

Children's mental health and the life course model: Identifying sensitive periods in development

Erin C. Dunn, ScD, MPH

Assistant Professor

Massachusetts General Hospital
Harvard Medical School

edunn2@mgh.harvard.edu

www.thedunnlab.com

 @ErinDunnScD

 @TheDunnLab

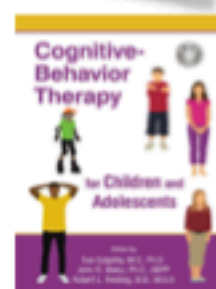


How a focus on when can help optimize prevention efforts for child mental health

Who



What



When



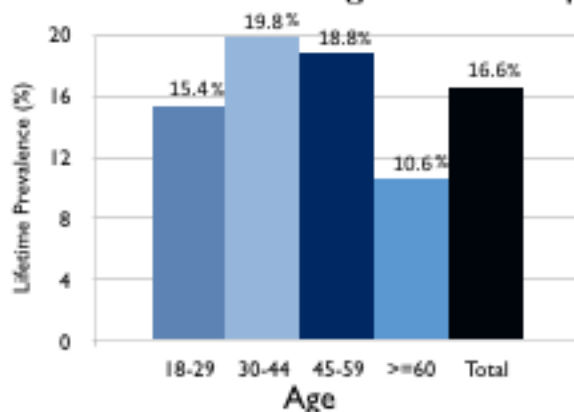
Where



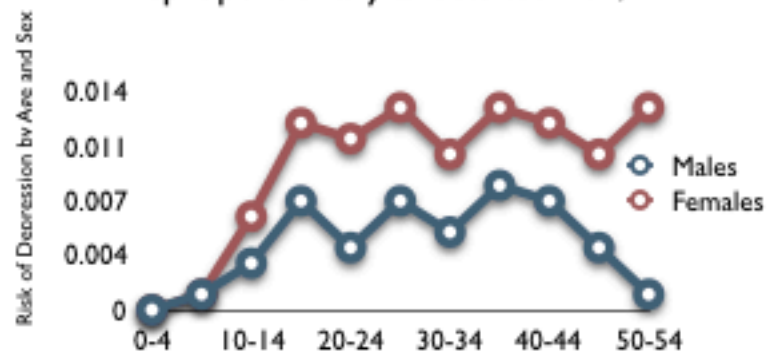
How

Depression: a major public health issue

It is common throughout the lifespan,



disproportionally affects women,



is associated with many consequences,



and is the leading cause of disability worldwide.



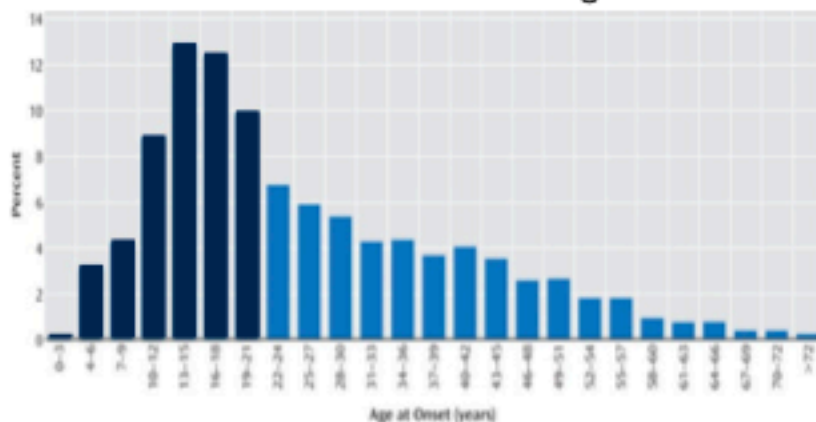
Kessler RC, et al. (2005). *Archives of General Psychiatry*.

Kessler RC & Bromet E (2013). *Annual Review of Public Health*. 3

Preventing depression is key

...because it strikes when people are young and once it emerges, it is highly recurrent.

20-40% of people with major depressive disorder had their first onset before age 18.



3/4 of people with depression will experience a relapse at some point in their lives.



Conclusion: We need to better understand the etiology of depression in order to prevent its occurrence as early on in the lifespan as possible.

The focus of my research laboratory

Identify people at highest risk for depression using genetic and other markers of vulnerability



Who

Understand how stress gets “under the skin”



How

Identify stages in the lifespan when experience, including stress, differentially matters



When

Exposure to childhood adversity is a major social determinant of depression



Divorce/marital discord



Poverty



Accidents/Injury



Natural disasters



Death of a loved one



Abuse/neglect



Witnessing violence



Parent psychopathology/
substance use



Illness



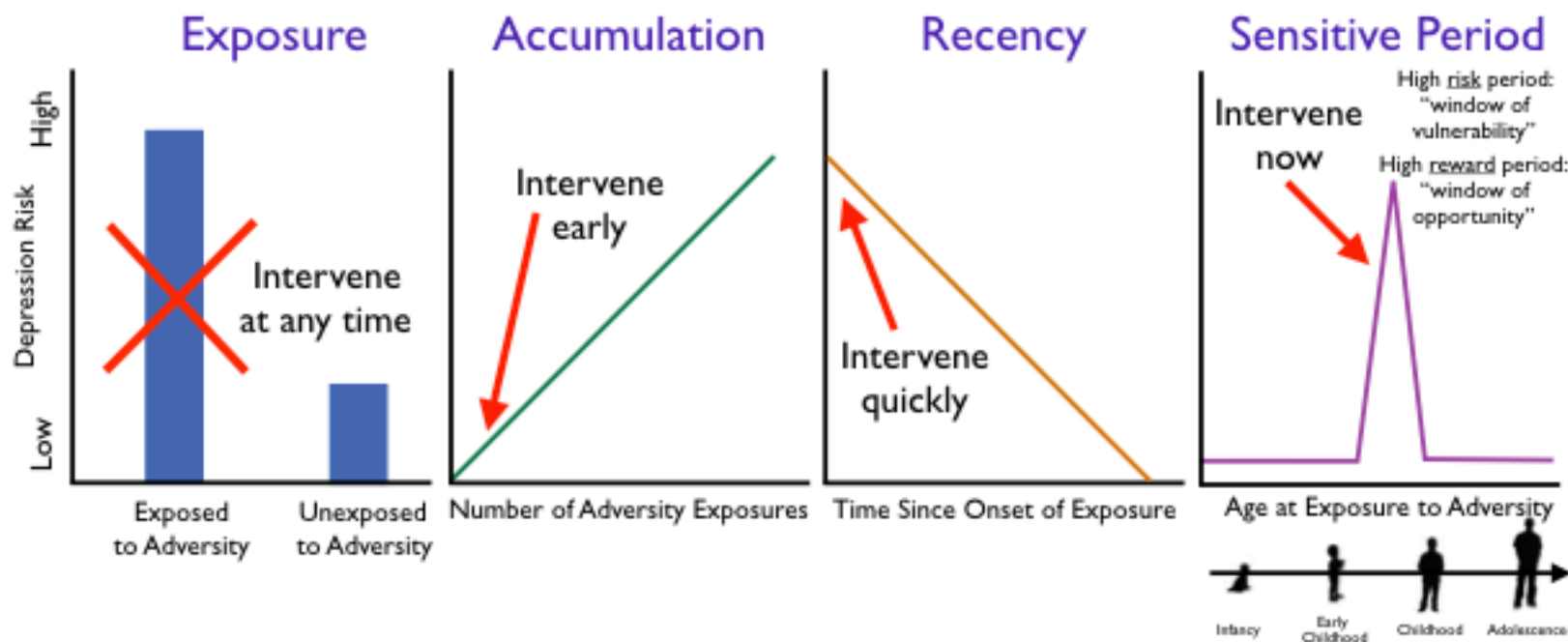
Household
Incarceration

Do all these terms mean the same thing?

Concept	Definition
Stress	• Feeling experienced when the demands of our lives exceed our personal and social responses to mobilize
Stressor	• External stimuli (positive or negative life event)
Trauma	• Shocking and emotionally overwhelming situation that involves actual or perceived death, serious injury, or threat to physical integrity • Serious adversity or terror
Toxic Stress	• Response to stress (excess activation of stress response system) • Explains how stress gets under the skin • Occurs following exposure to extreme, long-lasting, and severe stressors without adequate support from a caregiving adult
Childhood adversity	• Circumstances or events that threaten child's physical or psychological well-being • Deviation from expected life experiences for our species
ACEs (adverse childhood experiences)	• Term coined by Felitti, Anda, et al • Captures 10 childhood adversities

How might childhood adversity increase subsequent risk for depression?

Implications for Intervention



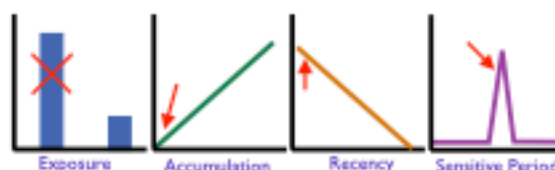
My goal: Generate research evidence that will enable scientists to make more precise recommendations about when to intervene, on a high-resolution time scale.

