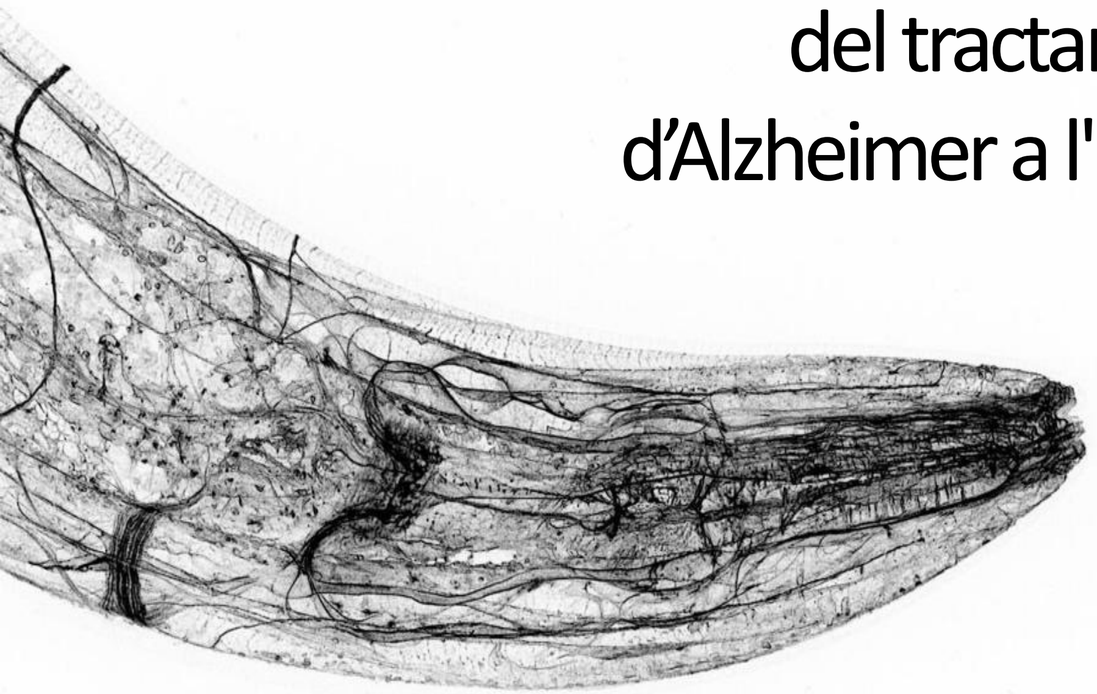
La metiltranferasa G9a: del tractament de la Malaltia d'Alzheimer a l'herència de la memòria.



Dr. Christian Griñán-Ferré

Seminari de Recerca

26 de Maig 2022

Universitat de Barcelona
Facultat de Farmàcia i Ciències de l'Alimentació

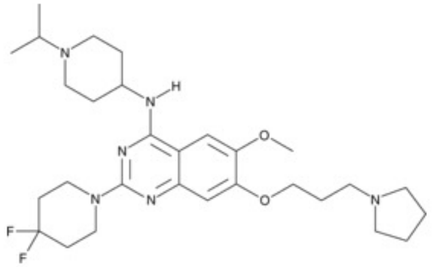
Institut de Neurociències
Universitat de Barcelona

Excelencia María de Maeztu

Facultat de Farmàcia i Ciències de l'Alimentació

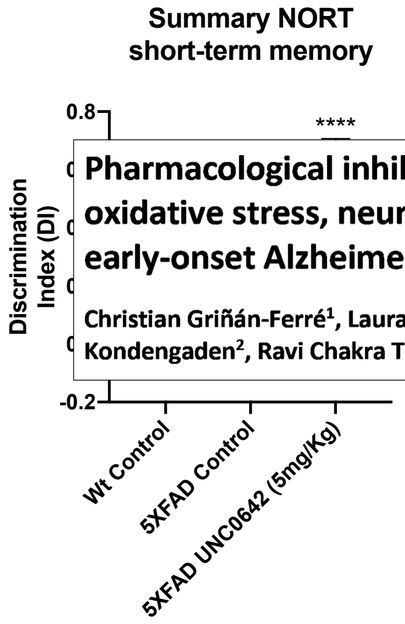
Proof-of-Concept (PoC)

UNC0642 an *in vivo*
BBB penetrant
G9a inhibitor
IC_{50} < 2.5 nM



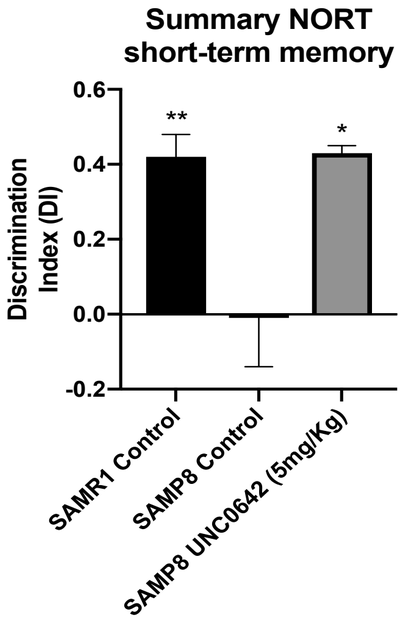
Pharmacological inhibition of G9a/GLP restores cognition and reduces oxidative stress, neuroinflammation and β-Amyloid plaques in an early-onset Alzheimer's disease mouse model

Christian Griñán-Ferré[1], Laura Marsal-García[1], Aina Bellver-Sanchis[1], Shukkoor Muhammed Kondengaden[2], Ravi Chakra Turga[3], Santiago Vázquez[4], Mercè Pallàs[1]



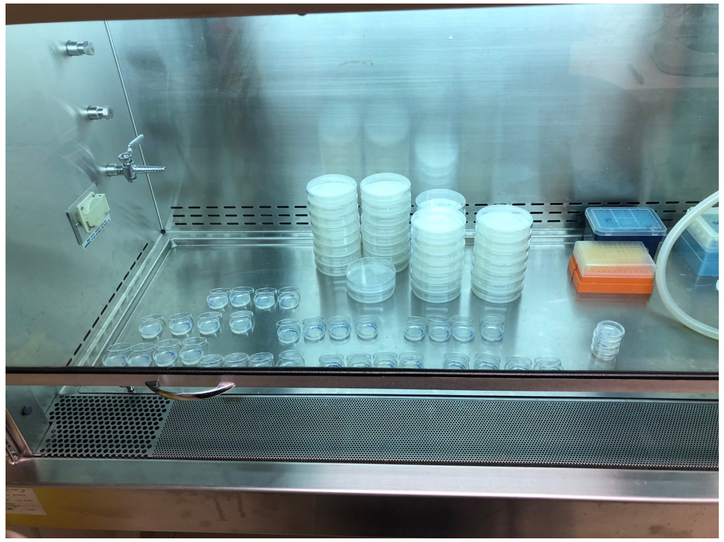
Inhibition of EHMT1/2 rescues synaptic and cognitive functions for Alzheimer's disease

