Maastricht University

MHENS School for Mental Health and Neuroscience

Epigenetics in Neurodegeneration: Contributor or Bystander?

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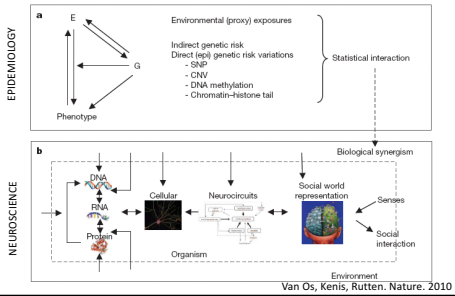
Debate / discussion Bressanone

Questions to you by Alfredo & Bart

- How does interplay between genetic variants and environmental exposure influence the onset and course of neurodegenerative disorders?
- Monozygotic twins – discordance in phenotype (e.g. dementia)
- What explains the missing heritability?
  => gap between molecular and twin-based estimates of heritability
- How are neurodegenerative disorders linked to environmental factors?
- Do your experiences during life influence your offspring via non-genetic inheritance?

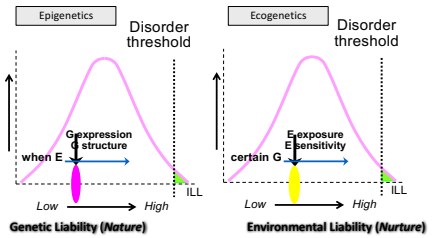
Environmental impact and sensitivity in relation to mental disorders and neuroscience



Van Os, Kenis, Rutten. Nature. 2010

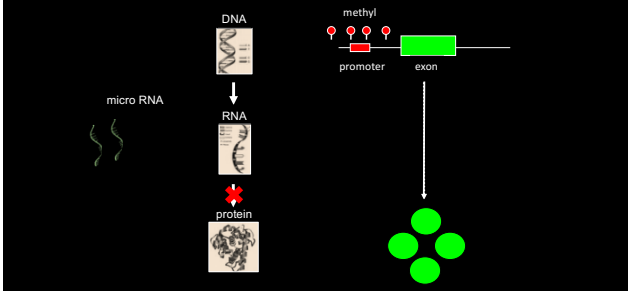
Taking into account etiological complexity of mental and neurodegenerative disorders

complex etiology involving many genes, small effects;
several environmental factors, moderate effects, across lifespan



2008, 2009 2015 Schiz Bull 2010 Nature. 2012 Molecular Psychiatry.

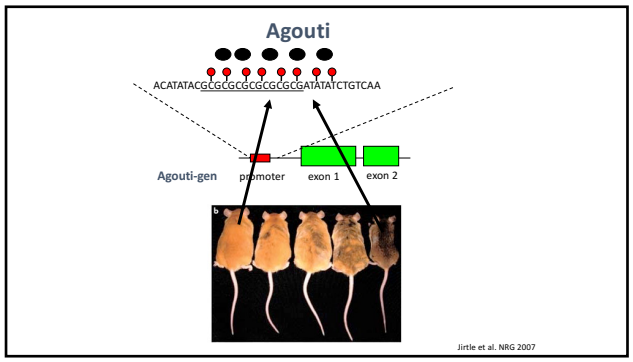
Epigenetic mechanisms regulate gene expression

