Early Adversity and Depression

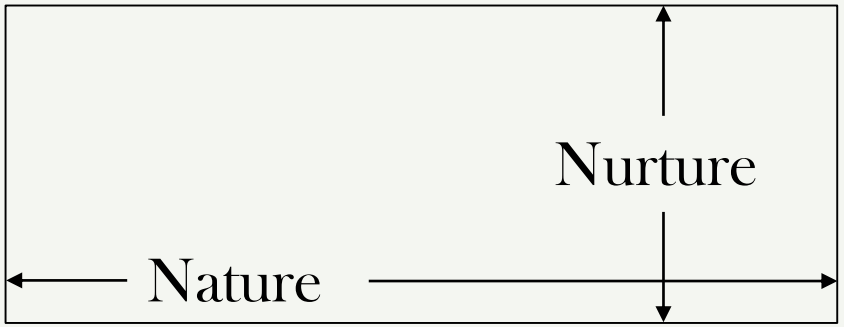
Chris Smart
Academic Clinical Fellow
Wolfson Centre

Nature vs nurture

Ideas:

~ Original sin (St Augustine) vs innate goodness (Rousseau)

~ *Tabula rasa* (Locke)



~ Donald Hebb:

~ Francis Galton: “convenient jingle of words”

Nature vs nurture

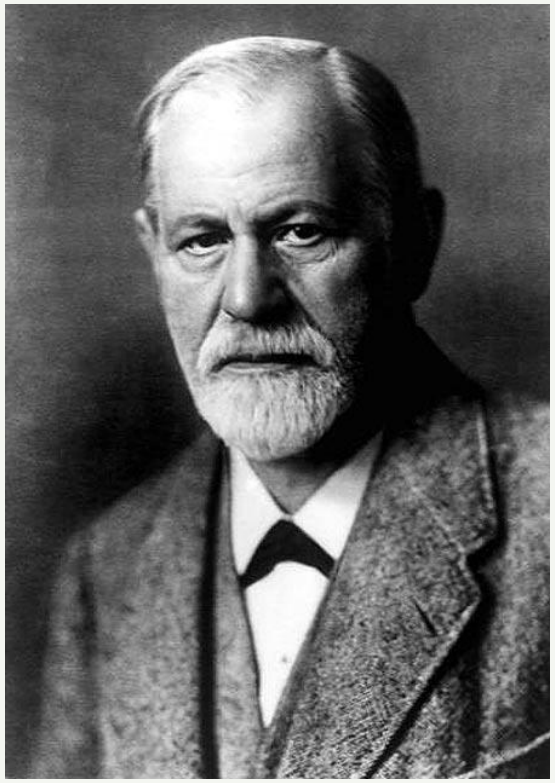
Psychiatry:

- Descartes/ Morel: "degenerate reflexes" (nature)

- Freud = psych environmentalist (nurture)

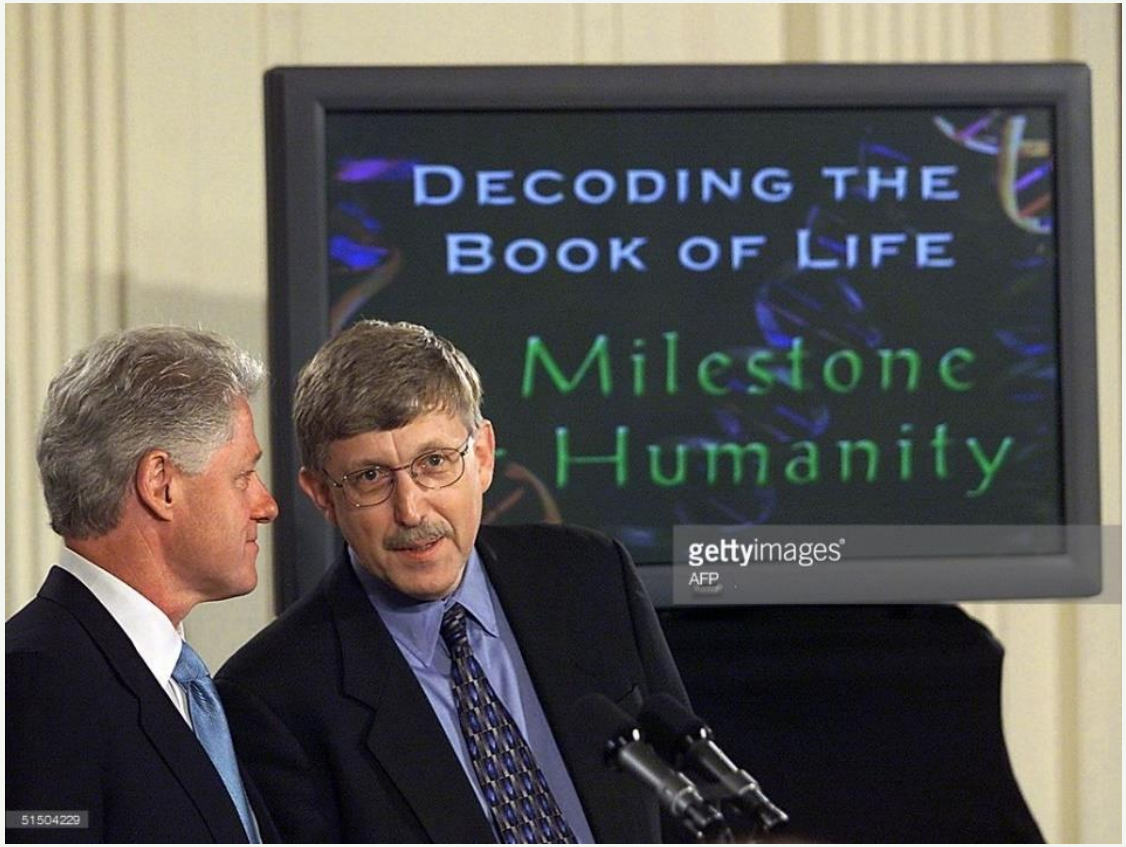
- Sexual seduction theory rejected, repression/ impulses from 1897