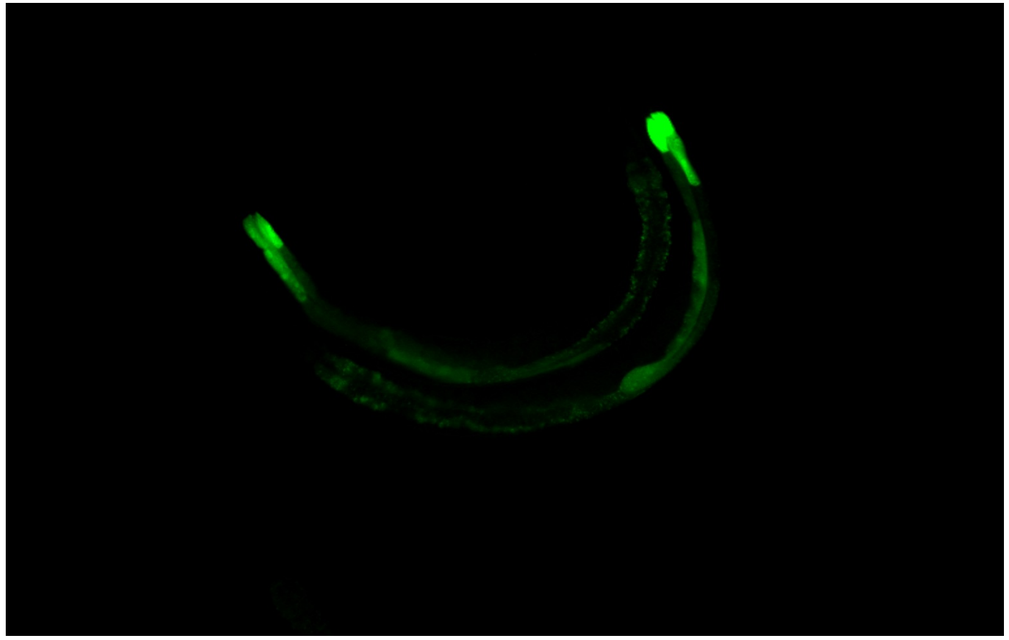
Yan Zheng,[1,2,*] Aiyi Liu,[1,3,*] Zi-Jun Wang,[1,4,*] Qing Cao,[1] Wei Wang,[1] Lin Lin,[1] Kaijie Ma,[1,4] Freddy Zhang,[1] Jing Wei,[1,4] Emmanuel Matas,[1] Jia Cheng,[1] Guo-Jun Chen,[3] Xiaomin Wang[2] and Zhen Yan[1,4]



