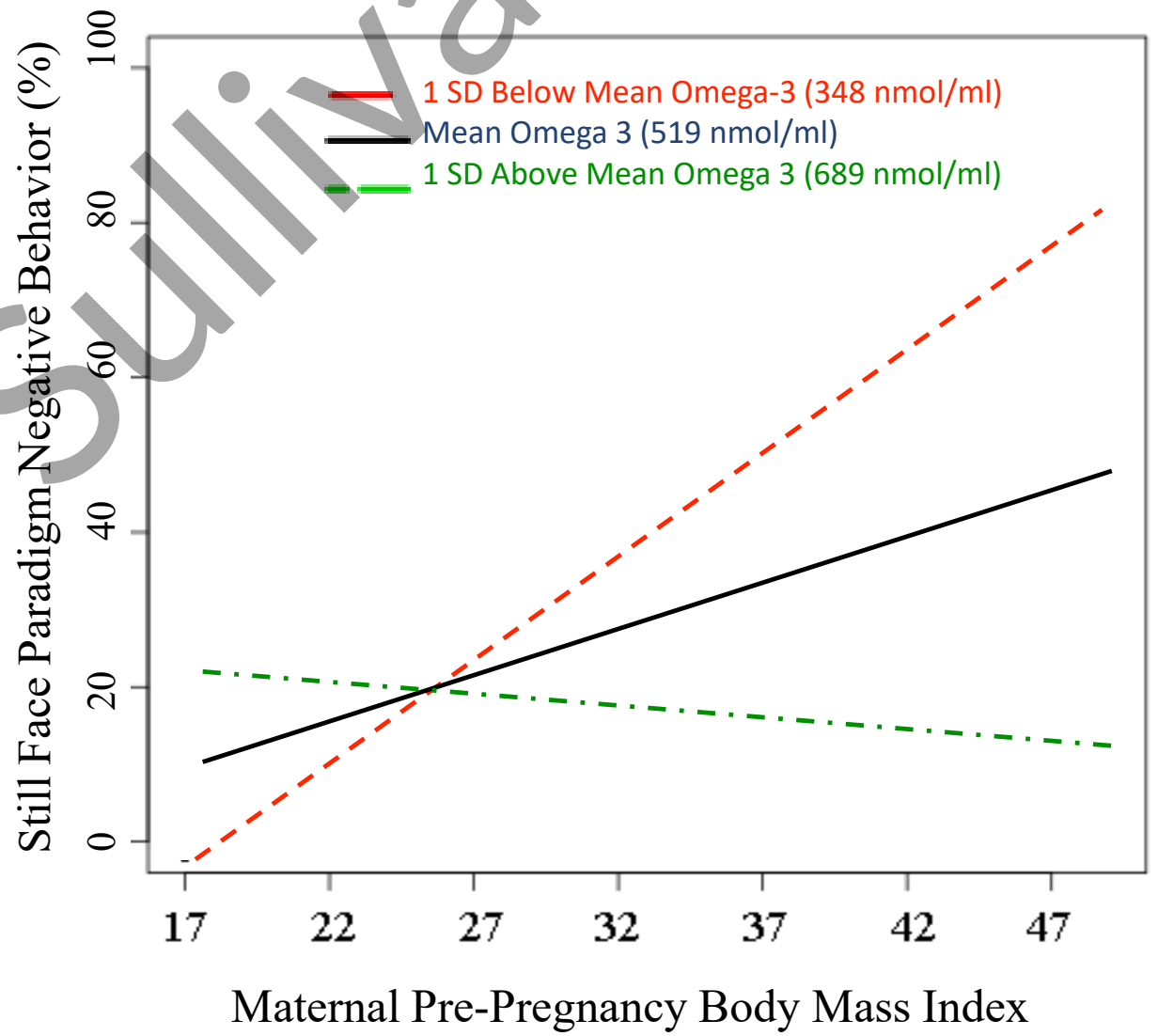
Note: χ^2 (1, N=68)=.09, p=.76, CFI=1.00, RMSEA=.00. Indirect effect β=.20, p = .01. *p< .05, **p< .01. Dashed line indicates a path that was estimated but was not statistically significant.