- Concerns = latency, single stimulus, abuse too common, veracity, Rx outcomes



Human Genome Project

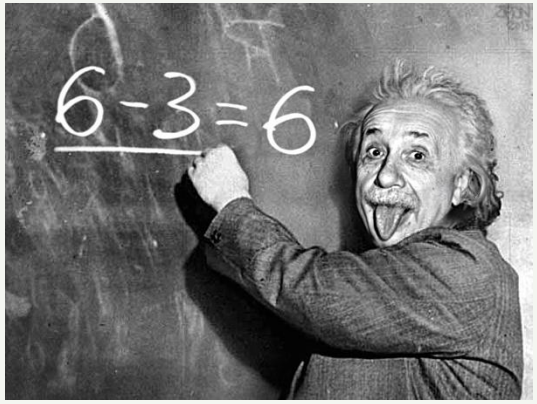
Promise and 'Problems'……..



Human Genome Project

17,000 genes

23,000 genes



3.3 billion bp

50,000 genes

0.13 billion bp

132 billion bp

98% 'dark matter'

Human Genome Project

Defining the role of common variation in the genomic and biological architecture of adult human height

Wood et al., Nature Genetics, 2014

- Simple trait.
- 80% heritability.
- 250,000 individuals.
- 10,000 SNPs.
- <30% of phenotype variability accounted for.

HGP and depression

Whole genome sequencing fails to predict risk of most common diseases

Susan Mayor

BMJ, 2012

Genetic Studies of Major Depressive Disorder: Why Are There No Genome-wide Association Study Findings and What Can We Do About It?

Douglas F. Levinson, Sara Mostafavi, Yuri Milaneschi, Margarita Rivera, Stephan Ripke, Naomi R. Wray, and Patrick F. Sullivan

Biol Psych, 2014

-Heritability of depression ≈ 40%
Linkage studies and GWAS unsuccessful

HPA Axis and depression

- Decades of evidence.
- Raised cortisol/ abnormal dex-CRH.
- In line with empirical findings.
- Associated with early adversity.

Early Adversity

THE BATTERED-CHILD SYNDROME

C. HENRY KEMPE, M.D., DENVER, FREDERIC N. SILVERMAN, M.D., CINCINNATI, BRANDT F. STEELE, M.D., WILLIAM DROEGEMUELLER, M.D., AND HENRY K. SILVER, M.D., DENVER

Professor and Chairman (Dr. Kempe) and Professor of Pediatrics (Dr. Silver), Department of Pediatrics; Associate Professor of Psychiatry (Dr. Steele), and Assistant Resident in Obstetrics and Gynecology (Dr. Droegemueller), University of Colorado School of Medicine; and Director, Division of Roentgenology, Children's Hospital (Dr. Silverman).