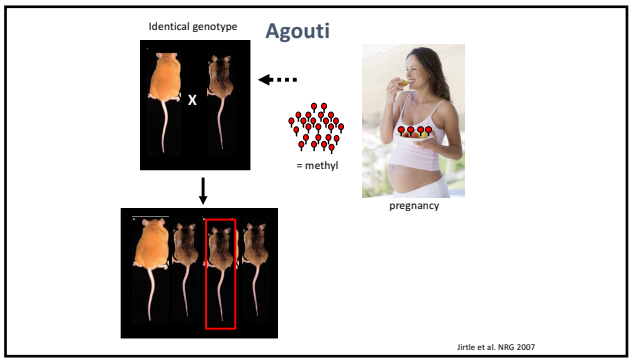


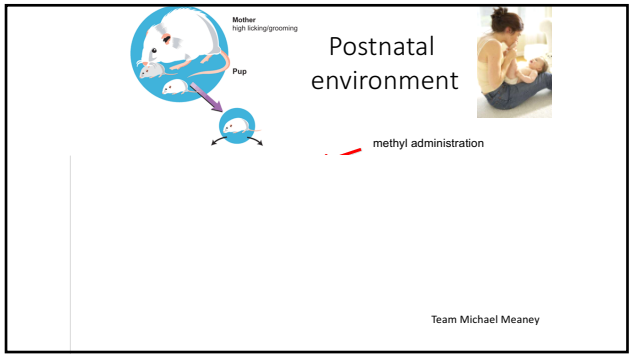
Epigenetics & environmental exposures

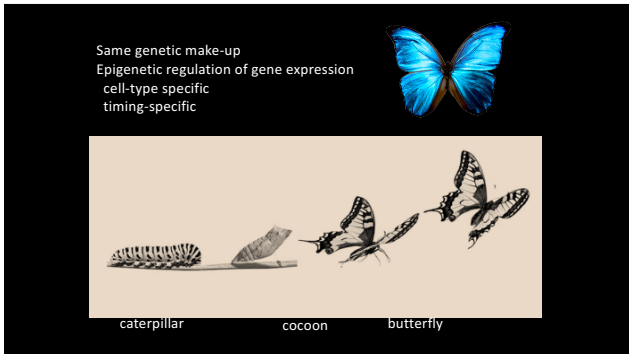
= alterations in gene expression by mechanisms ot

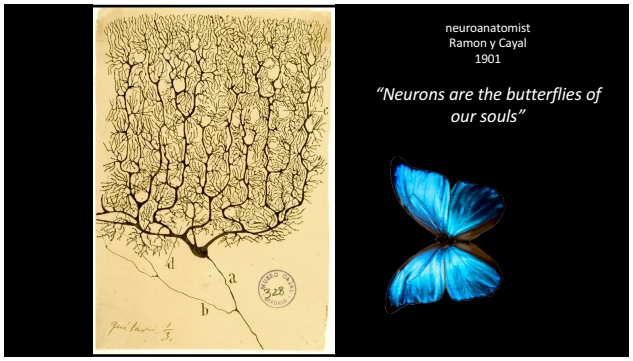
ENVIRONMENT

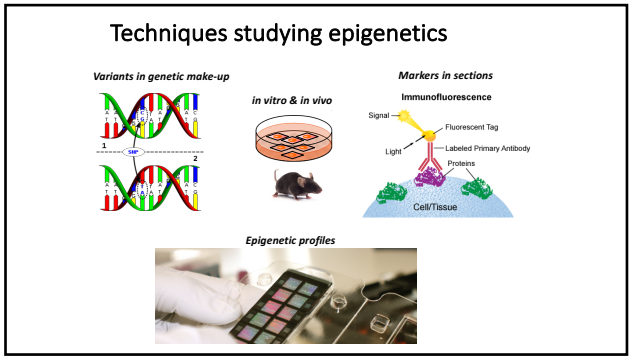

Agouti
ACATATACGCGCGCGCGCGCGCGATATATCTGTCAA
Agouti-gen
promoter
exon 1
exon 2
Jirtle et al. NRG 2007


Identical genotype
Agouti
X
= methyl
pregnancy
Jirtle et al. NRG 2007


Mother
high licking/grooming
Pup
Postnatal environment
methyl administration
Team Michael Meaney

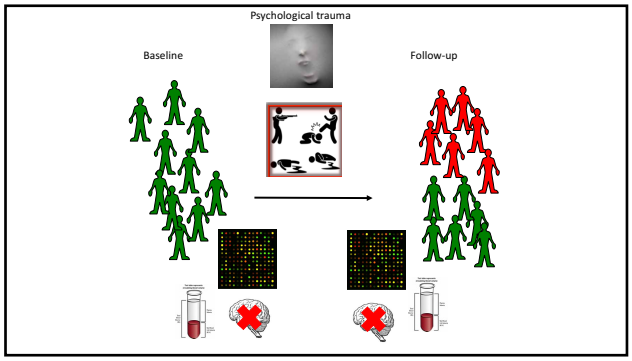

Same genetic make-up
Epigenetic regulation of gene expression
cell-type specific
timing-specific
caterpillar
cocoon
butterfly

