Biological transmission of parental life-course adversity across generations

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April 9, 2018

Fetal programming and biological embedding

Fetal programming, or **prenatal programming**, is the idea that physiological processes can be reset or reprogrammed during embryonic and fetal development

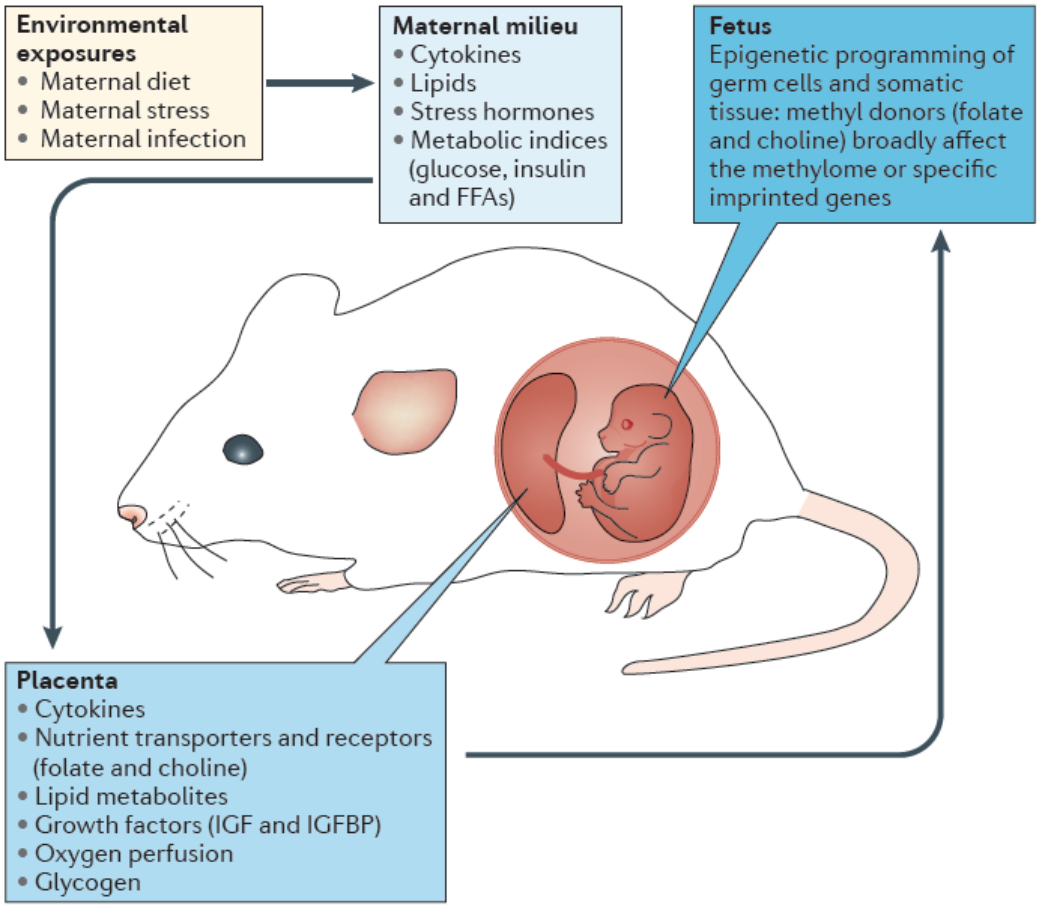
- These changes are capable of persisting into adulthood and across generations

Neurodevelopmental programming: the implementation of the genetic and epigenetic blueprints that guide and coordinate normal brain development

- Tightly regulated transcriptional processes
- Epigenetic processes
  - Reprogram the epigenome
  - Epigenetic marks within germ cells

Bale TL. *Nat Rev Neurosci.* 2015;16(6):332-344

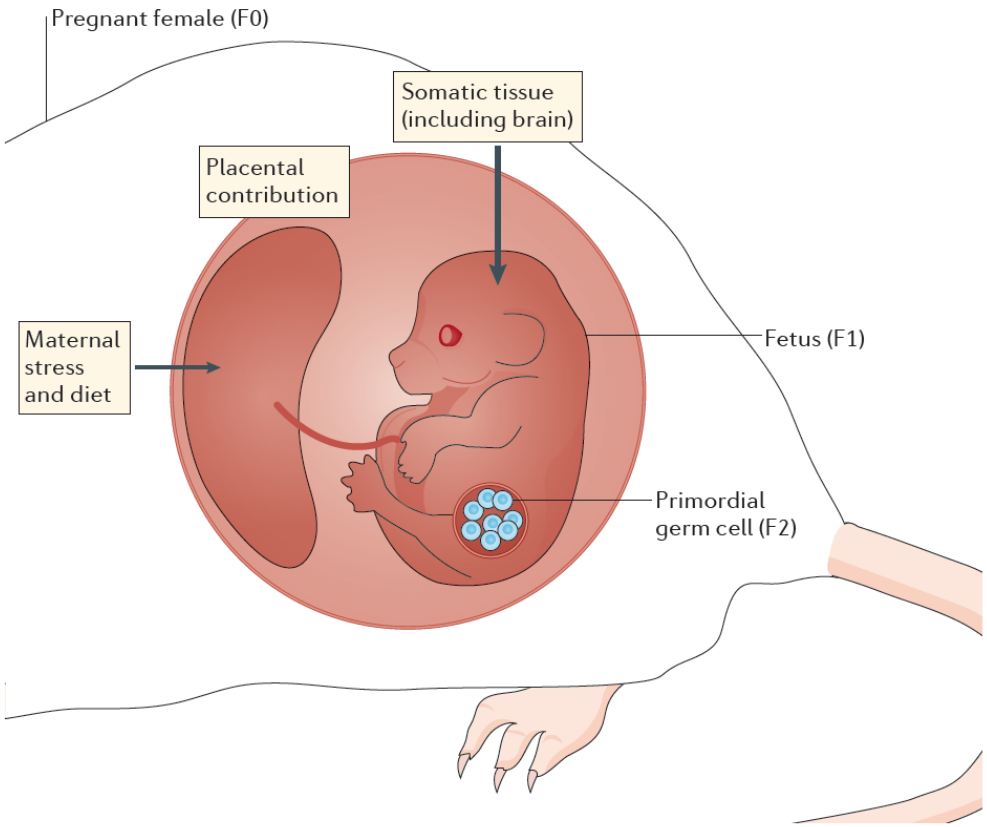
Complex interactions during gestation



1. Endocrine disruptions in the **maternal milieu**
2. Environmental exposures can indirectly alter **placental development and function**
3. Changes can affect fetal development or germ line

Bale TL. *Nat Rev Neurosci.* 2015;16(6):332-344

Programming of phenotypes and disease risk can skip generations

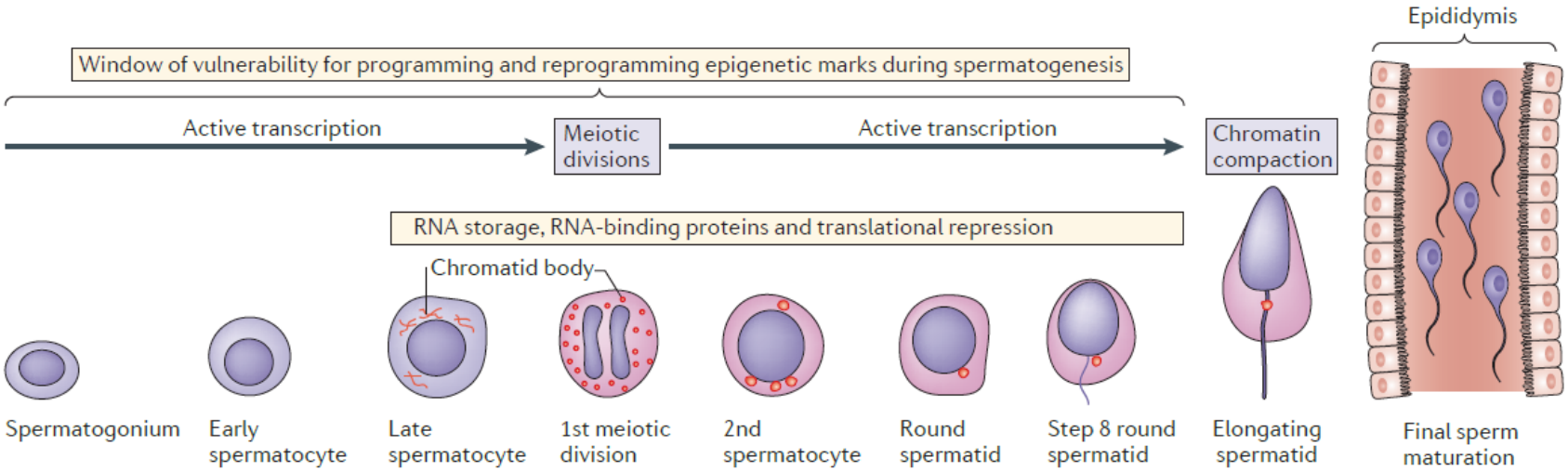


Maternal stress, *in utero,* upsets hormonal milieu

- F1 generation: direct changes to the placenta
- F2 generation: changes to primordial germ cells
  - Germ cells are present and undergo reprogramming during embryonic development.