Unanswered questions that we are tackling in my research group

Exactly when are the developmental periods of greatest vulnerability to depression following exposure to stress and adversity?



What matters more: just being exposed, the accumulation of exposure, the recency of exposure, or its developmental timing?



How exactly does exposure to stress and adversity during sensitive periods “get under the skin” to increase risk for depression?



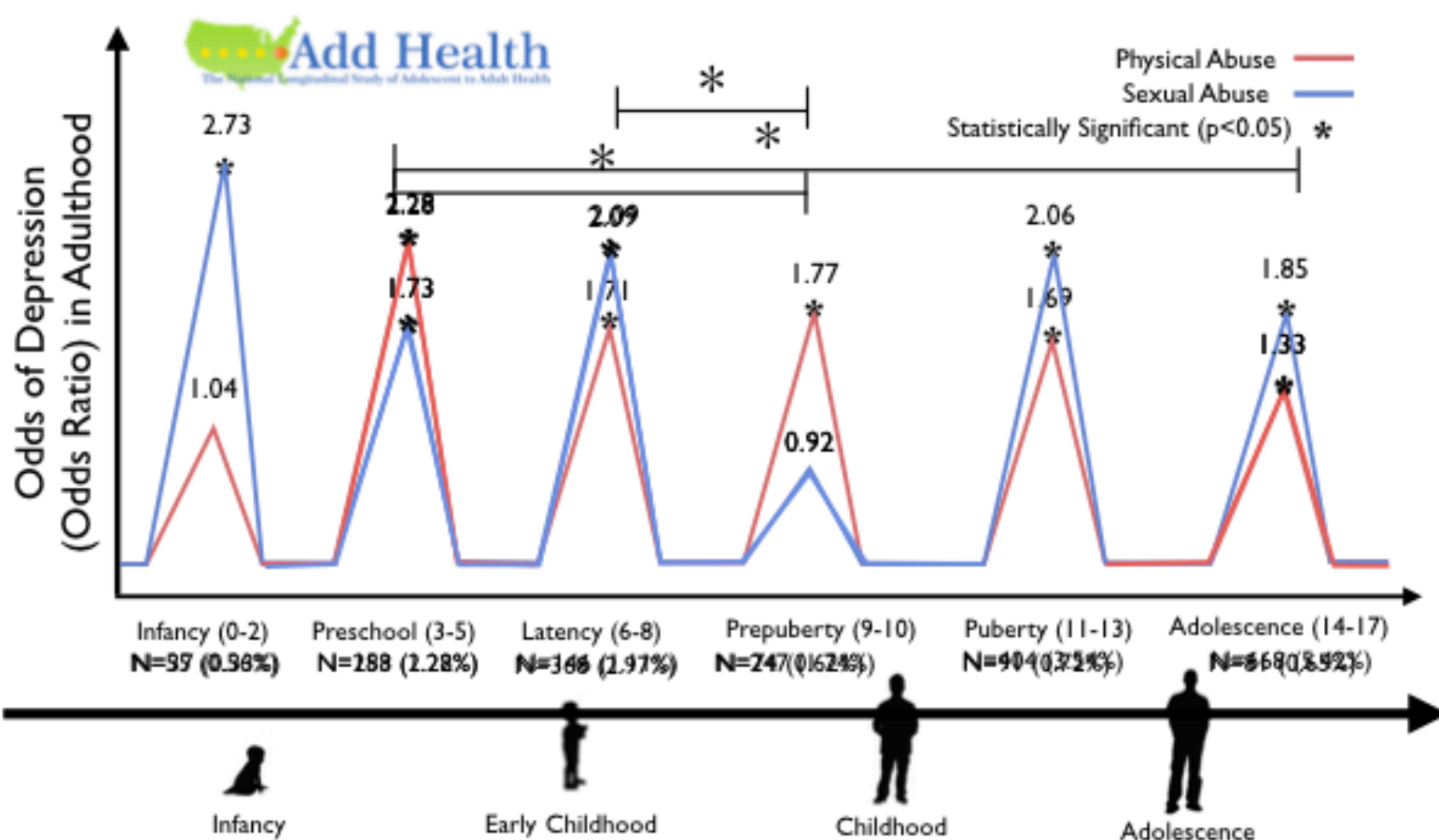
Do genes regulate when sensitive periods occur? If so, what genes are involved? And do these genes play a role in shaping risk for depression?



Answers to these questions are critical to:

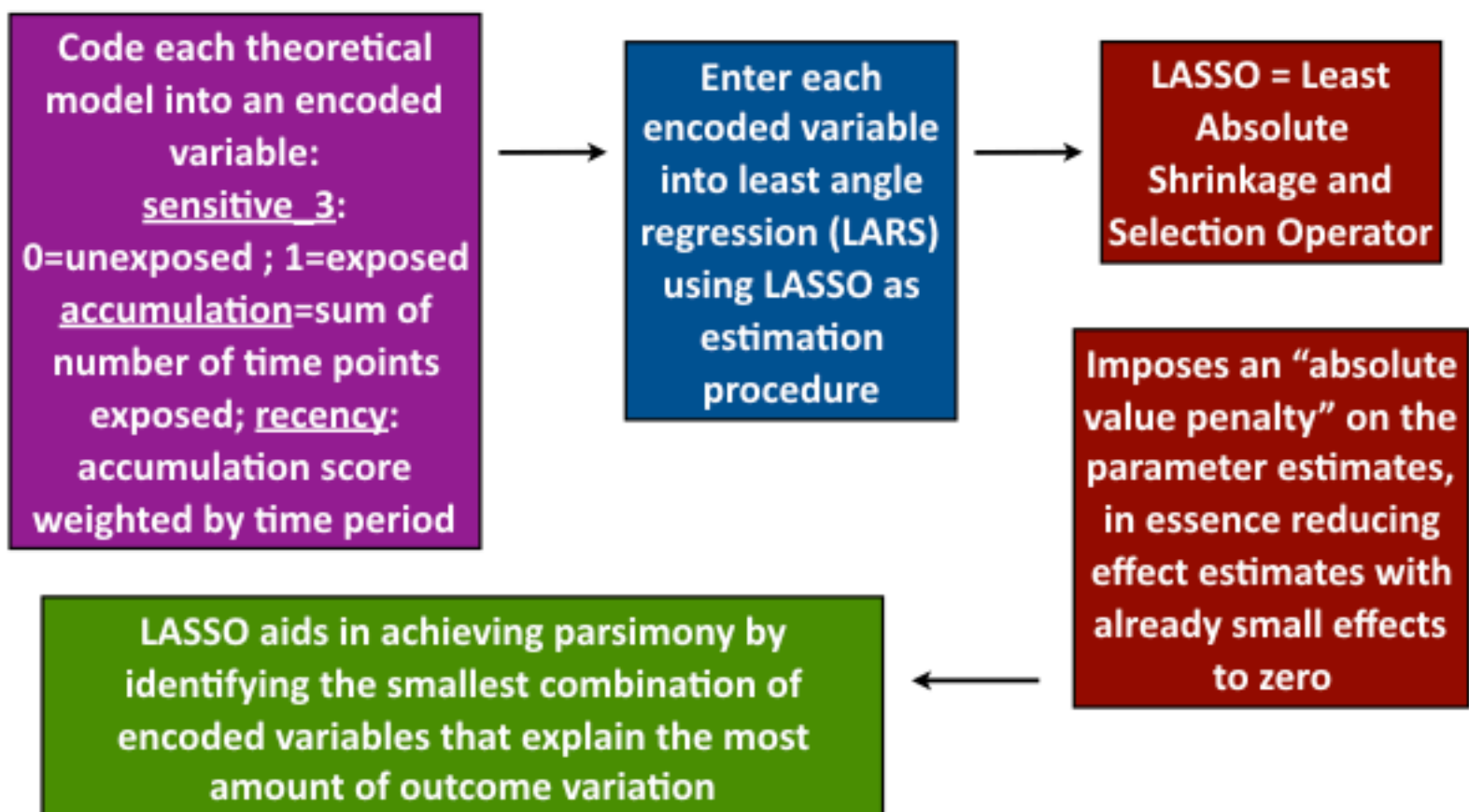
- Understand the mechanisms underlying risk for depression
- Develop targeted interventions that are *uniquely timed* to be most effective and efficient at preventing depression and other brain health conditions