Gustafsson et al. 2019, Front Neurosci. 2019 Oct 1;13:1035

Maternal Pre-Pregnancy BMI and Fatty Acid Levels Influence Child Negative Affect

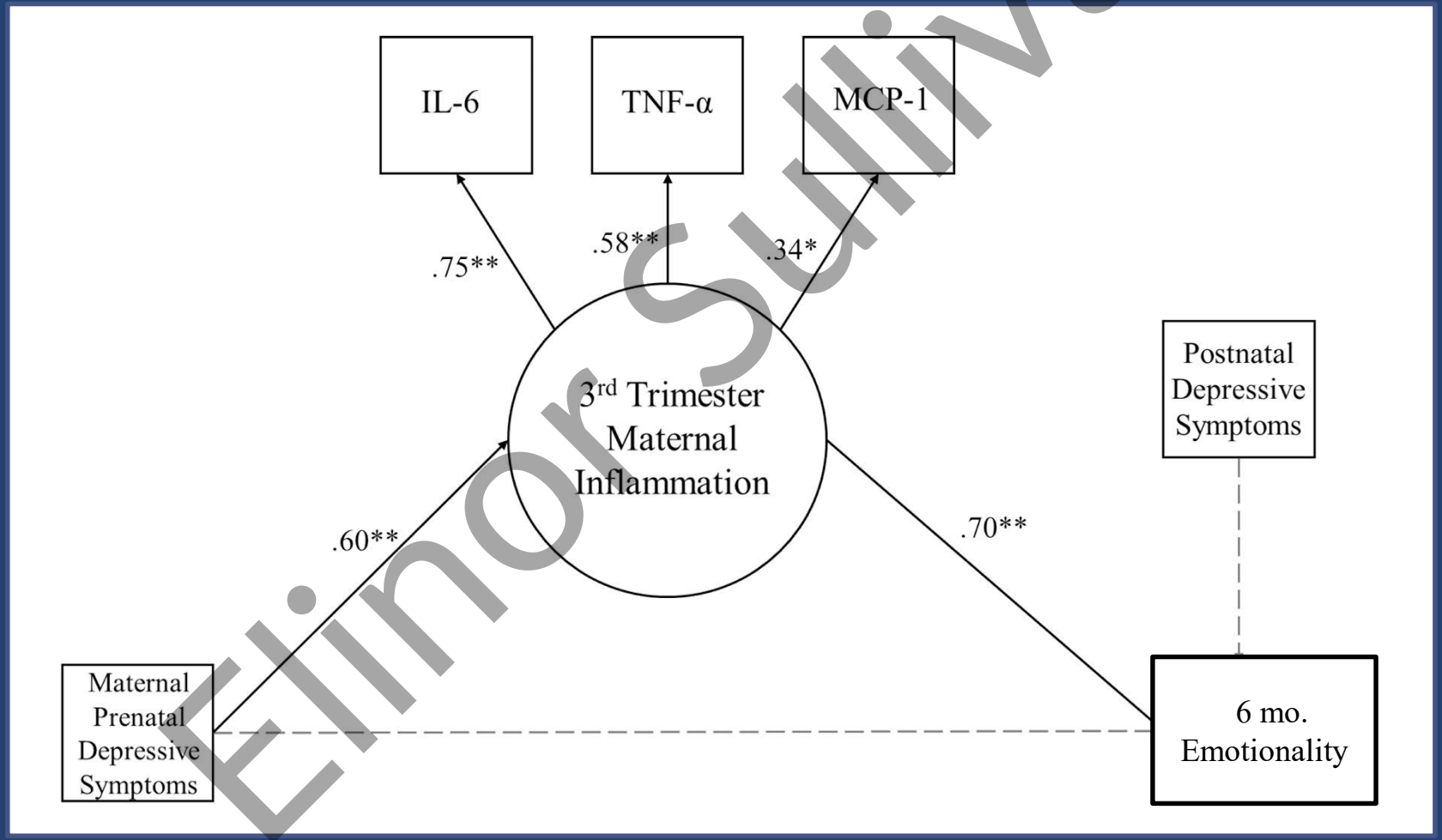


- Increased maternal BMI predicts increased offspring negative valence behaviors (p=0.004)
- But more maternal omega 3 fatty acid (Eicosapentaenoic Acid (EPA) in blood protected from this effect (p=0.001).