Bale TL. *Nat Rev Neurosci.* 2015;16(6):332-344

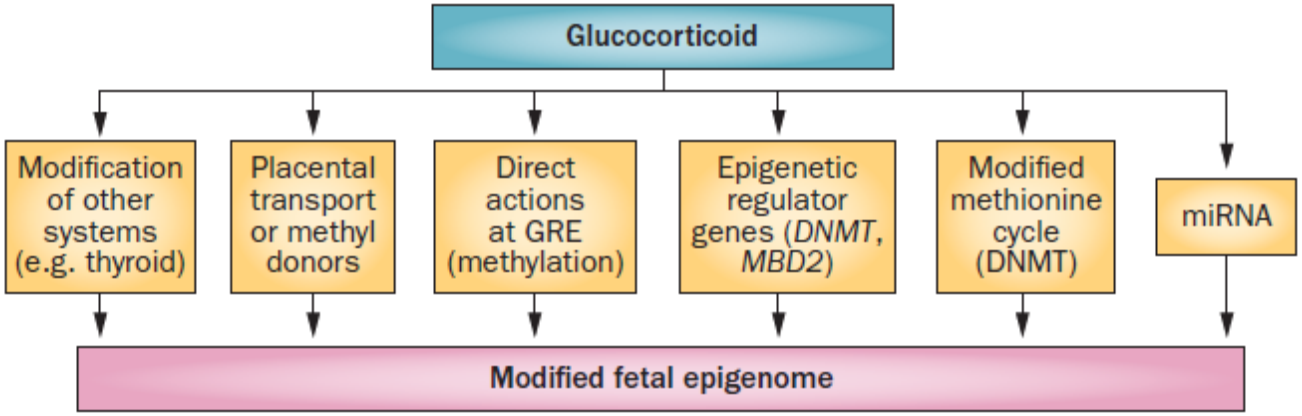
Timing of exposure during spermatogenesis

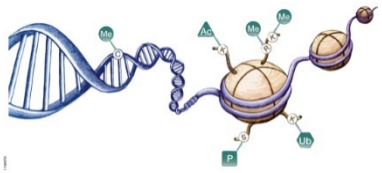


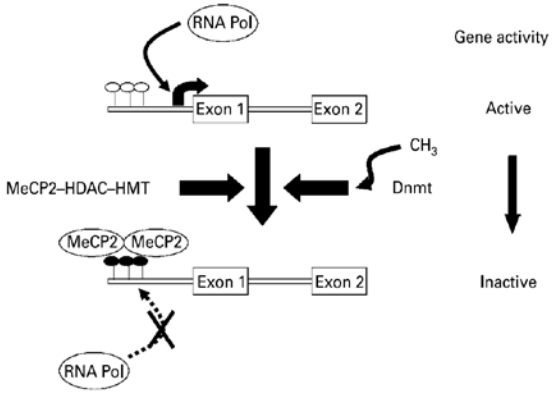
Bale TL. *Nat Rev Neurosci.* 2015;16(6):332-344

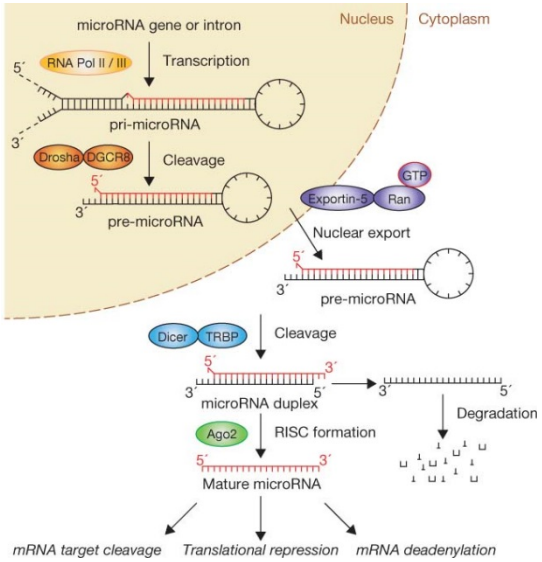
Mechanisms of biological programming

Immune/Inflammatory, nutritional, endocrine, and…





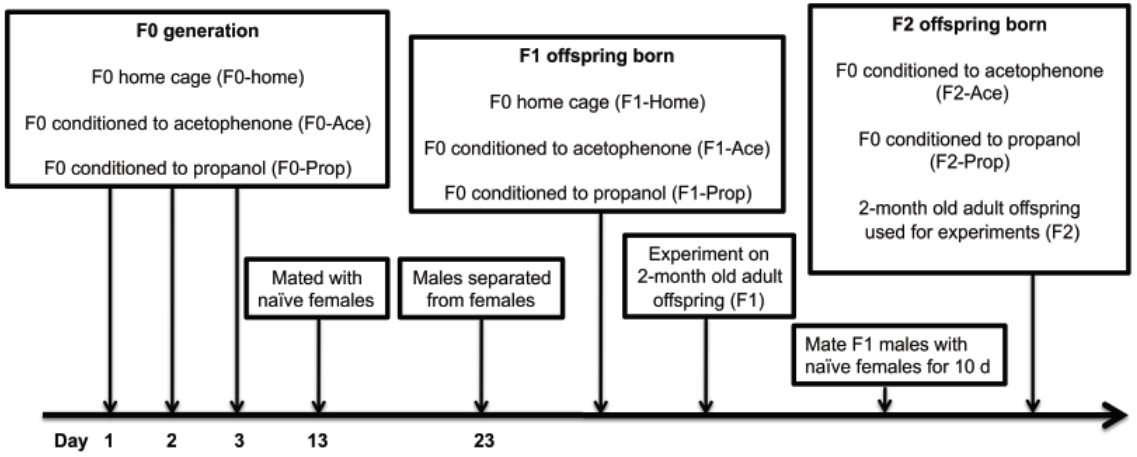




Moisiadis VG & Mathhews SG. *Nat Rev Endocrinology.* 2014;10: 403-411
Burdge GC, *et al. Br J Nutr. 2007:*97(6):1036-1046
www.promega.com

Empirical transgenerational studies: Olfactory conditioning

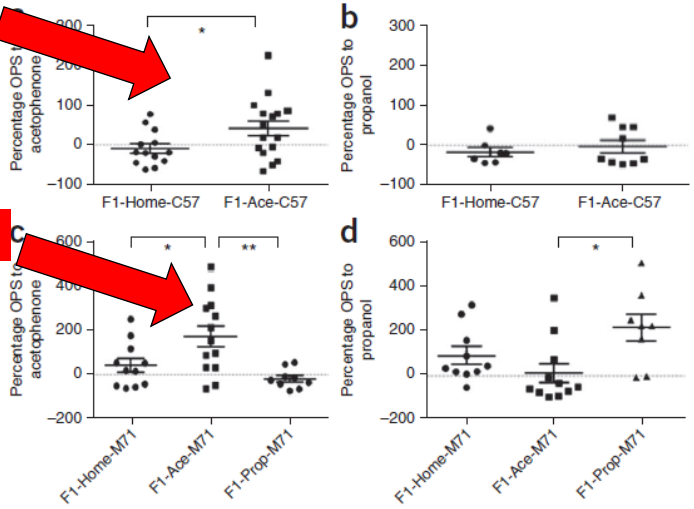
Experimental design



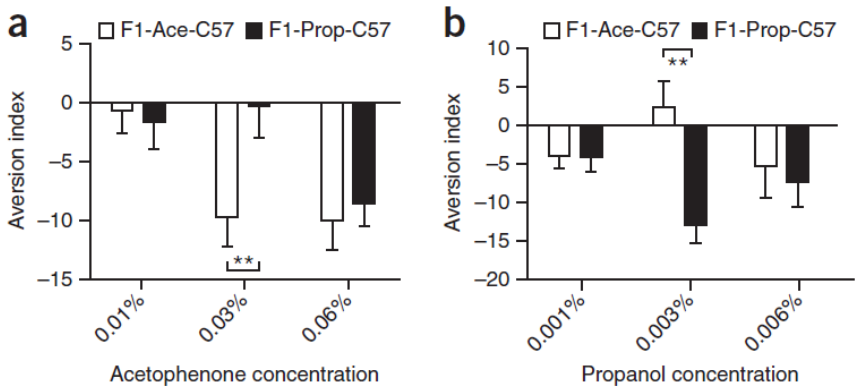
Odor potentiated startle

Sensitivity

Specificity

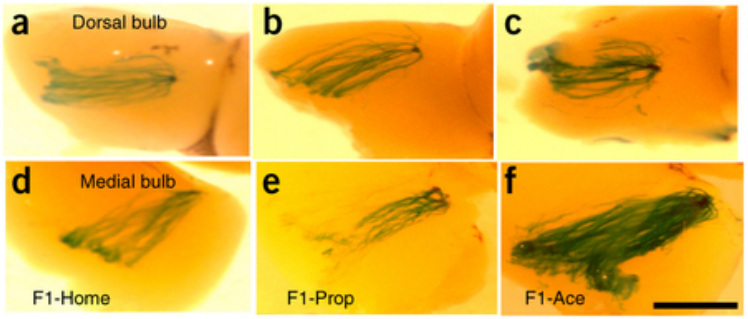


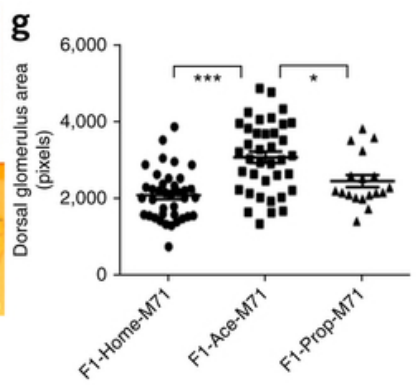
Odor sensitivity

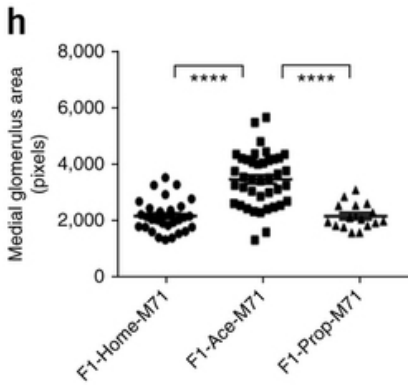


Dias BG & Ressler K. *Nat Neurosci*. 2014;17(1):89-96.