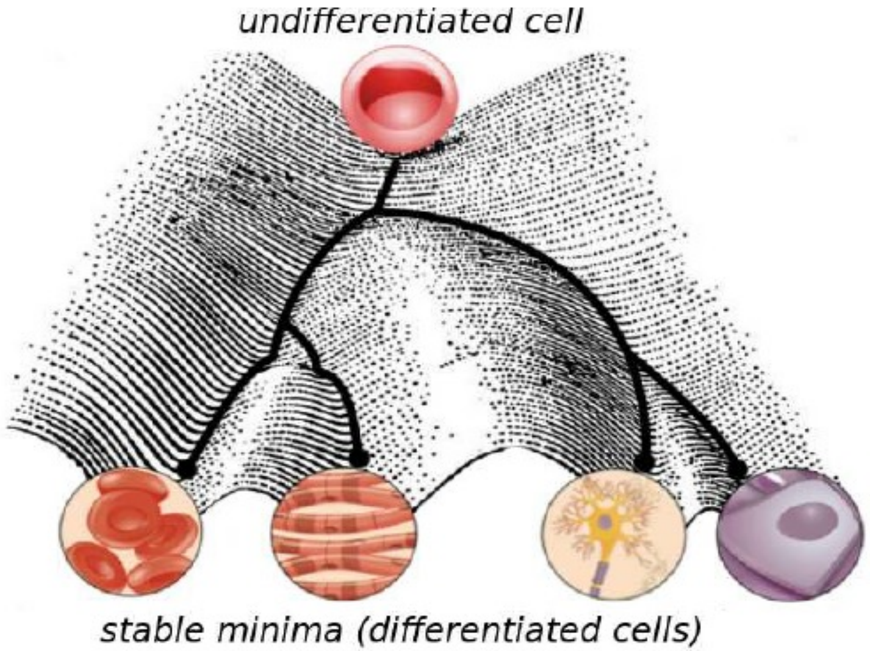
← Final results

C. elegans study in Budapest





EPIGENETICS



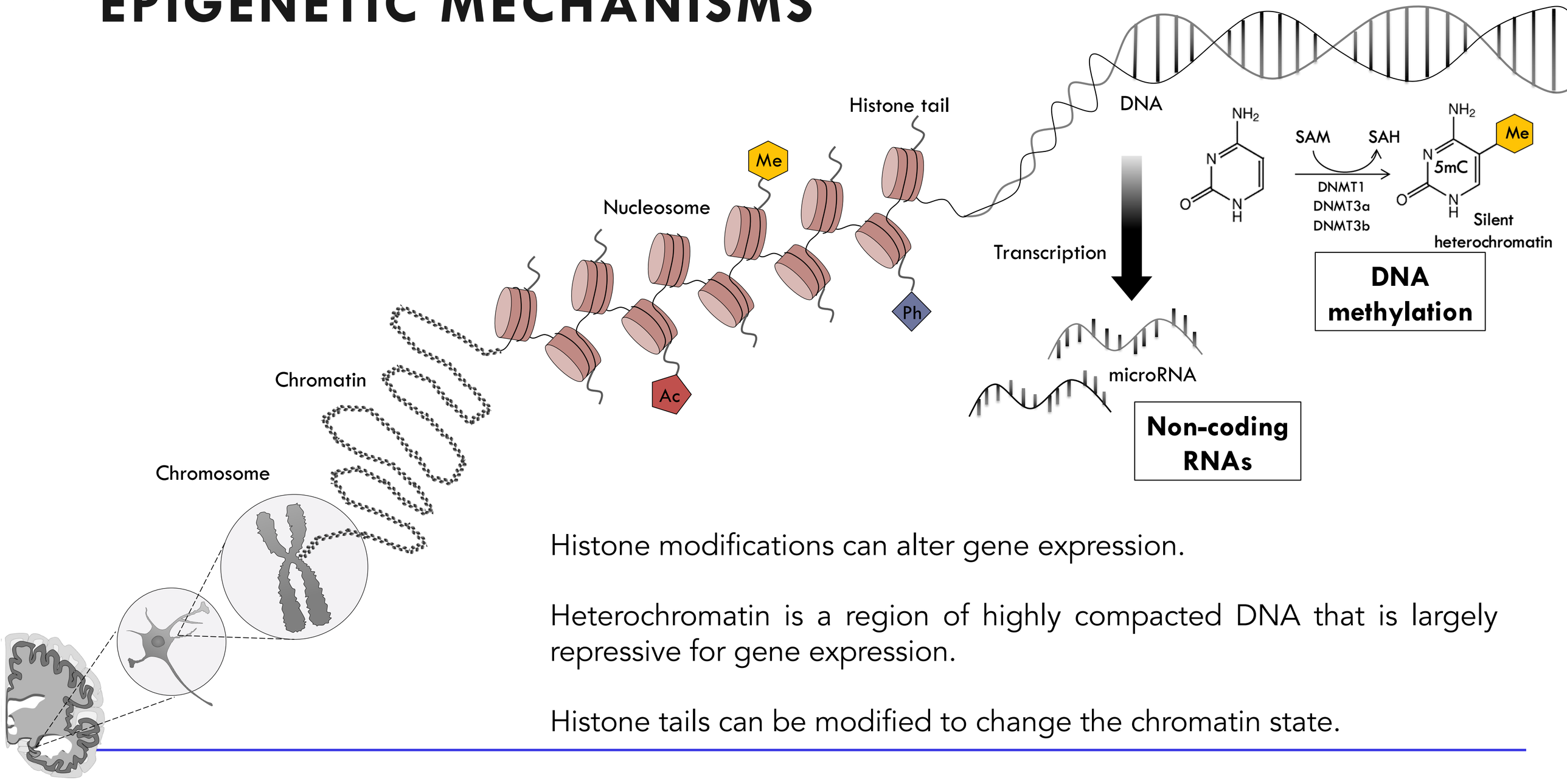
Epigenetic landscape, 1940

Nature Reviews | Genetics

Conrad Hal Waddington (1905-1975)
Developmental biologist

Epigenetics is the study of how your behaviors and environment can cause changes that affect the way your genes work. Unlike genetic changes, epigenetic changes are reversible and do not change your DNA sequence, but they can change how your body reads a DNA sequence.

EPIGENETIC MECHANISMS

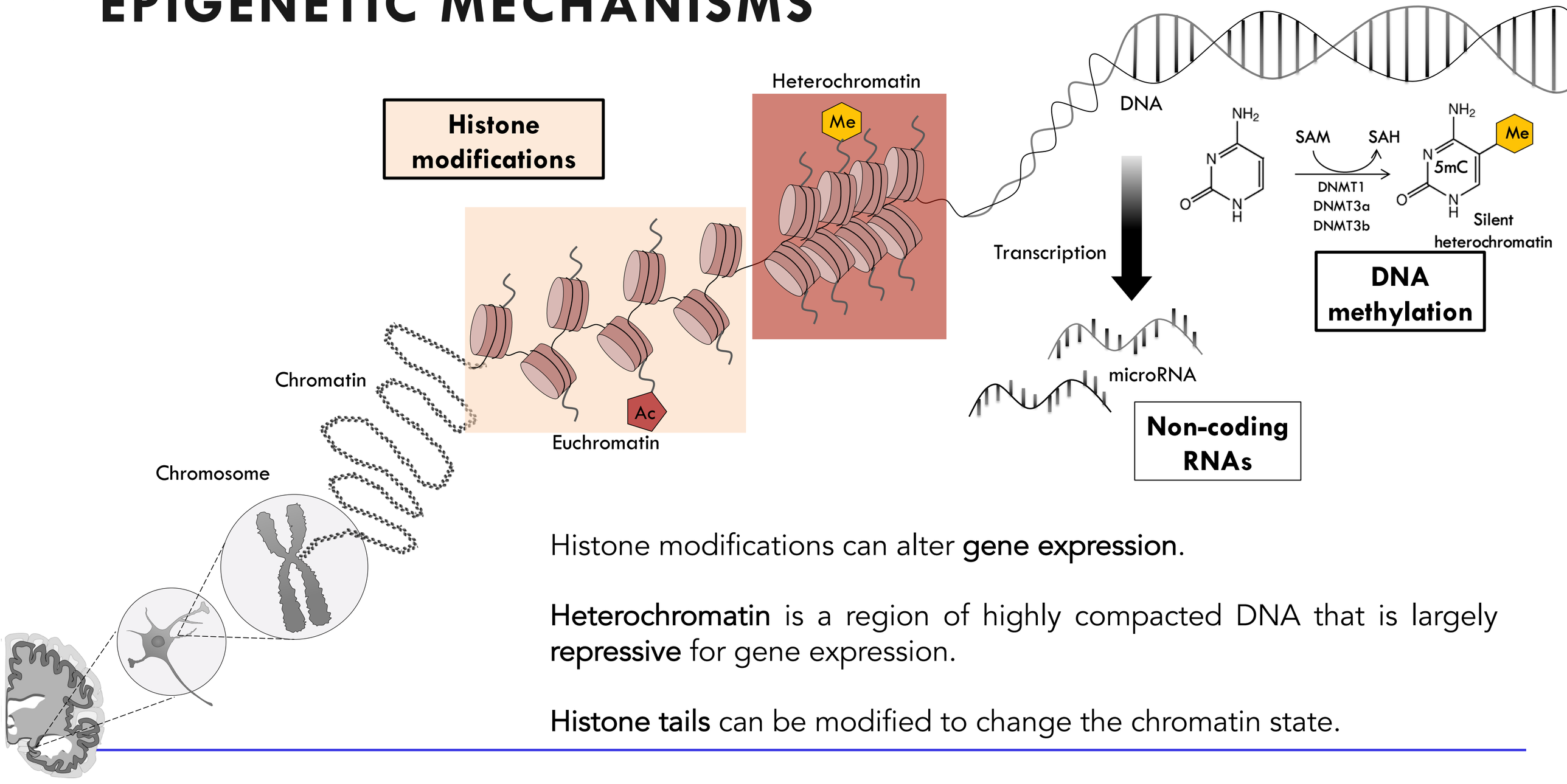


Histone modifications can alter gene expression.

Heterochromatin is a region of highly compacted DNA that is largely repressive for gene expression.

Histone tails can be modified to change the chromatin state.

EPIGENETIC MECHANISMS



Histone modifications can alter **gene expression**.

Heterochromatin is a region of highly compacted DNA that is largely **repressive** for gene expression.