Retrospective Study of Young Adults



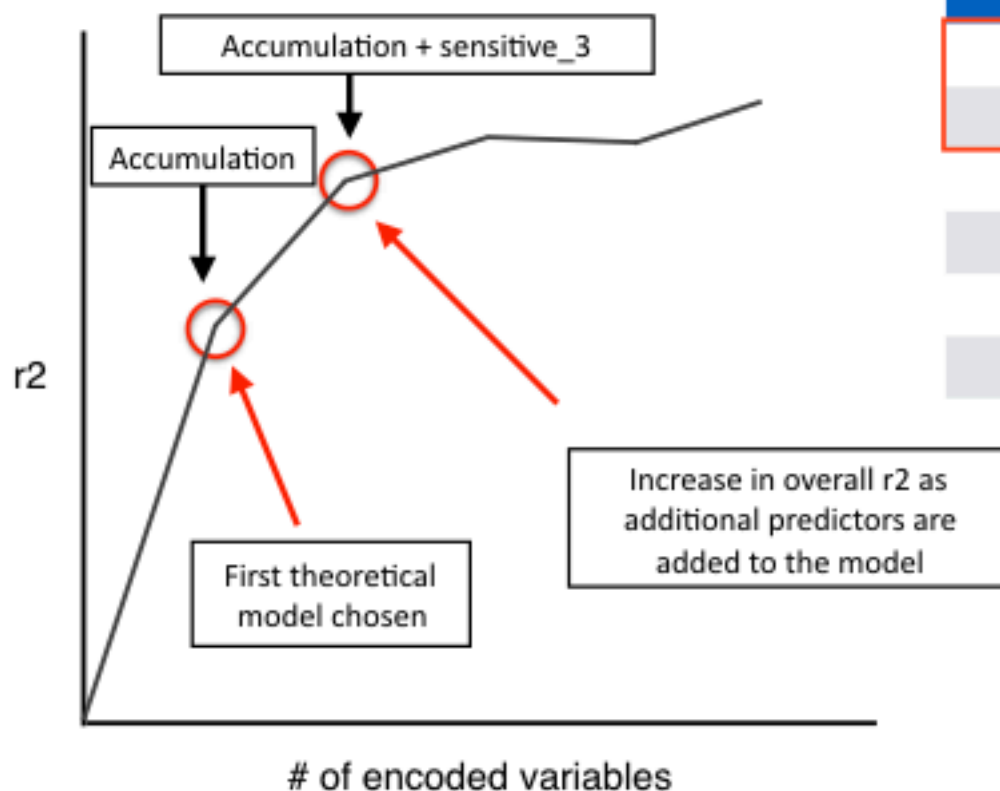
Dunn, E.C., McLaughlin, K.A., Slopen, N., Rosand, J., & Smoller, J.W. (2013). *Depression and Anxiety*.

Overview of Structured Lifecourse Modeling Approach (SLCMA)



Interpreting LARS Results

Results are summarized in an “elbow plot”



Variable	Drop in covariance	P Value
1	17.396	0.0012
2	1.2234	0.0438
3	0.8836	0.1734
4	0.0023	0.5672
5	0.0001	0.9738
6	0.0020	0.9803

Also evaluate quantitatively through covariance hypothesis test

Prospective Study of Young Children

Avon
Longitudinal
Study of Parents
and Children
(ALSPAC)
n=~6,000

What theoretical model best explains variation:
Accumulation, recency, or sensitive period?

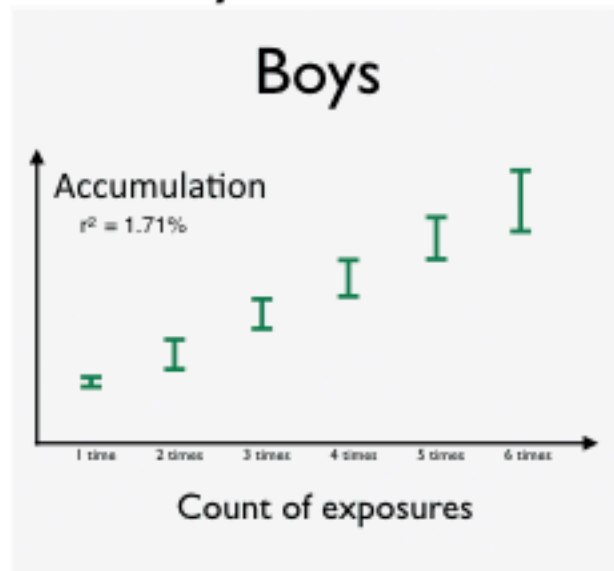
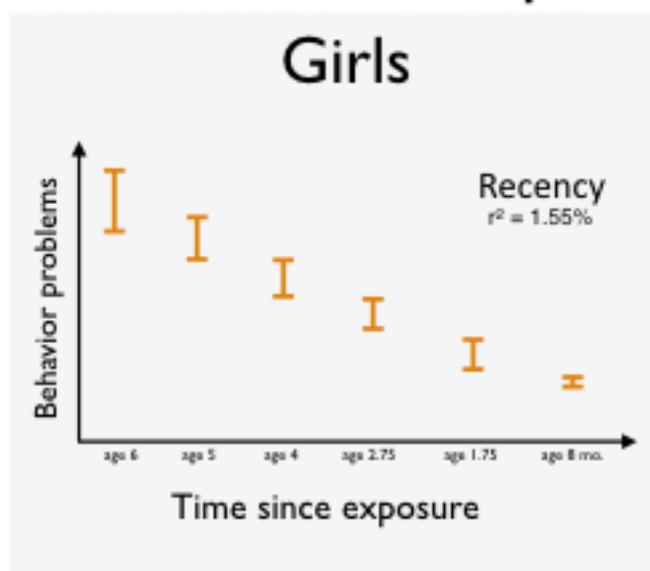
Behavior problems

1.5 years 2.5 years 3.5 years 4.75 years 5.75 years 6.75 years 8 years

Exposure to adversity



Caregiver
physical or
emotional
abuse



Can studying intermediates help identify sensitive periods sooner and more reliably?

Intermediate phenotype: A trait that could measure the most immediate impact of the exposure

Exposure to
child adversity



Intermediate Phenotypes

- Coping with stress
- Insomnia symptoms
- Emotion recognition skills
- Executive

Depression

molecular targets
(i.e., epigenetic
processes, cellular
aging)



Exposure to adversity appears to have measurable biological effects

Avon Longitudinal Study of Parents and Children (ALSPAC)
n~6,000

What theoretical model best explains variation:
Accumulation, recency, or sensitive period?

DNA_m at 485,000 sites in the genome

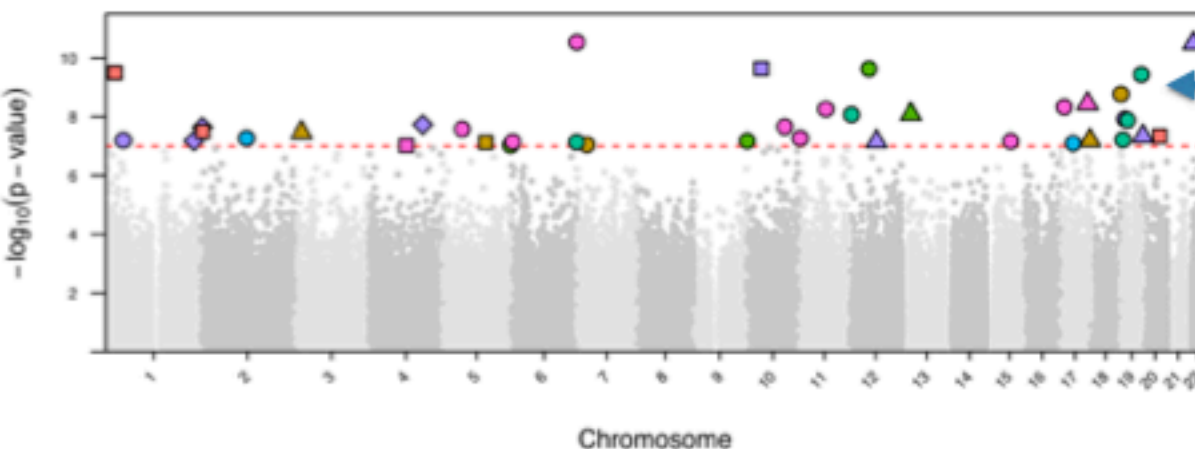
1.5 years 2.5 years 3.5 years 4.75 years 5.75 years 6.75 years 7 years