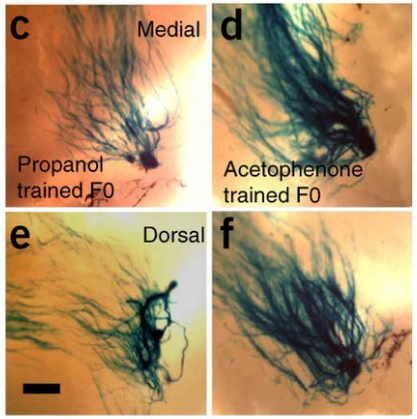
Olfactory conditioning in parent alters F1 neuroanatomy

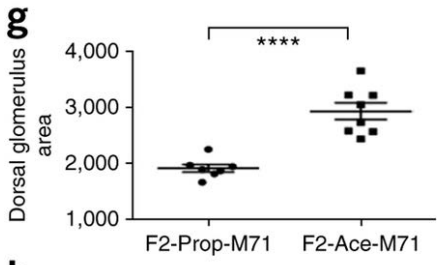


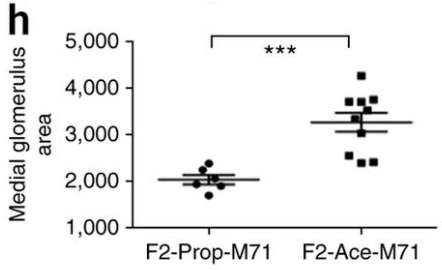


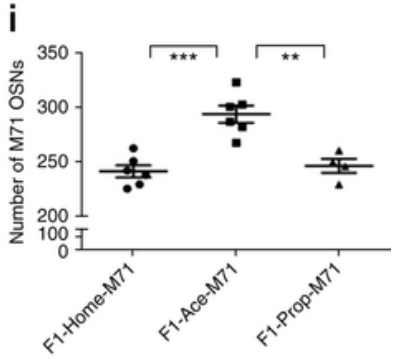


F2 generation





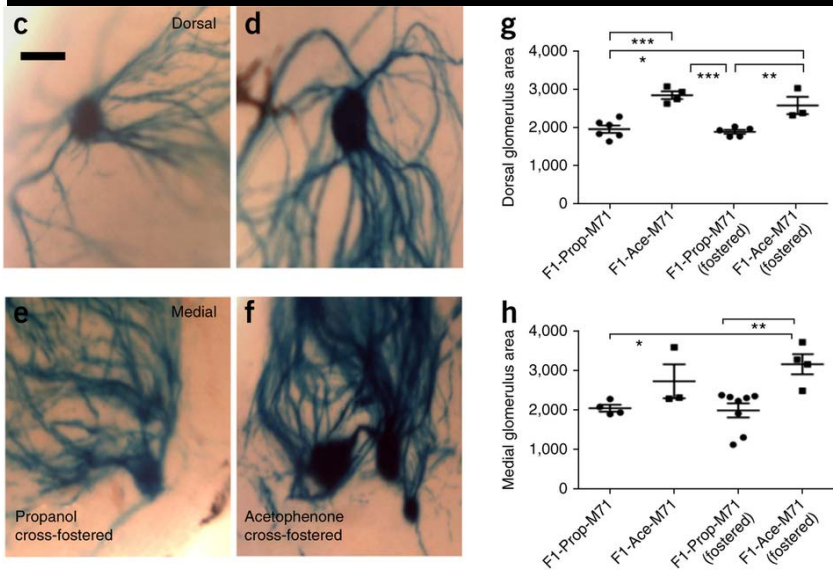


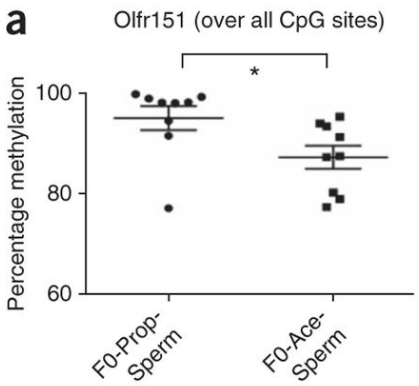


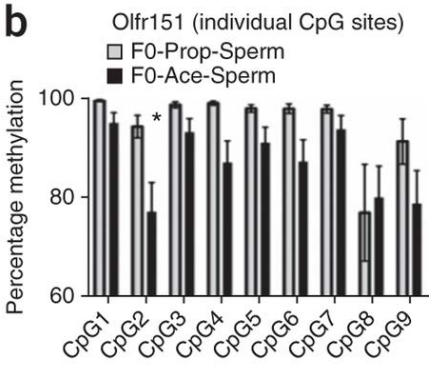
Dias BG & Ressler K. *Nat Neurosci*. 2014;17(1):89-96.

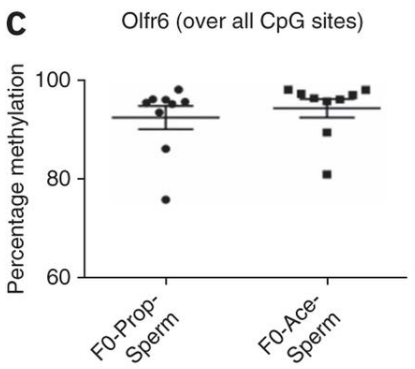
Transmission through DNA methylation of sperm?

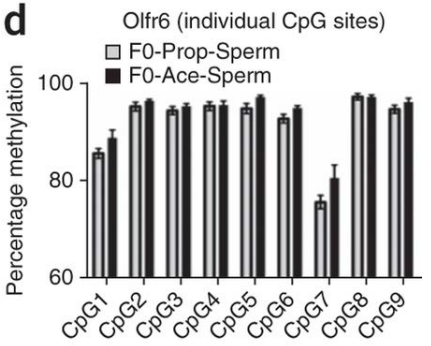
Cross-fostering has no impact

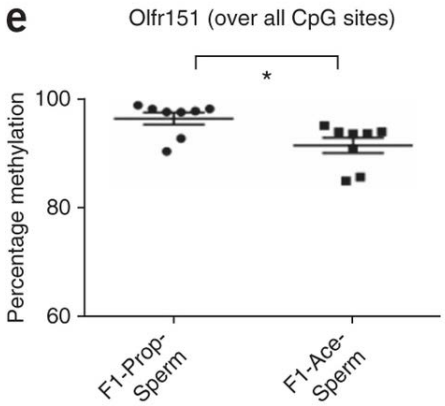


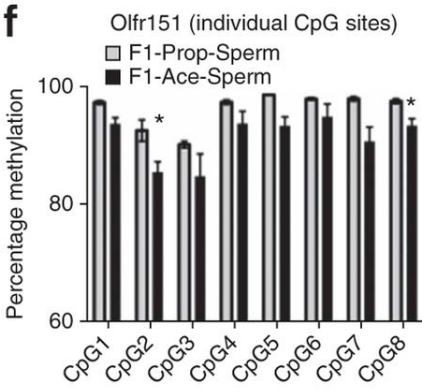












Dias BG & Ressler K. *Nat Neurosci*. 2014;17(1):89-96.

Transgenerational inheritance via sperm hypomethylation

F0-conditioned odor information transferred to male offspring:

Biological inheritance via gametes, epigenetic mark

Changes in F1,F2 behavioral phenotypes and olfactory neuroanatomical structure

- F1 & F2 offspring from F0-odor conditioned mothers or fathers, exhibit a behavioral sensitivity to the F0-conditioned odor and increased odor specific glomerulus area and olfactory sensory neuron number
  - The *Olfr151* gene, encoding for the odor specific M71 receptor shows hypomethylation in sperm from F0-odor conditioned males

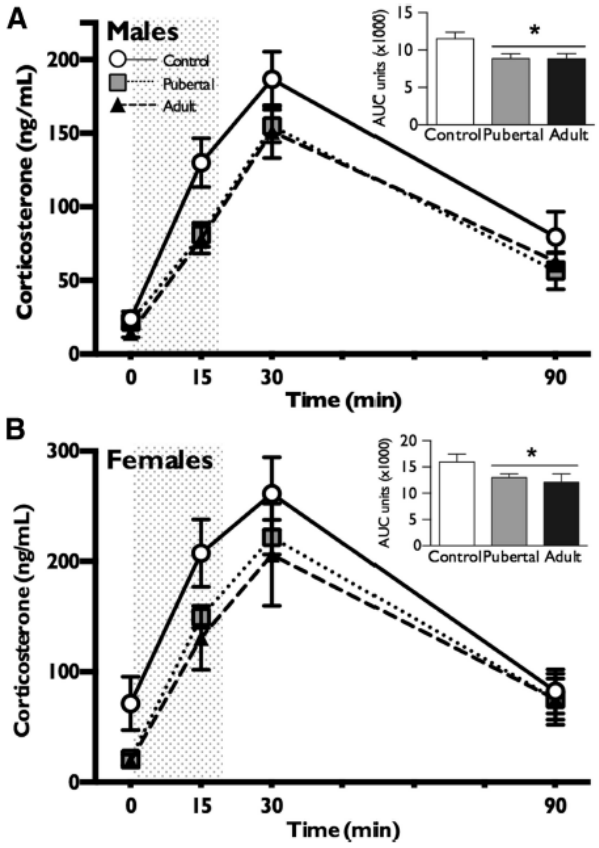
The results of the study support a transgenerational inheritance model

Dias BG & Ressler K. *Nat Neurosci*. 2014;17(1):89-96.

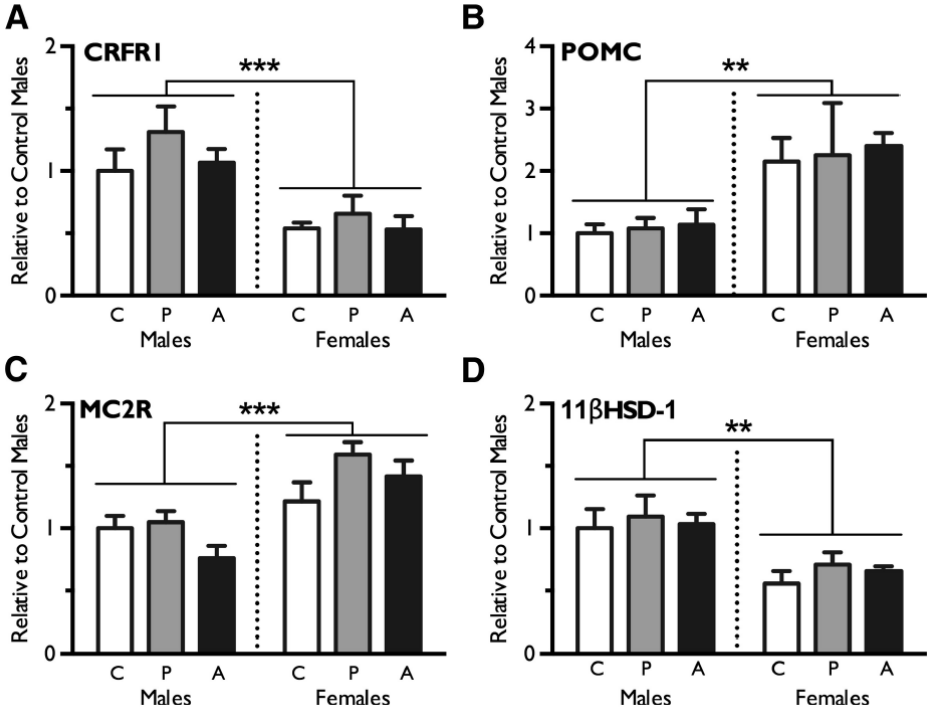
Paternal prenatal stress on offspring neural HPA-axis regulation and function

