Epigenetic Programming by Early-Life Stress: Translational approaches from Rodent to Human and back

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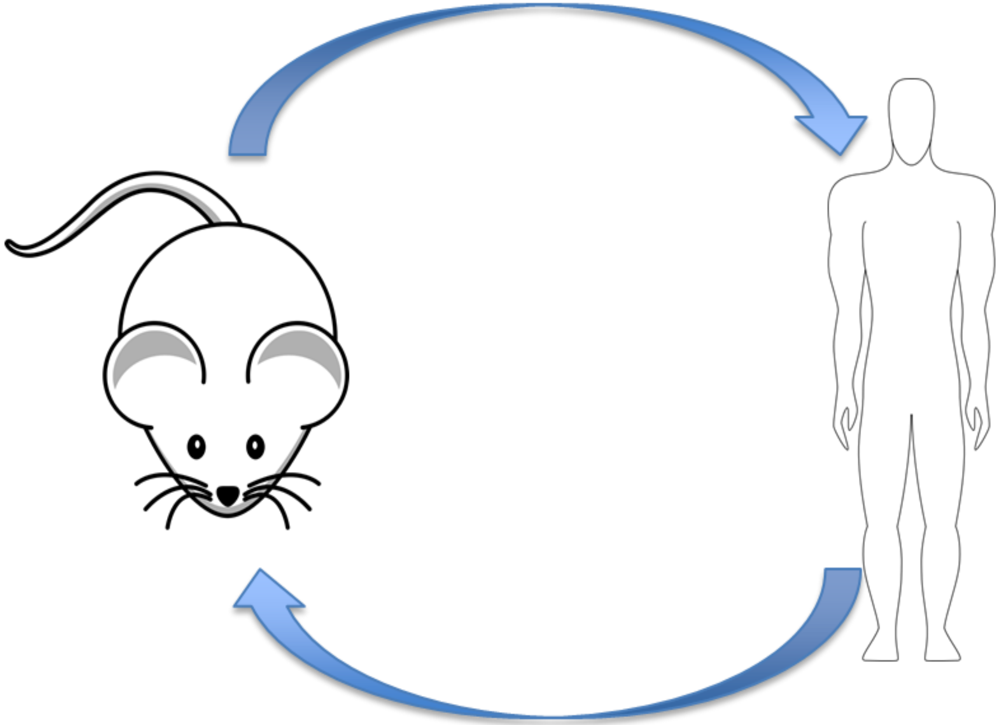
Manchester Metropolitan University

Translational animal models



Animal models for stress: testing/developing hypotheses

Control for environment and genetics

Generation of different animal model paradigms

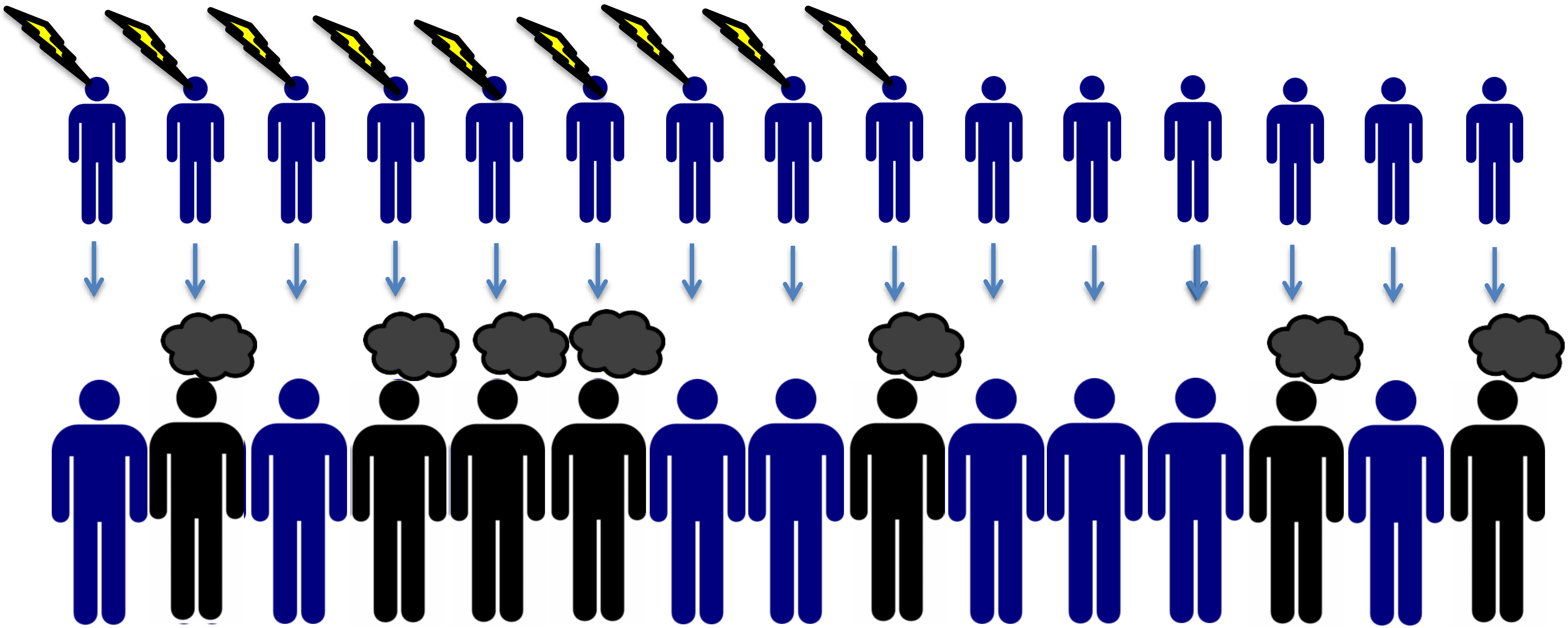
Different tests

Access to tissues, e.g. brain

Transgenics

Selective breading

Childhood trauma leads to increased risk of depression in adulthood

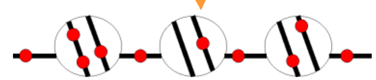


Adaption

Genome

Adaptation

Stress



epigenome

Programming of Endocrine Circuits

„good“ adaptative

Neuroendocrine Phenotype

maladaptative

Adult environment

susceptibility to mood disorders

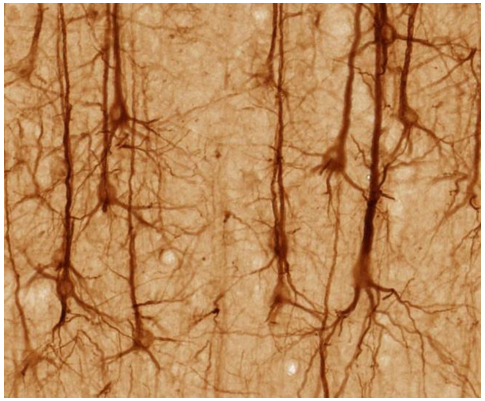
Murgatroyd & Spengler Front Psychiatry 2011

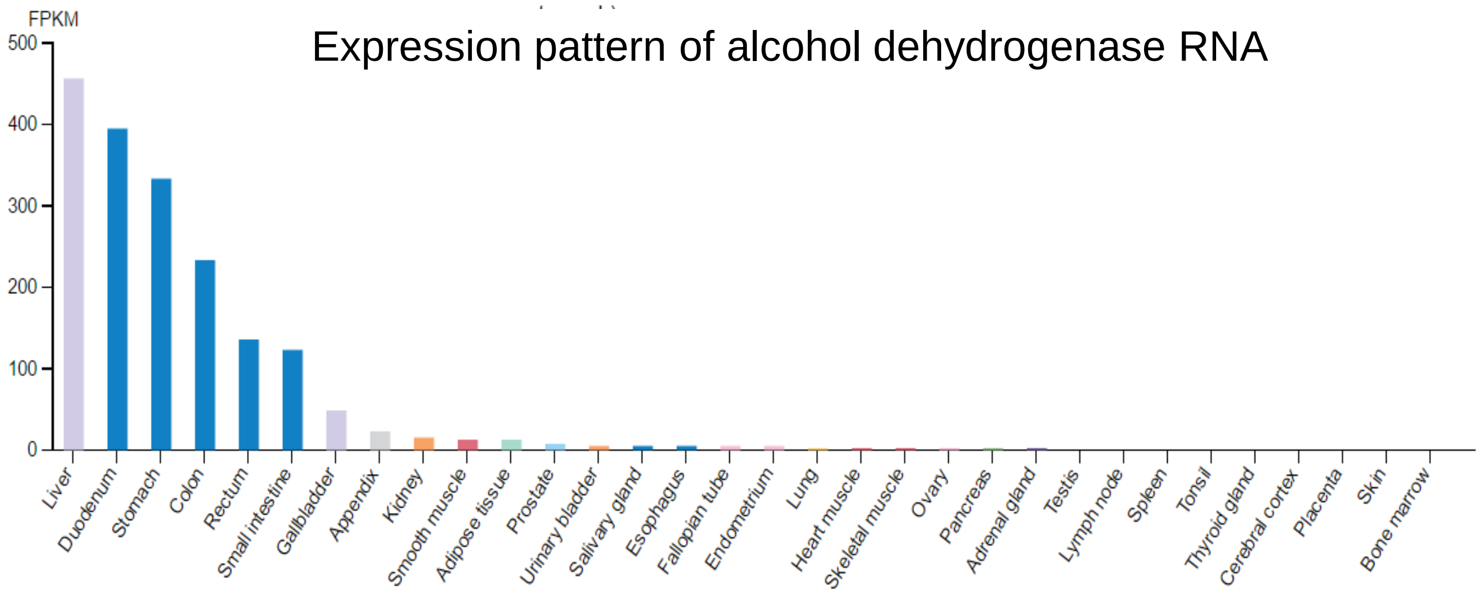
Epigenetic programming of early-life stress

Early-life stress epigenetically programs the expression of genes regulating stress

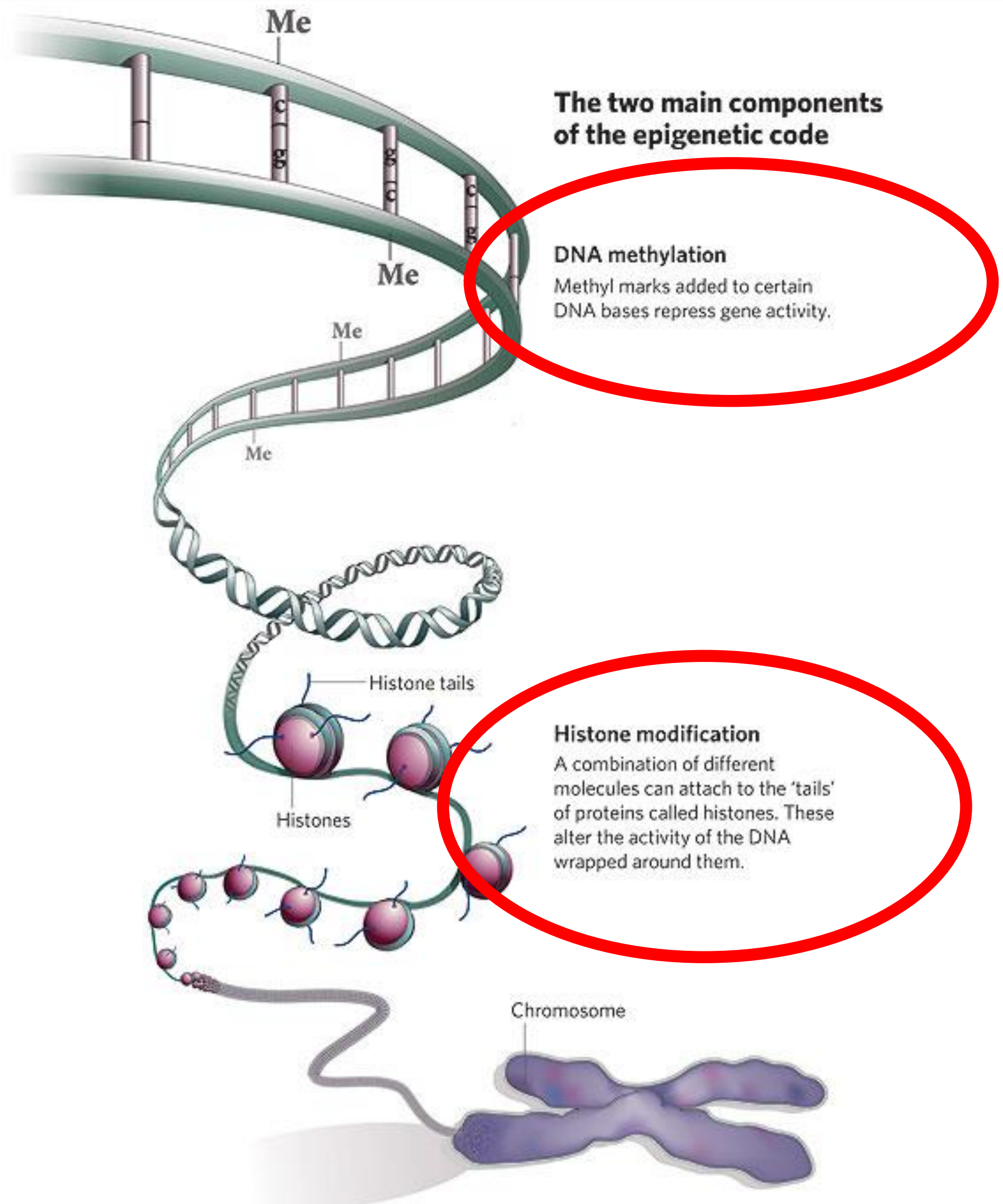
epi = above/upon, genetics

Only 10-20% of genes are active in any cell.