JAMA, 1962

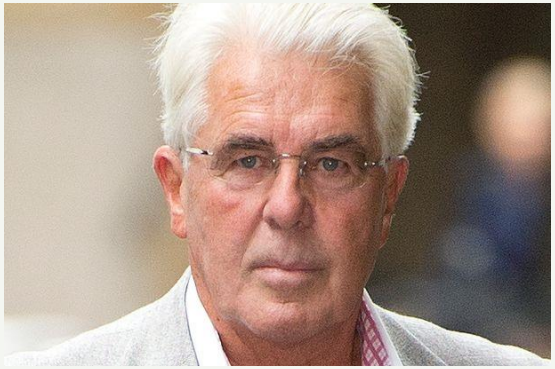
Resilience in the Face of Adversity

Protective Factors and Resistance to Psychiatric Disorder*

MICHAEL RUTTER

B J Psych, 1985

Early Adversity



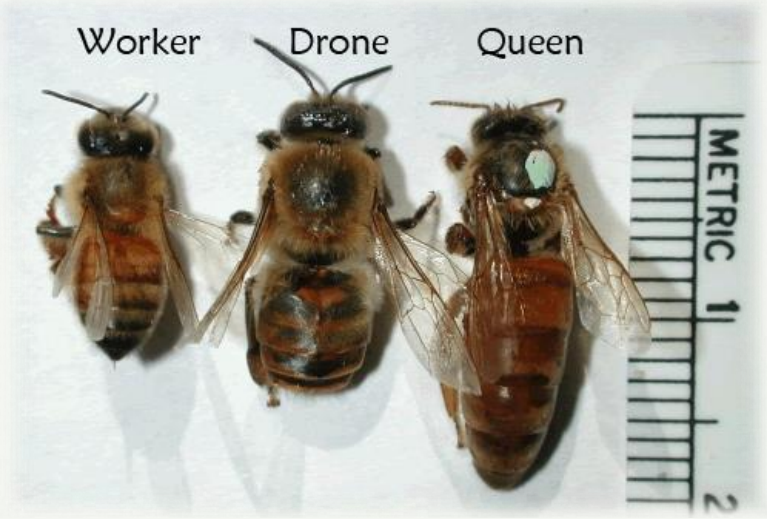
Early Adversity

- Rotherham, Rochdale, Plymouth, Telford, Oxford.
- NSPCC 0.5million maltreatment/ yr.

- How does it (environment) get “under the skin”?
- Why a latency?

Epigenetics

How genotype becomes phenotype.