Pubertal: CVS 28-70; Adult: CVS 56-98

Blunted offspring stress responsivity



Sex differences in expression in adrenal & pituitary

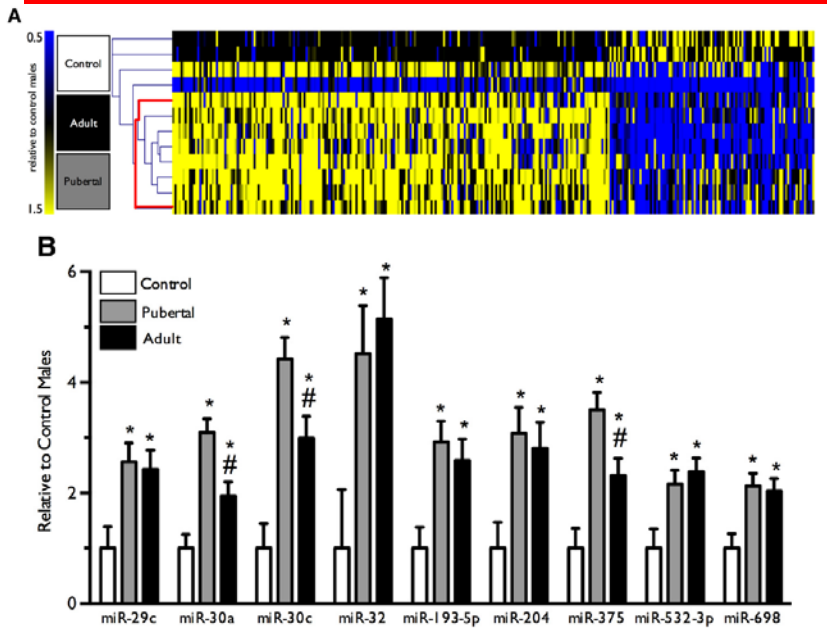


PNMS induced gene expression changes in PVN & BNST of offspring

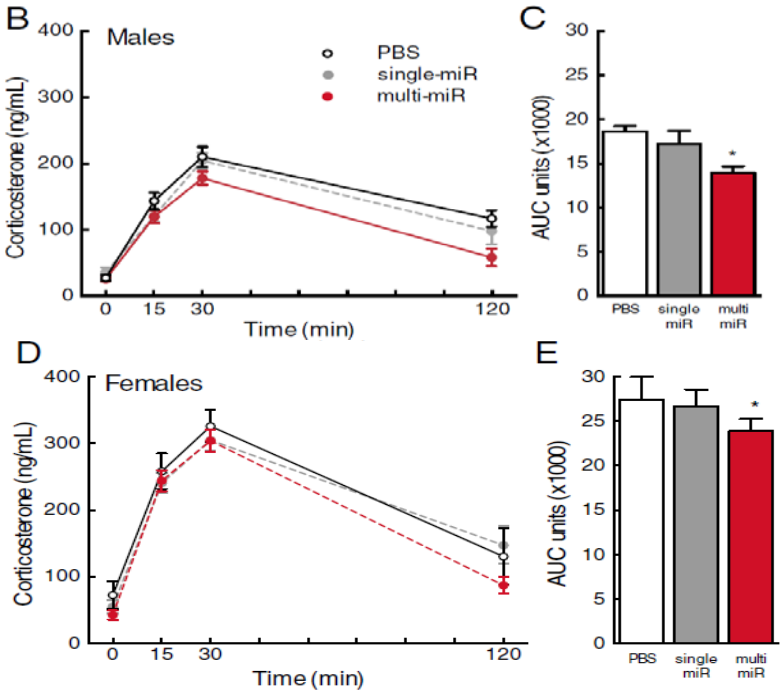
Rodgers AB, *et al*. *J Neurosci. 2013*:33(21):9003-9012

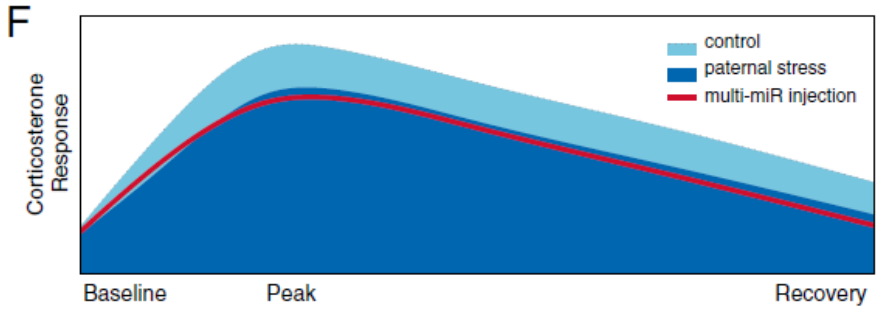
MicroRNAs implicated in experience-dependent transgenerational transmission of altered HPA stress responsivity

Altered sperm miRNA expression



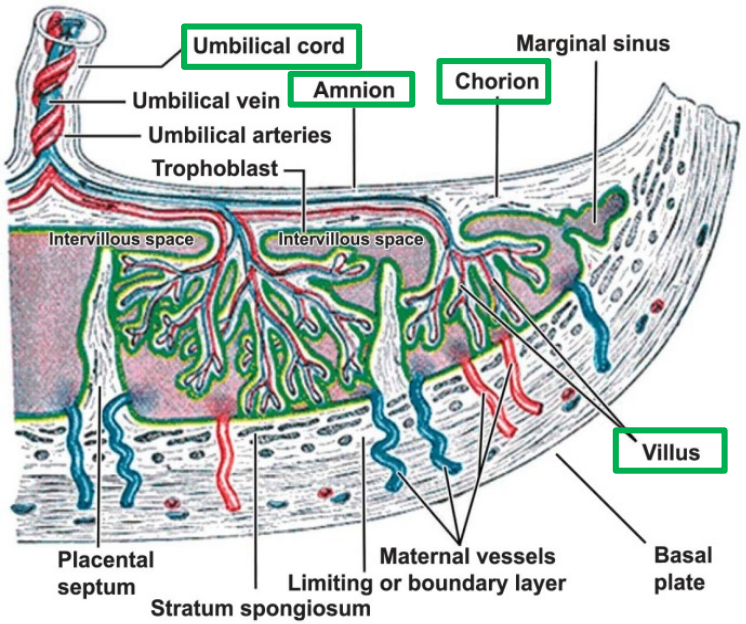
Recapitulation of stress transmission via sperm

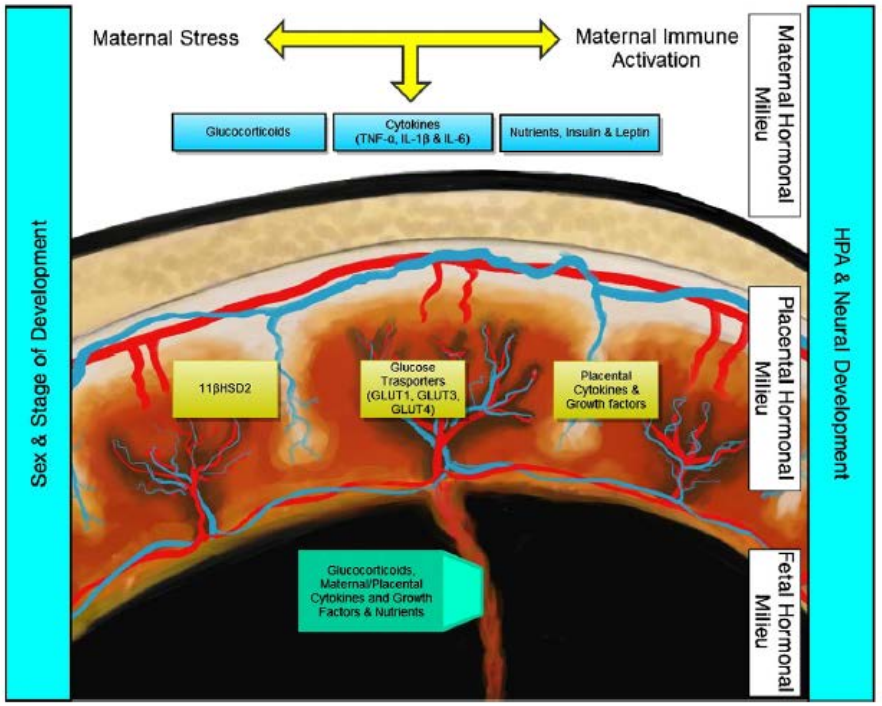




Rodgers AB, *et al. J Neurosci. 2013:*33(21):9003-9012
Rodgers AB, *et al. PNAS. 2015:*112(44):13699-13704

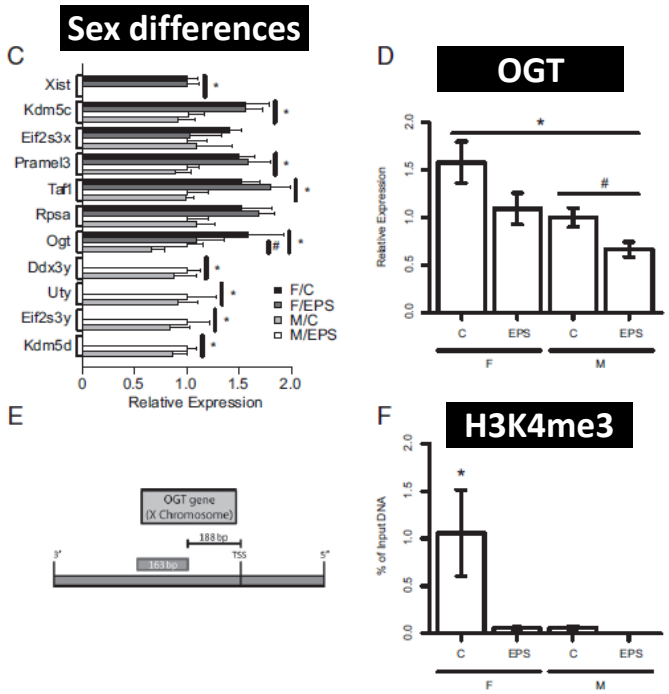
The role of the placenta

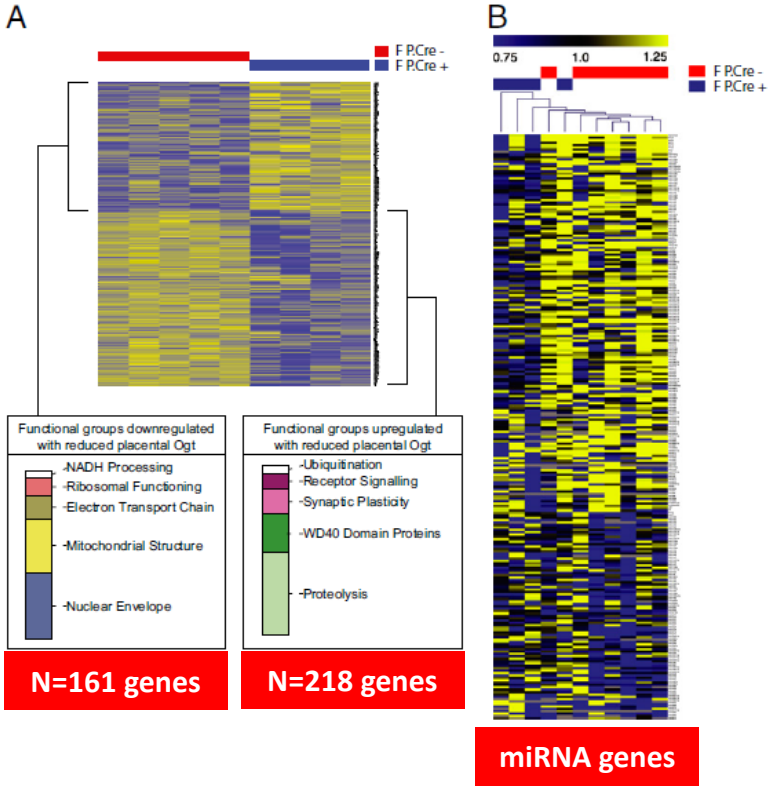




Serov AS, *et al*. *Journal of Applied Physiology.2015;* jap-00543
Howertown CL & BaleTL. Hormones and Behavior. 2012; 62:237-242