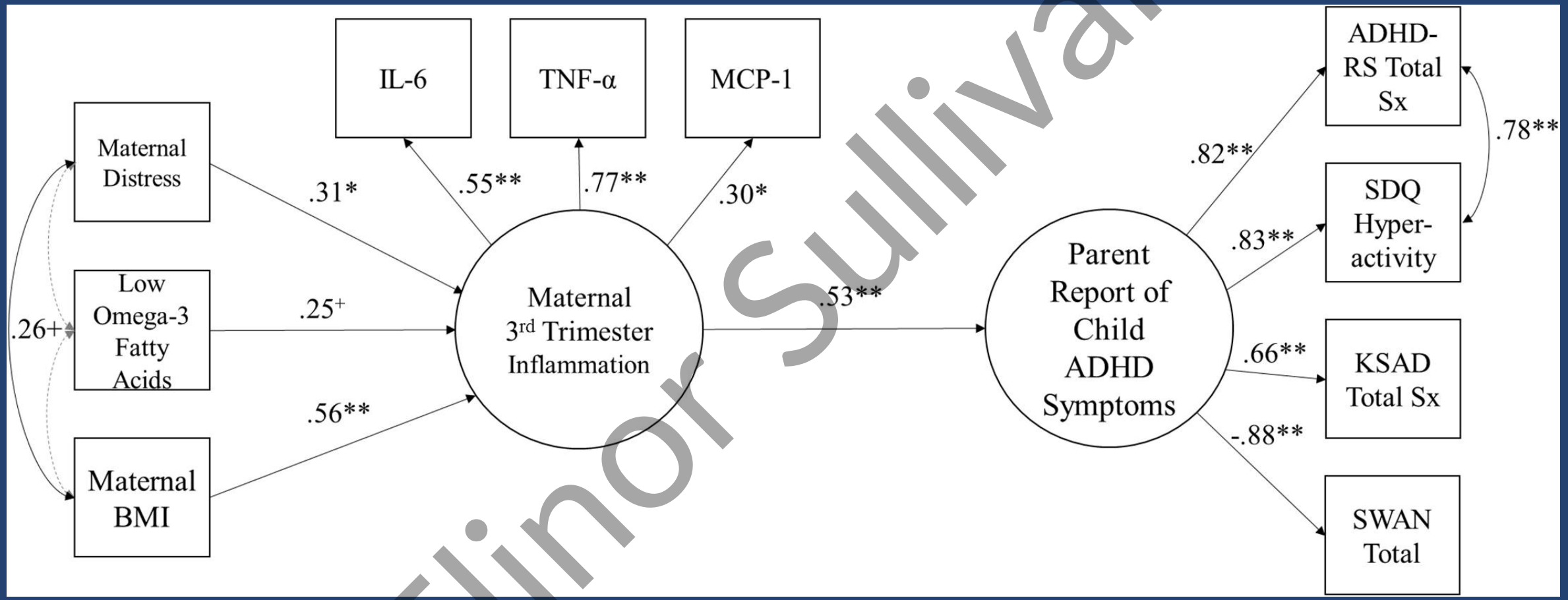
Gustafsson et al. 2019, Front Neurosci. 2019 Oct 1;13:1035

Maternal Depression Predicts Infant Sadness & Emotionality via Maternal **Inflammation**