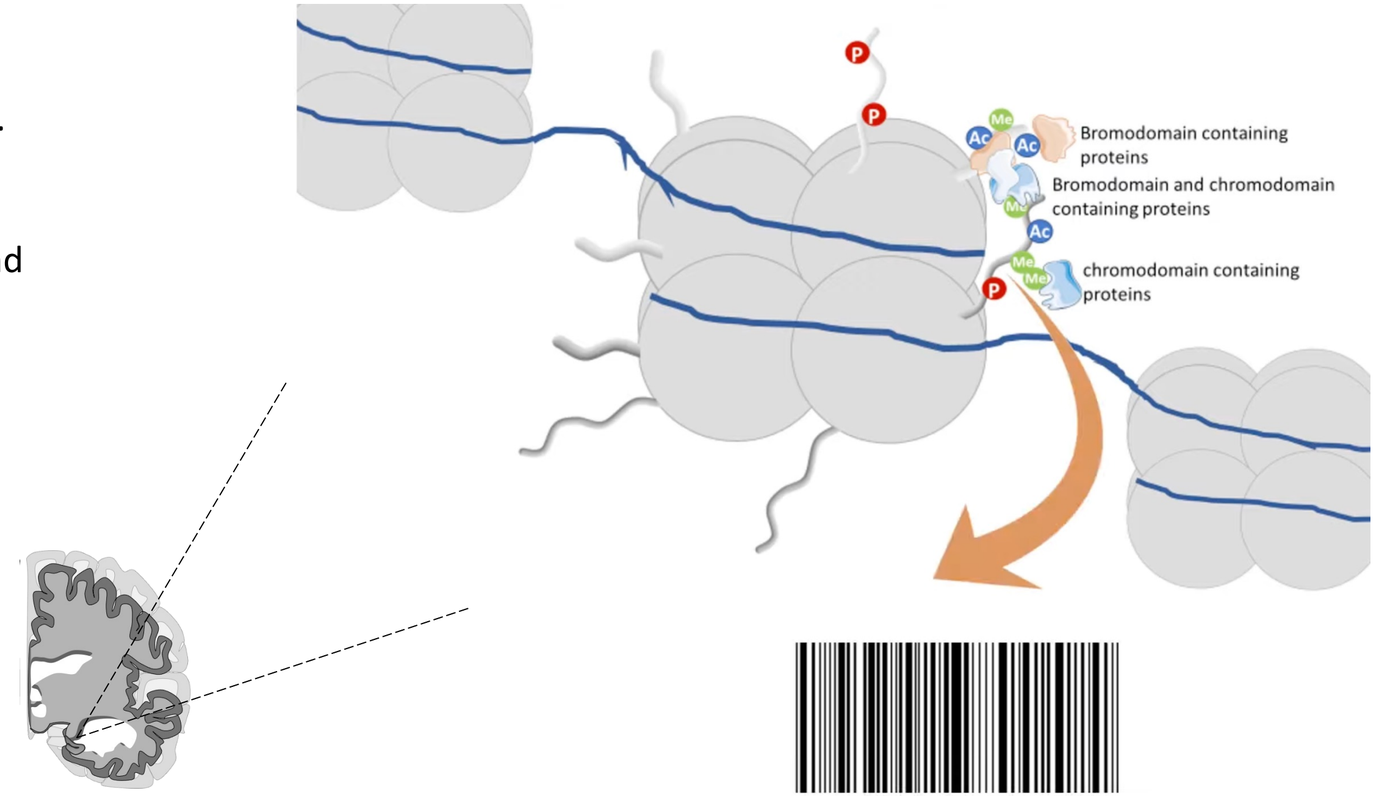
Histone tails can be modified to change the chromatin state.

HISTONE MODIFICATIONS

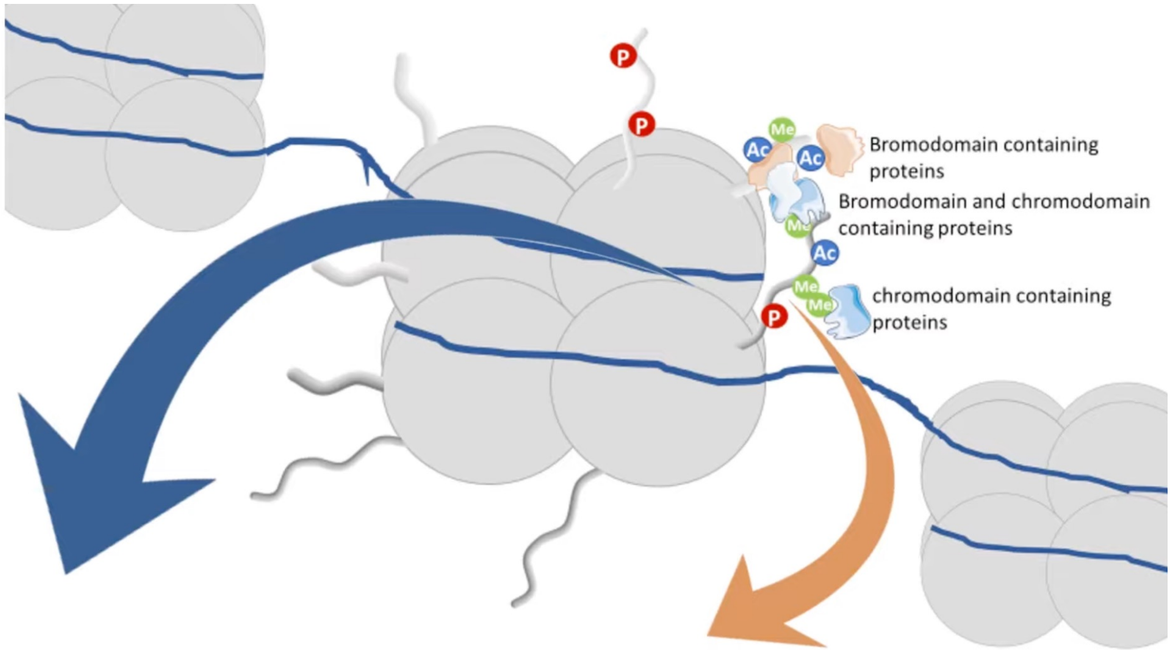
Readers: Bromo and chromodomains…

Writers: histone methyltransferases and histoine acetyltransferases

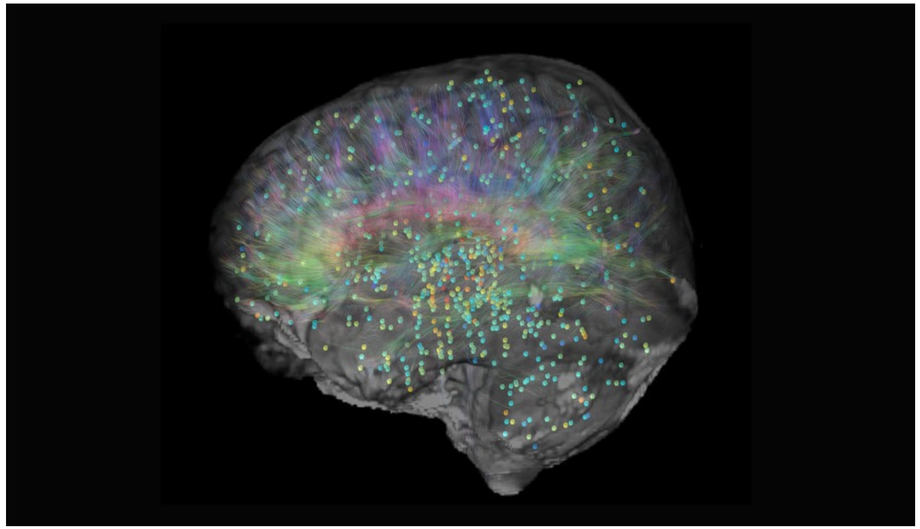
Erasers: histone deacetylases and demethylases



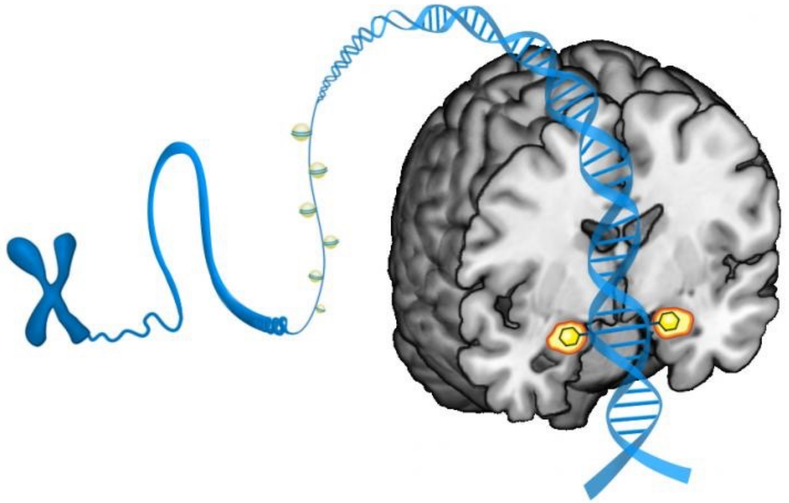
HISTONE MODIFICATIONS



EPIGENETICS IN THE NERVOUS SYSTEM



The human brain expresses numerous genes; approximately 80–95%



Neuronal activity *per se* modifies DNA methylation and histone modifications patterns, and further, that learning and memory depend on these epigenetic changes.