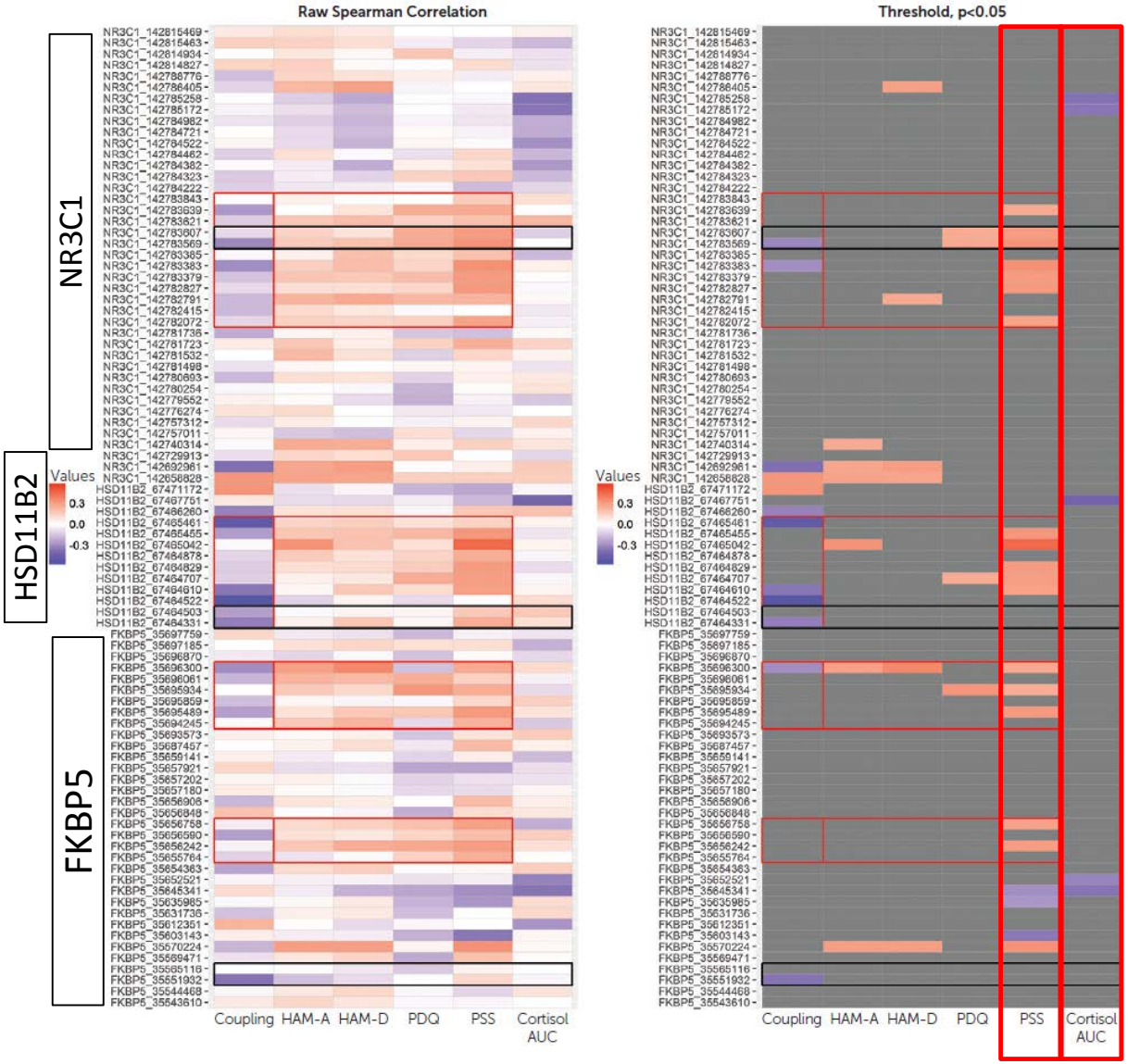
Sex differences and PNMS on placental gene expression





Howerton CL, *et al. PNAS. 2013;110(13): 5169-5174.*

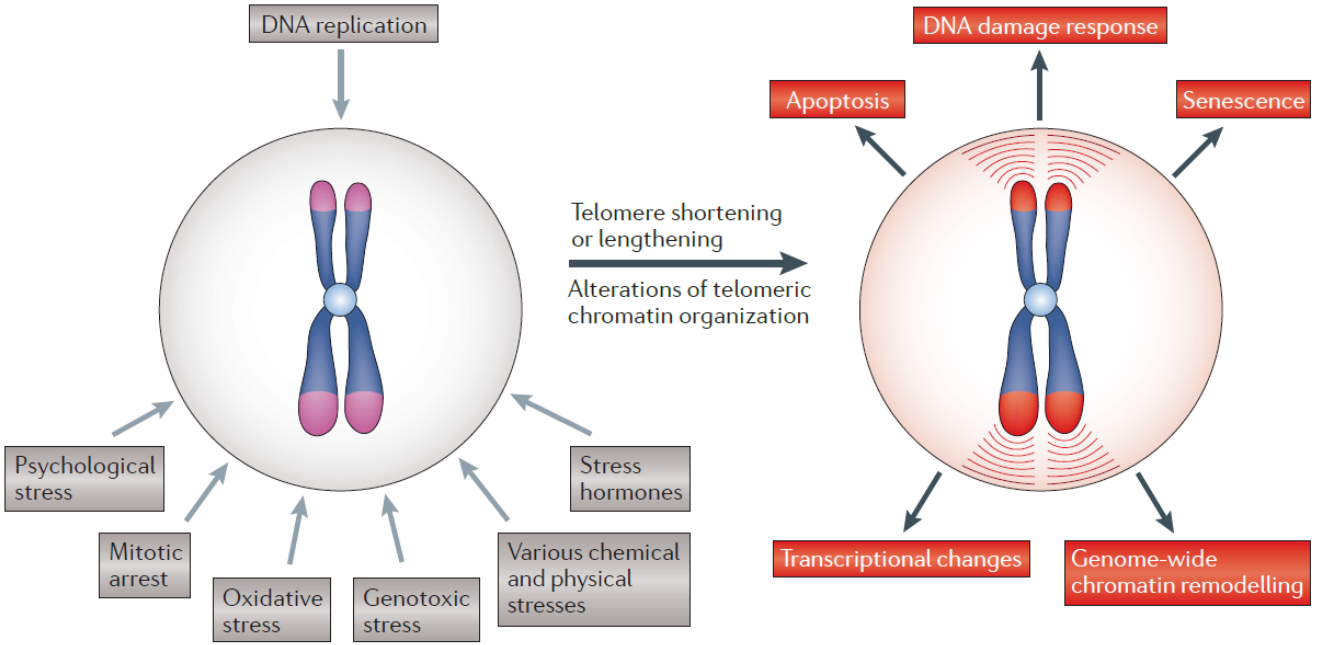
Human Placental DNA methylation and perceived stress



Monk C, *et al*. *Am J Psychiatry. 2016;173: 705-713.*

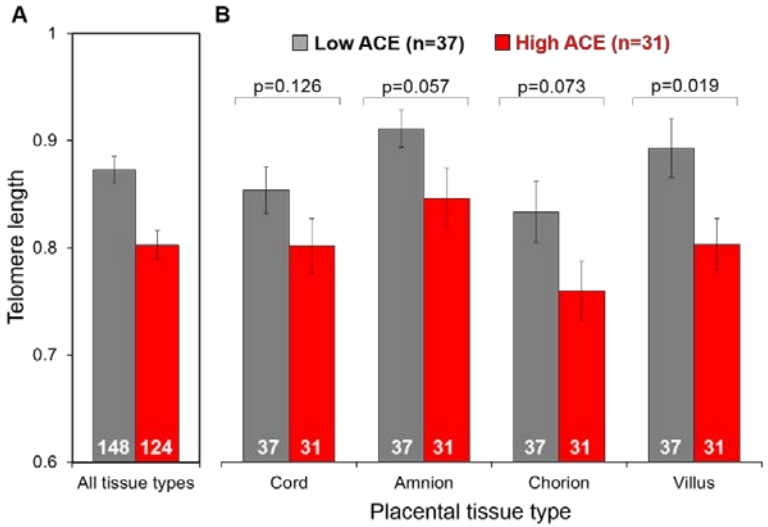
Mechanisms of preconception programming: Telomere length