Gustafsson et al. 2018, Brain Behavior Immunity 2018 Oct;73:470-481

Common Inflammatory Pathway to ADHD

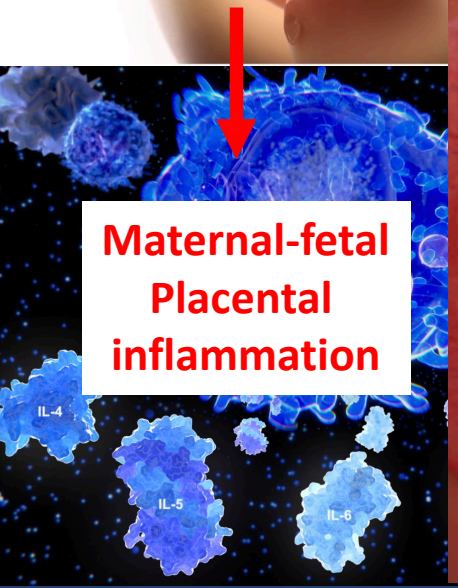


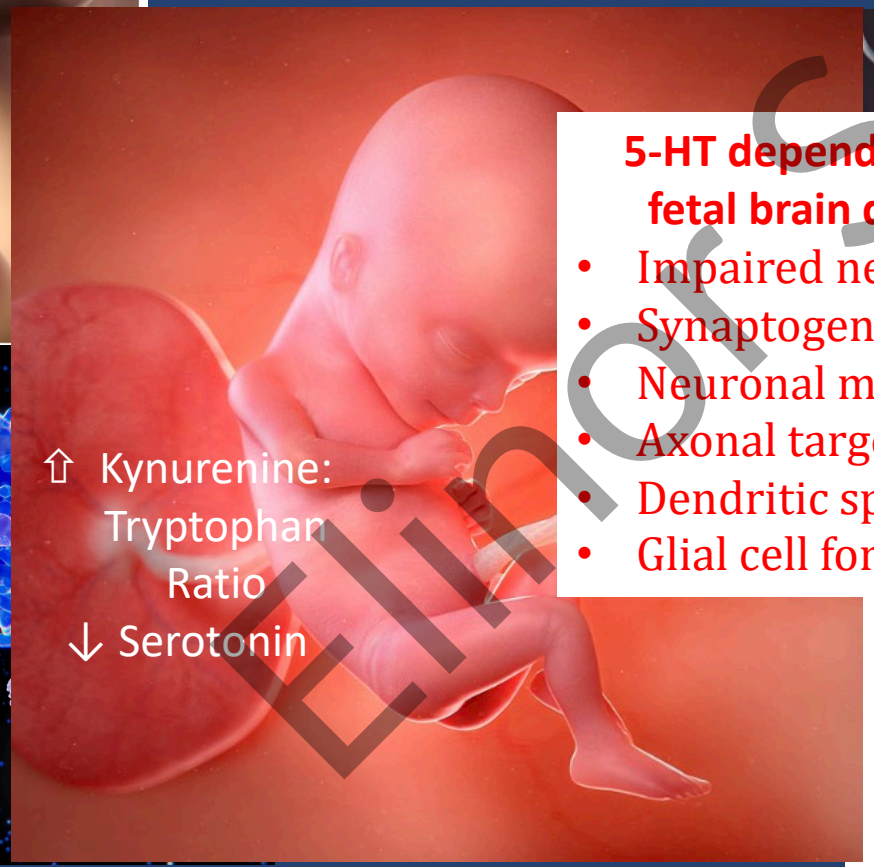
Gustafsson et al. 2020 Brain Behav Immun. 2020 Oct;89:350-356.

Best Current Methods to Address Identified Gaps

- Rigorous analysis of biological markers that can be collected noninvasively in humans.
  - Inflammation: Plasma cytokines, peripheral blood mononuclear (PBMC) isolation→ baseline and stimulated response.
  - Collection of delivery samples
    - **Cord blood**-assess fetus.
    - **Placenta**-assess placental inflammation, serotonin, kynurenine, isolate Hofbauer Cells *(cellular microglia-like models).*
    - **Umbilical cord--**isolate and expand mesenchymal stem cells (can be differentiated into adipocytes, osteoblasts, chondrocytes, and possibly into hepatocytes, cardiomyocytes, skeletal myocytes and neurons.