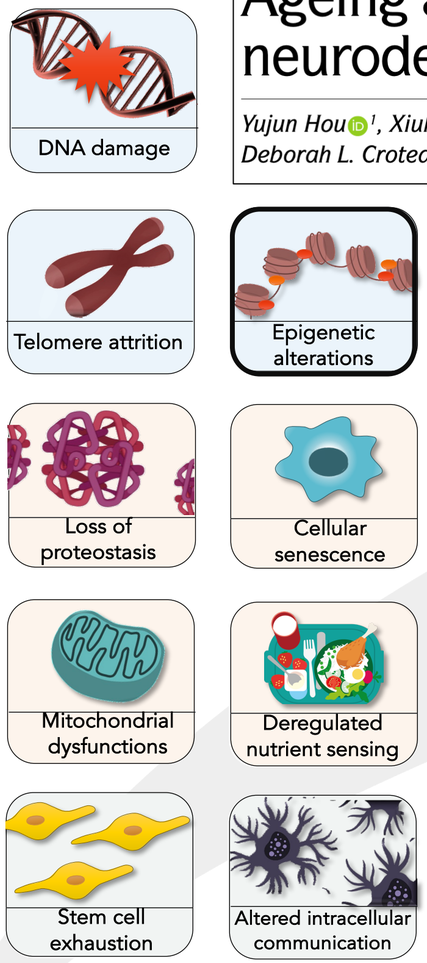
Bae B, Jayaraman D, Walsh CA. Genetic Changes Shaping the Human Brain. *Developmental cell*. 2015;32(4):423-434.

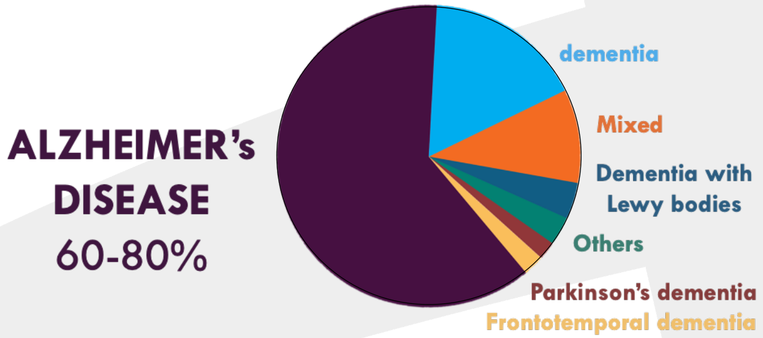
Levenson J. M., Sweatt J. D. (2005). Epigenetic mechanisms in memory formation. *Nat. Rev. Neurosci.* 6 108–118.

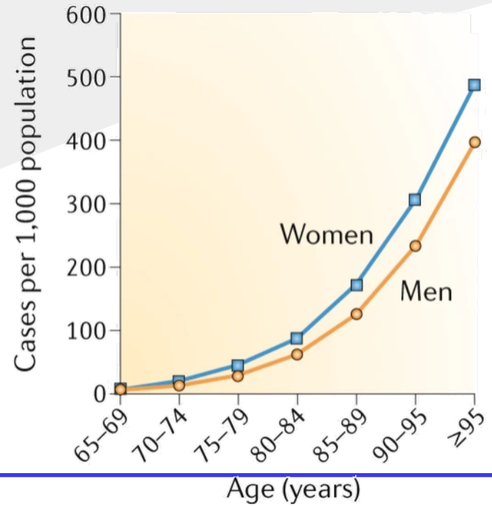
ALZHEIMER'S DISEASE

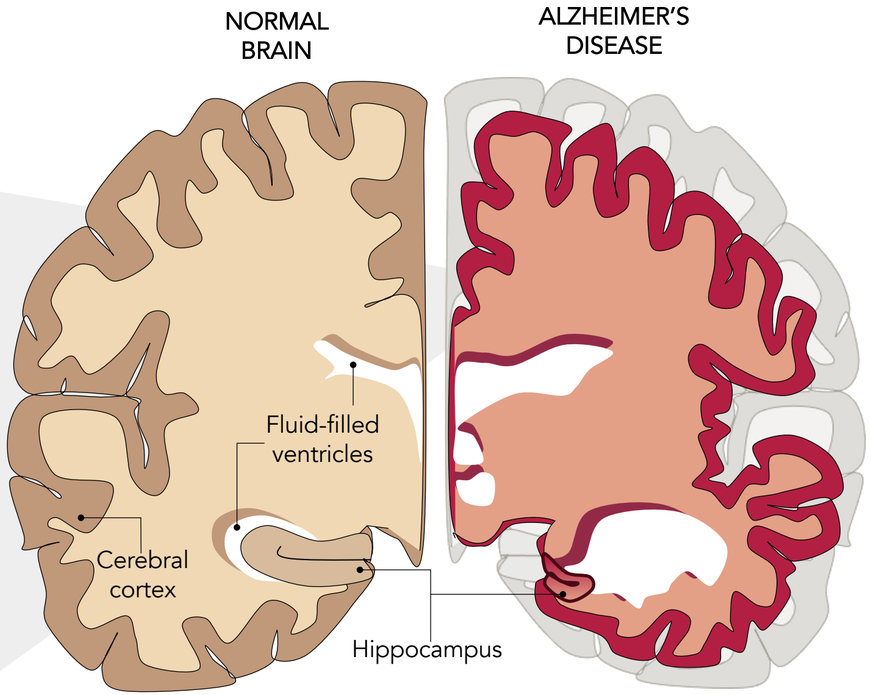
Ageing as a risk factor for neurodegenerative disease

*Yujun Hou[1], Xiuli Dan[1], Mansi Babbar[1], Yong Wei[1], Steen G. Hasselbalch[2], Deborah L. Croteau[1] and Vilhelm A. Bohr[1,3]**