Integration of exogenous and endogenous signals → **Altered cell fate**

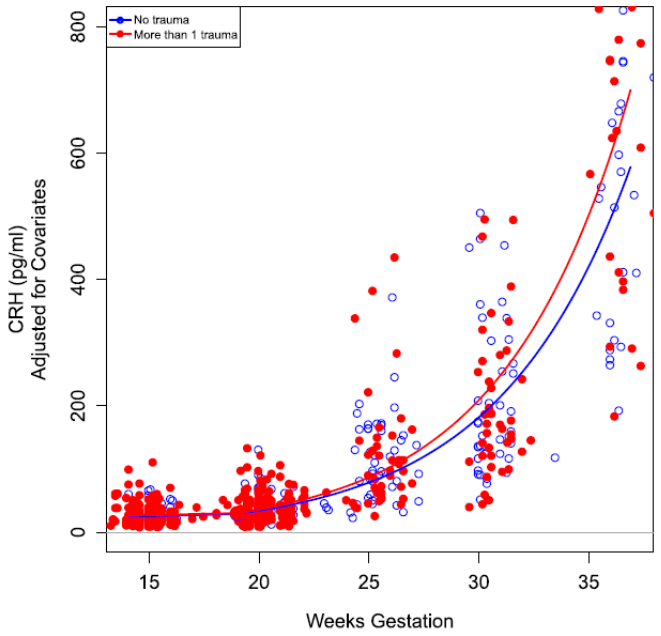


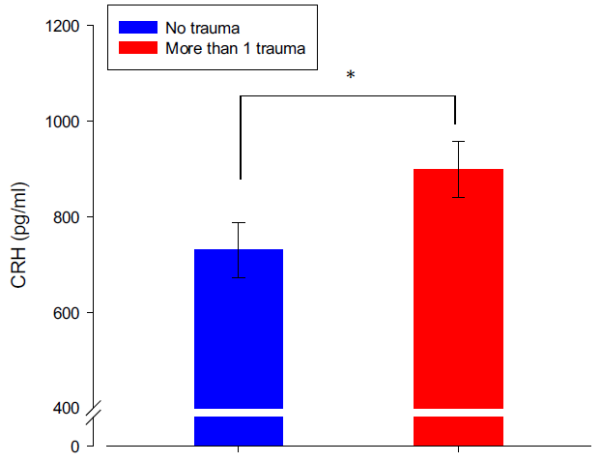
Ye J, *et al. Nat Rev Genet.* 2014: *15*(7):491-503.

Maternal preconception adversity induces placental changes



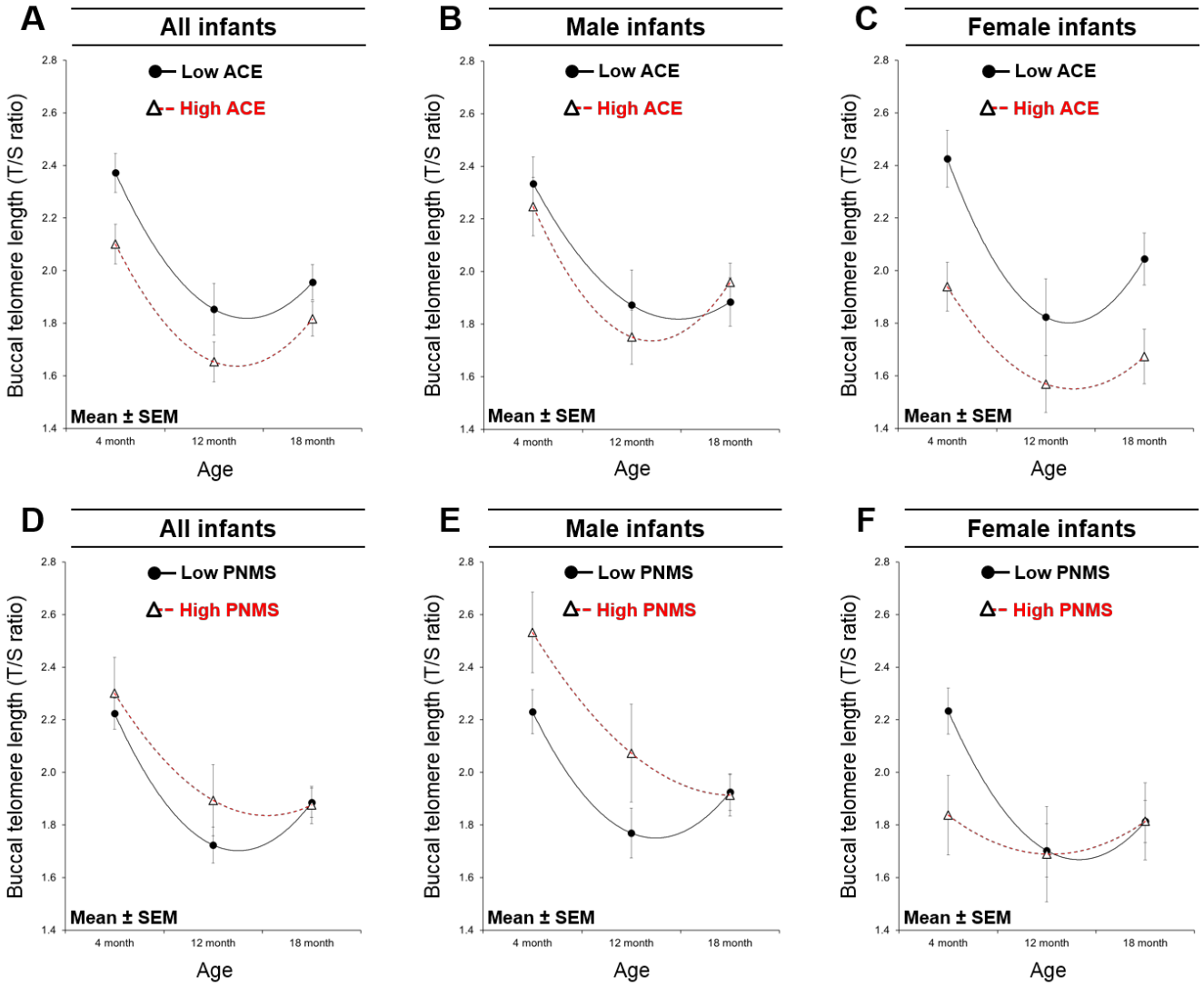
High maternal ACE exposure predicted shorter TL (β=-0.0736; p=0.018).





Data from BANGL. *In preparation*.
Moog NK, *et al. Biological Psychiatry*. 2016; 79:831-839

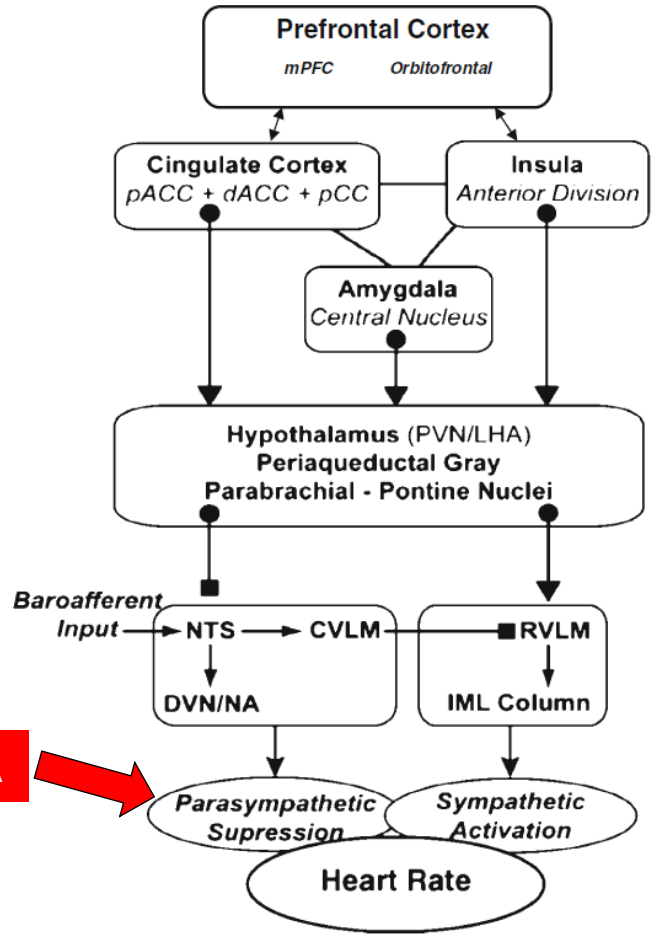
Preconception adversity and PNMS influence infant TL trajectory

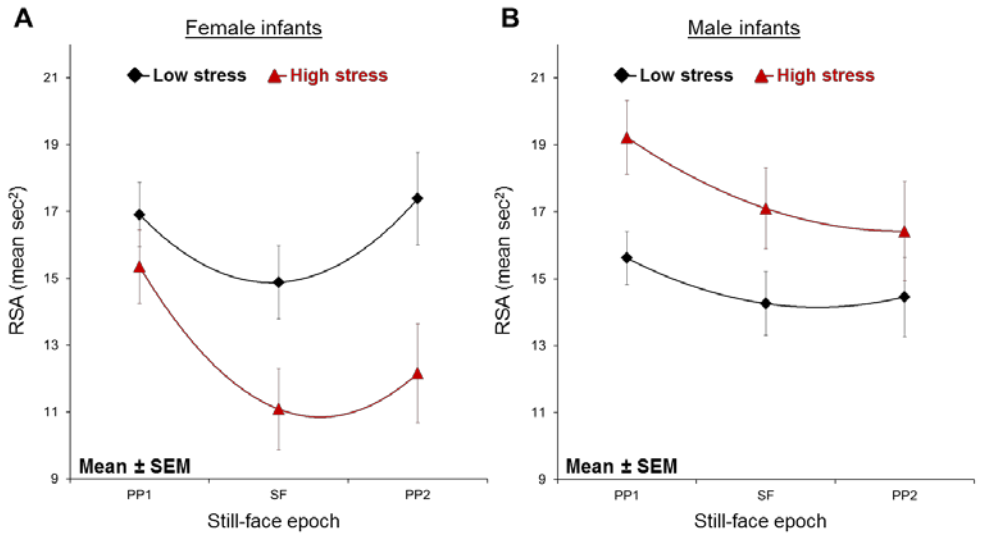


Esteves K.C., Jones C.W., *et al. Under review.*

Preconception and prenatal stress influences infant ANS stress response differently