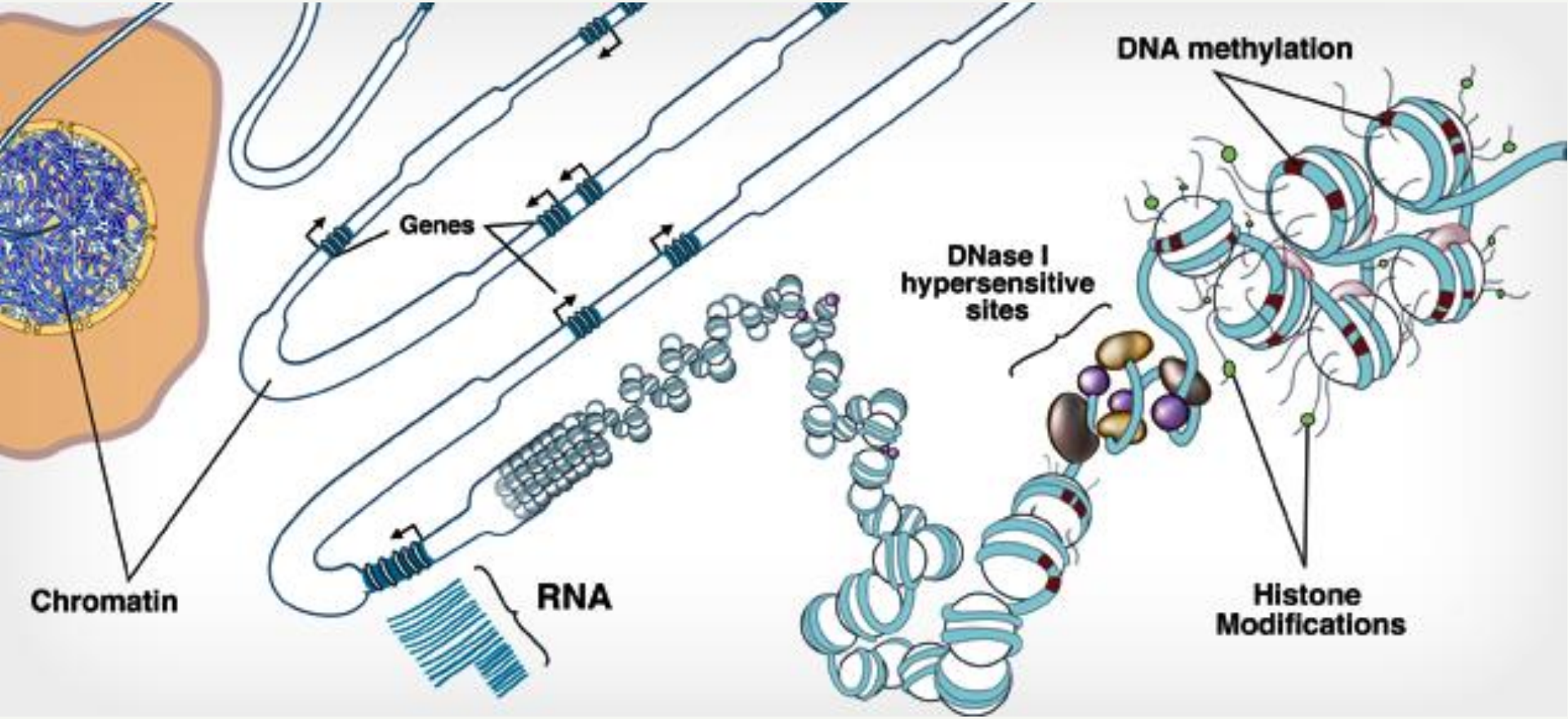


Conrad Waddington

"The structural adaptation of chromosomal regions so as to register, signal or perpetuate altered activity states".

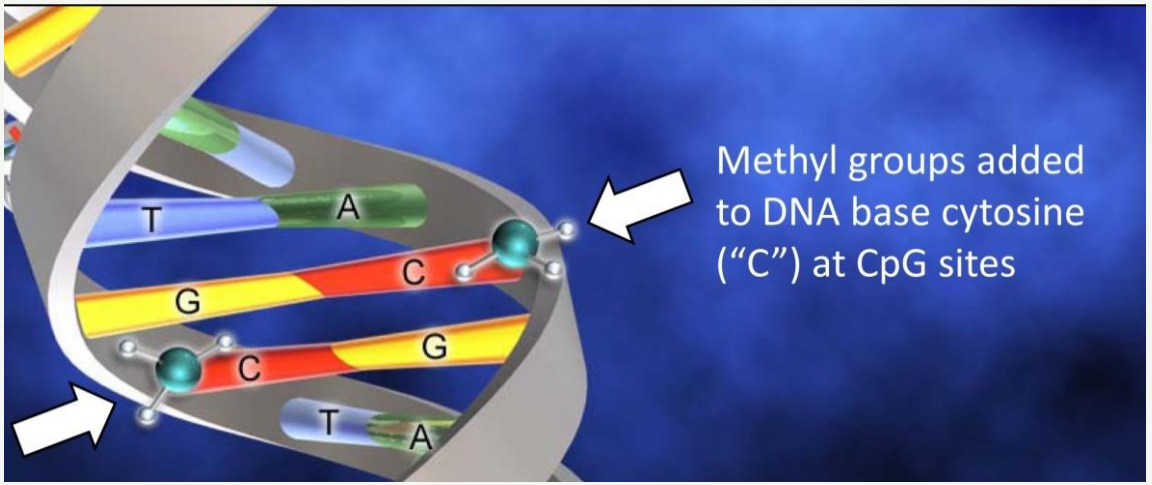
Adrian Bird, (Nature, 2007)

Epigenetics ~ mechanisms



DNA methylation

- At cytosine-guanine (CG/CpG) dinucleotides.
- Covalent bonds.
- CG 'islands' in gene promoters.



- Methylation silences genes.
- Transcription Factors inhibited directly or by Methyl Binding Proteins.