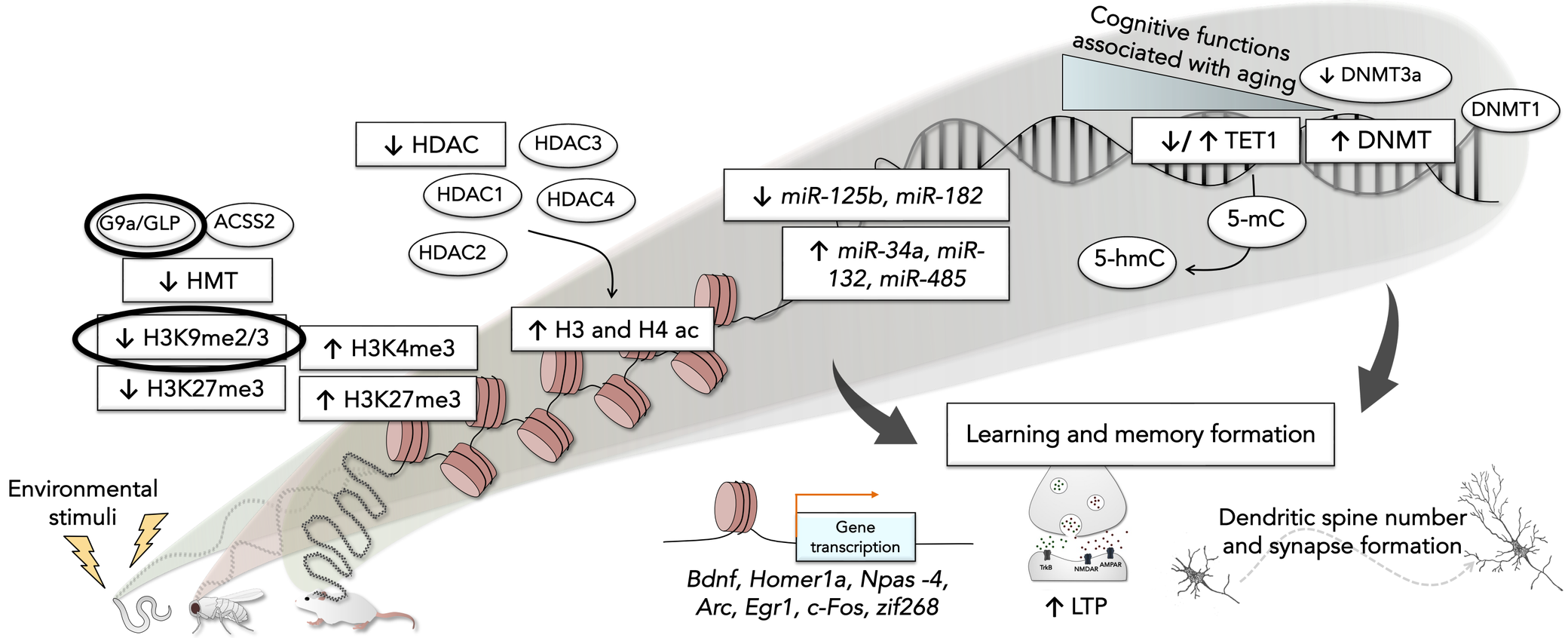




The most common cause of dementia.

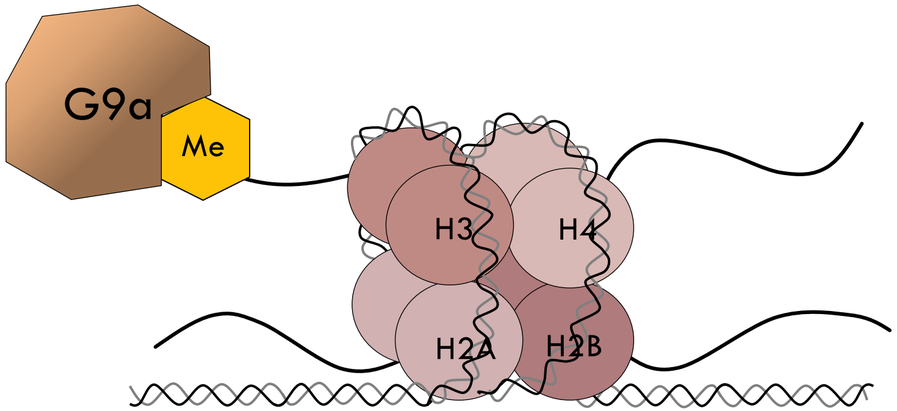
A **progressive** and **irreversible** age-dependent **neurodegenerative diseases** characterized by cognitive decline and memory loss.

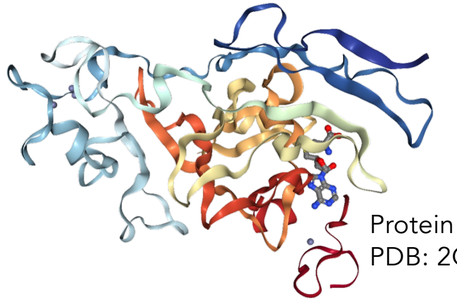
EPIGENETIC ALTERATIONS ASSOCIATED WITH ALZHEIMER'S DISEASE



Bellver-Sanchis et al., 2021. Epigenomes, MDPI.

G9a METHYLTRANSFERASE





Protein Data Bank
PDB: 2O8J

Lysine methyltransferase.

H3K9me and H3K9me2 are repressive marks.

Its inhibition restores the neuropathological hallmarks of AD.

2019

Inhibition of EHMT1/2 rescues synaptic and cognitive functions for Alzheimer's disease

Yan Zheng,[1,2,*] Aiyi Liu,[1,3,*] Zi-Jun Wang,[1,4,*] Qing Cao,[1] Wei Wang,[1] Lin Lin,[1] Kaijie Ma,[1,4] Freddy Zhang,[1] Jing Wei,[1,4] Emmanuel Matas,[1] Jia Cheng,[1] Guo-Jun Chen,[3] Xiaomin Wang[2] and Zhen Yan[1,4]

2019

Epigenetics and memory: Emerging role of histone lysine methyltransferase G9a/GLP complex as bidirectional regulator of synaptic plasticity

Karen Ka Lam Pang[a,b], Mahima Sharma[a,b,c], Sreedharan Sajikumar[a,b,*]

Epigenetic regulation by G9a/GLP complex ameliorates amyloid-beta 1-42 induced deficits in long-term plasticity and synaptic tagging/capture in hippocampal pyramidal neurons

Mahima Sharma,[1,2] Tobias Dierkes[1,3,4] and Sreedharan Sajikumar[1,2]