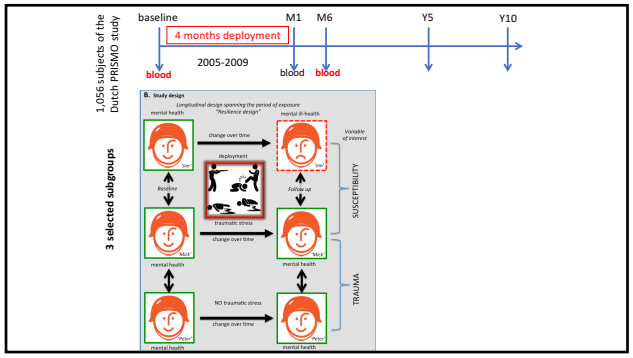

neuroanatomist
Ramon y Cayal
1901
"Neurons are the butterflies of our souls"

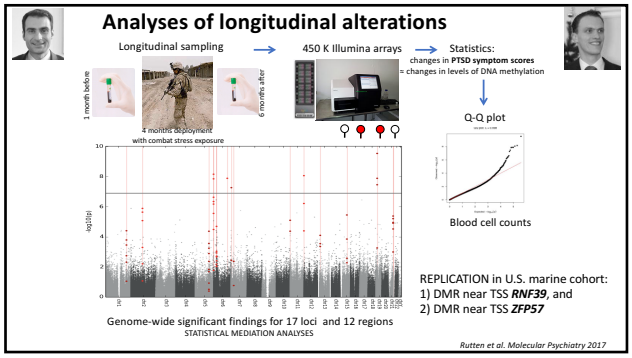

Techniques studying epigenetics
Variants in genetic make-up
in vitro & in vivo
Markers in sections
Immunofluorescence
Signal
Fluorescent Tag
Light
Labeled Primary Antibody
Proteins
Cell/Tissue
Epigenetic profiles

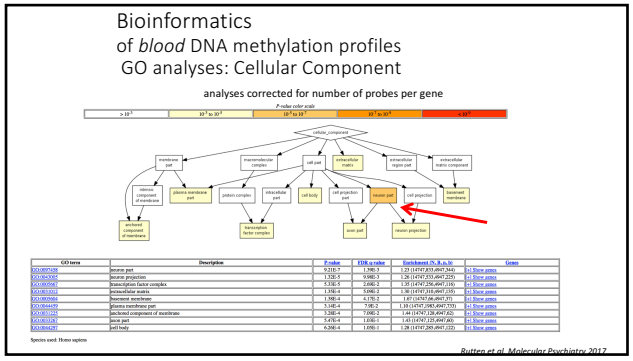
Research example

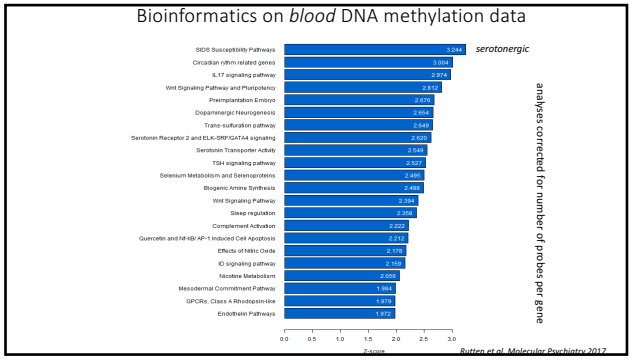
Is the differential behavioral/mental response to exposure to *severe psychological trauma* mediated by differential ***epigenetic*** profiles?