Obesity-Induced Inflammation Alters Serotonin-Kynurenine Pathways and Child Neurobehavioral Development

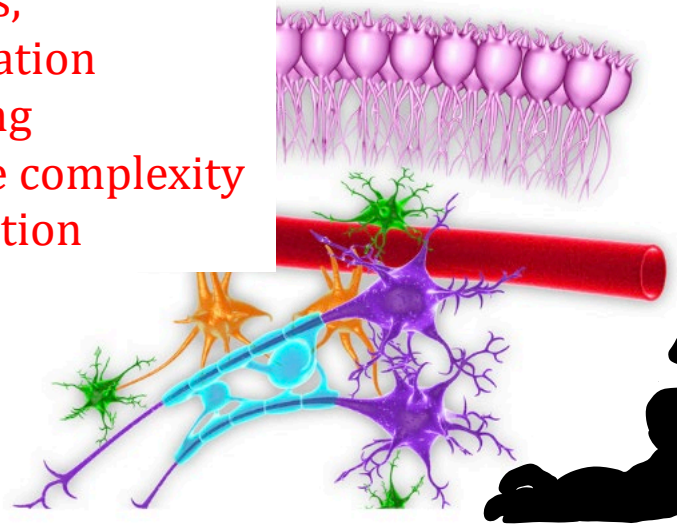




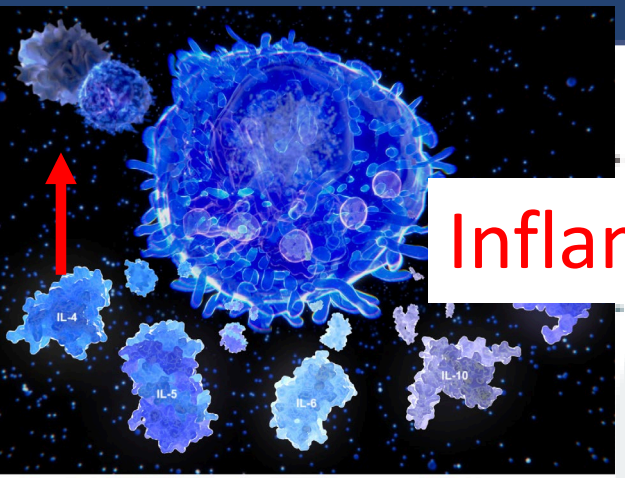
5-HT dependent effects on fetal brain development

- Impaired neurogenesis
- Synaptogenesis,
- Neuronal migration
- Axonal targeting
- Dendritic spine complexity
- Glial cell formation