2017

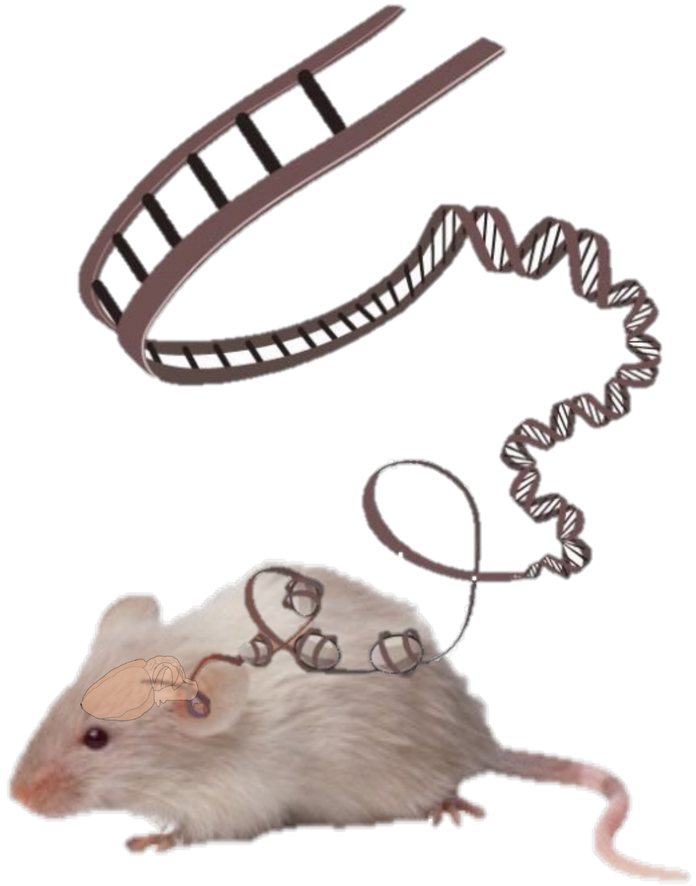
Pharmacological inhibition of G9a/GLP restores cognition and reduces oxidative stress, neuroinflammation and β-Amyloid plaques in an early-onset Alzheimer's disease mouse model

Christian Griñán-Ferré[1], Laura Marsal-García[1], Aina Bellver-Sanchis[1], Shukkoor Muhammed Kondengaden[2], Ravi Chakra Turga[3], Santiago Vázquez[4], Mercè Pallàs[1]

2019 – Second study in vivo in AD transgenic mice model

THE SAMP8 MOUSE MODEL

Epigenetics can explain in part the senescent phenotype that characterizes SAMP8



frontiers in
AGING NEUROSCIENCE

ORIGINAL RESEARCH ARTICLE
published: 20 March 2014
doi: 10.3389/fnagi.2014.00051

Epigenetic alterations in hippocampus of SAMP8 senescent mice and modulation by voluntary physical exercise

*Marta Cosín-Tomás[1,2†], María J. Alvarez-López[1,2†], Sandra Sanchez-Roige[3], Jaume F. Lalanza[3], Sergi Bayod[1], Coral Sanfeliu[2], Merce Pallàs[1], Rosa M. Escorihuela[3] and Perla Kaliman[2]**

[1] *Unitat de Farmacologia, Facultat de Farmàcia Institut de Biomedicina Universitat de Barcelona (IBUB), Nucli Universitari de Pedralbes, Barcelona, Spain*
[2] *Department of Brain Ischemia and Neurodegeneration, Institut d'Investigacions Biomèdiques de Barcelona (IIBB)-Consejo Superior de Investigaciones Científicas (CSIC), Barcelona, Spain*
[3] *Departamento de Psiquiatría y Medicina Legal, Facultad de Medicina, Instituto de Neurociencias, Universitat Autònoma de Barcelona, Barcelona, Spain*

frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 18 October 2016
doi: 10.3389/fnagi.2016.00241

Environmental Enrichment Modified Epigenetic Mechanisms in SAMP8 Mouse Hippocampus by Reducing Oxidative Stress and Inflammaging and Achieving Neuroprotection

*Christian Griñan-Ferré[1], Dolors Puigoriol-Illamola[1], Verónica Palomera-Ávalos[1], David Pérez-Cáceres[2], Júlia Companys-Alemany[1], Antonio Camins[1], Daniel Ortuño-Sahagún[3], M. Teresa Rodrigo[2] and Mercè Pallàs[1]**

Journal of Alzheimer's Disease 62 (2018) 943–963
DOI 10.3233/JAD-170664
IOS Press

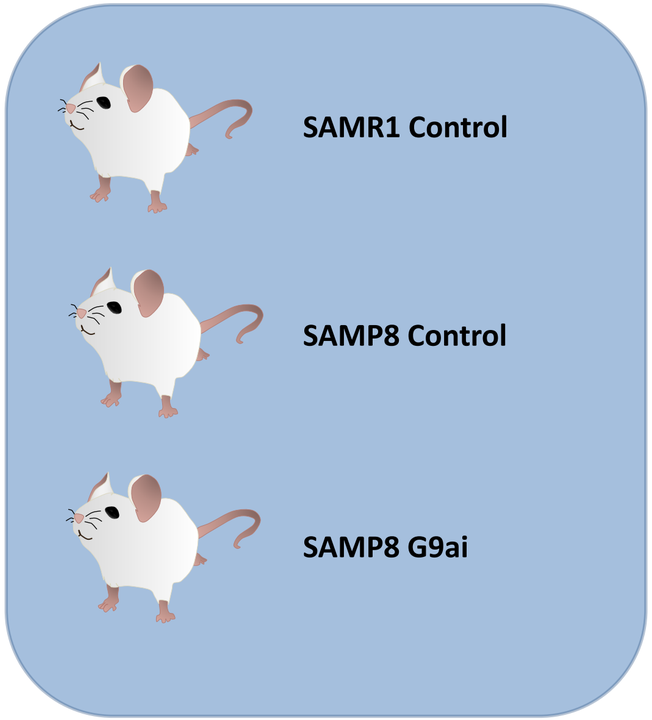
Review

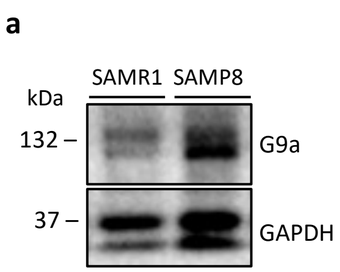
Understanding Epigenetics in the Neurodegeneration of Alzheimer's Disease: SAMP8 Mouse Model

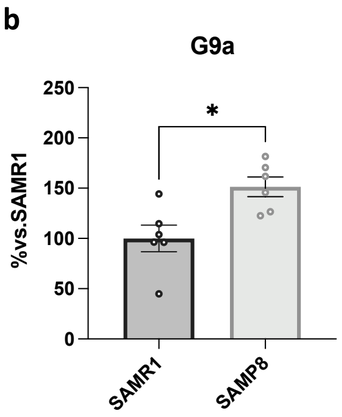
Christian Griñán-Ferré[a], Rubén Corpas[b], Dolors Puigoriol-Illamola[a], Verónica Palomera-Ávalos[a], Coral Sanfeliu[b] and Mercè Pallàs[a,*]
[a]*Department of Pharmacology, Toxicology and Therapeutic Chemistry (Pharmacology Section) and Institute of Neuroscience, University of Barcelona and CIBERNED, Barcelona, Spain*
[b]*Institut d'Investigacions Biomèdiques de Barcelona (IIBB), CSIC, IDIBAPS and CIBERESP, Barcelona, Spain*