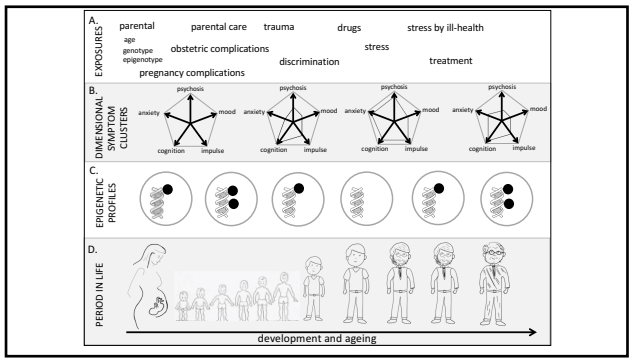




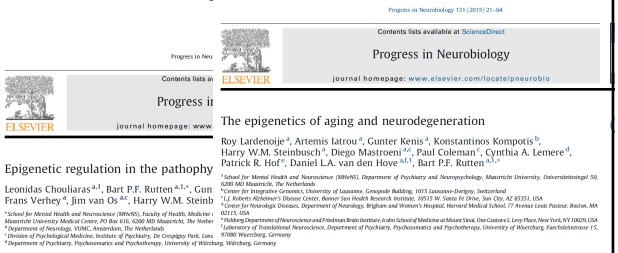








Research example
Ageing and dementia



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ELSEVIER

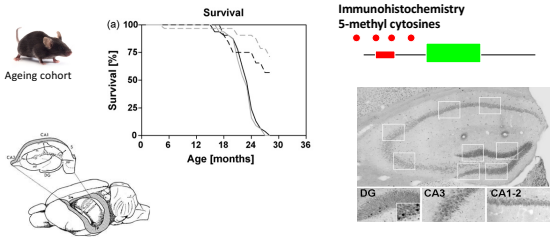
The epigenetics of aging and neurodegeneration

Roy Lardenoije [a], Artemis Iatrou [a], Gunter Kenis [a], Konstantinos Kompotis [b], Harry W.M. Steinbusch [a], Diego Mastroeni [a,c], Paul Coleman [c], Cynthia A. Lemere [d], Patrick R. Hof [e], Daniel L.A. van den Hove [a,f,1], Bart P.F. Rutten [a,1,*]

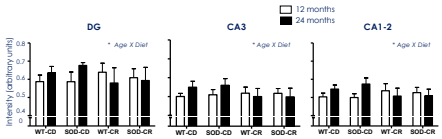
Epigenetic regulation in the pathophy

Leonidas Chouliaras [a,1], Bart P.F. Rutten [a,1,*], Gun
Frans Verhey [g], Jim van Os [a,c], Harry W.M. Steinb

Immunohistochemistry of epigenetic marks in the hippocampus with ageing



Age-related changes attenuated by caloric restriction



- **Increased levels with aging, prevented by caloric restriction**
- No effect of SOD overexpression
- Similar patterns for surface area measurements

(Chouliaras et al., Brain, Behavior and Immunity, 2011)

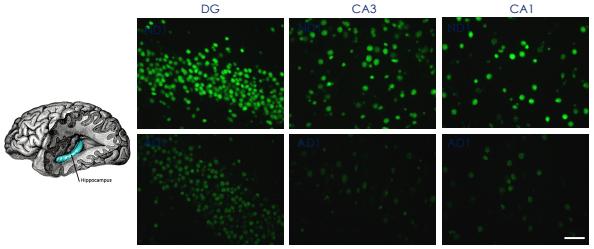
The Banner Sun Health Research Institute

Dr. Leonidas Chouliaras, Prof. Dr. Paul Coleman, Dr. Diego Mastroeni

- ✓NIH Alzheimer's Disease Center (BSHRI, AZ, USA)
- ✓Subjects tested cognitively annually (**average folluw-up > 8 years**)
- ✓Diagnosis on the basis of clinical and neuropathological consensus
- ✓Medication noted
- ✓**Average PMI 2,8 hours**
- ✓Age range 60-100; Braak stages I-VI

DNA (hydroxy)methylation in the human AD hippocampus: opposite direction to normal age-related changes

Similar patterns for 5-mC and 5-hmC



(Chouliaras et al., Neurobiol. Aging, 2013)