Exposure to adversity

Adversity

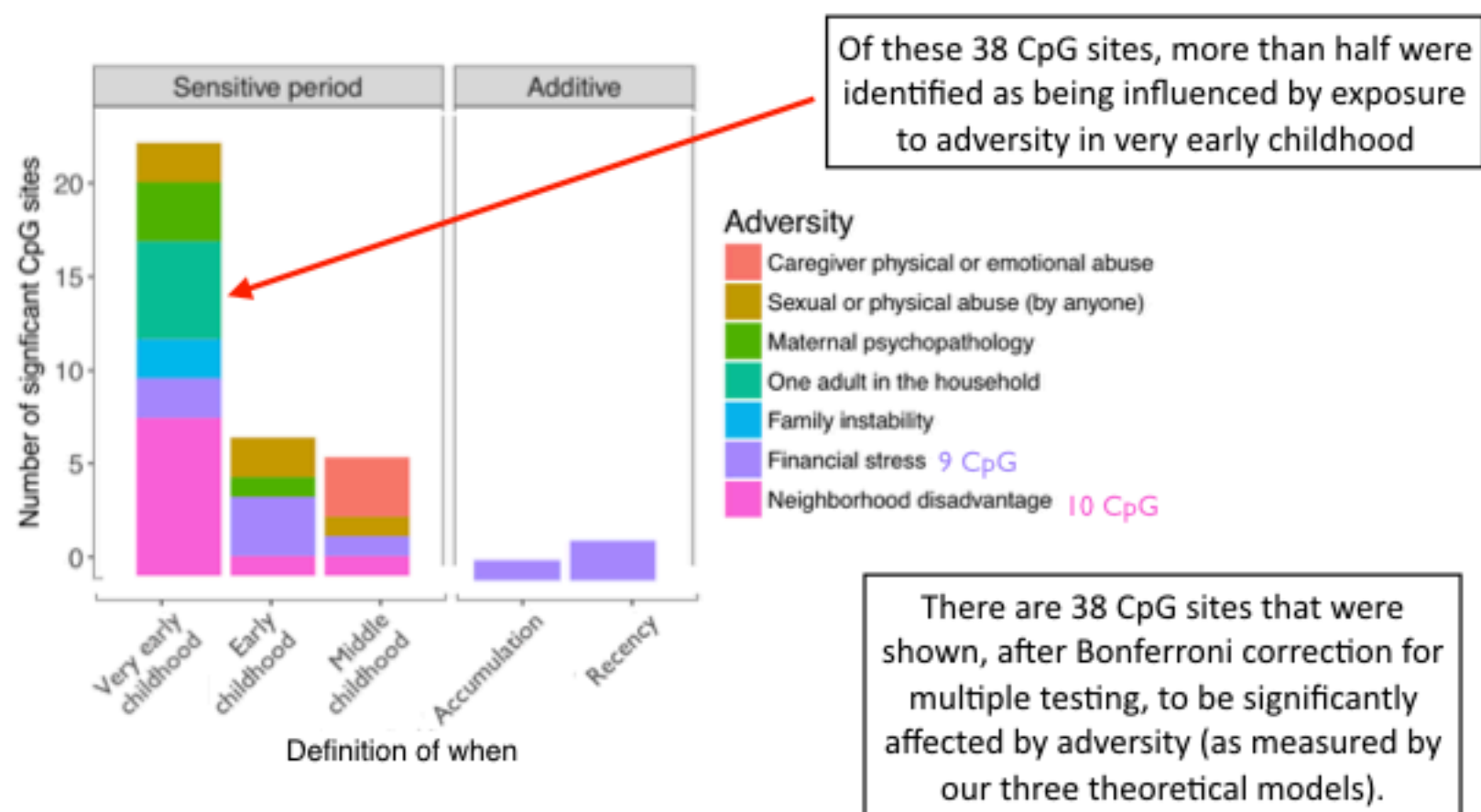
- Caregiver physical or emotional abuse
- Sexual or physical abuse (by anyone)
- Maternal psychopathology
- One adult in the household
- Family instability
- Financial stress
- Neighborhood disadvantage

Accessible Resource for Integrated Epigenomics Studies (ARIES) (n=1,018 mother-child pairs)

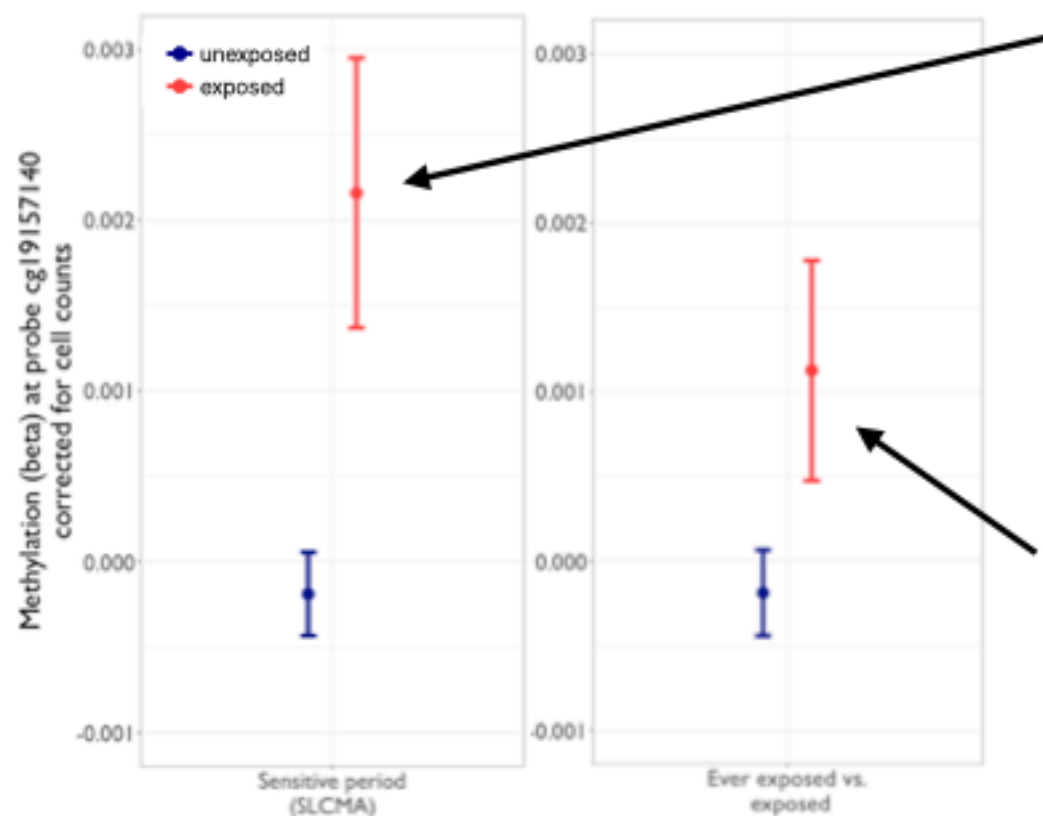


38 significant loci distributed throughout the genome

Timing of adversity seems to matter most in shaping DNAm patterns



How do these results compare to analyses of exposed vs. unexposed?



At the top “hit”, our modeling approach identified a sensitive period during very early childhood for the effect of neighborhood disadvantage ($p < 3 \times 10^{-11}$)

Using a simple ever exposed vs. unexposed analysis, the effect was nominally significant ($p=0.0002$), but not readily detectable when correcting for multiple comparisons (as in standard EWAS).

Summary of Findings for Intermediates

Study	Population	Design	Exposure	Outcome	Evidence for sensitive periods?
Dunn et al (2018); JCPP	children	prospective	abuse and other adversity	emotion recognition	
Crawford et al (under review)	children	prospective	abuse	social cognitive skills	
Marini et al (2020); Psychoneuro.	children	prospective	abuse	epigenetic aging	✓
Dunn et al (2019); BioPsychiatry	children	prospective	abuse and other adversity	DNA methylation	✓
Vaughn-Coaxum (2018); JYA	adolescents	cross-sectional	abuse and other trauma	copng with stress	
Wang (2016); Sleep Medicine	adolescents	cross-sectional	abuse and other trauma	insomnia	✓
Dunn et al (2016); CA&N	young adults	retrospective	abuse	memory	✓

But current measures of adversity have serious limitations

Retrospective

Problems with prospective methods: Problems with retrospective methods:

- Parents may be susceptible to biases in recall or reluctant to impart to their children when asked in relation to when events occurred
- Parents could be unaware of some exposures
- There is often low levels of agreement between parents and their children
- Official reports, such as health or social services records, represent an alternative strategy, but these often fail to detect all cases

Prospective

Very Early Childhood (0-2 years) Early Childhood (3-5 years) Middle Childhood (6-7 years) Late Childhood (8-10 years) Adolescence (11-18 years) Adult (+18 years)

Can children's shed teeth serve as a novel biomarker of ACE exposure?