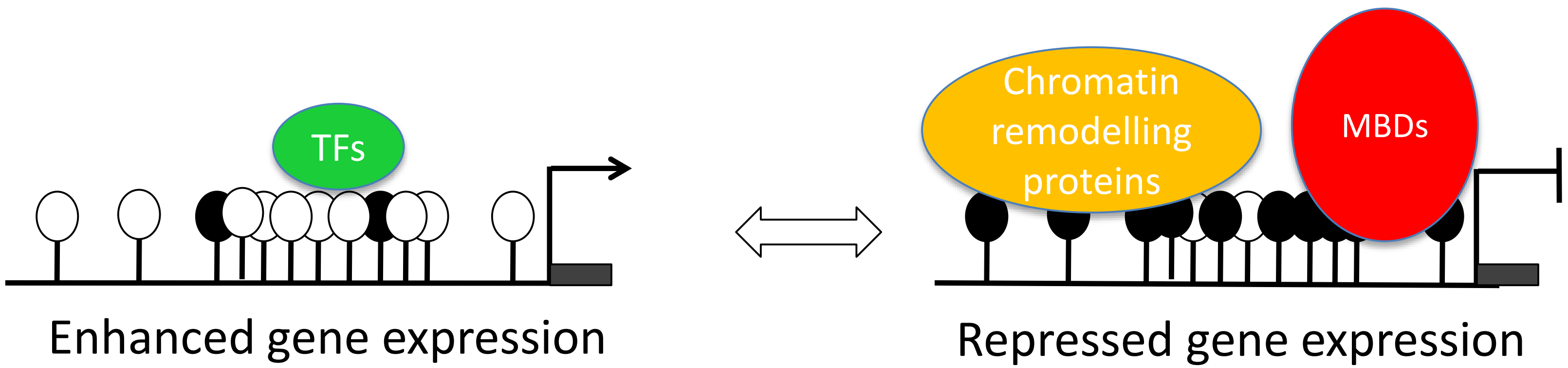


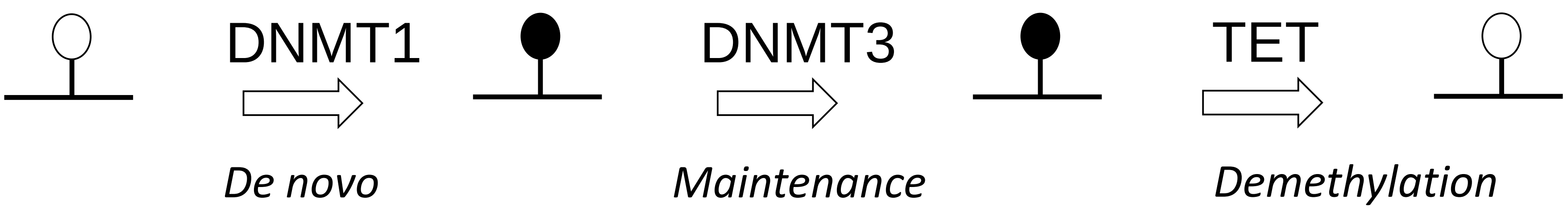


Gene silencing that occurs without changes in the DNA sequence

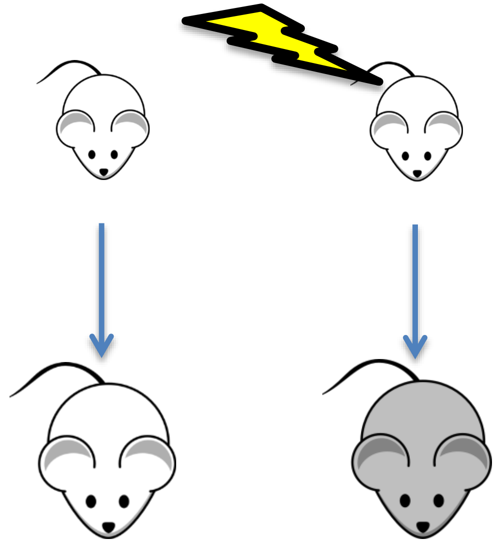


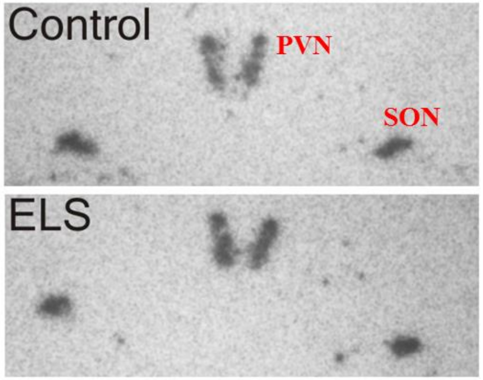
DNA methylation at gene regulatory regions can inhibit transcription



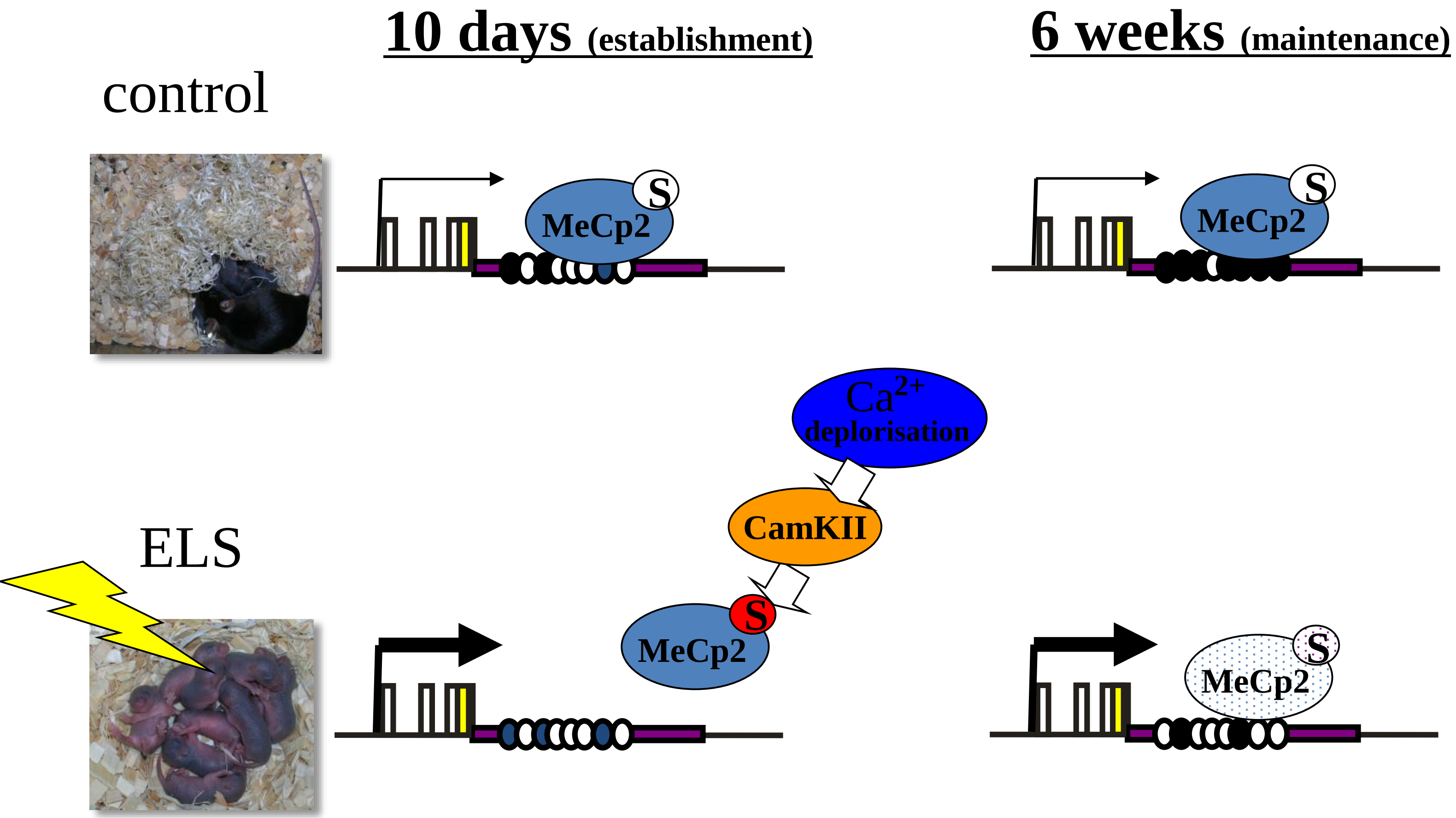


Early-life programming of anxiety & depression





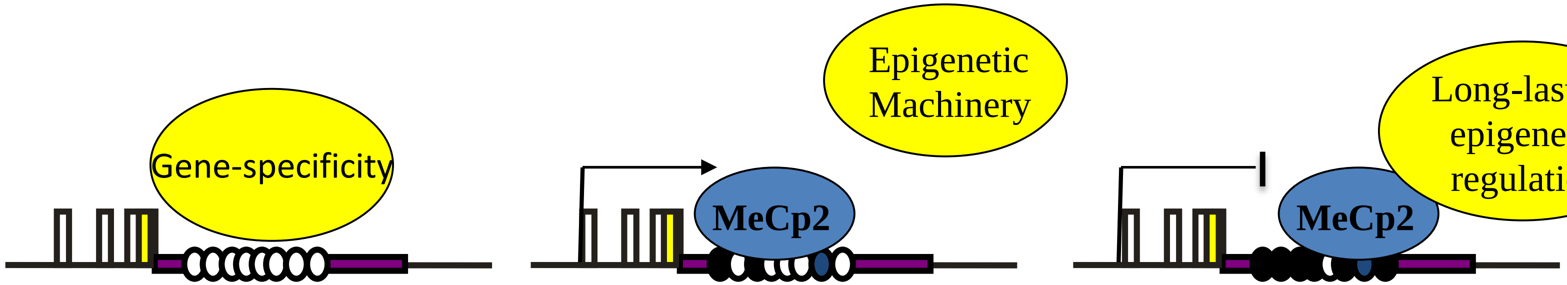
Molecular model for early-life stress programming



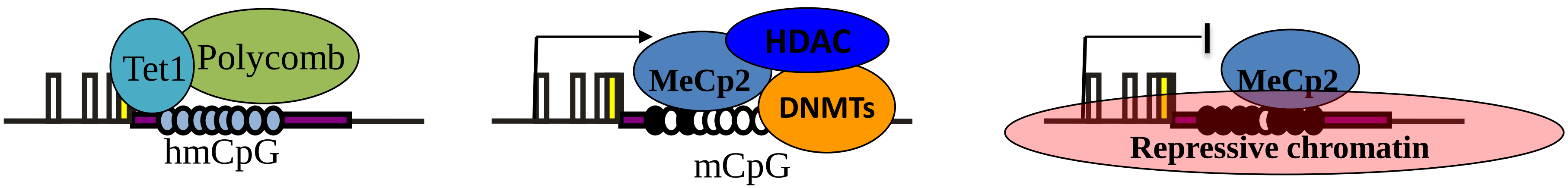
Murgatroyd et al. *Nat Neuro* 2009

What are the mechanisms for the gene-specific marking

“Factor(s)”?