ANS stress response



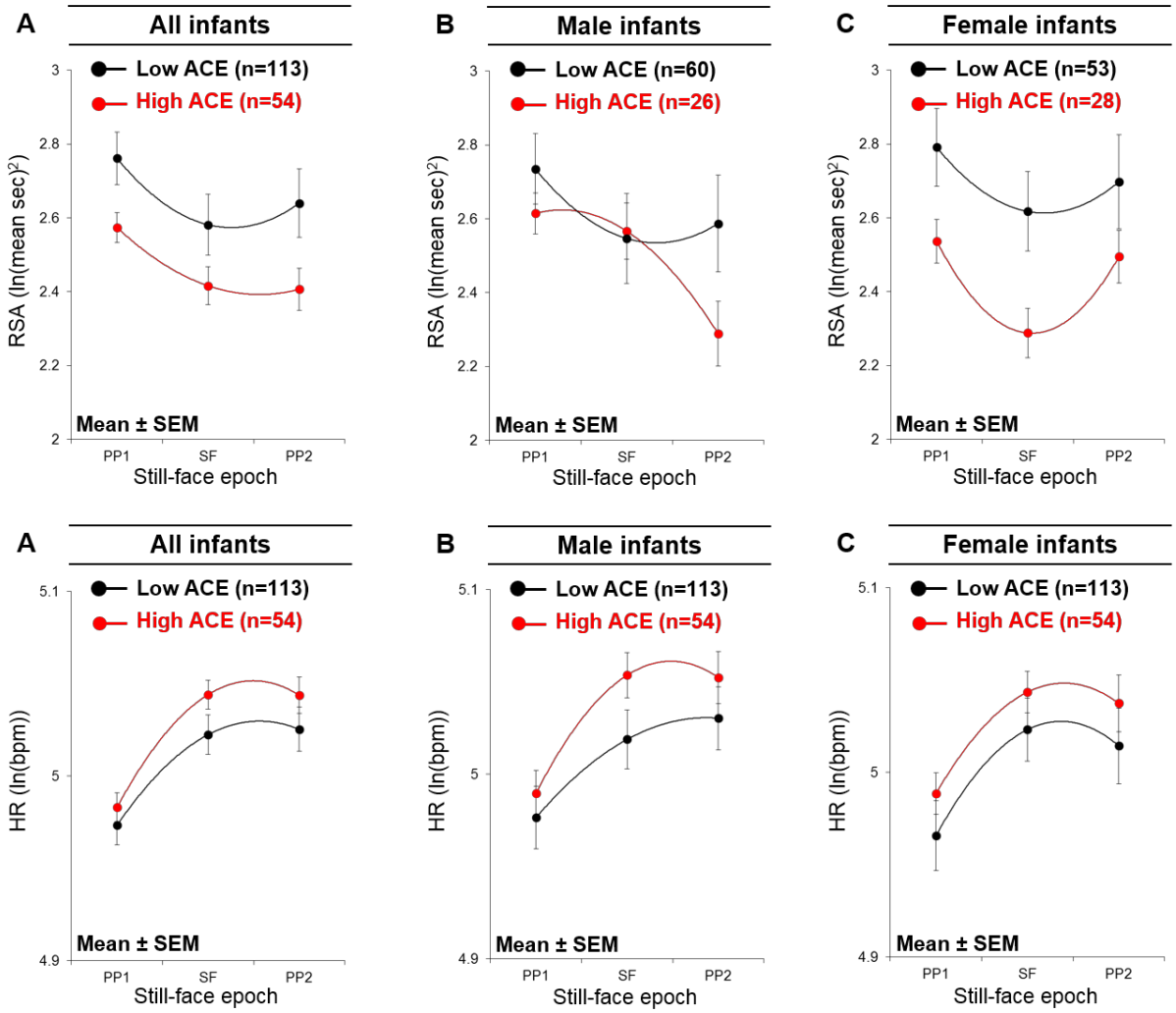


Infant RSA	B (SE)	*p* Value
Intercept	**3.22 (0.89)**	**<.001**
Time	**–0.48 (0.13)**	**<.001**
Time^2	**0.07 (0.03)**	**.05**
Sex	0.03 (0.09)	.75
Race	0.09 (0.02)	.26
Prenatal stress	**0.75 (0.04)**	**.05**
ACEs	**–0.20 (0.09)**	**.04**
Gestational age	–0.00 (0.02)	.84
Maternal education	–0.02 (0.03)	.55
Prenatal stress×time^2	**–0.02 (0.01)**	**.05**
Prenatal stress×sex	**–0.43 (0.18)**	**.02**
Time^2×sex	**0.02 (0.01)**	**.02**

Note: Data in boldface indicate significant effects.

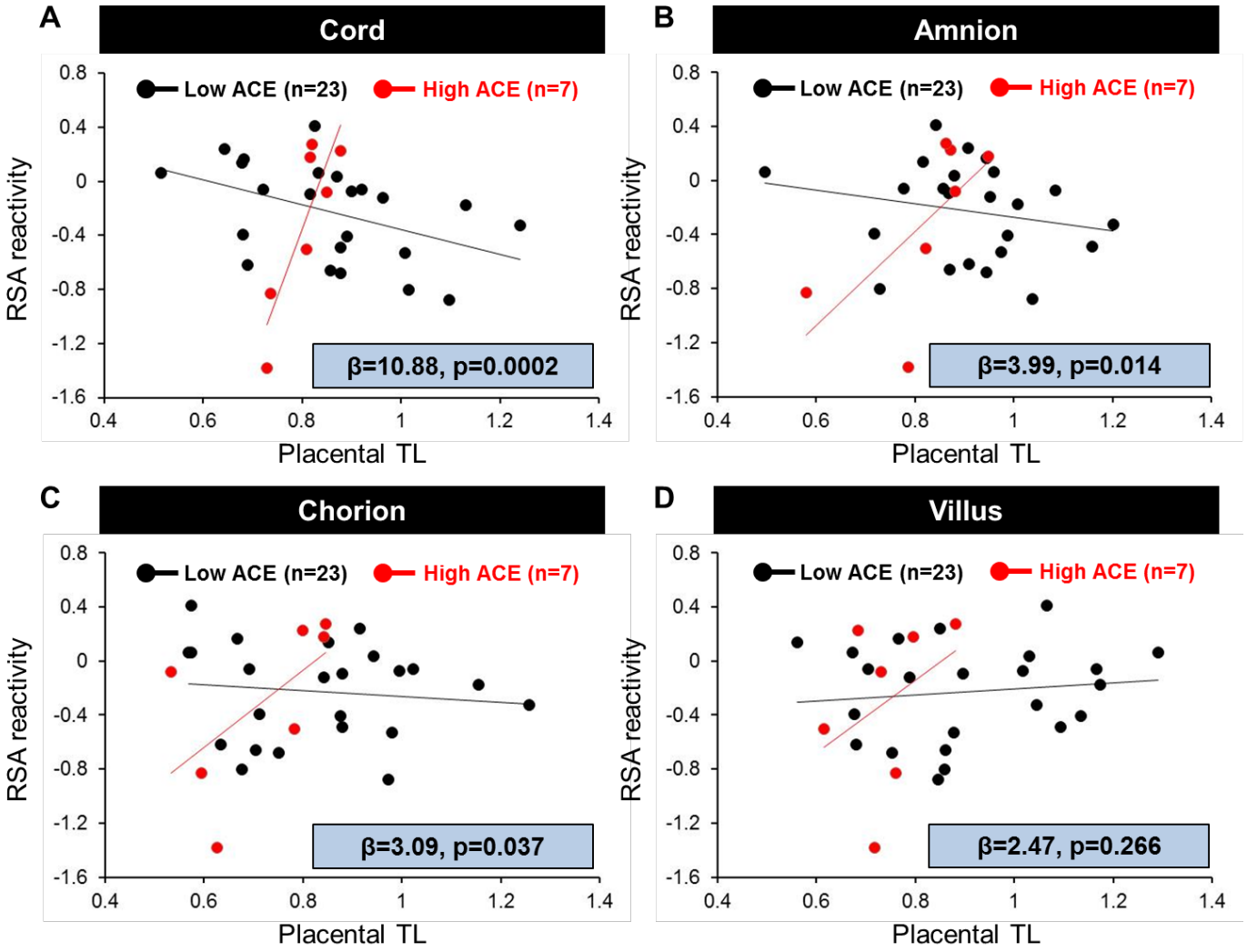
Gray S.A.O., *et al. J Am Acad Child Adolesc Psychiatry. 2017;56(11): 922-929*
Thayer, et al. 2009. *Annals of Behavioral Medicine*

Preconception influences infants in a sex-specific fashion



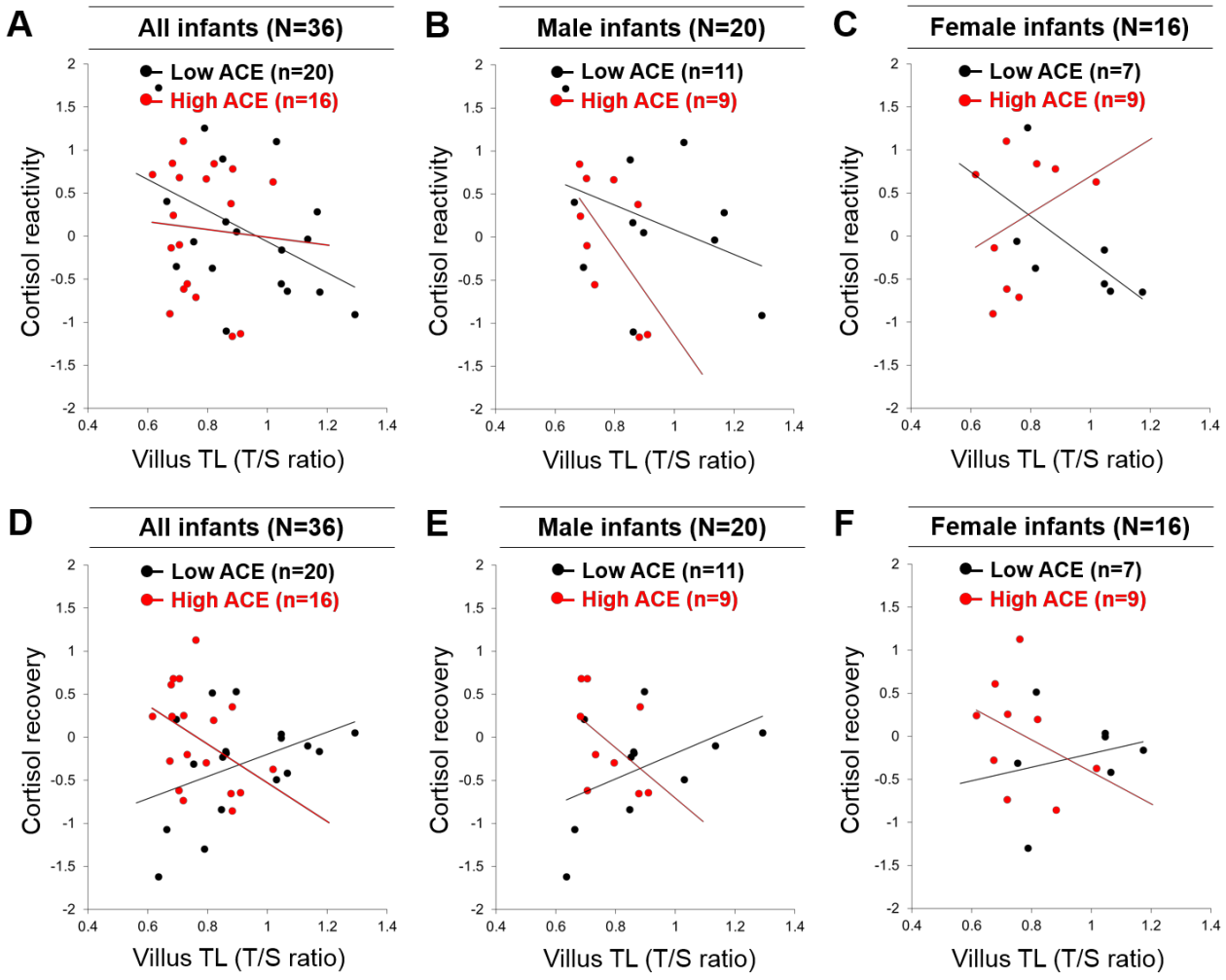
Gray S.A.O., *et al. J Am Acad Child Adolesc Psychiatry. 2017;56(11): 922-929*