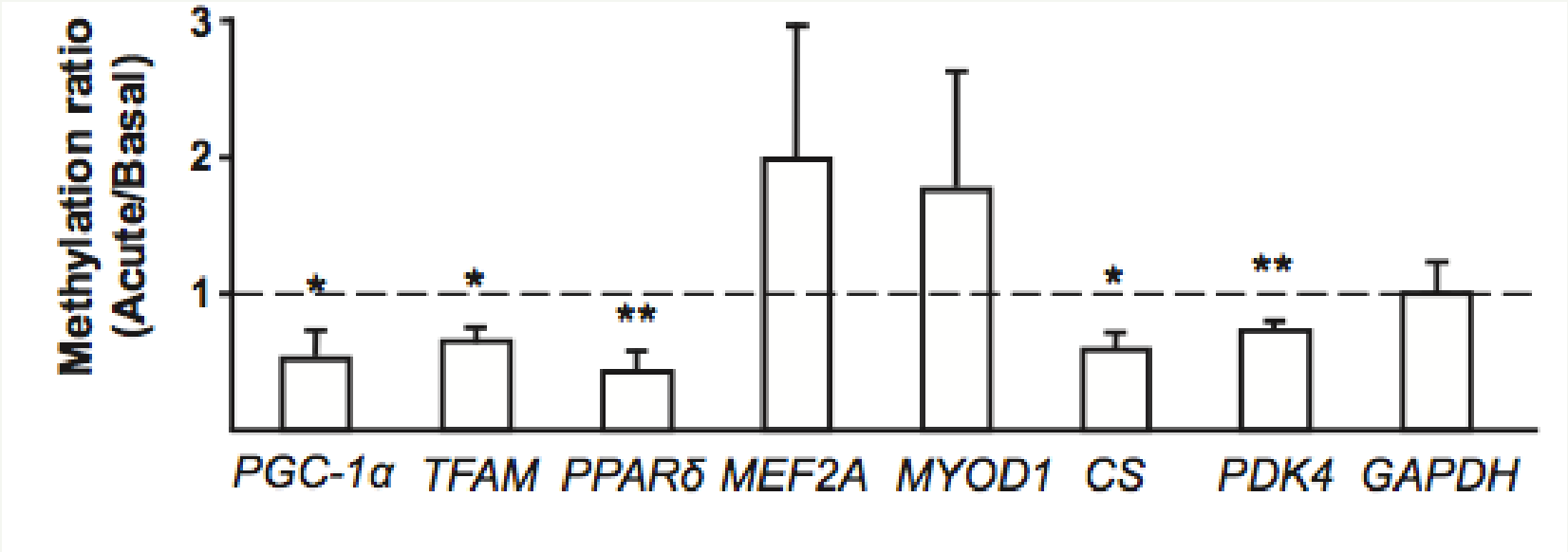
DNA methylation

Stable but dynamic…….

Acute Exercise Remodels Promoter Methylation in Human Skeletal Muscle

Romain Barrès,[1,4] Jie Yan,[1] Brendan Egan,[1,5] Jonas Thue Treebak,[4] Morten Rasmussen,[4] Tomas Fritz,[3] Kenneth Caidahl,[2] Anna Krook,[1] Donal J. O'Gorman,[5] and Juleen R. Zierath[1,4,*]

Cell Metab, 2012



Epigenetic programming by maternal behavior

Ian C G Weaver[1,2], Nadia Cervoni[3], Frances A Champagne[1,2], Ana C D'Alessio[3], Shakti Sharma[1], Jonathan R Seckl[4], Sergiy Dymov[3], Moshe Szyf[2,3] & Michael J Meaney[1,2]

Nat Neurosci, 2004

- Cross-fostered offspring.
- 'Caring' adoptive mothers › low NR3C1 methylation; 'poor' mothers › high methylation.
- Correlated with hippocampal glucocorticoid receptor expression.
- Persisted to day 90.
- Differences went with Trichostatin A.