„some" of the factors…

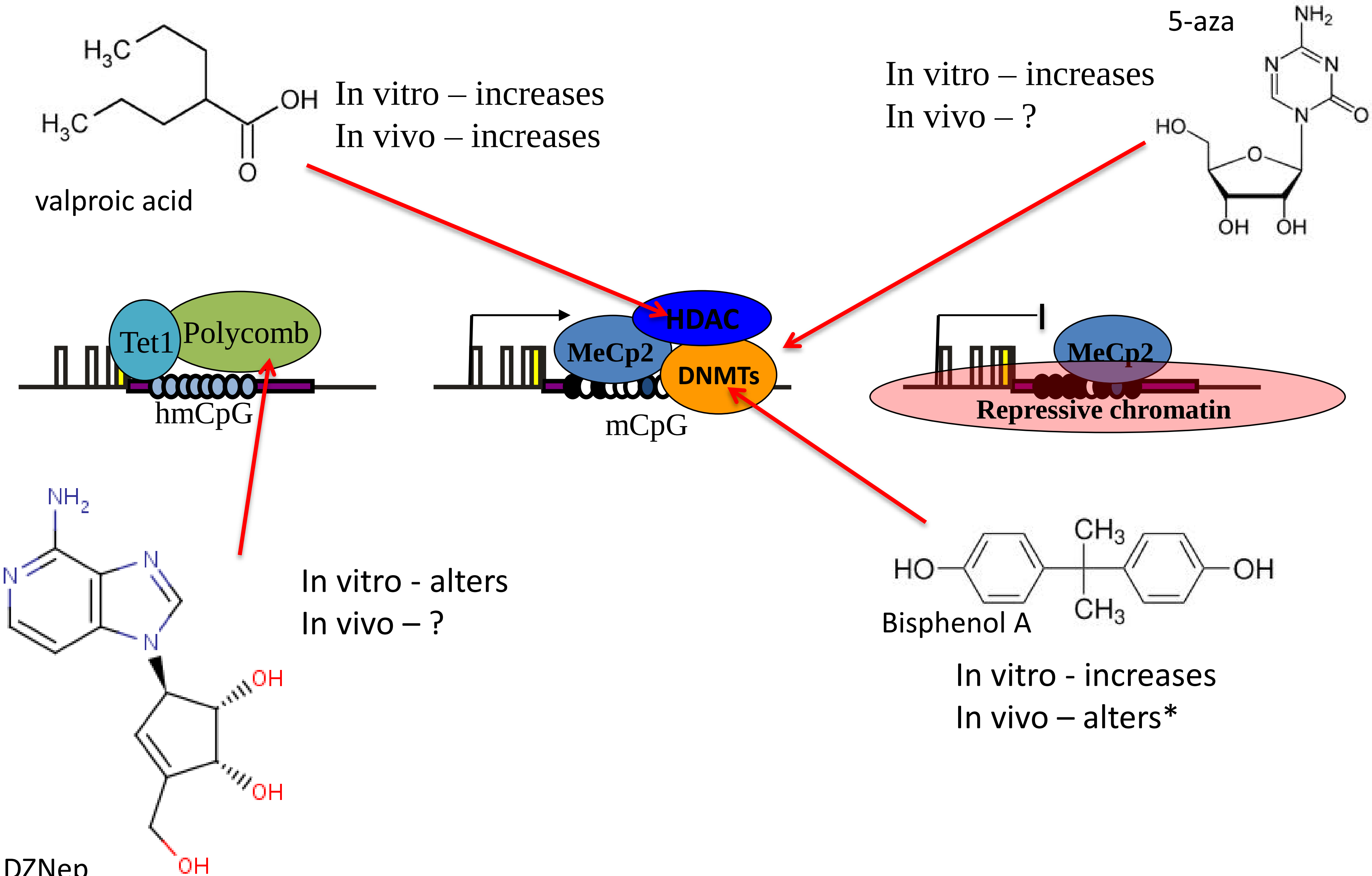


ESC → Hypothalamic progenitors → Vasopressin Neurons

→ prenatal → postnatal → Adult

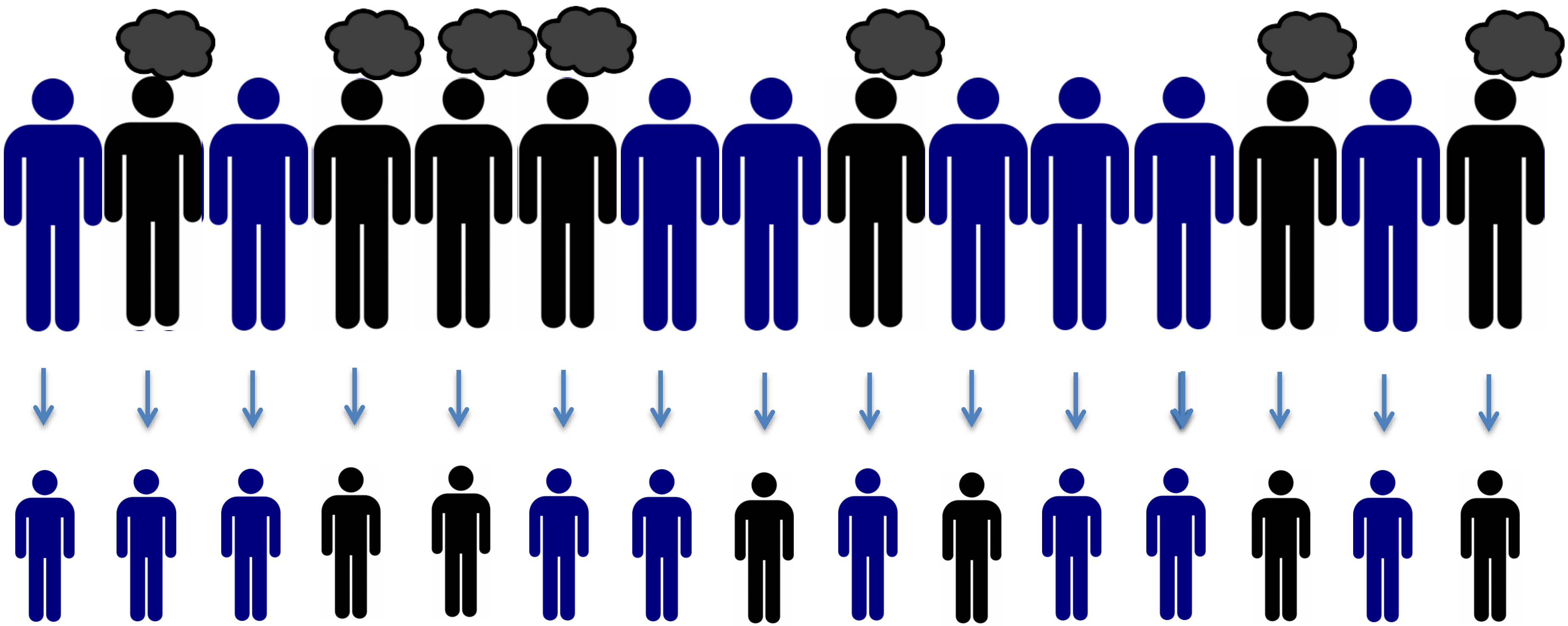
Murgatroyd & Spengler, *PloS one*, 2014

Pharmacologically targeting epigenetic regulation of AVP



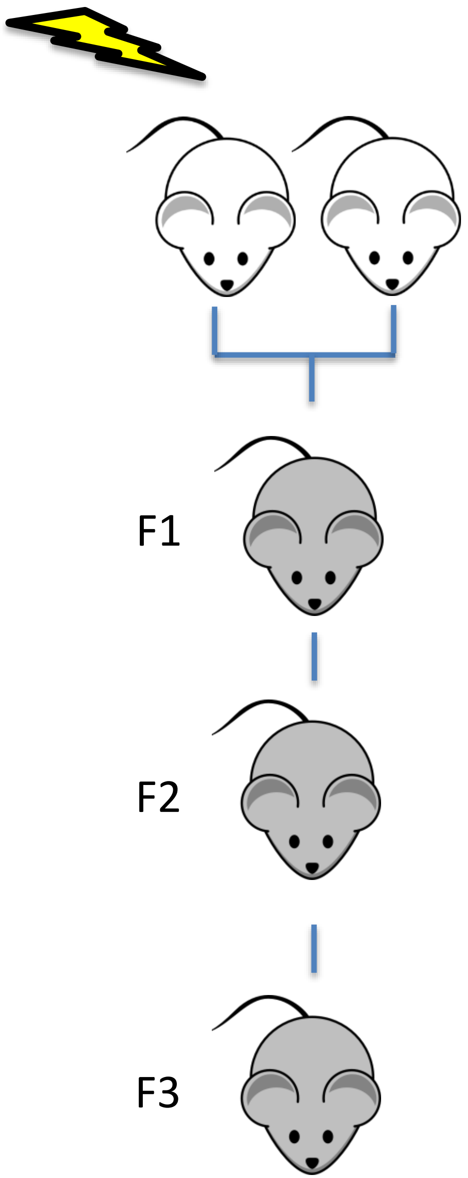
Murgatroyd & Spengler, *PloS one*, 2014

Children of depressed parents are at high risk for depression themselves



Inheritance of acquired stress

Inheritance of acquired stress



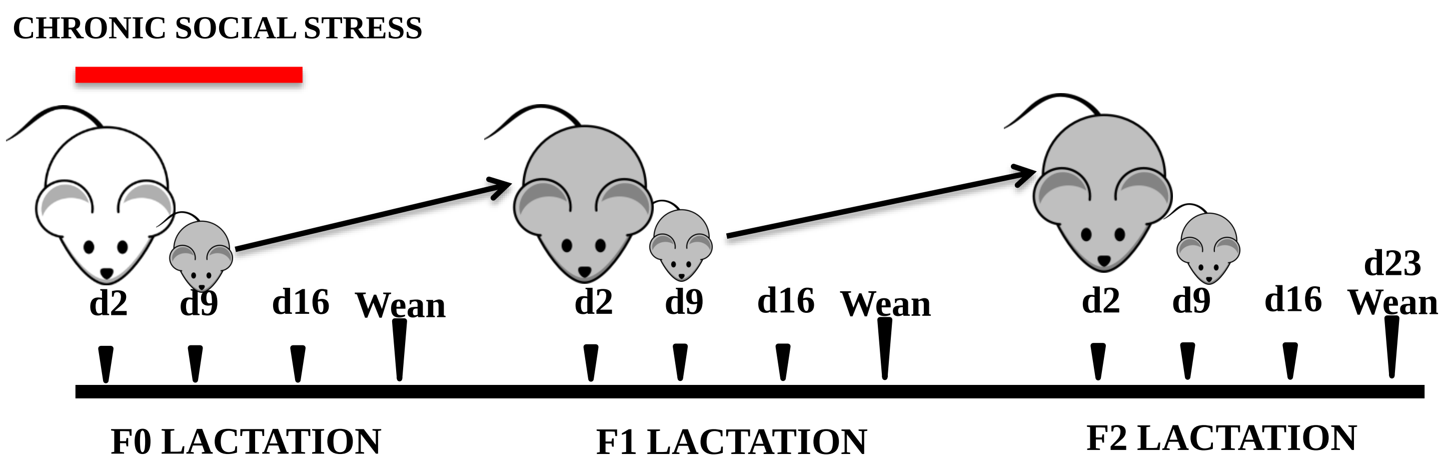
Epigenetic

Behaviour

Endocrine & Immune

Milk (lactocrine programming)

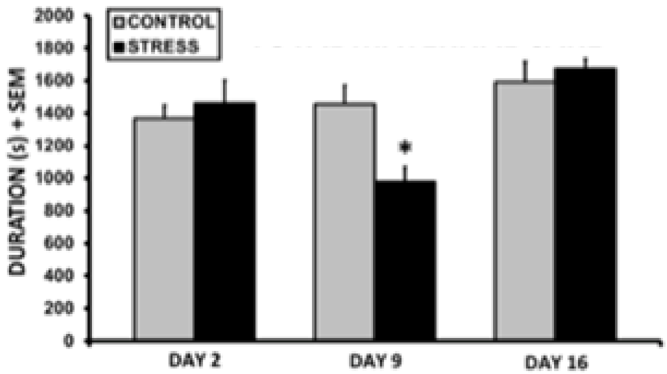
Generational chronic social stress model for maternal behaviour



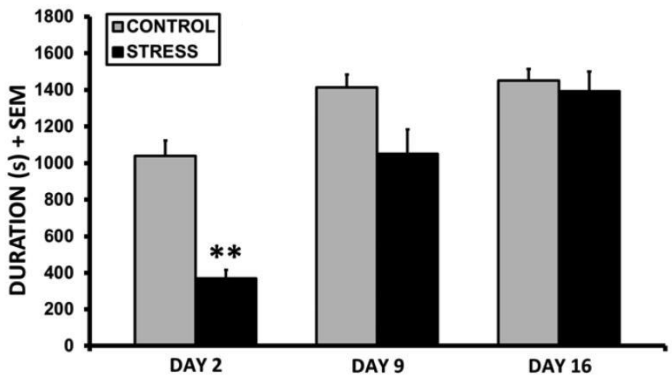
Murgatroyd & Nephew Psychoneuroendocrinol. 2013

Reduced maternal care (including pup grooming)

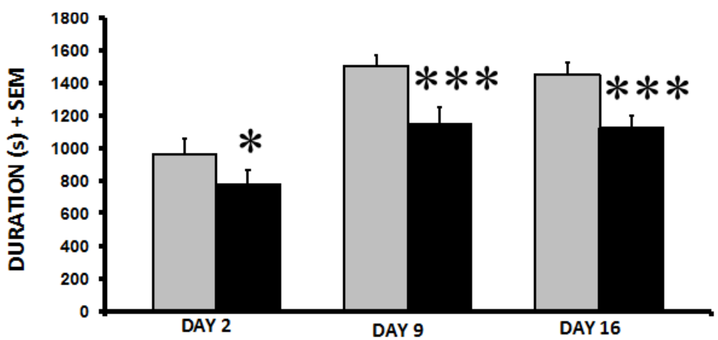
F0

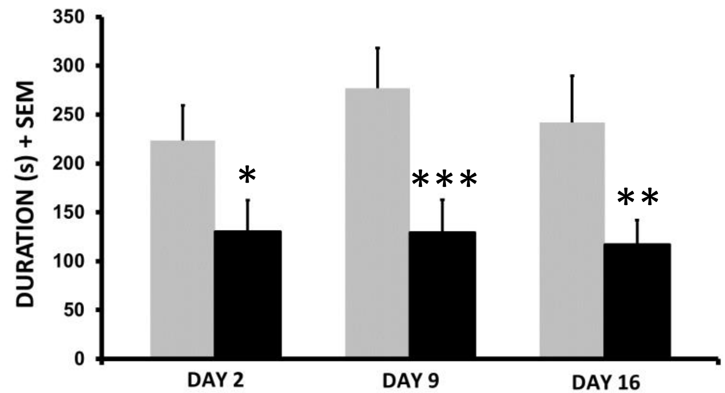


F1



F2





Intergenerational transmission of maternal measures

MATERNAL FACTORS	F0			F1			F2		
	Day 2	Day 9	Day 16	Day 2	Day 9	Day 16	Day 2	Day 9	Day 16
MATERNAL CARE	-----	↓	-----	↓	-----	-----	↓	↓	↓
MATERNAL RESTLESSNESS	-----	↑	-----	↑	-----	-----	↑	-----	↑
MATERNAL AGGRESSION	-----	↑	↑	↑	-----	-----	-----	-----	-----
MILK INTAKE	-----	↓	↓	↓	-----	-----	-----	-----	-----
Corticosterone (Day 23)	-----			↑			↓		
Prolactin (Day 23)	-----			↓			-----		
Gene Regulation	PVN: ↑ GR MeA: ↓ OXT			PVN, SON, CeA, MeA: ↓ OXT PVN: ↓ OXTR, PRLR, AVP			-----		
Nr3c1 exon 1.7 Methylation	PVN: ↑ CpG2			PVN: ↑ CpG3 Hipp: ↓ CpG1-6			-----		
ICAM-1 (Day 23)	-----			-----			↓		

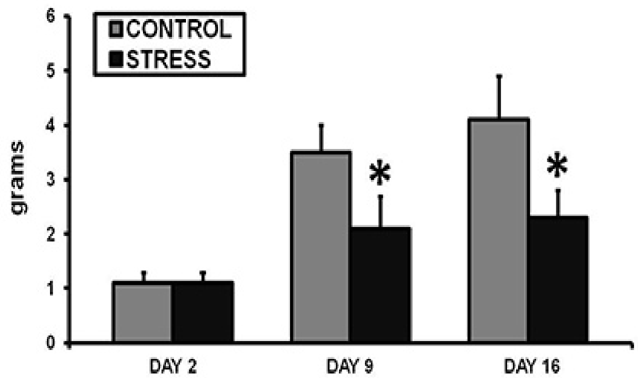
Nephew et al. *Psychoneuroendocrnology* 2017

Milk production (intake), Milk Corticosterone

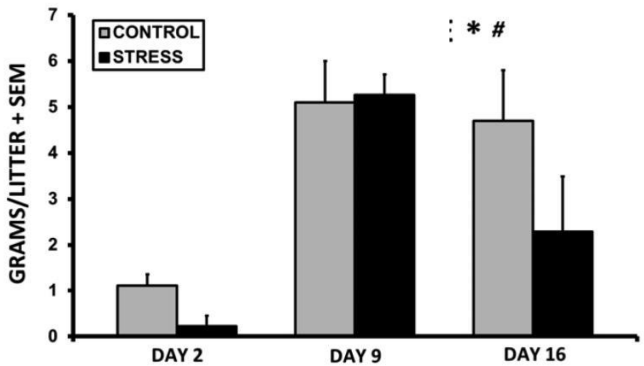
Milk production

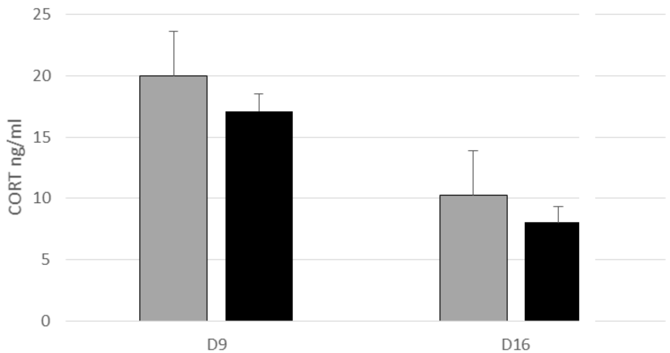
Milk corticosterone

F0



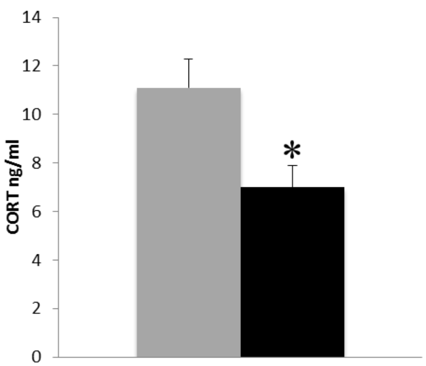
F1





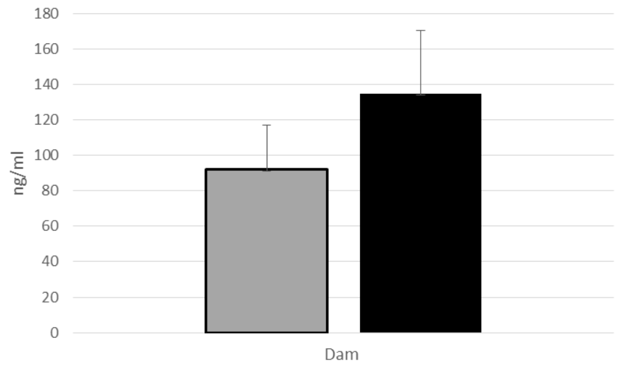
F2

No differences

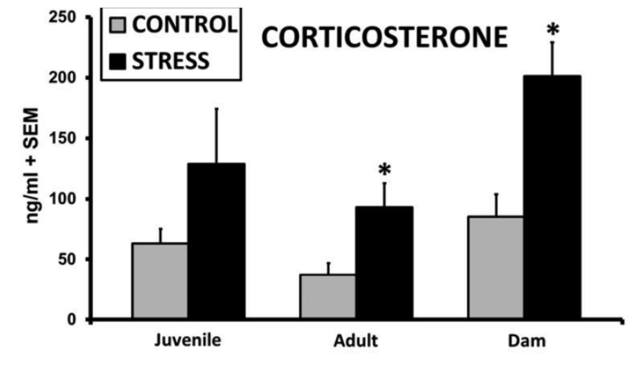


Serum Corticosterone

F0



F1



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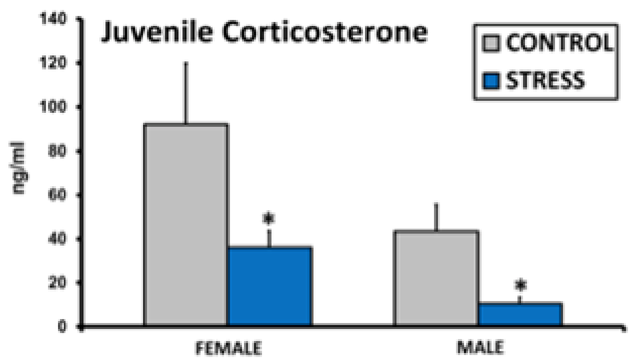
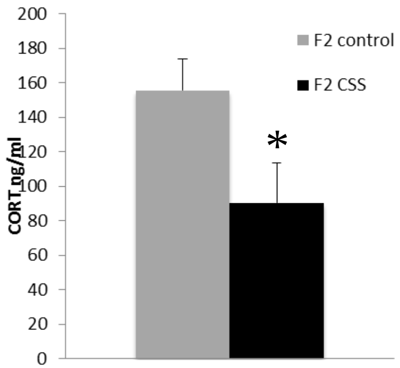
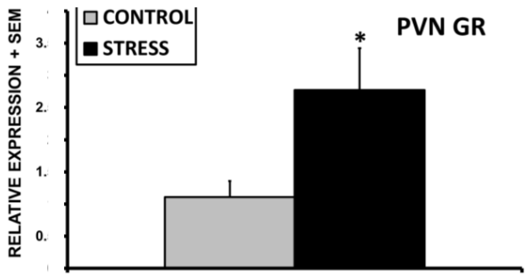