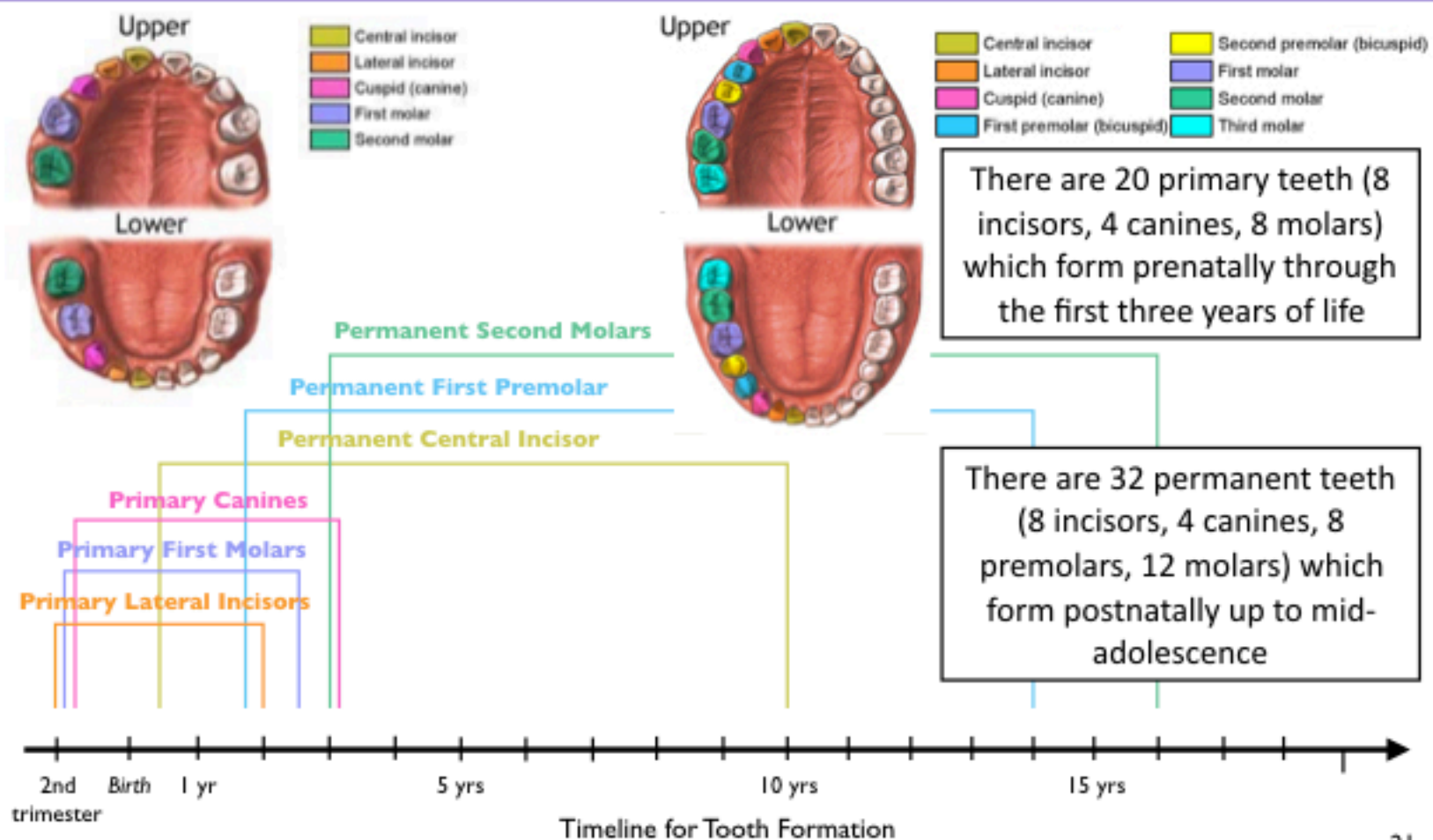
Teeth as Potential New Tools to Measure Early-Life Adversity and Subsequent Mental Health Risk: An Interdisciplinary Review and Conceptual Model

Kathryn A. Davis, Rebecca V. Mountain, Olivia R. Pickett, Pamela K. Den Besten, Felicitas B. Bidlack, and Erin C. Dunn



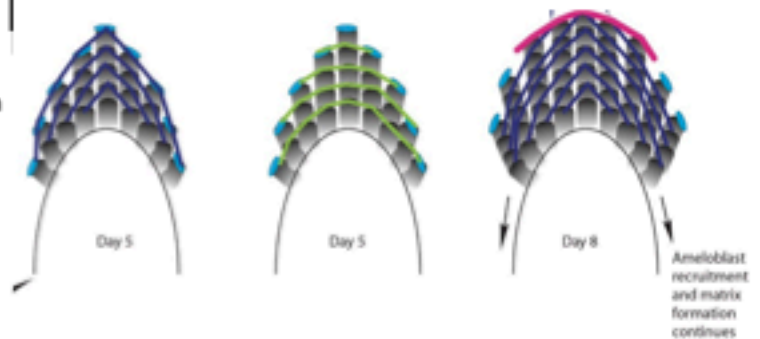
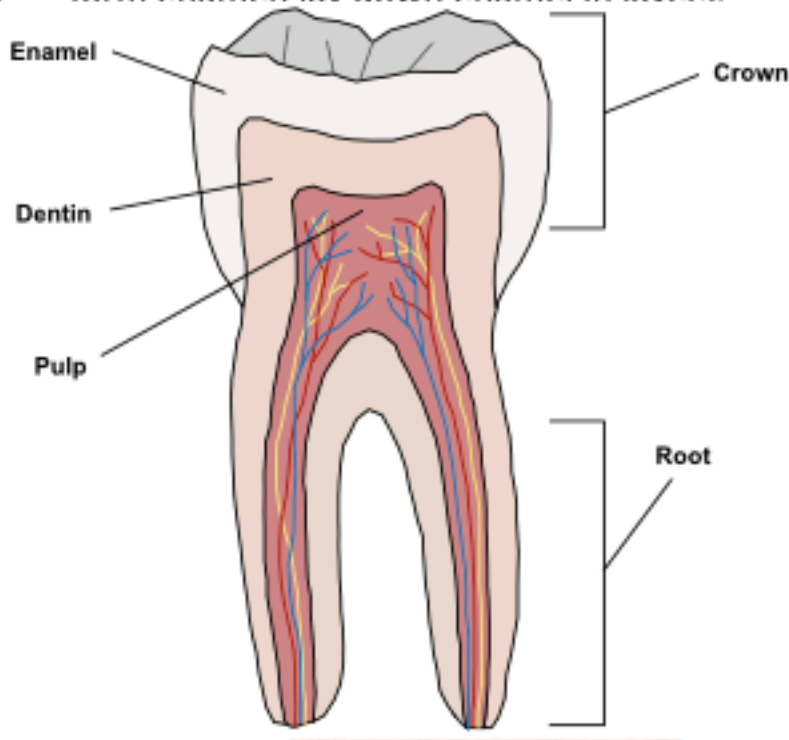
Davis, K.A., Mountain, R.V., Pickett, O.R., DenBesten, P.K., Bidlack, F.B., & Dunn, E.C. (in press). *Biological Psychiatry*

Tooth biomarkers



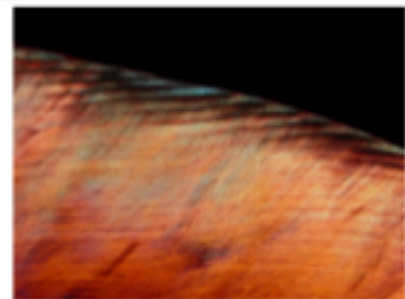
Teeth record the timing of their incremental growth

During development, ameloblasts (the cells that form enamel) lay down enamel in layers.



ded in the
ge.

Tooth



Tooth growth diagram retrieved from: <http://paleopix.com/blog/2013/07/18/how-teeth-grow/>.

Tooth incremental lines image courtesy of Tim Bromage. Retrieved from: <https://d2r55xnwy6nx47.cloudfront.net/uploads/2016/12/teeth-may-reveal-a-multi-day-biological-clock-20161213.pdf>

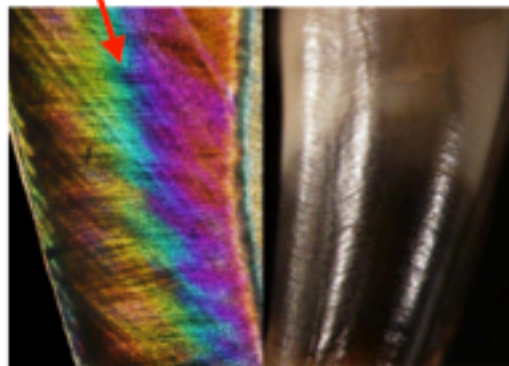
This recording of development is the same across different species

We see the same rings within teeth across different mammals.

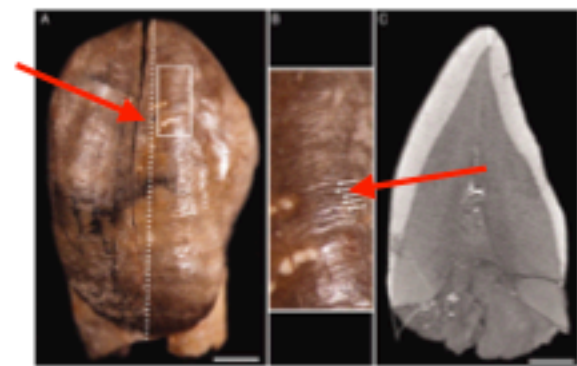
Primate



Neanderthal



Human



Smith T.M., Boesch C. *Am J Phys Anthropol* (2015).
Image retrieved from <https://onlinelibrary.wiley.com/>.

Smith, T.M. Image retrieved from <https://www.mpg.de/549054/pressRelease20071203>.

Smith T.M., Tafforeau P., Reid, D.J., Grün, R., Eggins, S., Boutakiout, M., & Hublin, J.J. *PNAS* (2007). Image retrieved from <http://www.pnas.org/>.

Teeth also record insults or disruptions that occur during their development



Illness

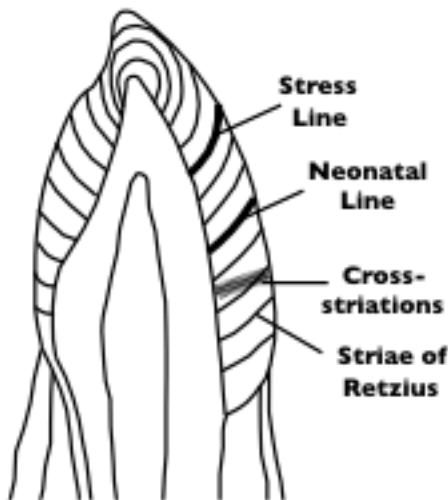


Malnutrition



Heavy metals

Teeth can tell us not just whether a stressor occurred during development, but *when*.