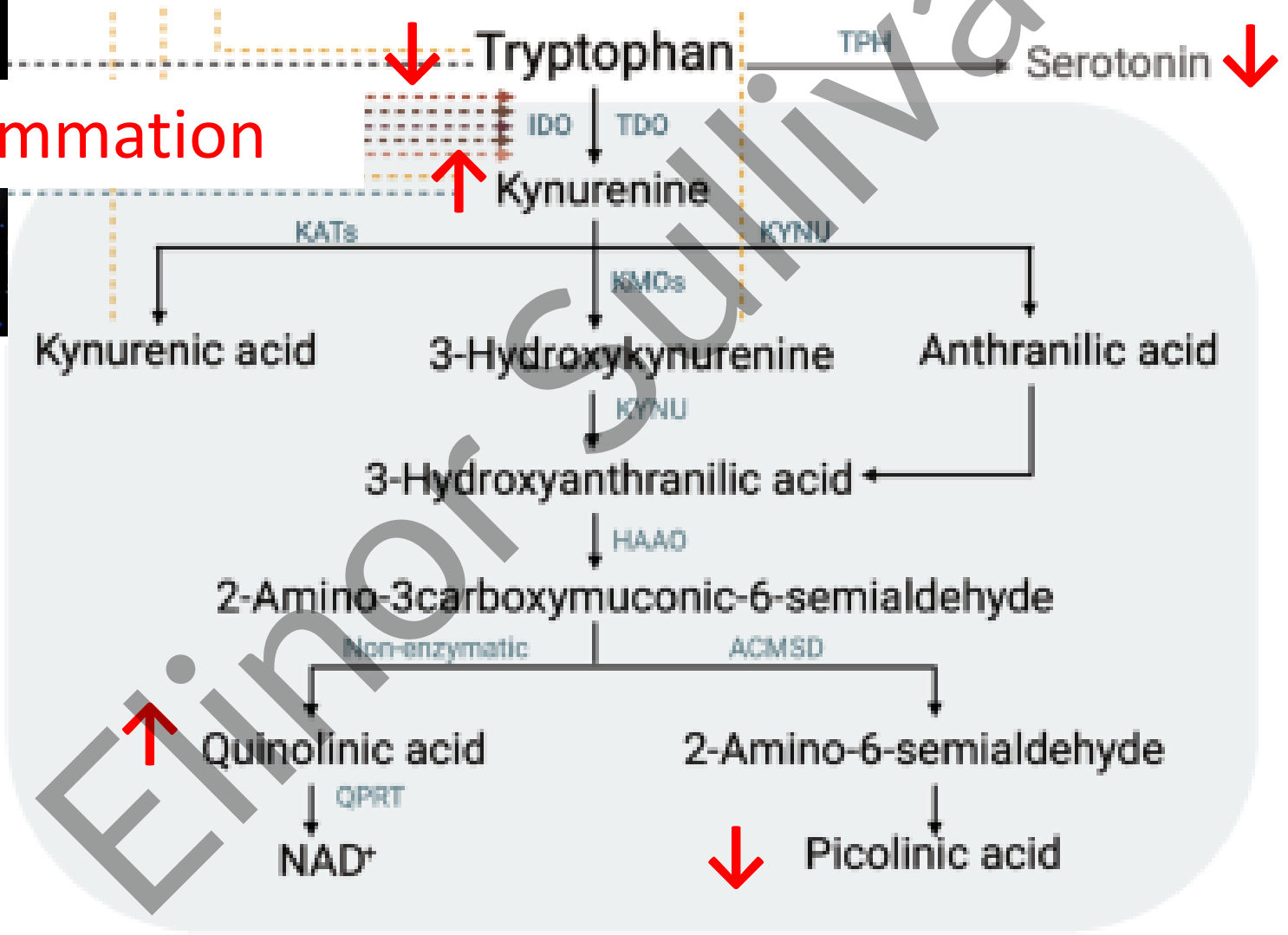
- Altered Brain Function
- Increased risk of neurodevelopmental disorders