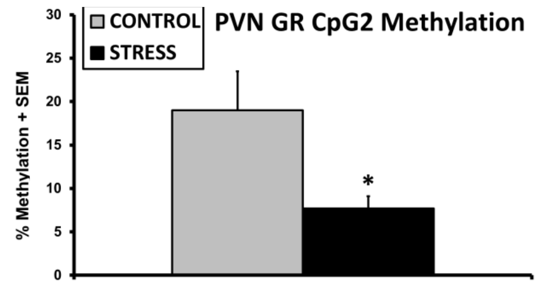


GR regulation

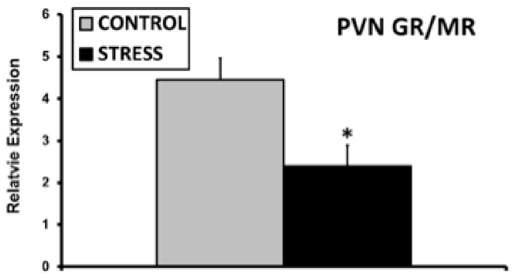
PVN expression | PVN Methylation | Hippocampus Methylation

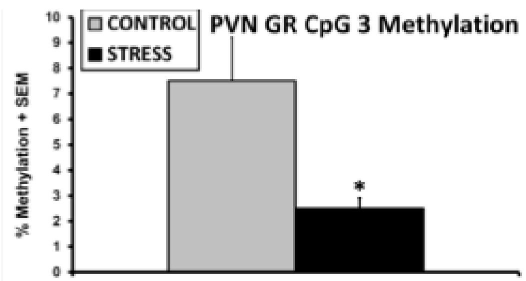
F0

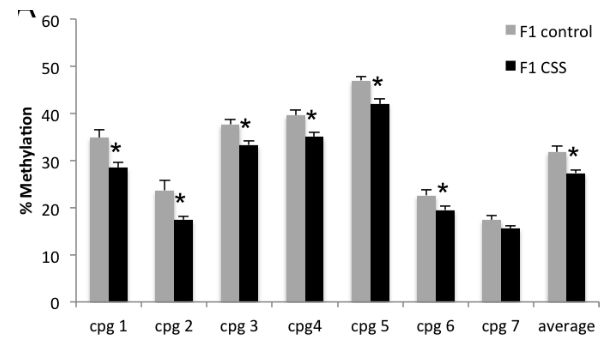




F1

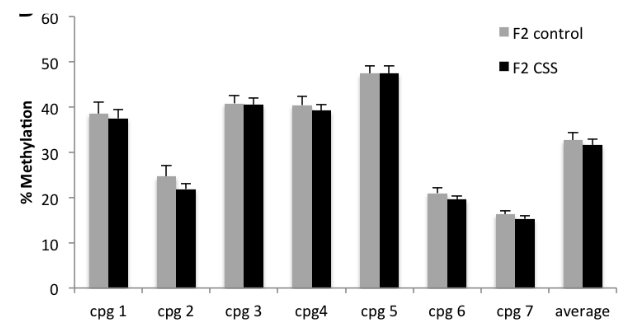






F2

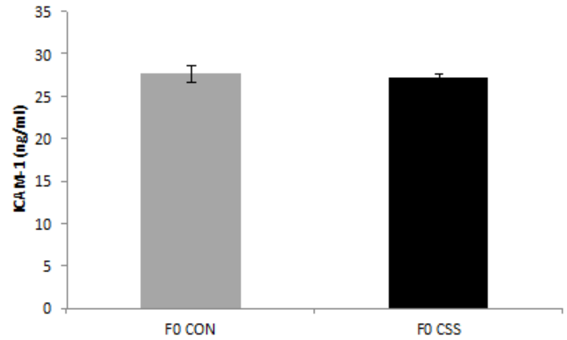
No differences



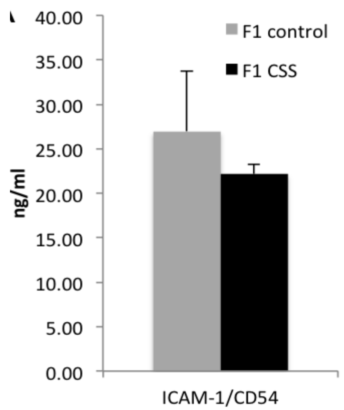
*Intergenerational genomewide analysis ongoing

Immune markers (ICAM-1)