Low-resolution time scale



High-resolution time scale



Smith T.M. *Annual Review of Anthropology* (2013). Image retrieved from: <https://www.knowablemagazine.org/article/living-world/2018/truth-baby-teeth>.

To date, most of this work has focused on physiological stressors



Top Left: Source: Valerie Andrushko. In Armelagos G.J., Goodman A.H., Harper K.N., & Blakey M.L. *Evolutionary Anthropology* (2009). Image retrieved from <https://onlinelibrary.wiley.com/>.

Bottom Left: Smith T.M., Green D. Image retrieved from <https://phys.org/news/2018-11-teeth-environments-ancient-humans-neanderthals.html>.

Top Right: Goodman A.H., Rose J.C. *Yearbook of Physical Anthropology* (1990). Image retrieved from <https://onlinelibrary.wiley.com/>.

Bottom Right: Savabieasfahani M., Ali S.S., Bacho R., Savabi O., Alsabbak M. *Environ Monit Assess* (2016). Image retrieved from <https://link.springer.com>.

But primate studies suggest that teeth may also capture psychosocial stress

Summary of the literature on the association between psychosocial stress and markers of disrupted tooth development in non-human primates

Study	Primate	Psychosocial Stressor	Evidence in teeth?
Bowman 1991	Rhesus macaques	Separation from mothers; intro of new males to social group	✓
Dirks 1998	Gibbon	Weaning	?
Dirks et al. 2002, 2010	Baboons	Mother's return to mating during the weaning process	?
Schwartz et al. 2006	Juvenile gorilla	Caregiving disruptions; enclosure transfers	✓
Smith et al. 2015	Wild chimpanzees	Mother's aggression; sibling's death	?
Austin et al. 2016	Rhesus macaques	Separation from social group for biobehavioral assessment	✓

Stressors recorded in teeth have been shown to predict neuropsychiatric risk

Environmental Toxicants

Organic Toxicants
(e.g., pesticides)



Heavy Metals
(e.g., lead)



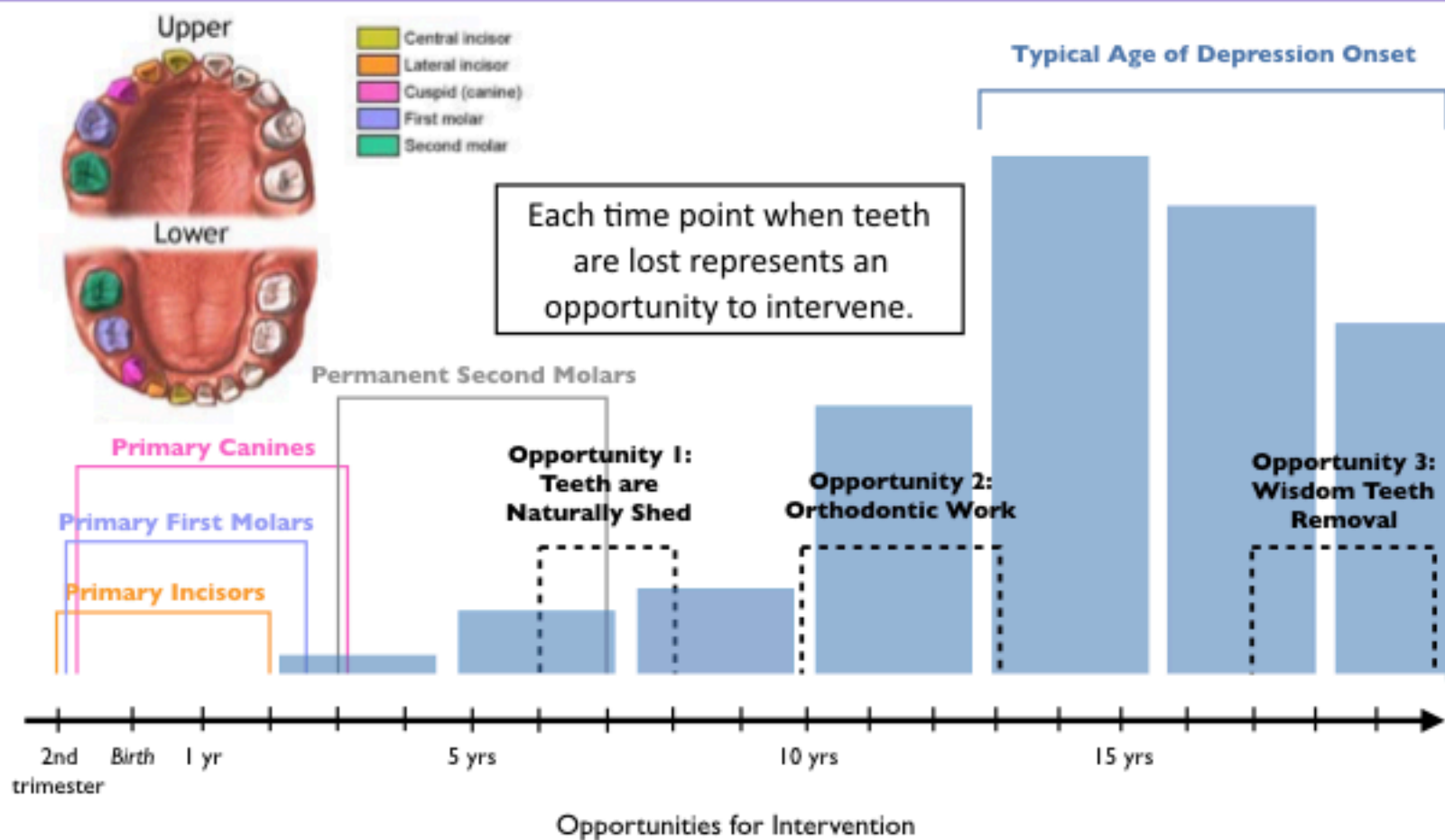
To date, studies using teeth as a marker of neuropsychiatric risk have focused on environmental exposures that can be inhaled or ingested.

Examples of studies on the link between tooth-based measures of environmental exposures and neuropsychiatric outcomes

Study	Population Studied	Exposure of Interest	Teeth	Outcome	Main Findings
Modabbernia et al., 2016	Adults with schizophrenia and healthy controls	Heavy metals (manganese, lead, cadmium, copper, magnesium, zinc)	Shed primary teeth	Schizophrenia diagnosis	Higher early-life lead exposure among individuals with schizophrenia
Arora et al., 2017	Adolescent twin pairs	Heavy metals (manganese, lead, zinc)	Shed primary teeth	Autism spectrum disorder diagnosis (ASD)	Differences in uptake of heavy metals between ASD cases and controls, especially during prenatal life and first 5 months postnatal
Chiu et al., 2017	Adolescents	Heavy metals (manganese)	Shed primary teeth	Neuromotor function	Evidence of sex-specific sensitive periods for early life manganese exposure and measures of neuromotor function

Arora M, Reichenberg A, Willfors C, Austin C, Gennings C, Bergen S, ...Bölke S. *Nature Communications* (2017).
 Chiu Y, Henn B, Hsu H, Pendo M, Coull B, Austin C, ...Arora M. *Environmental Research* (2017).
 Modabbernia A, Velthorst E, Gennings C, De Haan L, Austin C, Sutterland A, ...Reichenberg A. *European Psychiatry* (2016).

Teeth may provide enormous and unique opportunities for primary prevention



THE SCIENCE TOOTHFAIRY



The STRONG Study

STORIES TEETH RECORD OF NEWBORN GROWTH

Were you pregnant during or 1-year prior to
the Boston Marathon bombings and manhunt in
April 2013?

www.teethforscience.com

We wrote a children's book to communicate our goals to children/parents

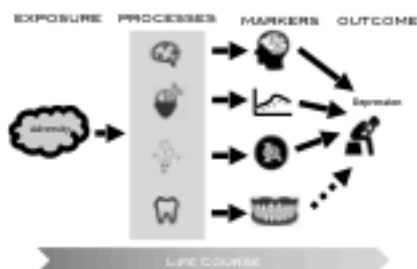
www.teethforscience.com



What we are sinking our teeth into

Conceptual

What do we believe to be the model linking adversity exposure to teeth, and teeth to depression risk?



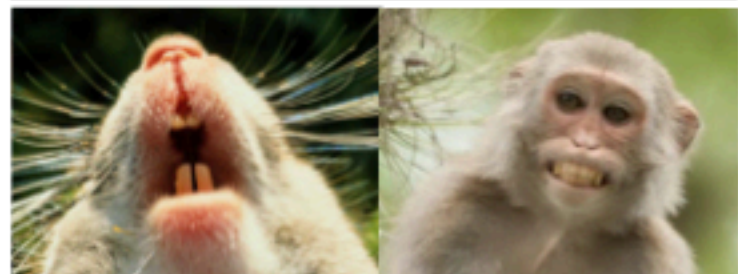
Mechanistic

What are the biological processes linking adversity exposure to tooth development?