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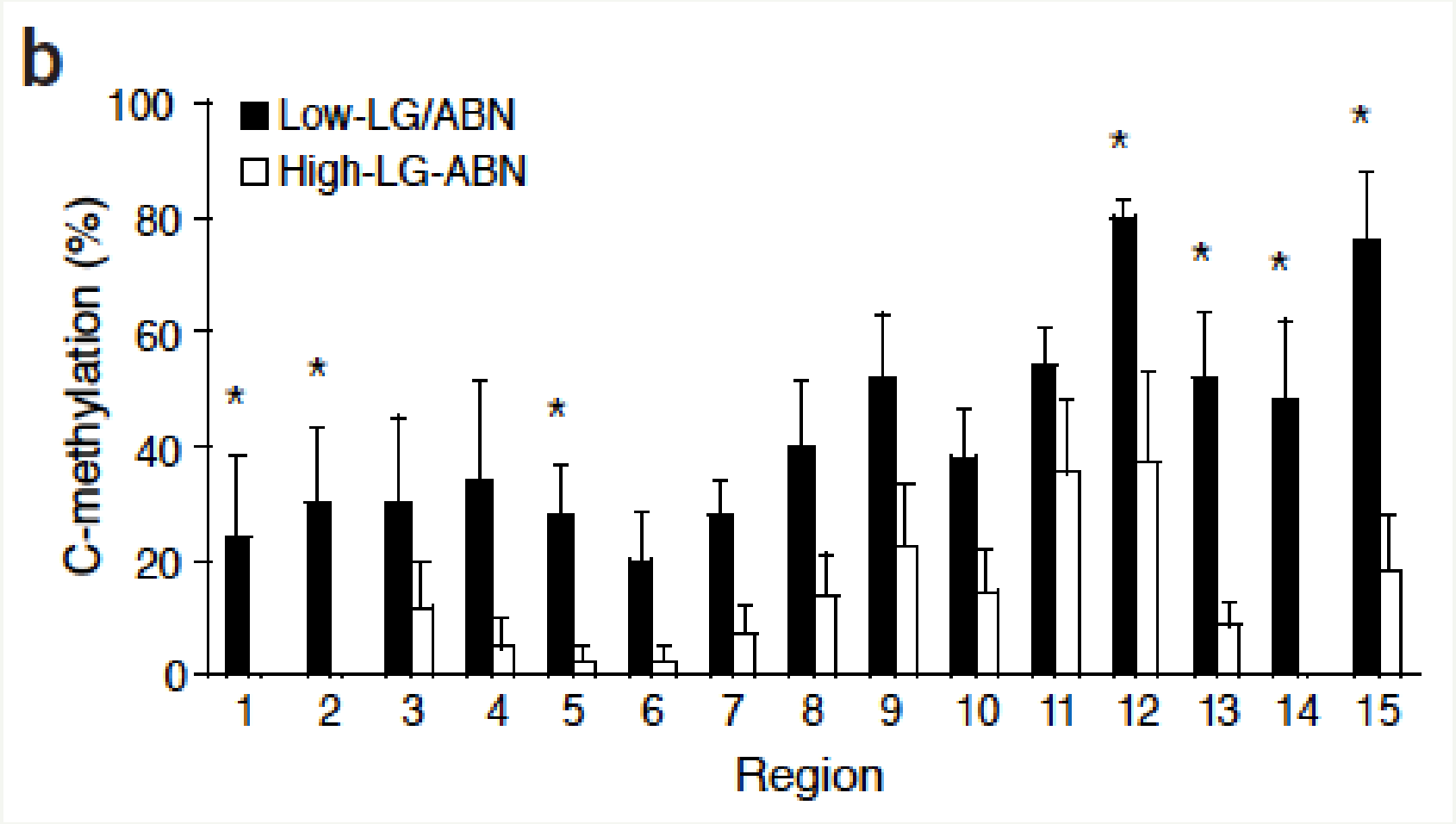

Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (*NR3C1*) and infant cortisol stress responses

Tim F. Oberlander,[1,2,*] Joanne Weinberg,[2,3] Michael Papsdorf,[1] Ruth Grunau,[1,2] Shaila Misri[4] and Angela M. Devlin[1,2]

Epigenetics, 2008

- In utero exposure to maternal depression (medicated, n=33; unmedicated, n=13; controls, n=36).
- Newborn cord blood.
- 3rd trim depression associated with NR3C1 methylation.
- Single CG site correlated to cortisol response.
- SSRIs = no effect on methylation.

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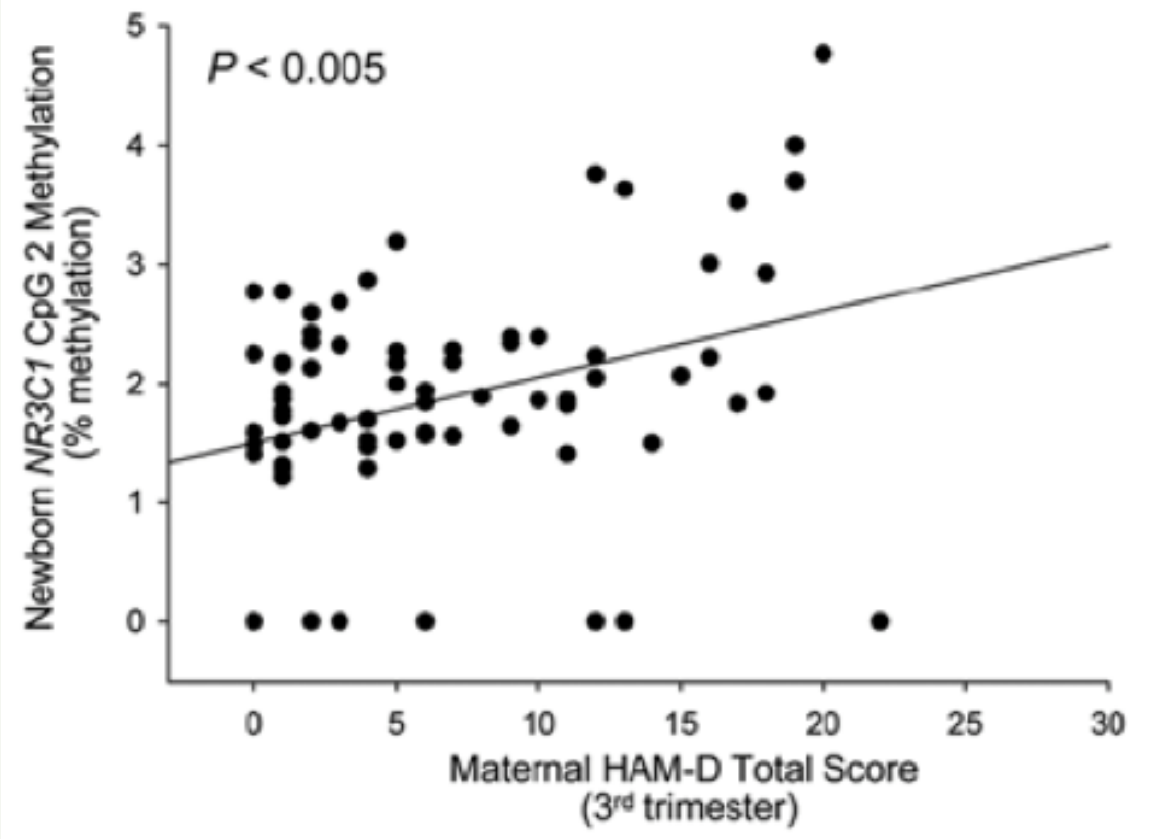