F0

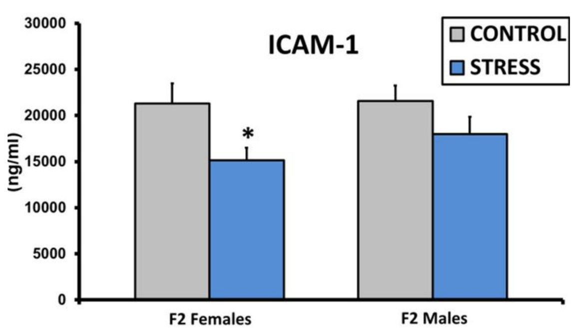


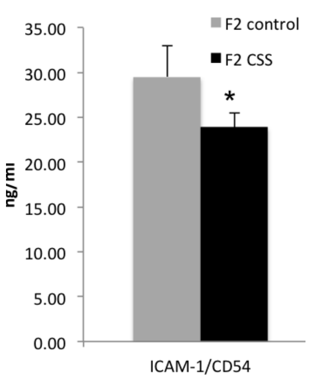
F1



F2

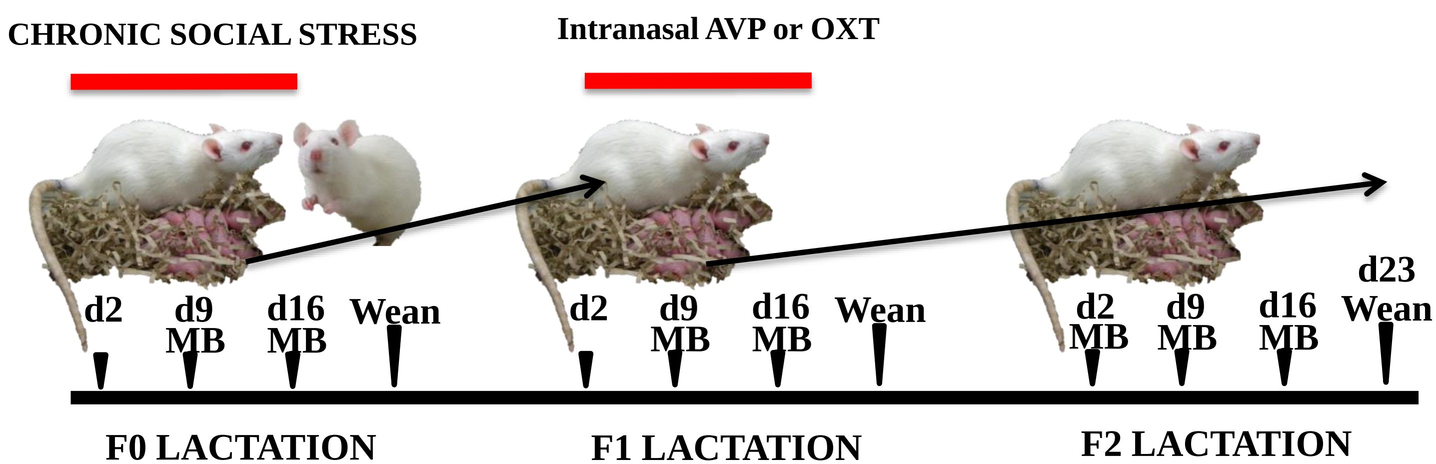
IFNg
IL18,
a1AGP,
BDNF

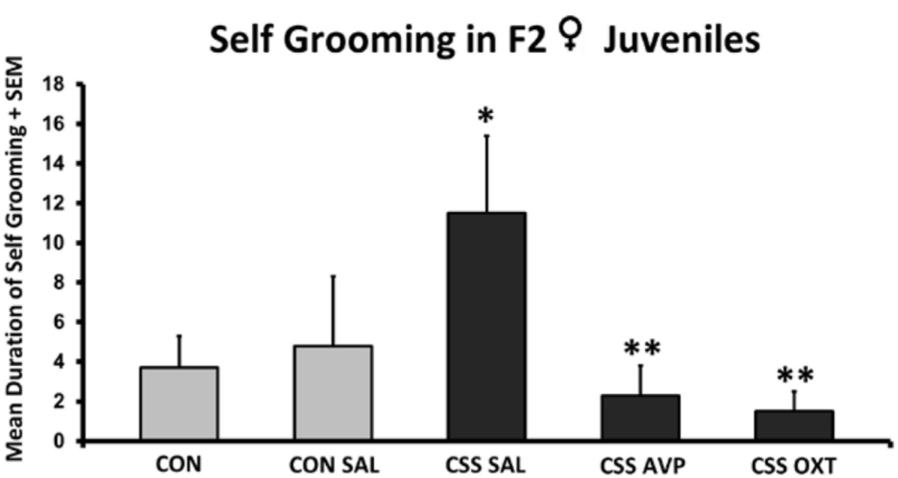


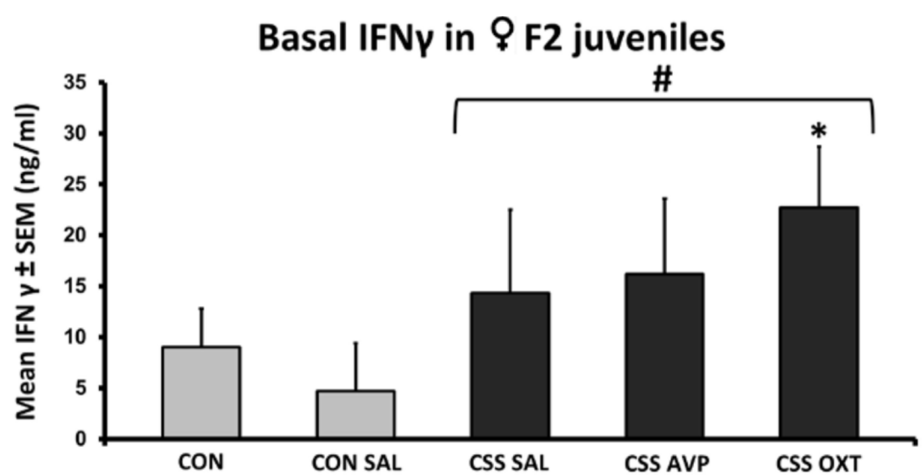


Murgatroyd et al. *Front Ecol.Evol.* 2016

Effects of AVP and OXT treatment of CSS dams on female offspring

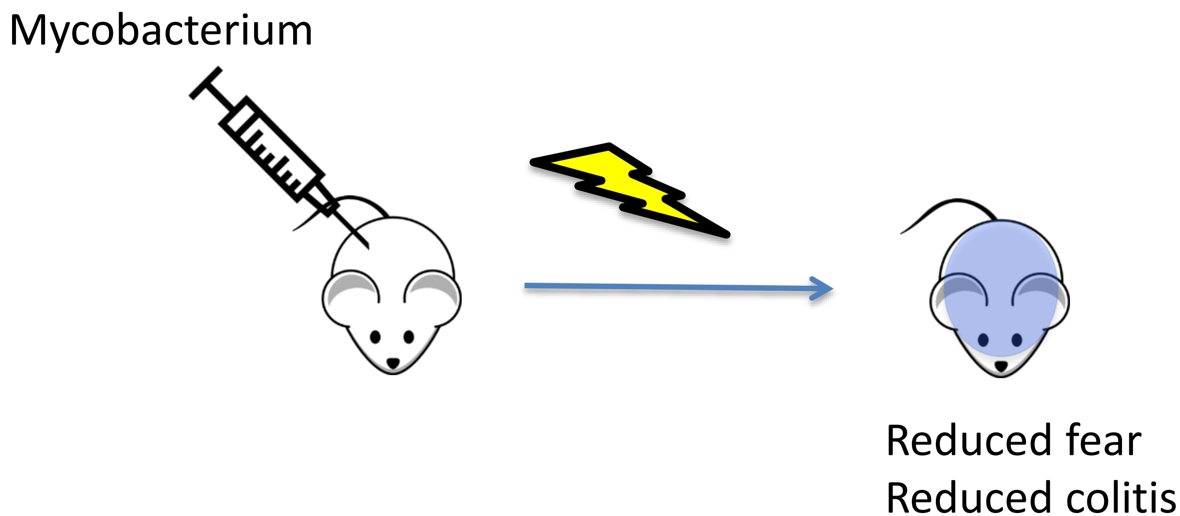






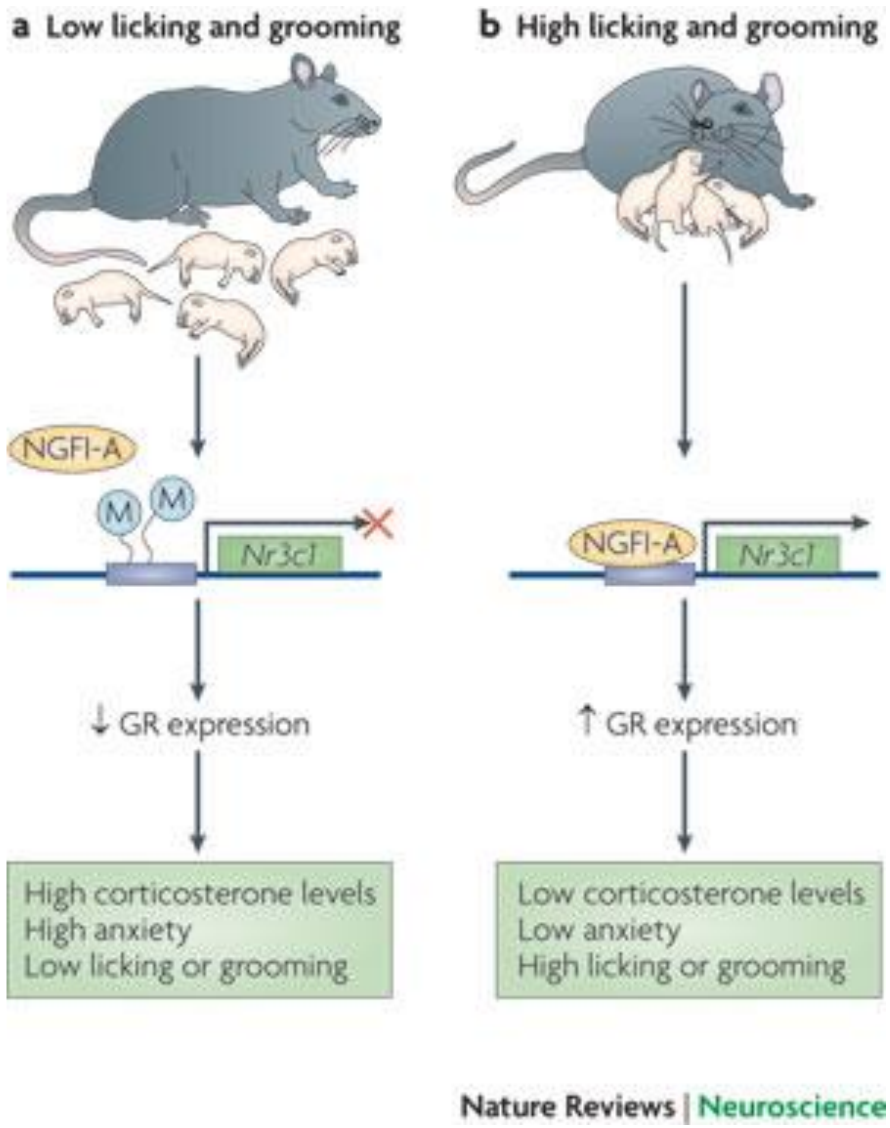
Murgatroyd et al. *Front.Endo*.2016

Immunisation promotes stress resilience



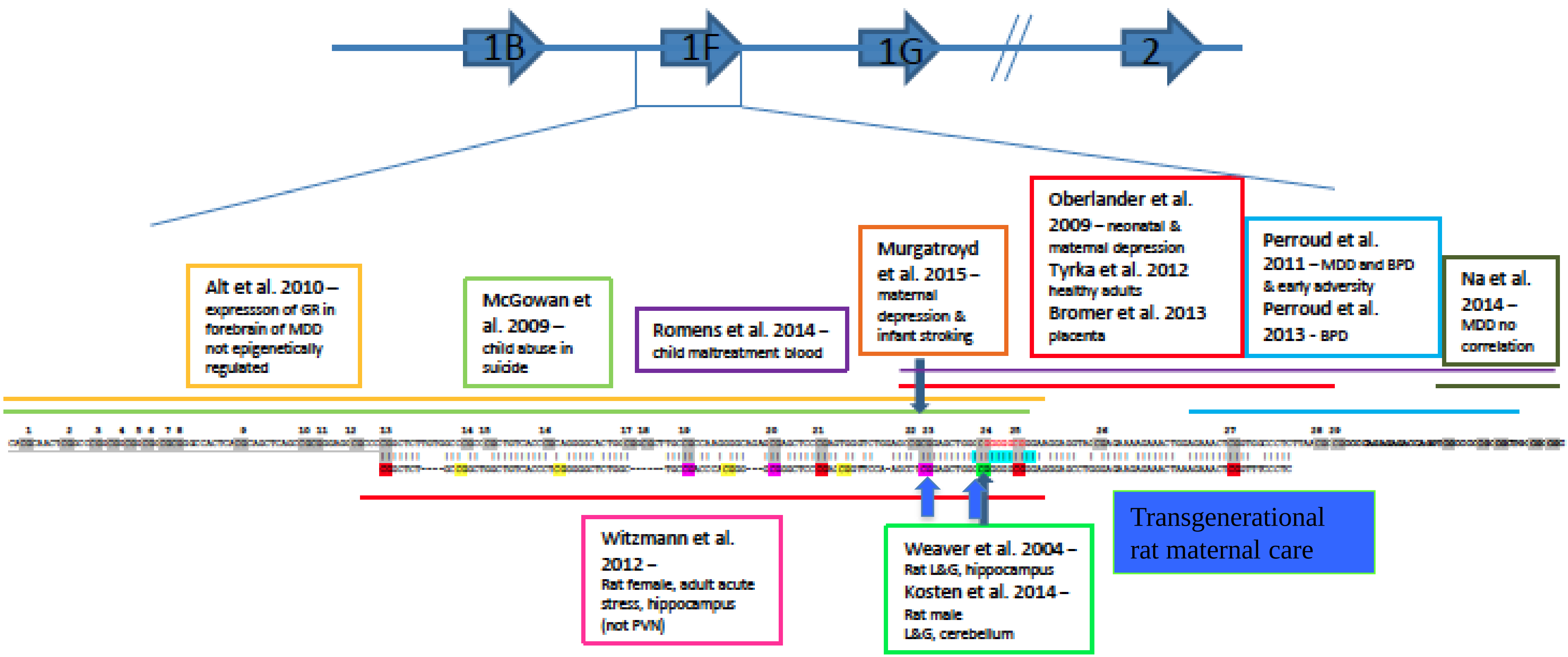
Reber et al. PNAS 2016

Nr3c1 methylation and early life licking/grooming

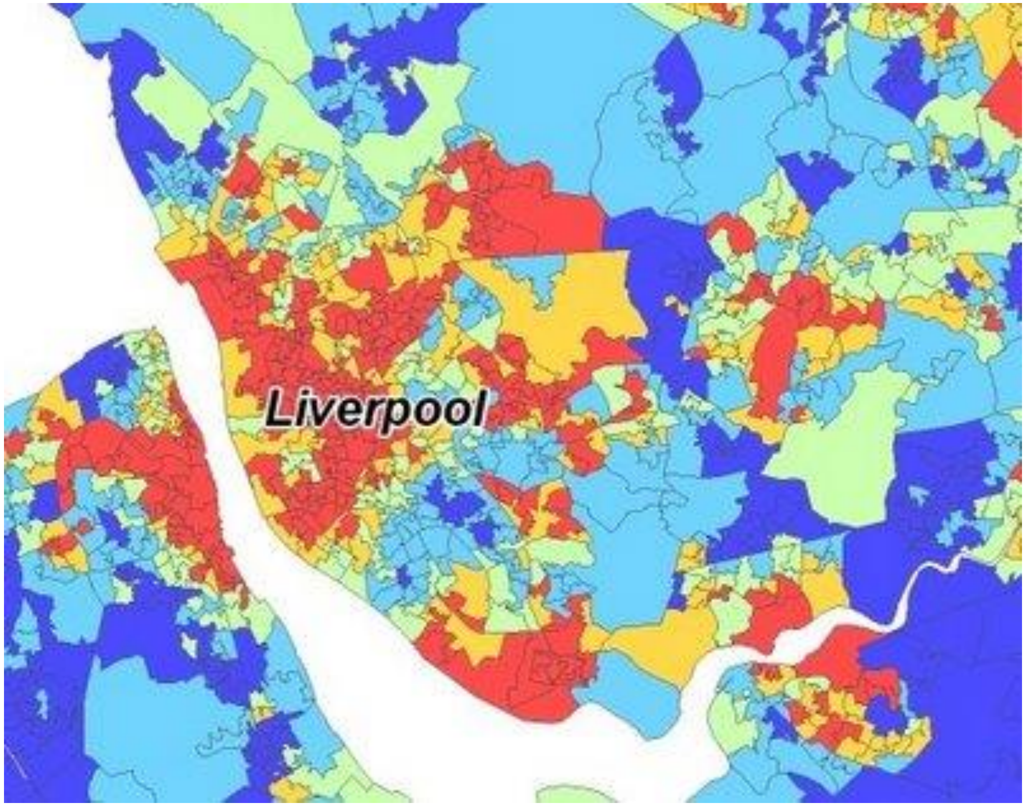


Weaver et al. (2004) Nat. Neuro.

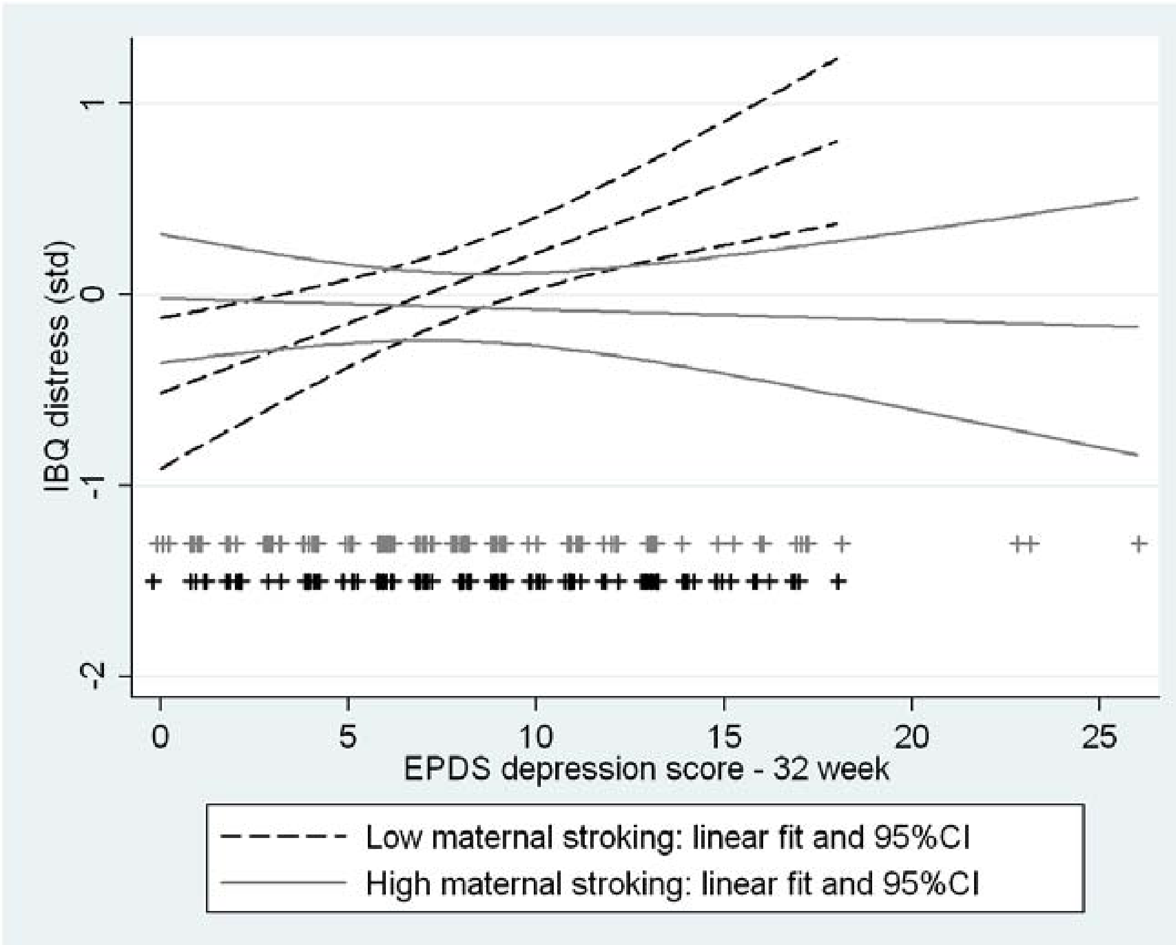
Methylation of human & rat GR exon 1F/7 in the literature



WCHADS - Wirral Child health and Development Study

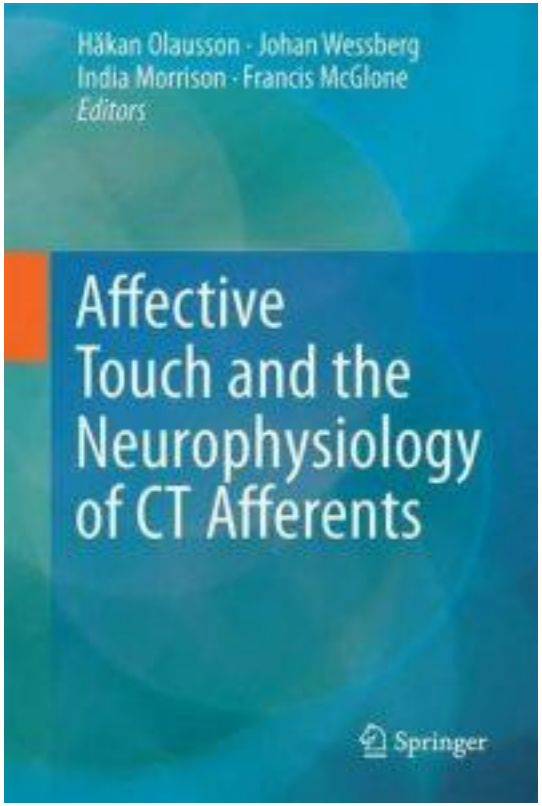


Maternal stroking moderates effect of prenatal depression on infant behaviour



Sharp et al. *PlosOne* 2014
Sharp et al. Psychol Med. 2015


IASAT
International Association for
the Study of Affective Touch
IASAT2017
2nd Congress Programme
Friday 1st September - Sunday 3rd September
in Liverpool, UK at Liverpool John Moores University
UCL
li.u


Håkan Olausson · Johan Wessberg
India Morrison · Francis McGlone
Editors
Affective
Touch and the
Neurophysiology
of CT Afferents
Springer

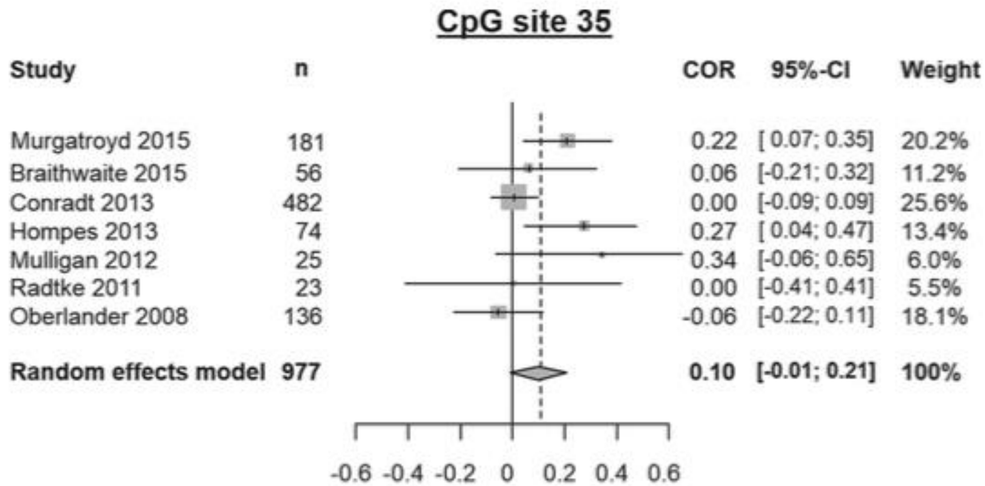
C-tactile afferents: Cutaneous mediators of oxytocin release during affiliative tactile interactions?