Empirical

What types of adversity exposure are captured in teeth? What dose of exposure is required?



Feasibility

What are the social and cultural factors that could make the widespread use of teeth as a novel biomarker more or less feasible?



We desperately need breakthrough discoveries in the field of brain health.

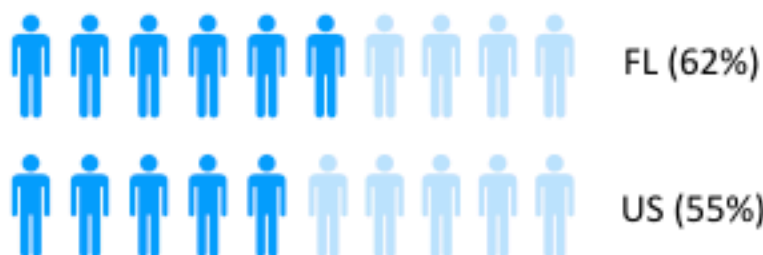
- Brain health problems affect 1 in every 3 people worldwide.



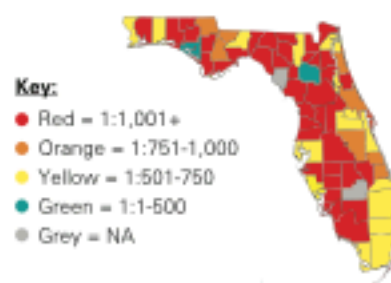
- There is limited understanding of the causes of brain disease. This limits our ability to:
 - Treat brain disease once it emerges.
 - Prevent brain disease before it occurs.
 - Promote brain health across the lifespan.
- Discovering the basis of brain health may be *the most* important medical challenge of our time.

This need exists nationwide, and especially in Florida.

Florida ranks 48th out of the 50 states for adults with mental illness who do not receive mental health services



Florida ranks 44th out of the 50 states for the number of available mental health providers per capita



Florida ranks 50th for per capita spending on mental health support



Florida ranked 32nd for the prevalence of youth with severe major depression



Top Left: Source: Mental Health in America - Adult Data, Mental Health America (2018). Image retrieved from <https://www.mhanational.org/issues/mental-health-america-adult-data-2018>

Bottom Left: National Association of State Mental Health Program Directors Inc. (NAMI-inc). 2014. SMHA Mental Health Actual Dollar and Per Capita Expenditures by State, FY 2014

Top Right: County Health Rankings, Mental Health America (2016). Image retrieved from https://cdn.ymaws.com/www.fadaa.org/resource/resmgr/files/Mental_Health/FADAA_SlipSheet1_Final.pdf

Bottom Right: State of Mental Health in America - Prevalence Data, Mental Health America (2017). Image retrieved from <https://www.mhanational.org/issues/2017-state-mental-health-america-prevalence-data>

The Brain Health Initiative: The Florida Gulf Coast and beyond



Overarching goal: Identify, develop, and implement interventions aimed at optimizing brain health and performance across the lifespan

www.brainhealthinitiative.org



To accomplish this goal, we will:

- Identify the factors that shape brain health, including the role of genes, lifestyle factors, and the social and physical environment.
- Understand how certain interventions promote brain health and reduce the risk of brain-related diseases.
- Determine how these factors unfold across development so we can efficiently and effectively target interventions to *when* they will have long-lasting impacts.

Our multi-disciplinary team of scientists and clinicians



Stephanie Peabody

Executive Director



Erin Dunn

Director of Research



Ana-Maria Vranceanu

Director of Community
Intervention Development &
Implementation



Shelley Carson

Director of Survey
Development



Heidi Hanna

Director of Corporate &
Media Relations

Local, National, and Global Investigators



Spanning Multiple Disciplines

- Epidemiology
- Psychiatry
- Integrative neuroscience
- Neurology
- Neuropsychology
- Public Health
- Statistics
- Economics
- Technology
- Urban planning
- Biological sciences
- Child development

How we will achieve our goals

Longitudinal observational study

Identify predictors of brain health among a multigenerational cohort



Living Laboratory

Test the impact of novel interventions to improve brain health and enhance performance



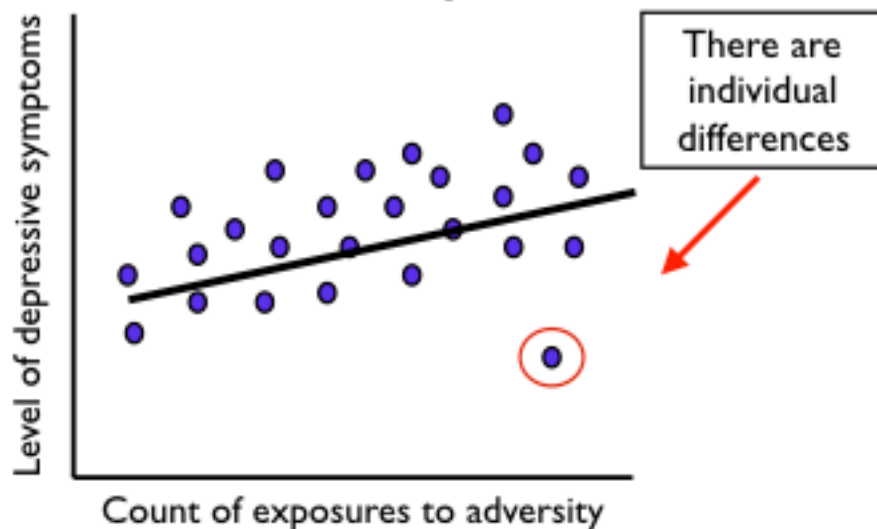
Community engagement/collective impact model

Engage multiple stakeholders within the community to increase sustainability

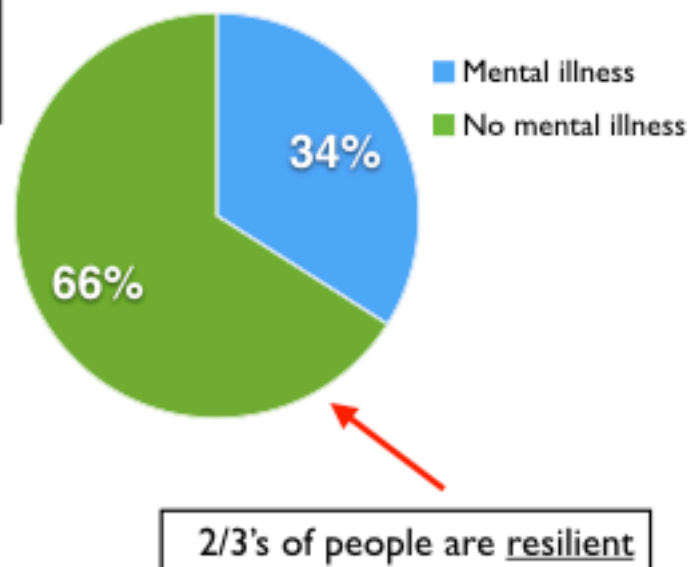


Not losing sight of hope.... because most people do OK

Association between adversity and risk for depression



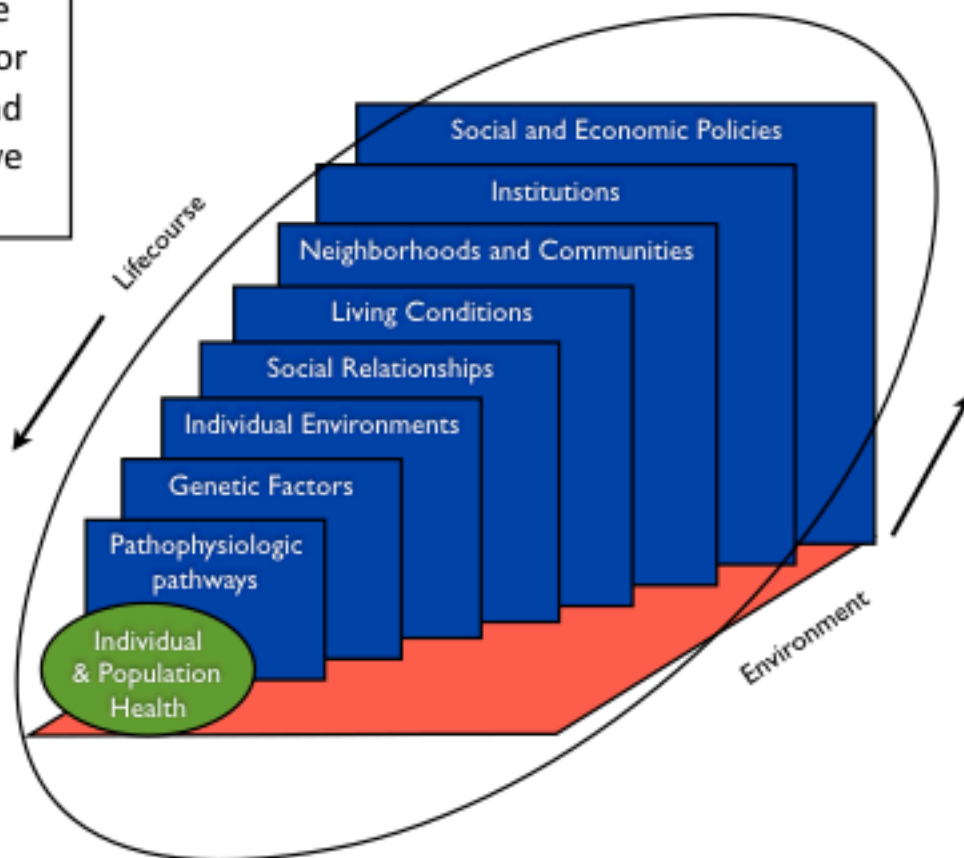
Mental health outcomes among children exposed to adversity