Obesity-Induced Inflammation Alters Serotonin-Kynurenine Pathways

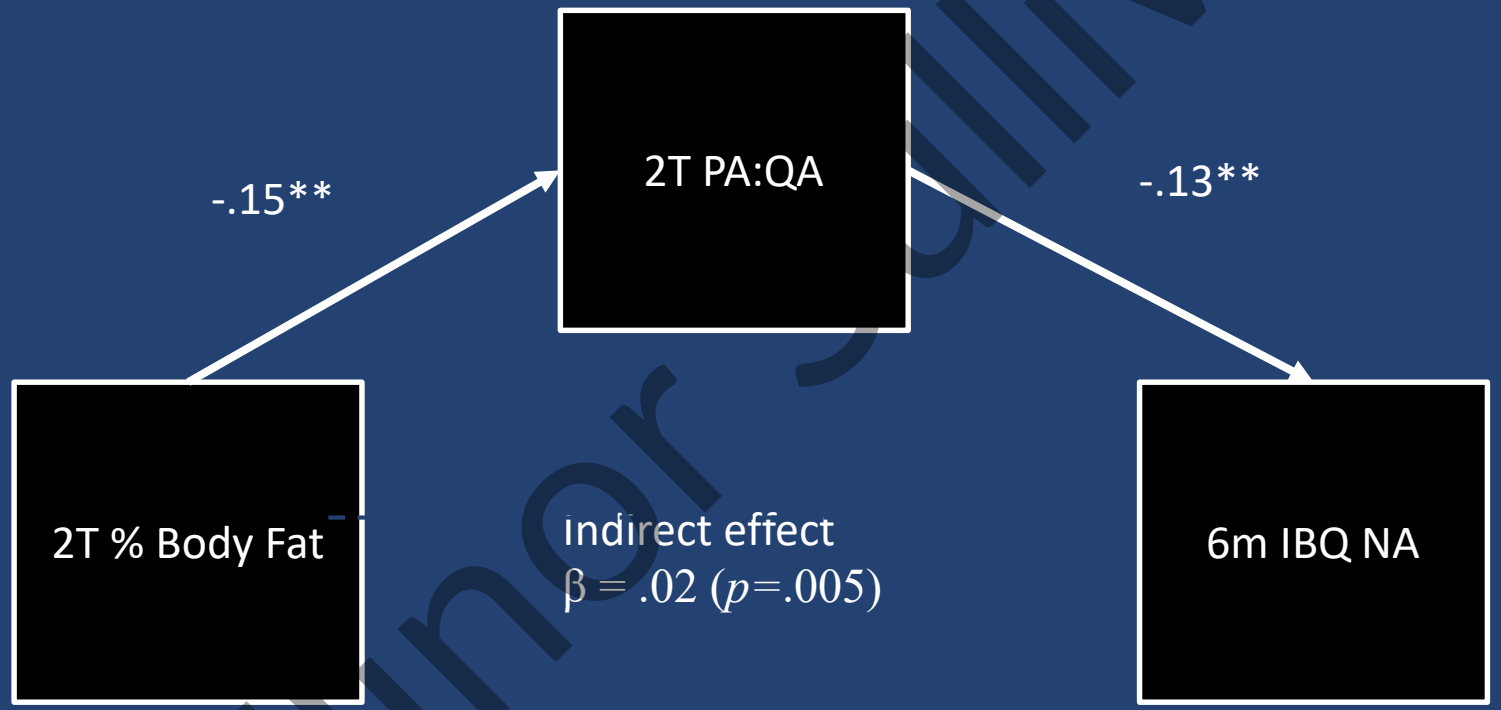


Inflammation



Adapted from Sha et al. 2022, *Transl Psychiatry* **12,** 35 (2022)

Picolinic Acid to Quinolinic Acid Ratio Mediates the Relationship Between Maternal Adiposity and Infant Negative Affect



N=224

- Controlled for child age at assessment and maternal depression (CESD) at 2T and 6 M
- See same pattern for infant sadness and distress to limitations

Summary

- Increased negative affect in infancy is associated with ADHD symptoms in childhood.
- Maternal obesity, distress and poor nutrition linked with ADHD symptoms in childhood.
- Inflammation as common pathway mediating association between prenatal factor and ADHD risk.
- Identified increased maternal omega-3 fatty acids as protective factors.
- Maternal obesity alters kynurenine metabolites which mediate relationship between maternal adiposity and infant negative emotionality.

Future Directions

- Discover the mechanisms by which prenatal environmental factors have a long-term influence on child behavior and risk for mental health disorders
- Identify and validate clinical biomarkers of risk for neurodevelopmental disorders
- Develop interventions:
  - Dietary intervention (reduction in saturated fat content, alterations in fat composition)
  - Omega 3 fatty acids (fish oil)
  - Anti-oxidant treatment (resveratrol)
  - Supplementation with critical amino acids (tryptophan)
- Define effective prevention strategies

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Learn more about the PEACH study here! →

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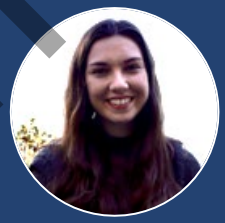

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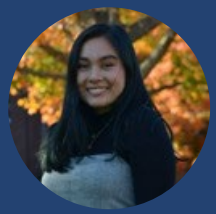

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