The roles of DNA methylation of *NR3C1* and *11β-HSD2* and exposure to maternal mood disorder in utero on newborn neurobehavior

Elisabeth Conradt[1,2,*], Barry M Lester[1,2,3], Allison A Appleton[4], David A Armstrong[4], and Carmen J Marsit[4]

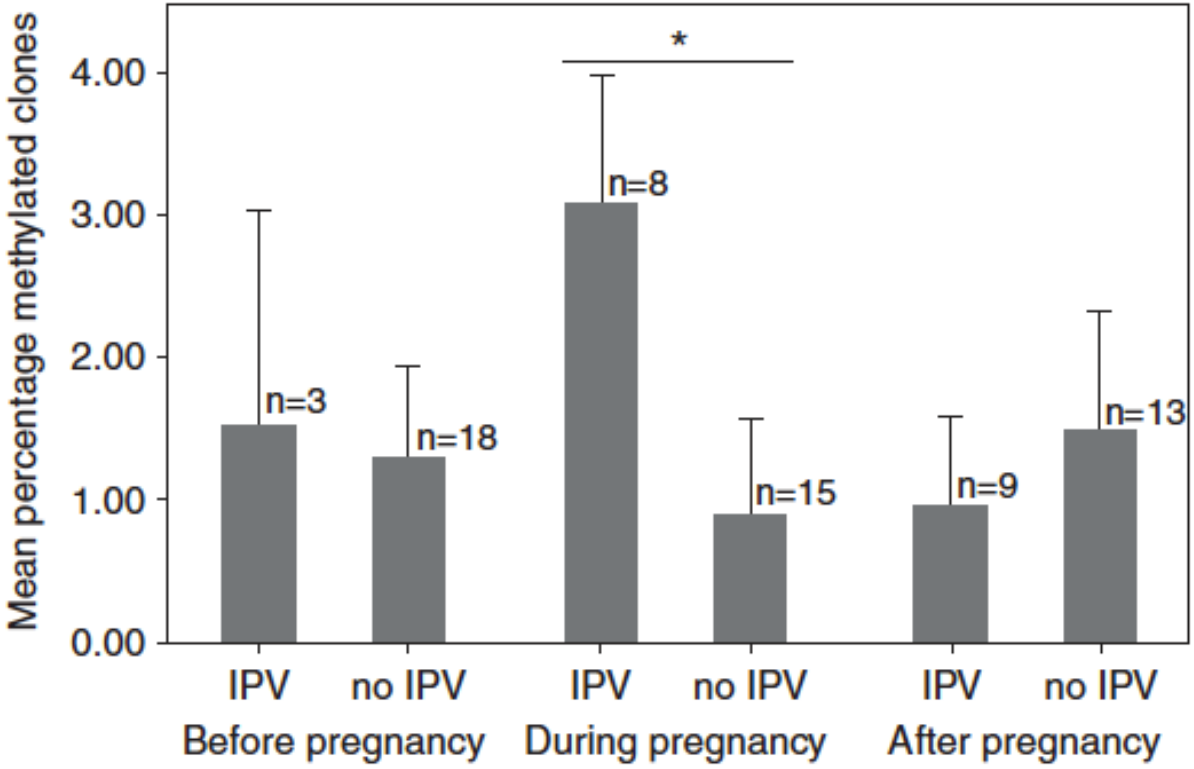
Epigenetics, 2013

- In utero exposure to maternal depression (n=66; controls n=398).
- Placenta.
- Depression led to increased methylation and worse neurobehavioural outcomes.