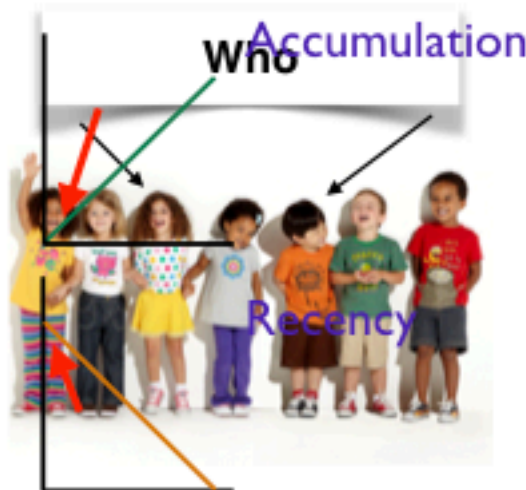
How do we promote resilience processes and outcomes?

Identify the buffers (or protective factors) that can offset risk for poor health outcomes for everyone, and especially among people who have been exposed to adversity.

10 PILLARS OF BRAIN HEALTH



How a focus on when can help optimize prevention efforts for child mental health



When

Sensitive Period

Where

Why neglecting **when** is a problem

- Accumulating evidence suggests its not just **THAT** you're exposed, but **WHEN** that matters

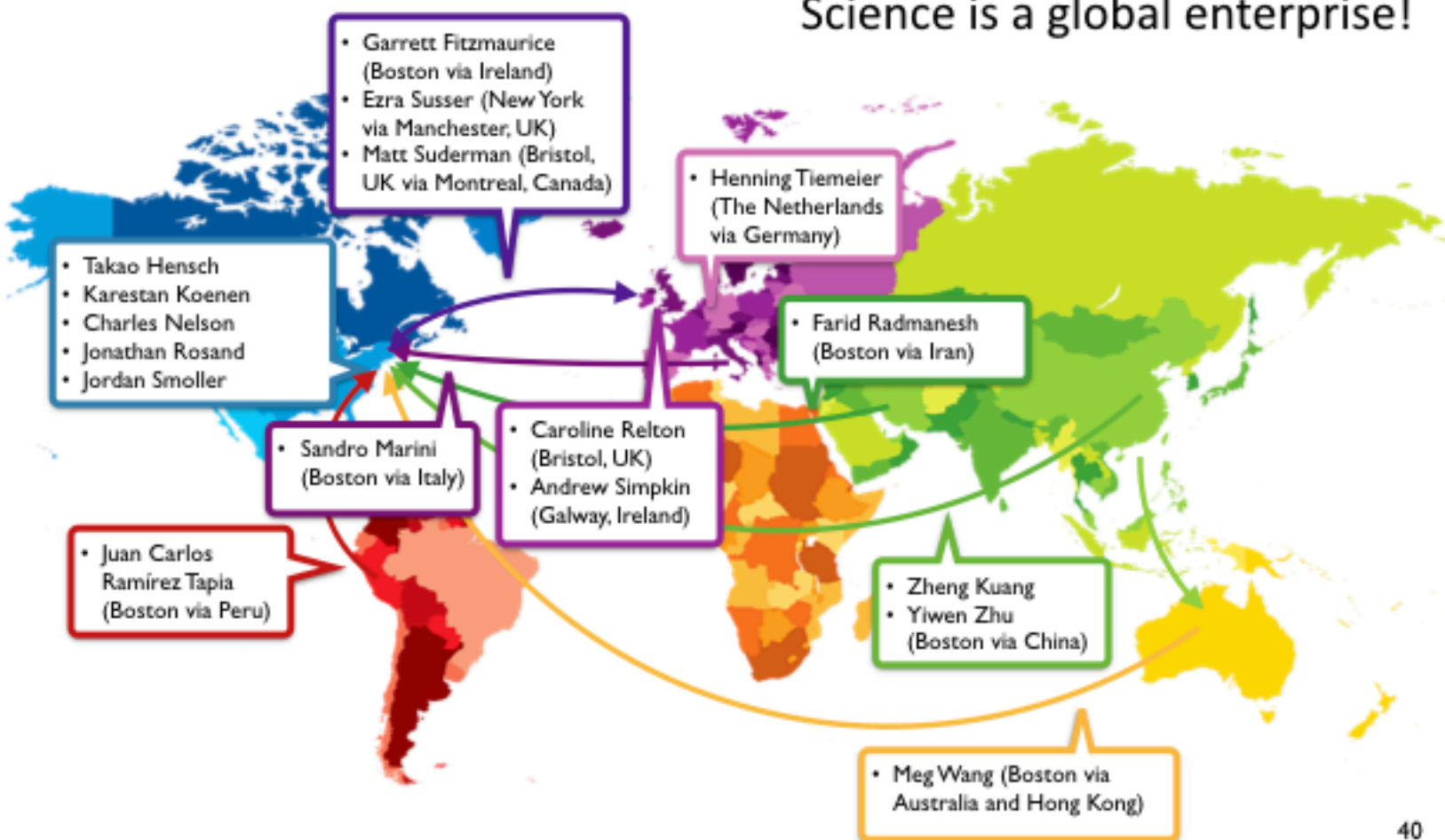
What's the potential impact of knowing when matters?

- It will help us better understand the etiology of depression and why certain people are most at risk
- It will help us to design interventions that are efficient, making the best use of our countries limited public health dollars, and effective - preventing depression before it ever even starts

How

Mentors and Collaborators

Science is a global enterprise!



The Dunn Lab Blog : Said & Dunn

SAID&DUNN

Scientific Findings, Musings, and Exploratory Pieces Written By Members of the Lab

The Latest Science Topics



HOW DOES STRESS GET UNDER THE SKIN? THE EPIGENETIC HYPOTHESIS

Can stressful experiences "get under the skin" and change the way our genes function? In this week's Said&Dunn post, Yiyen and Khalil explore the field of epigenetics, which is providing important new insights about how stress can affect the functioning of our DNA. This post also includes a video by Dr. Dunn, where she explains the meaning of epigenetics and how our lab group is studying the epigenetics of stress and depression.

By: Yiyen Zhu and Khalil Ziaoui



FIVE SENSITIVE PERIODS YOU DIDN'T KNOW EXISTED

In the Dunn Lab, a lot of our research is focused on identifying sensitive periods in development when life experiences may be particularly impactful in shaping brain health and risk for mental health problems. However, sensitive periods aren't just limited to mental health. Find out about some sensitive periods you probably didn't know existed in this week's Said&Dunn post.

By: Katie Davis



FIVE VIDEOS TO STAY ON TOP OF THE LATEST RESEARCH IN MENTAL HEALTH

Short on time, but want to learn more about the latest research in the field of mental health? Take the next 15 minutes to watch some videos—from our group and others—about depression, brain health, sensitive periods in development, science-based intervention strategies, and schizophrenia prevention.

By: Janine Corral

www.thedunnlab.com/blog/

Tips & How To's



CRACK THE CODE: FOUR TIPS FOR NEW R USERS

Have you ever tried to learn a new language? What about a new programming language? It can be a time-consuming, confusing and, at times, frustrating task. In this week's Said&Dunn post, our very own Data Analyst Yiyen Zhu shares her advice for beginners learning to code in R, and how to develop the skills to create inspiring, reproducible science.

By: Yiyen Zhu

Inspirations



HOW A MUSIC FESTIVAL CHANGED MY OUTLOOK ON SCIENCE

In this week's Said&Dunn post, Erin reflects on her experiences at One Mind Foundation's 24th Annual Music Festival for Brain Health and how it became one of the most transformative and career defining experiences of her life.

By: Dr. Erin Dunn

Lab Members and Funding Support



Lab Members

Janine Cerutti	Alex Lussier
Karmel Choi	Becky Mountain
Katie Davis	Kristen Nishimi
Emma Glickman	Clara Parsons
Natalie Harrington	Olivia Pickett
Kristina Jacobsson	Liv Sterns
Jessie Liu	Yiwen Zhu

Funding Support

Behavioral Research Award for Innovative New Scientists, NIMH (BRAINS; R01MH113930)

Center for Brain Health, MassGeneral

Harvard University Mind, Brain, Behavior

One Mind Rising Star Research Award

Jacobs Foundation

Russell Sage Foundation

Thank you!

Questions?:

edunn2@mgh.harvard.edu

www.thedunnlab.com

@ErinDunnScD



@TheDunnLab