Preconception adversity, placental TL, and ANS reactivity



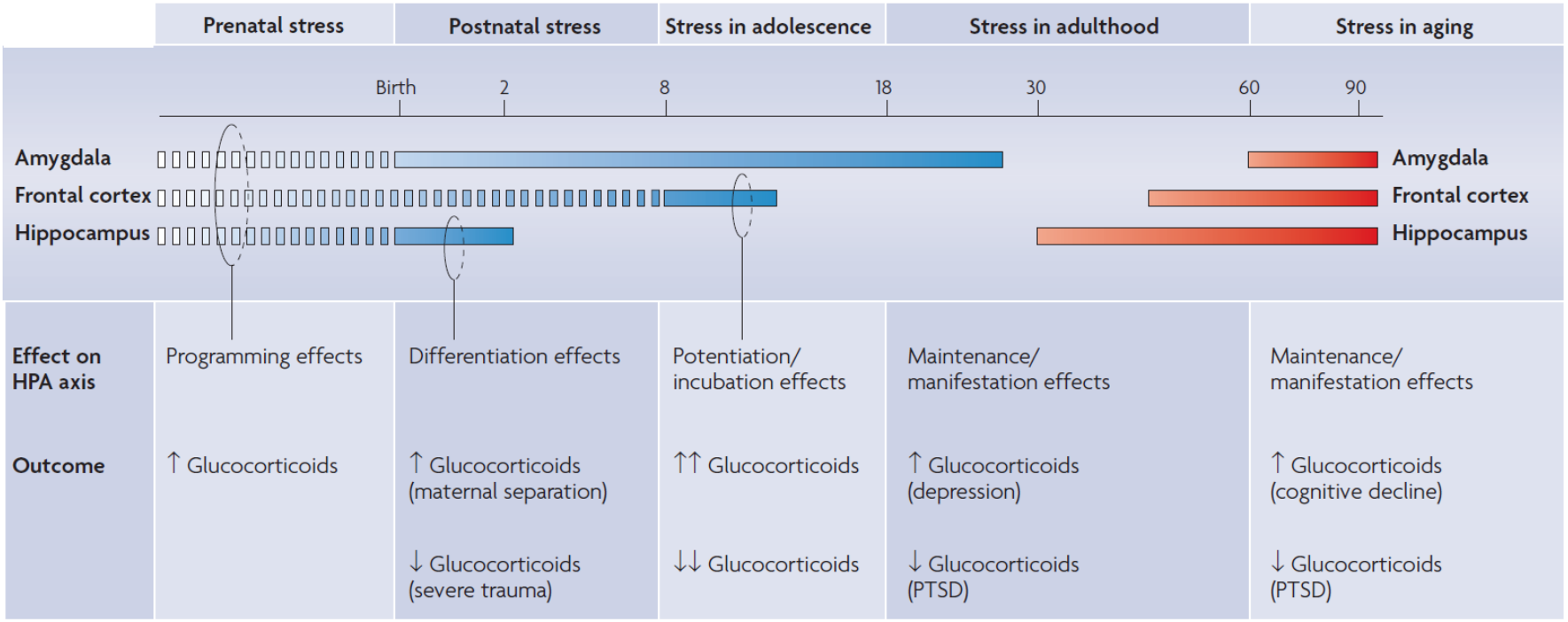
BANGL data. unpublished

Preconception adversity, placental TL, and cortisol



BANGL data. unpublished

Critical windows of vulnerability to stress across the life-course



- Brain regions develop and grow at different rates
- Exhibit differential age-related critical windows of exposure
- Overlapping cortico-limbic regulatory circuitry for HPA & ANS

Lupien, et al. 2009. *Nature Reviews Neuroscience*

Evolutionary and scientific round-up

- Preconception adversity and PNMS influences infant neurodevelopment
- Across domains, from genomic to humoral to behavioral levels
- Not only glucocorticoid signaling
- **Stress response is neither good nor bad**
  - Adaptive/maladaptive?
- Responsive to challenge and environment
  - Modifiable

Thanks

IDS:

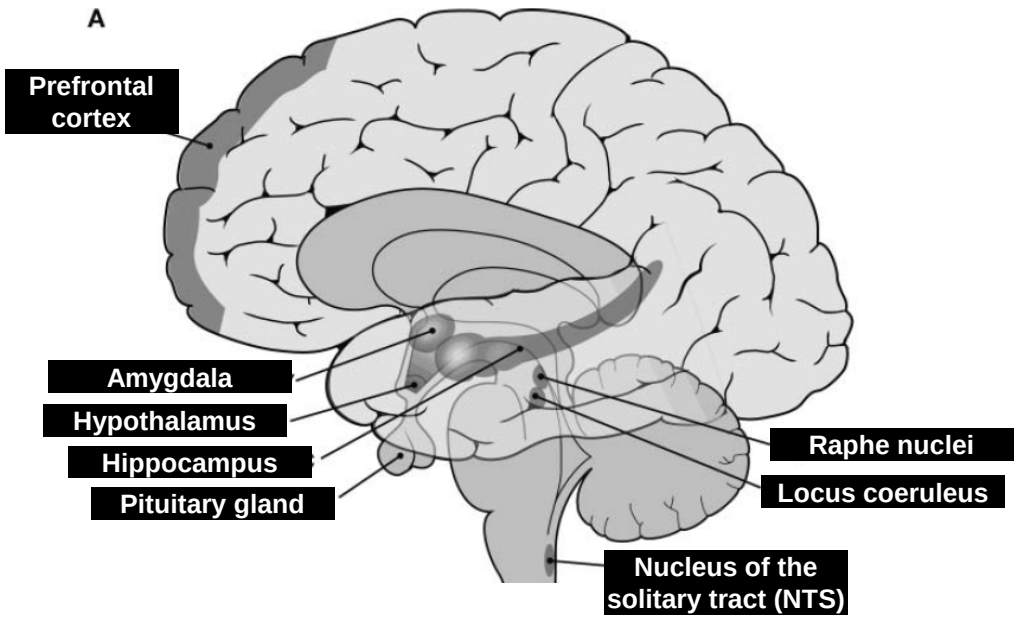
- **Stacy Drury, PI**
- Kyle Esteves
- Kelsey Confreda
- Tegan Clarke
- Michael Wren
- Andrew Dismukes
- Livia Merrill
- Jesse Smith
- Chanaye Jackson
- Rachel Lee
- Devin Videlefsky
- Keegan Collarame
- Megan Haney
- Cade Herman
- Sai Nedunchezhian

COLLABORATORS:

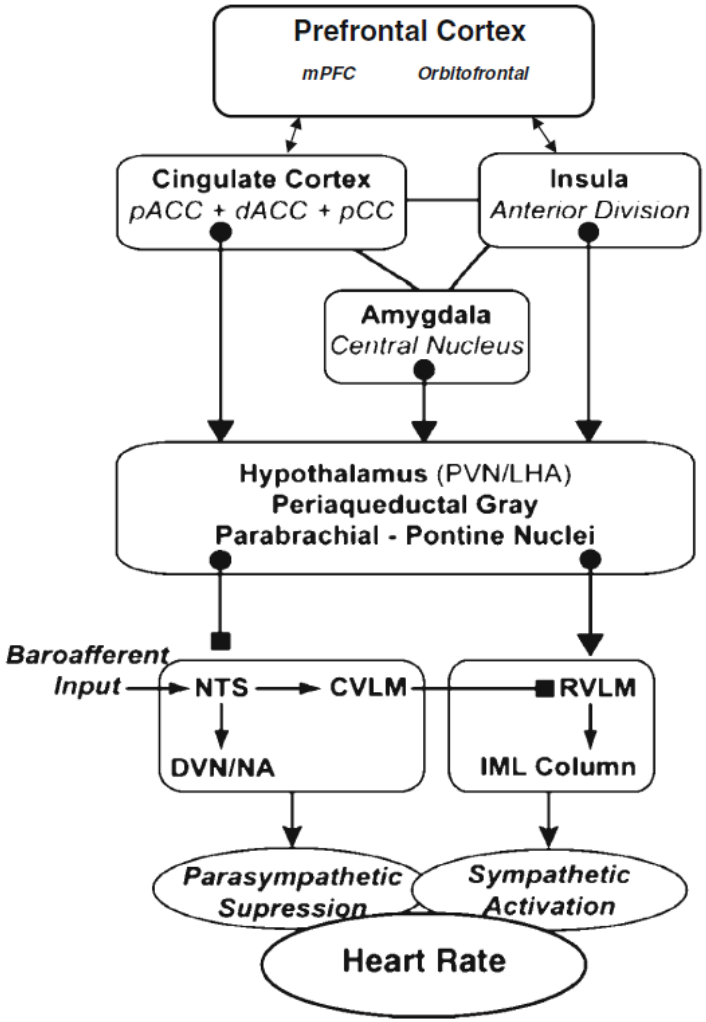
- Elizabeth Shirtcliff
- Charles Zeanah

Basic neuroanatomy of HPA & ANS regulation

HPA



ANS



Gunner, et al. 2007. *Annual Review of Psychology*
Thayer, et al. 2009. *Annals of Behavioral Medicine*