Transgenerational impact of intimate partner violence on methylation in the promoter of the glucocorticoid receptor

KM Radtke[1,2,4], M Ruf[1,4], HM Gunter[2,3,4], K Dohrmann[1], M Schauer[1], A Meyer[2] and T Elbert[1]

Transl Psych, 2011



Childhood Adversity and Epigenetic Modulation of the Leukocyte Glucocorticoid Receptor: Preliminary Findings in Healthy Adults

Audrey R. Tyrka[1,2*], Lawrence H. Price[1,2], Carmen Marsit[3], Oakland C. Walters[1], Linda L. Carpenter[1,2]

PLoS, 2012

- Healthy adult (n=99) blood.
- Methylation increased with child adversity, no expression data.

Differential expression of glucocorticoid receptor transcripts in major depressive disorder is not epigenetically programmed

Simone R. Alt[a,b], Jonathan D. Turner[a,b], Melanie D. Klok[c], Onno C. Meijer[c], Egbert A.J.F. Lakke[d], Roel H. DeRijk[c,e], Claude P. Muller[a,b,*]

Psychoneuroend, 2010

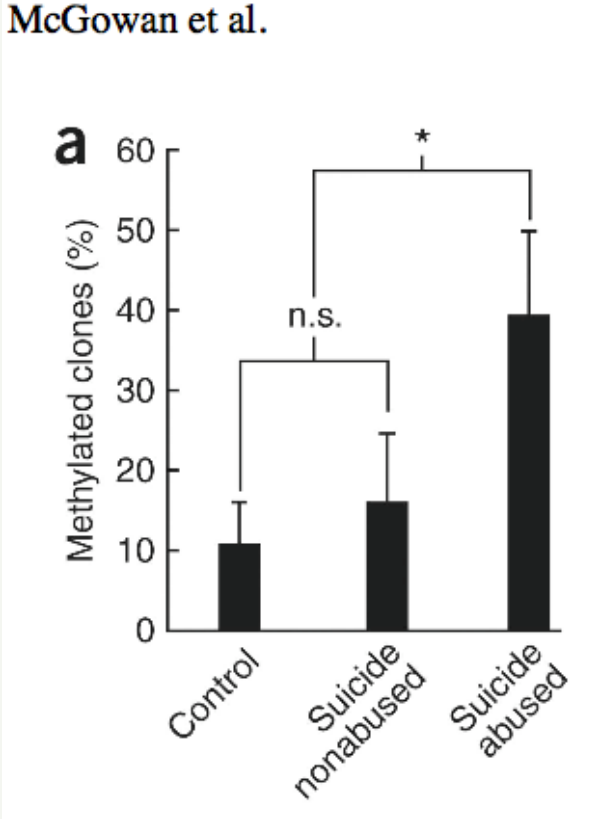
- Depressed PMs (n=6; controls=6).
- Hippocampal GR reduced, methylation unaffected.

Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse

Patrick O McGowan[1,2], Aya Sasaki[1,2], Ana C D'Alessio[3], Sergiy Dymov[3], Benoit Labonté[1,4], Moshe Szyf[2,3], Gustavo Turecki[1,4], and Michael J Meaney[1,2,5]

Nat Neurosci, 2009

- Depessed PM with (n=12) and without (n=12) child abuse; contols n=12.
- Methylation increased/ GR RNA fell with child abuse.



Genetic and epigenetic associations of *MAOA* and *NR3C1* with depression and childhood adversities

Philippe A. Melas[1,2], Yabin Wei[1,2], Chloe C. Y. Wong[3], Louise K. Sjöholm[1,2], Elin Åberg[1,2], Jonathan Mill[3], Martin Schalling[1,2], Yvonne Forsell[4] and Catharina Lavebratt[1,2]

Int J Neuropsychoph, 2013

- Depessed adults n=92, controls n=82.
- Saliva.
- Single CG site correlated with early parental death (n=9; 19% vs 14%), abuse not assessed.

Future studies

Early life trauma, depression and the glucocorticoid receptor gene – an epigenetic perspective

C. Smart[1]*, G. Strathdee[2], S. Watson[1,3], C. Murgatroyd[4] and R. H. McAllister-Williams[1,3]

Psych Med, 2015

Unify:

-Stressors

-Tissue

-DNA sequences

-Functional correlates

Longitudinal studies

Use comprehensive environmental data in psychiatry.

Our future work

- Funding for depressed (inpt+outpt) methylation of NR3C1, FKBP5 and SLC6A4.
- 100pts vs 50 controls.
- SNPs.
- RNA, protein and HPA function.
- Deep sequencing in Munich's Max Planck Institute.

Thanks