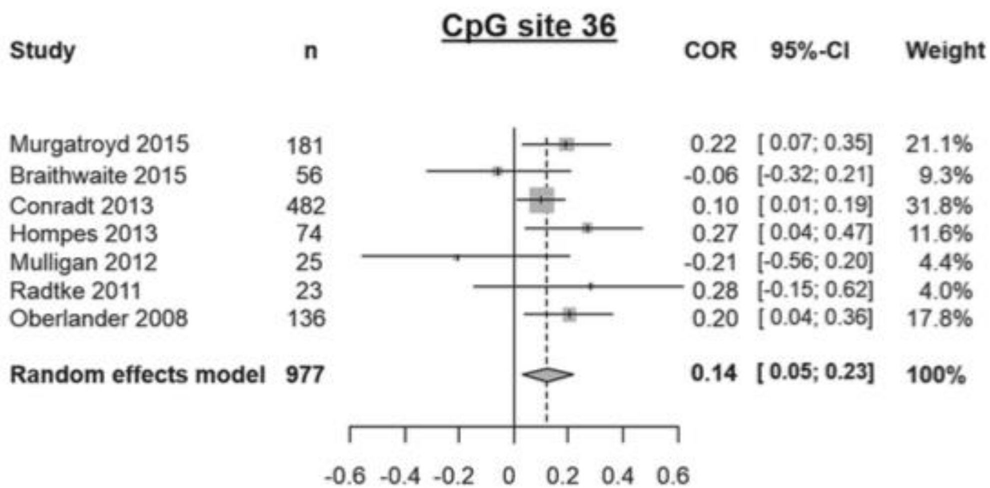
Walker SC, Trotter PD, Swaney WT, Marshall A, Mcglone FP. *Neuropeptides*. 2017

Stroking and DNA methylation in human

Early life stroking reduces GR methylation and stress behaviour in infants

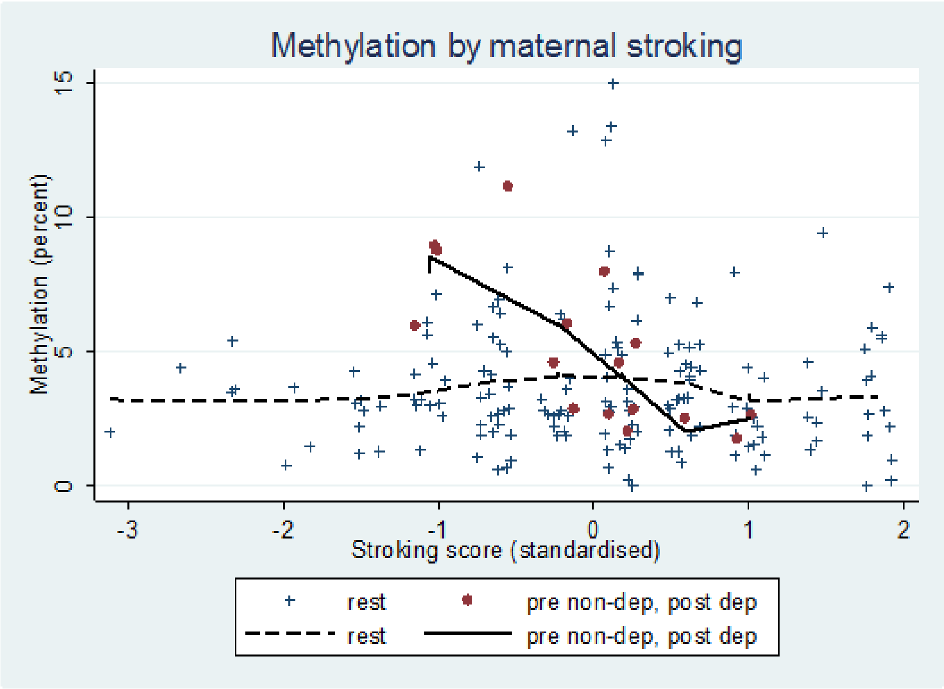
Specific CpGs associated with maternal depression and childhood stress





Palma-Gudiel et al. *Epigenetics* 2015

Maternal stroking (5 weeks age) reduces GR methylation



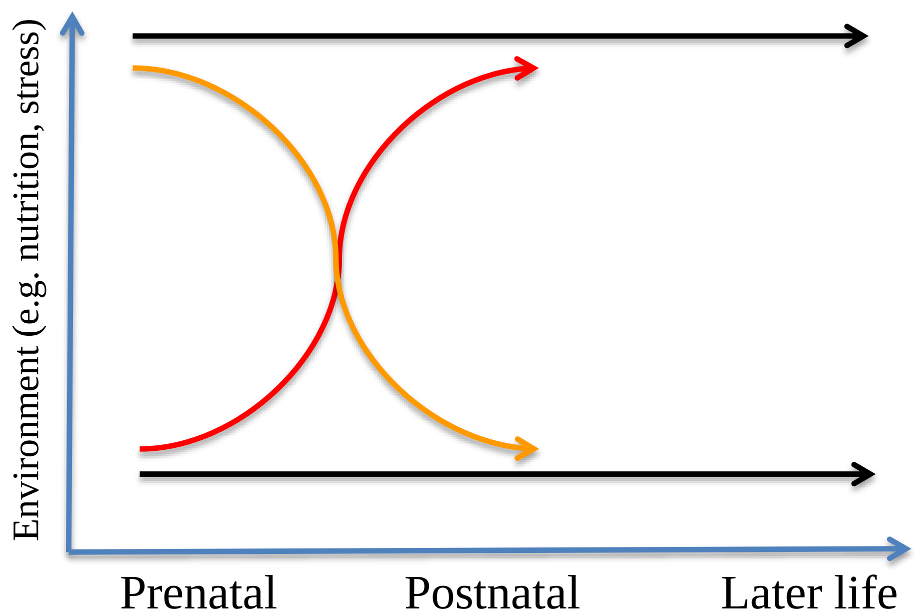
no effect of maternal stroking at 9 weeks of age

Murgatroyd et al. *Trans Psy*. 2015

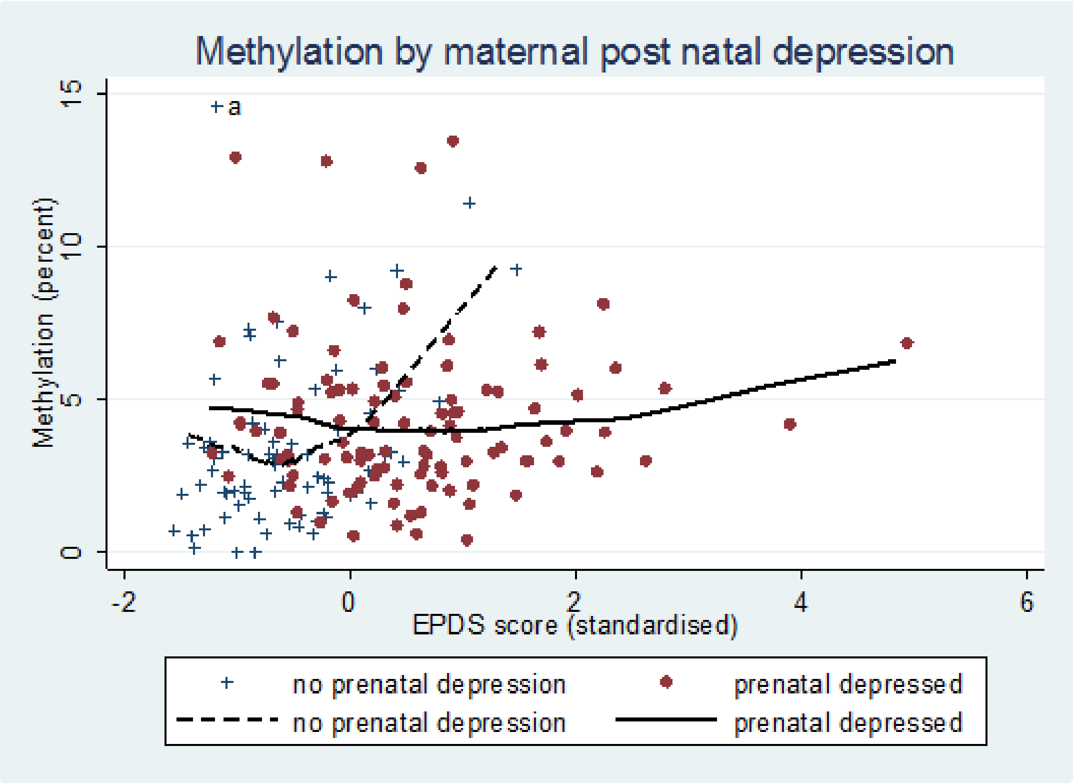
Predictive Adaptive Response & Mismatch

PAR hypothesis
Barker, Br Med Bull. 1997 53:96-108

An adaptive response to environmental cue acting early in life, where the advantage of the induced phenotype is primarily manifest in later life.



Infants of mothers with low prenatal depression were more vulnerable to the effects of postnatal depression



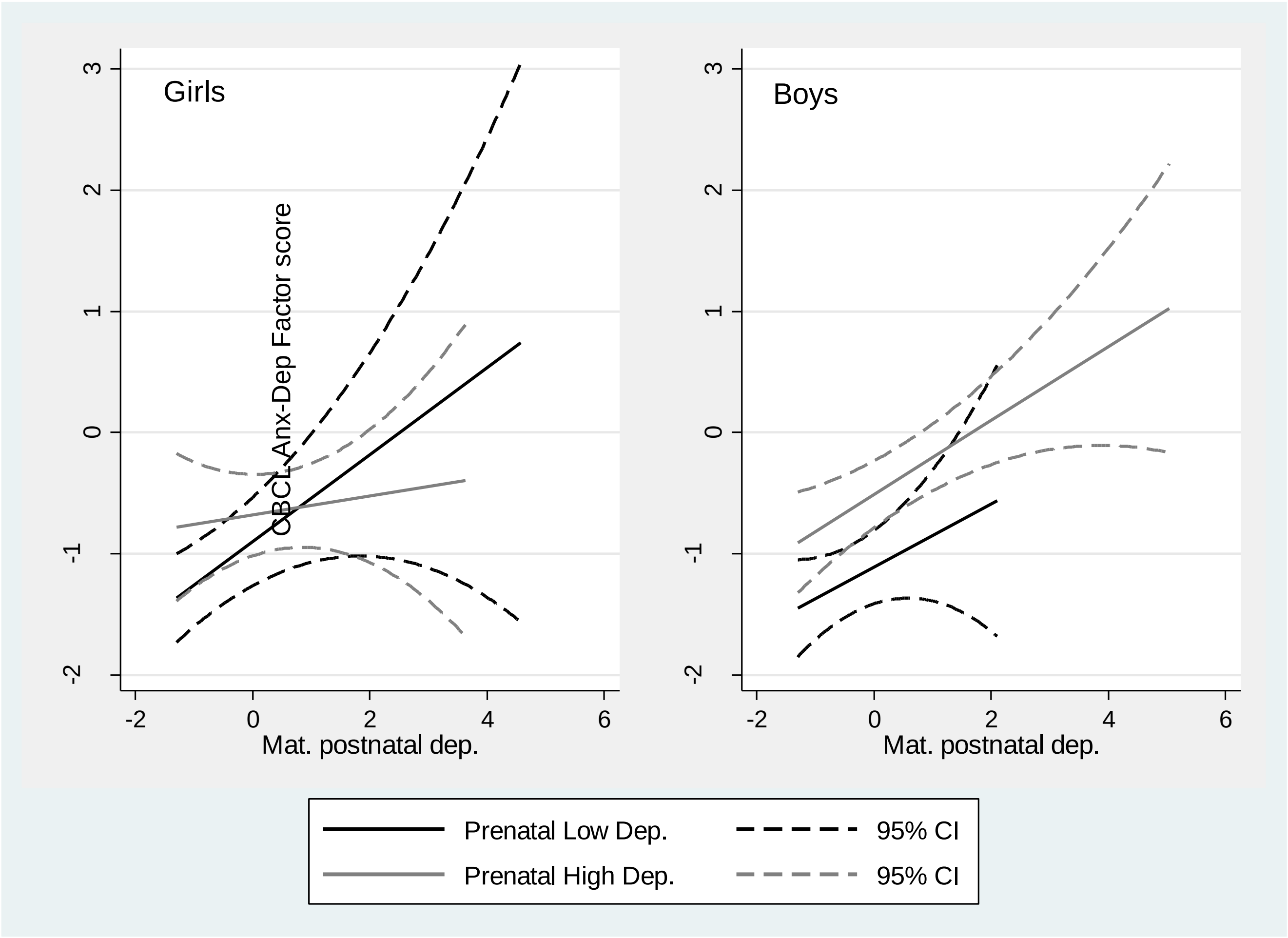
Murgatroyd et al. *Trans Psy*. 2015

Sex differences in interactions of pre- and postnatal depression

Trivers–Willard hypothesis
1973, Science 179 (4068): 90–9

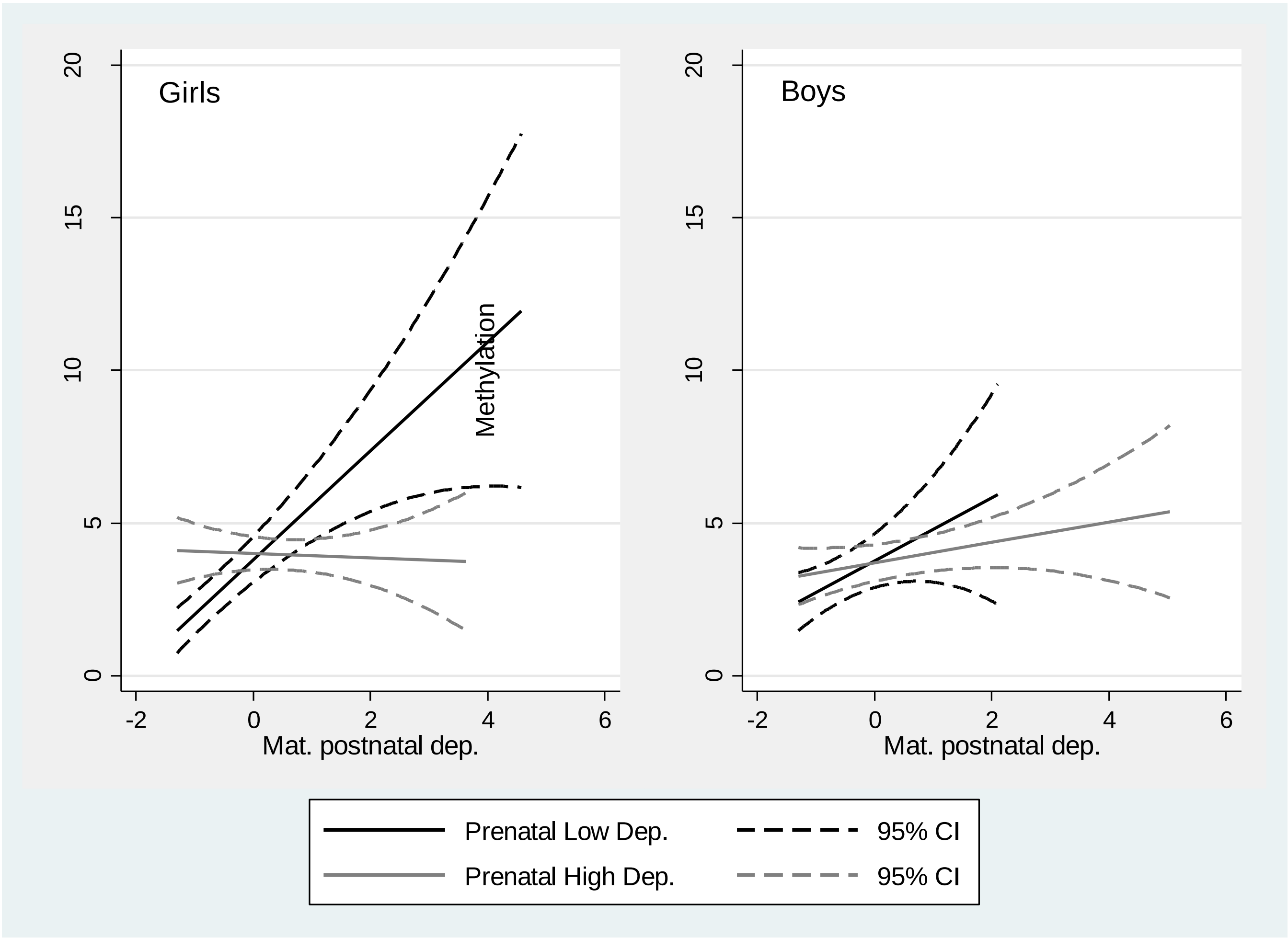
A good conditioned mother transfers competitive ability to male offspring for greater reproductive payoff