Global hypomethylation in Alzheimers disease

Ongoing

Human:

- **Genome-wide DNA (hydroxy)methylation in AD vs. control human brains**

  DNA from the middle temporal gyrus (MTG), and brainstem nuclei

  - Normal aging versus AD
  - According to Braak stage

DNA methylation in blood samples longitudinal

Research challenges

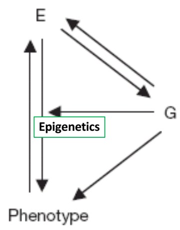
- Long-term, longitudinal (twin) epidemiological studies (e.g. mediation analyses)
- Collect cells/regions during prodromal phases
- Blood-brain correlations of epigenetic profiles
- Source and target of microRNAs
- Tissue composition, cell-type-specificity
- Sample sizes & confounders/co-variates
- Methodological validation and independent replication
- Genetics of epigenetics
- Integration with other – omics
- Phenotypical clinical assessments – quantitative, liability phenotypes
- From association to mediation - experimental studies
  - Ageing
  - Genetic variation, environmental exposures
  - Blood-brain
  - Epigenetic editing
- Reversibility of epigenetic marks *in vivo*, targeting epigenetics *in vivo*
- Inter- and transgenerational inheritance via epigenetics?

Take home

- Epigenetics is a very attractive area of research
- The environment matters
- Expression of genetic variants depends on environmental influences, and vice versa
- “Peripheral” cells may be informative
- Longitudinal studies needed
- Analyses
  - in relation to impact of E on functioning (in quantitative measures)
  - in relation to genetic background
  - In relation to cell type, timing
  - In relation to their biological levels -> system biology
- Lot of work needs to be done…….. Collaboration is essential!

What do you think?

“Is it their environment, their genes, or the interplay?



Twin studies - ageing

Epigenetic drift

Increasing difference between monozygotic twins

Int J Epidemiol. 2016 Aug;45(4):1146-1158. Epub 2016 Aug 6.

Epigenetic drift in the aging genome: a ten-year follow-up in an elderly twin cohort.

Tan Q[1,2], Heijmans BT[3], Hjelmborg JV[4], Soerensen M[4,2], Christensen K[4,2], Christiansen L[4].

⊕ **Author information**

Abstract

BACKGROUND: Current epigenetic studies on aging are dominated by the cross-sectional design that correlates subjects' ages or age groups with their measured epigenetic profiles. Such studies have been more aimed at age prediction or building up the epigenetic clock of age rather than focusing on the dynamic patterns in epigenetic changes during the aging process.

METHODS: We performed an epigenome-wide association study of intra-individual longitudinal changes in DNA methylation at CpG (cytosine-phosphate-guanine) sites measured in whole-blood samples of a cohort of 43 elderly twin pairs followed for 10 years (age at intake 73-82 years). Biological pathway analysis and survival analysis were also conducted on CpGs showing longitudinal change in their DNA-methylation levels. Classical twin models were fitted to each CpG site to estimate the genetic and environmental effects on DNA-methylation.

RESULTS: Our analysis identified 2284 CpG sites whose DNA-methylation levels changed longitudinally over the follow-up. Twin modelling revealed that the longitudinal change for 90% of these CpG sites was explained solely by individual unique environmental factors and only for 10% of these sites was it influenced by familial factors (genetic or shared environment). Over 60% of the identified CpG sites were replicated (same direction and replication $P < 0.05$) in an independent cross-sectional sample of 300 twins aged from 30 to 74 years. The replication rate went up to 91% for the top 53 CpGs with $P < 1 \times 10^{-07}$. Pathway analysis of genes linked to these CpGs identified biologically meaningful gene-sets involved in cellular-signalling events and in transmission across chemical synapses, which are important molecular underpinnings of aging-related degenerative disorders.

CONCLUSION: Our epigenome-wide association studies on a cohort of old twins followed up for 10 years identified highly replicable epigenetic biomarkers predominantly implicated in signalling pathways of degenerative disorders and survival in the elderly.

KEYWORDS: DNA methylation, longitudinal, twins, aging, survival