Prenatal-postnatal mismatch conditions associate with child symptoms in girls only

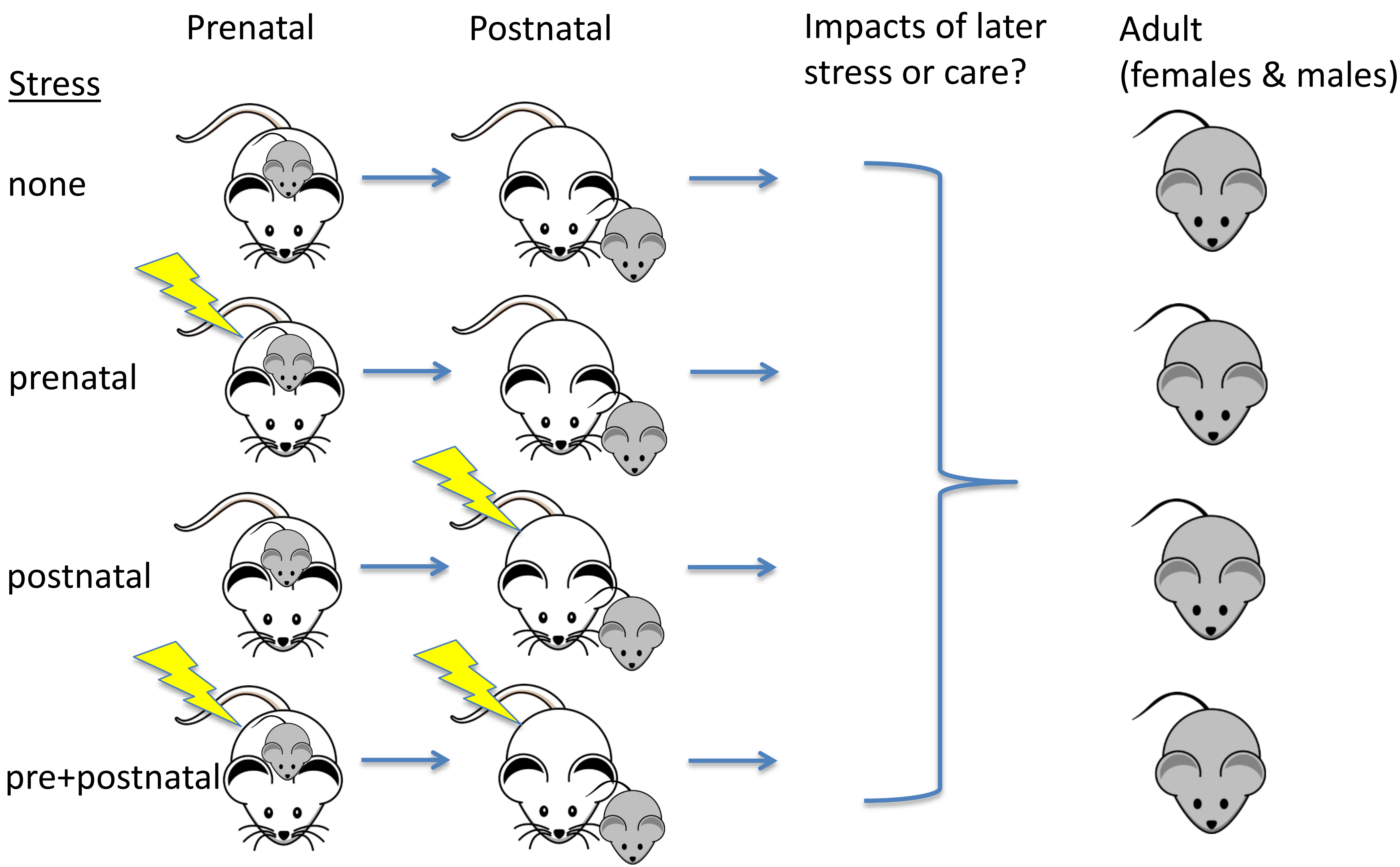


In submission

Prenatal-postnatal mismatch conditions significantly associate with methylation in girls only



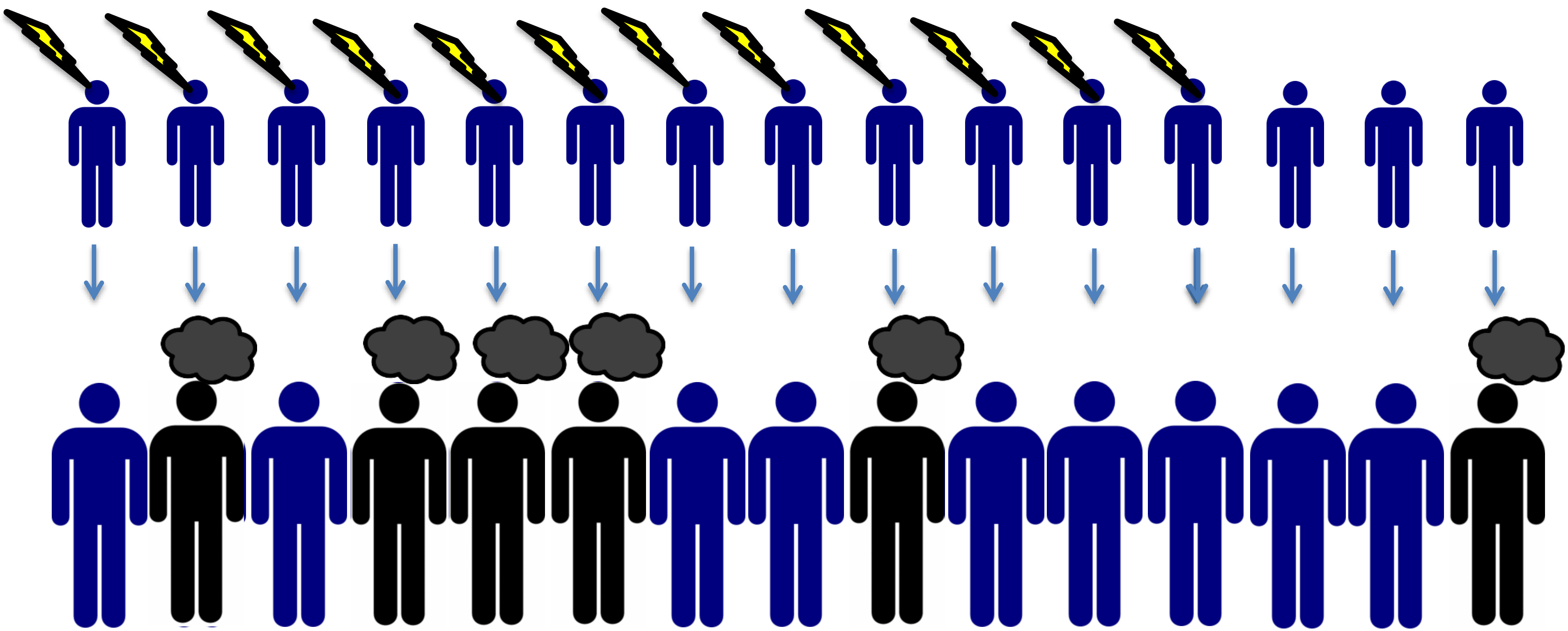
Animal model for Prenatal-postnatal mismatch conditions



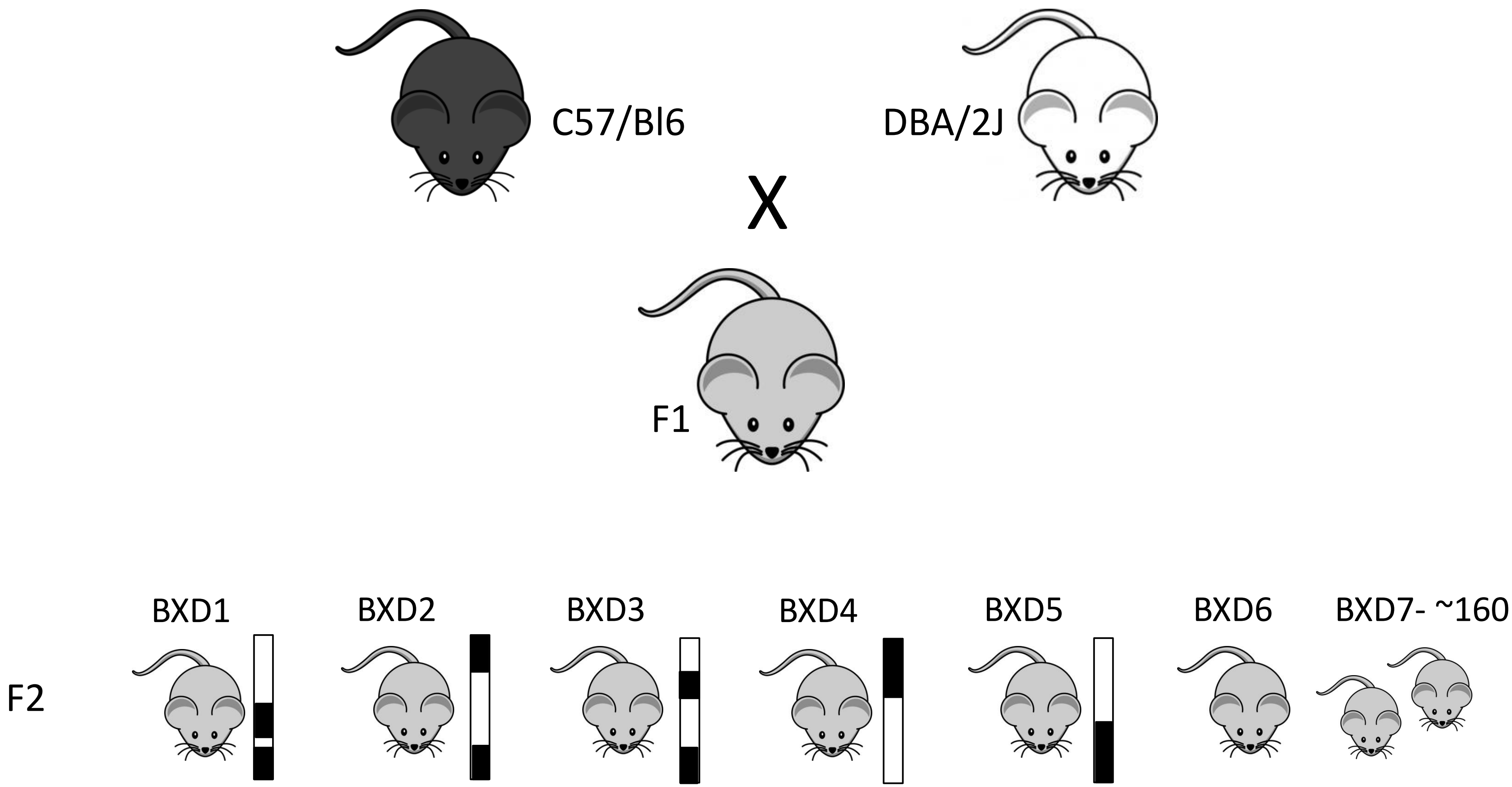
WCHADS - Longitudinal changes in DNA methylation

20wks	32wks	Birth	5wks	9wks	7mths	14mths	2.5yrs	3.5yrs	4.5yrs	7yrs
Env.	Env.			Env.	Env.	Env.	Env.	Env.	Env.	Env.
			stroking	stroking		stroking				
						DNA	DNA	DNA	DNA	DNA

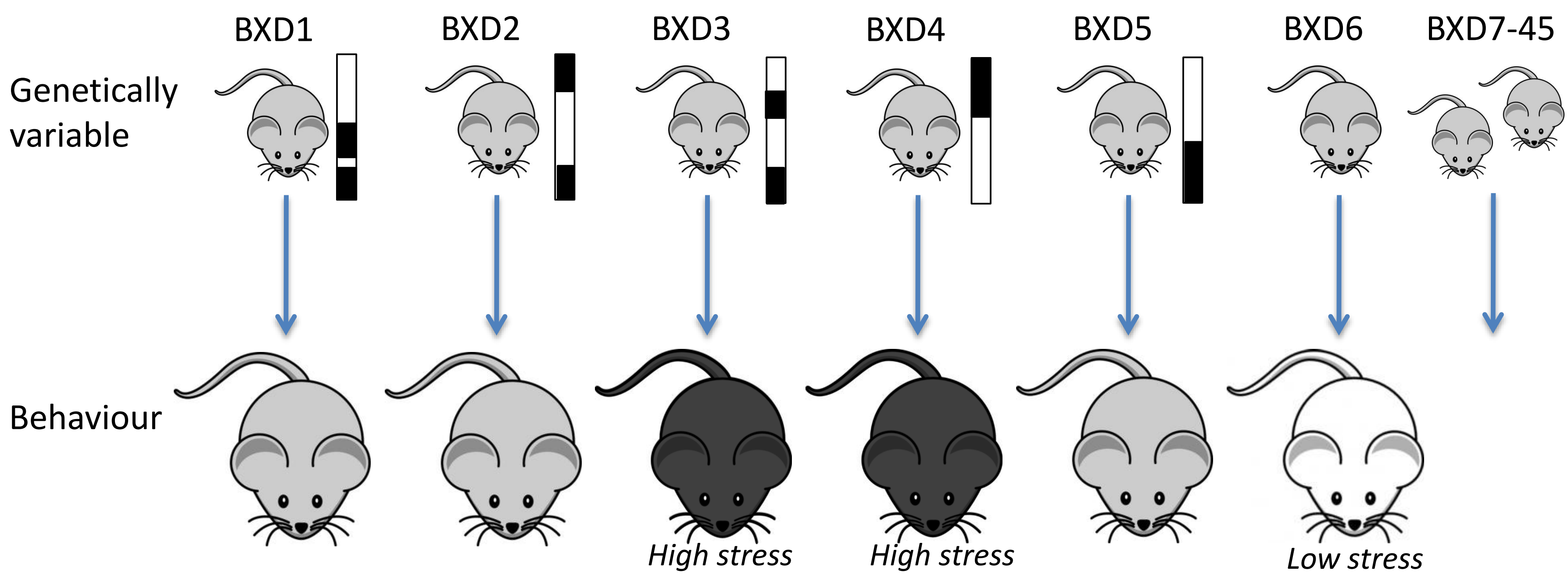
Not everyone with early-life stress develops depression
Not everyone with depression suffered early life stress



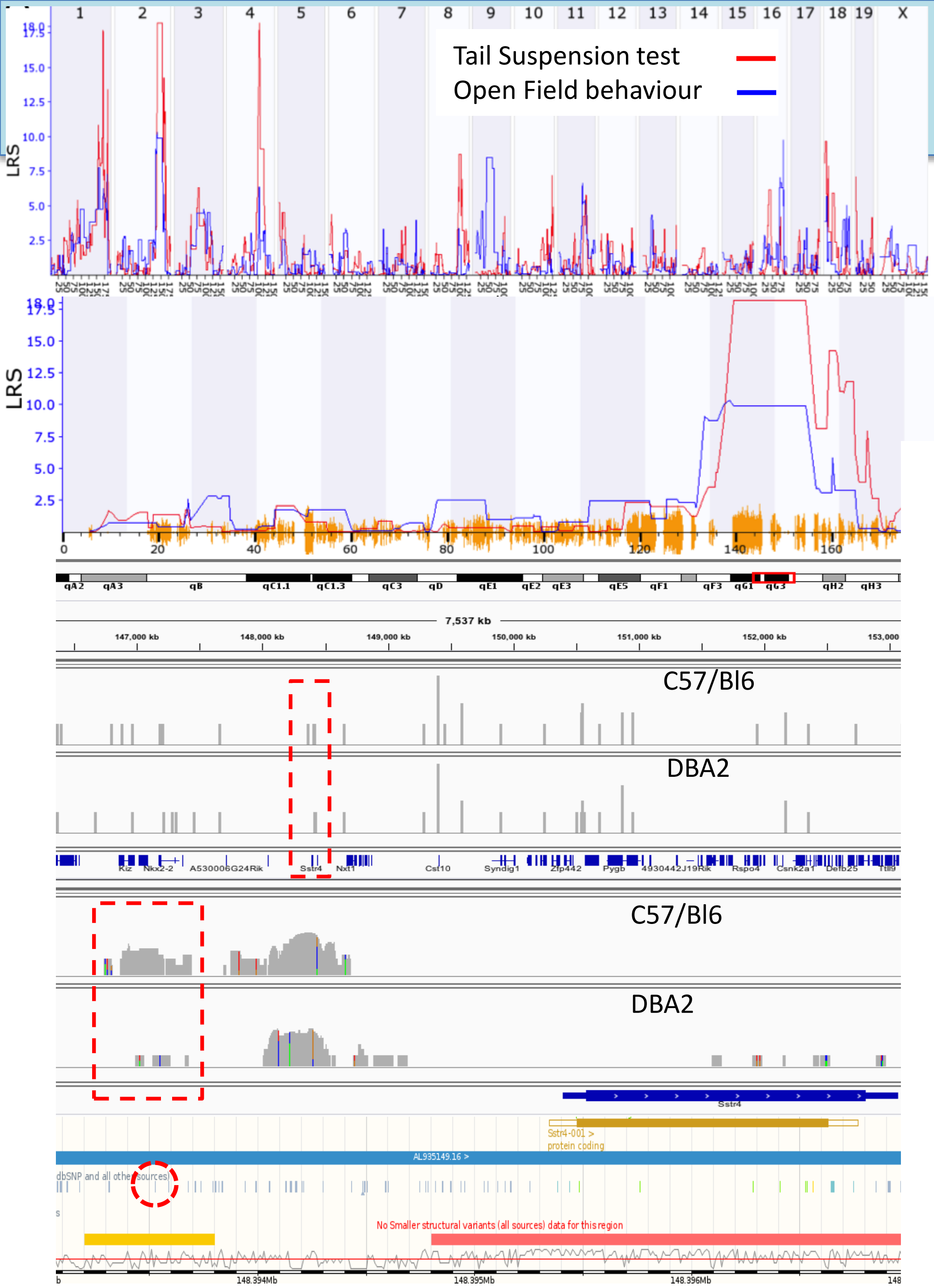
Recombinant inbred mouse strains



Animal model for genomewide analyses

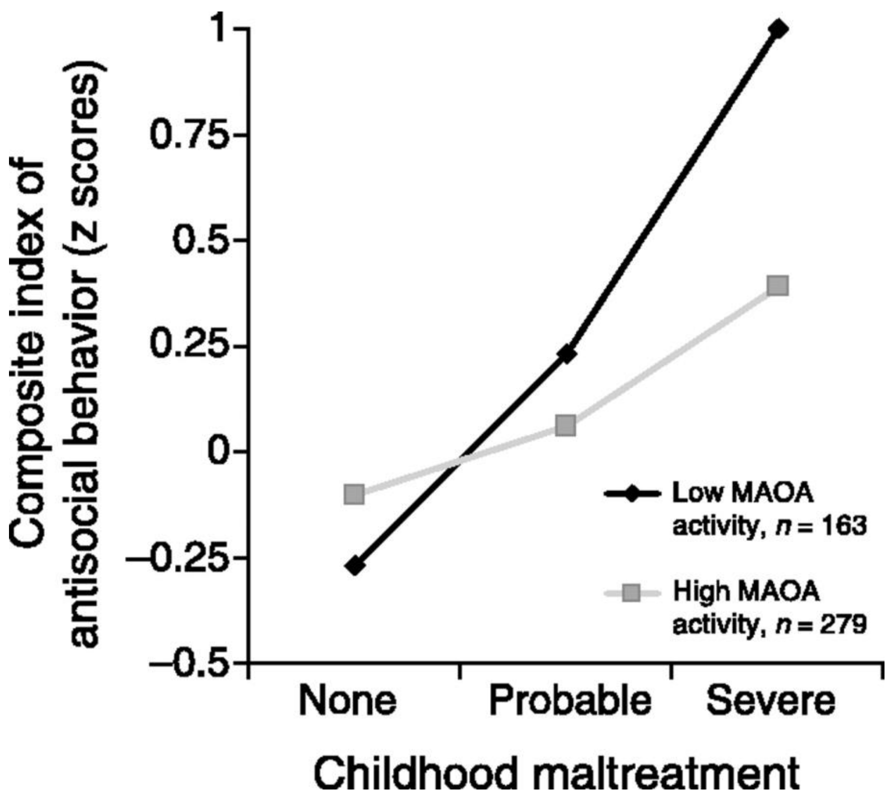


epiQTL for Stress-related behaviour



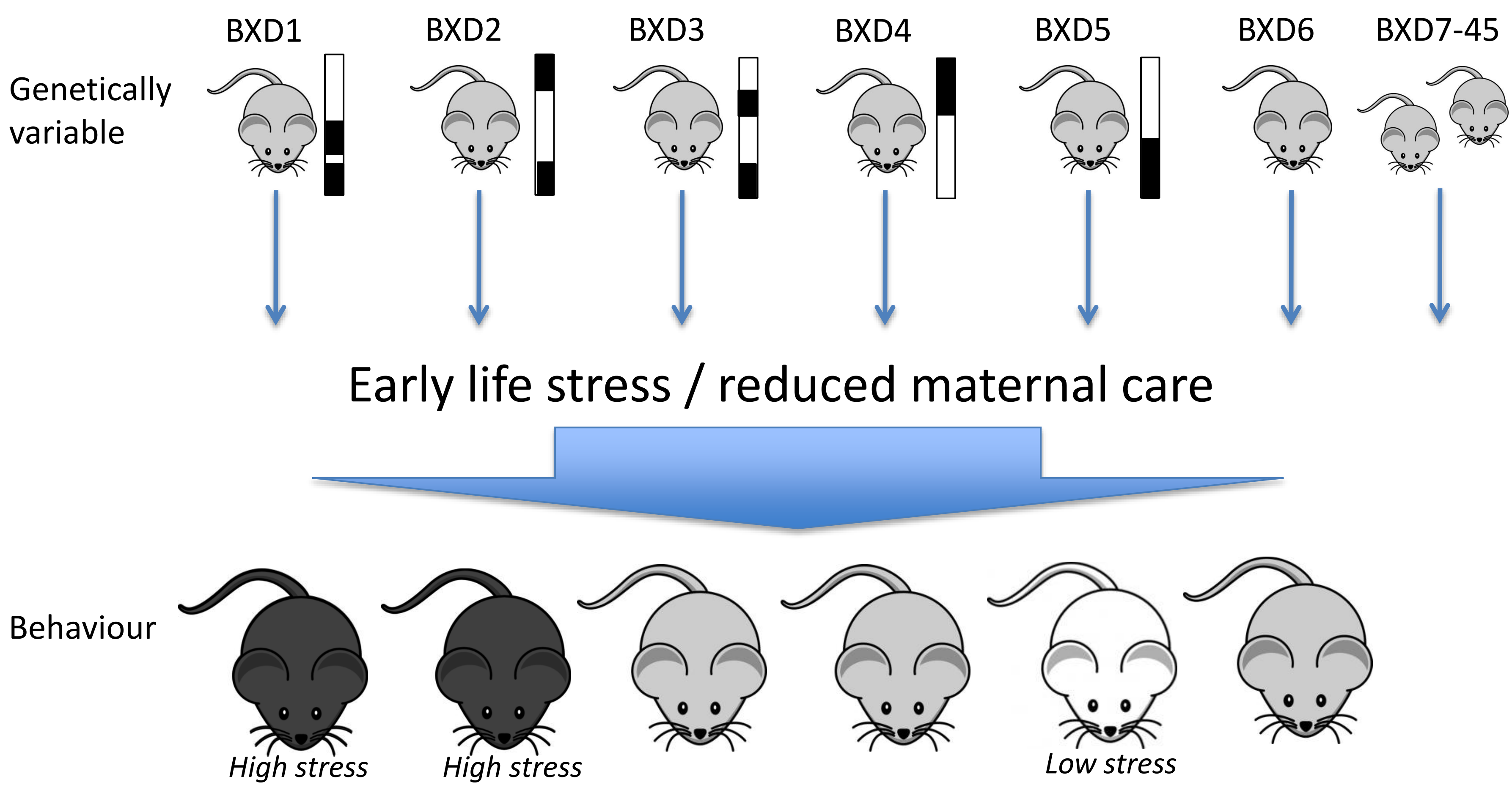
Scheich et al. 2016 Neuropharmacology. 101:204-15. Somatostatin receptor subtype 4 activation is involved in anxiety and depression-like behavior in mouse models.

Gene x Environment (GxE)



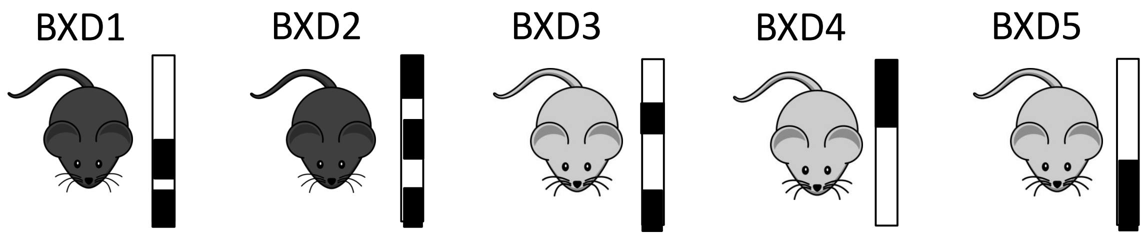
Caspi et al. Science 2002

Animal model for genomewide GxE analyses



Epigenetically programmmed expression QTL (epeQTL)

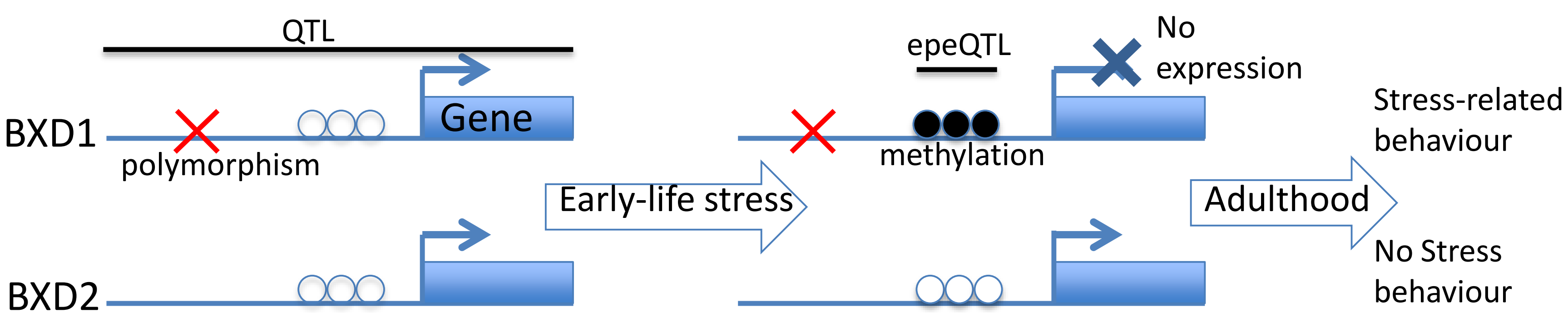
An epigenetically programmed expression QTL (epeQTL)



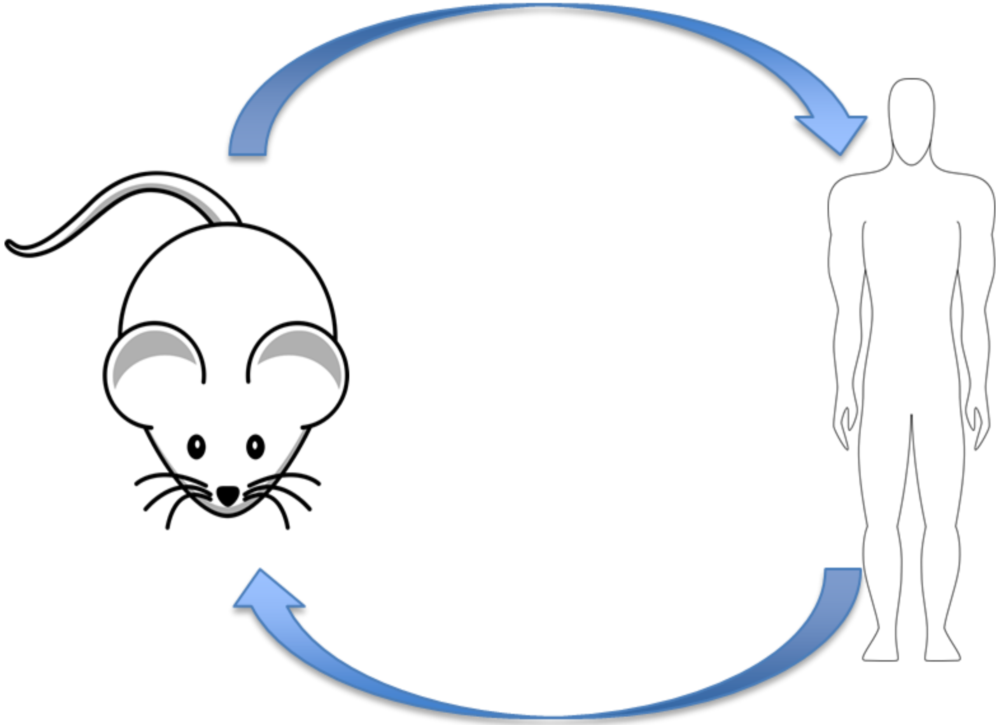
Which genetic regions are shared between sensitive (or insensitive) BXD lines (QTL)?

Which regions in QTL show differential mDNA following early-life stress (epeQTL)?

Which genes are differentially expressed in association with epeQTL



Translational animal models



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