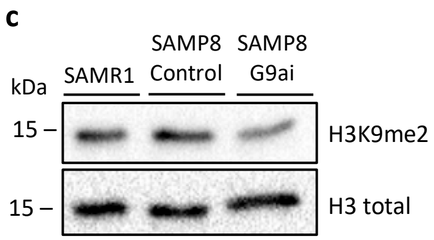
Accepted 11 January 2018

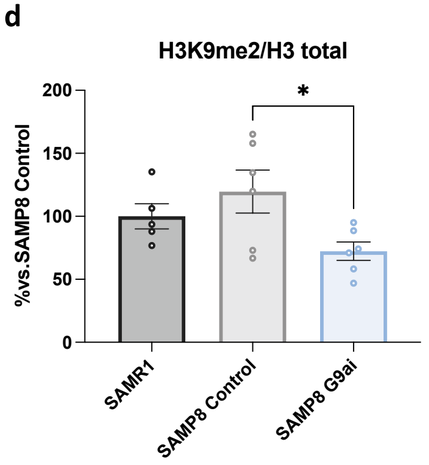
THE SAMP8 MOUSE MODEL





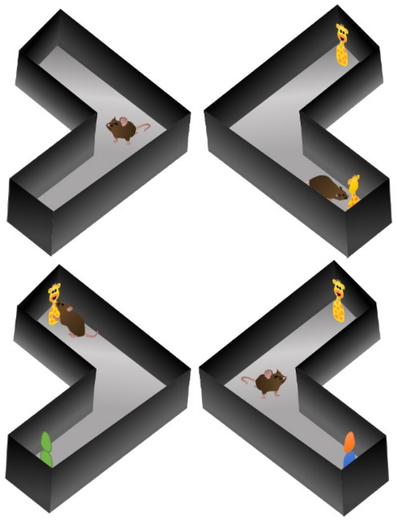


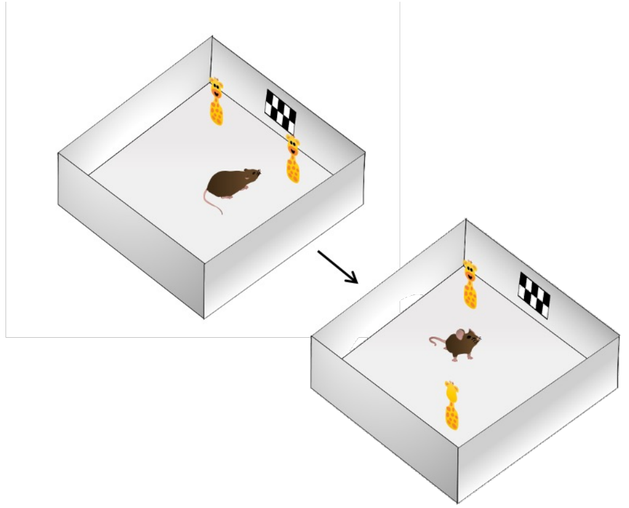




One-way ANOVA with Tukey post hoc analysis: *p<0.05; **p<0.01; ***p<0.001;****p<0.0001

PHARMACOLOGICAL G9A INHIBITION LEADS TO A REDUCTION IN H3K9ME2 AND AD HALLMARKS, RESTORING DENDRITIC SPINE DENSITY IN SAMP8 MICE



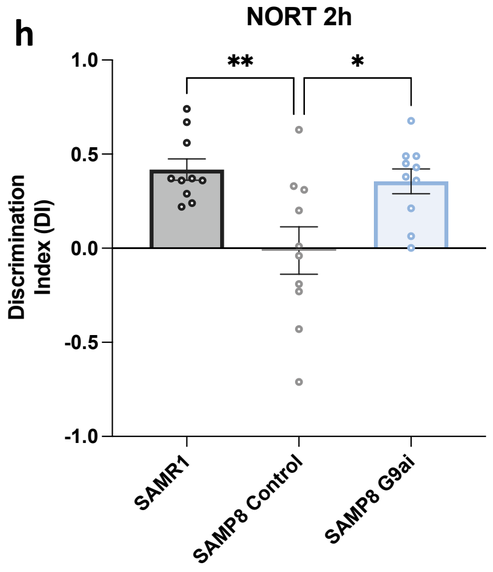


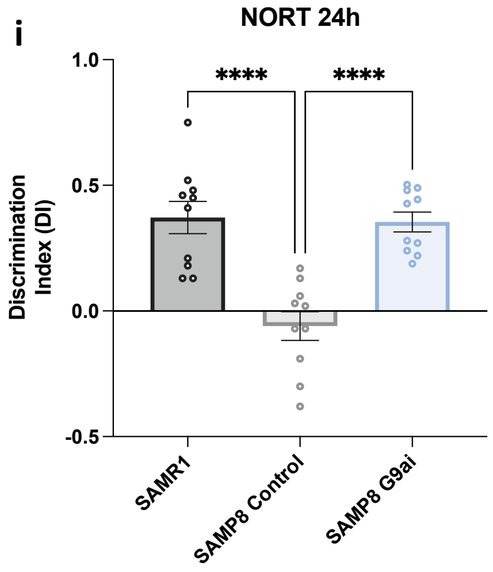
Discrimination Index

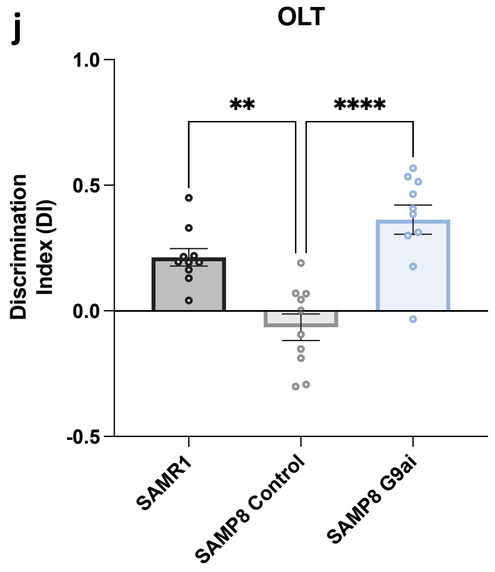
$$\frac{t_{(novel)} - t_{(old)}}{t_{(novel)} + t_{(old)}}$$

~0 : poor discrimination

>0 : increased discrimination







One-way ANOVA with Tukey post hoc analysis: *p<0.05; **p<0.01; ***p<0.001;****p<0.0001

SOME MEMORIES ARE ENCODED IN THE HERITABLE MATERIAL

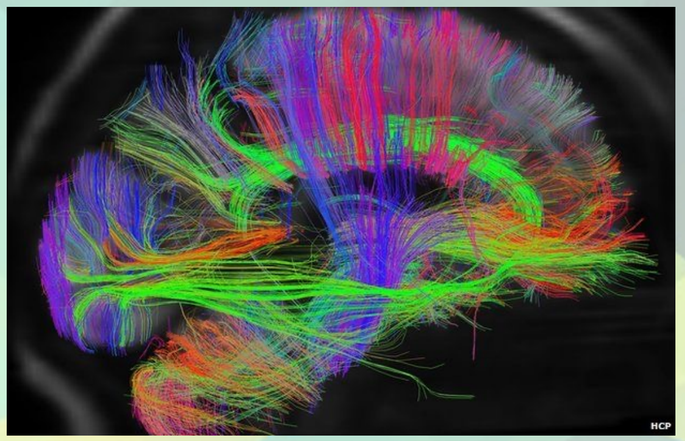
SOME MEMORIES ARE ENCODED IN THE HERITABLE MATERIAL

SOME MEMORIES ARE ENCODED IN THE HERITABLE MATERIAL

SOME MEMORIES ARE ENCODED IN THE HERITABLE MATERIAL

Wheres is this memory encoded?

CAENORHABDITIS ELEGANS

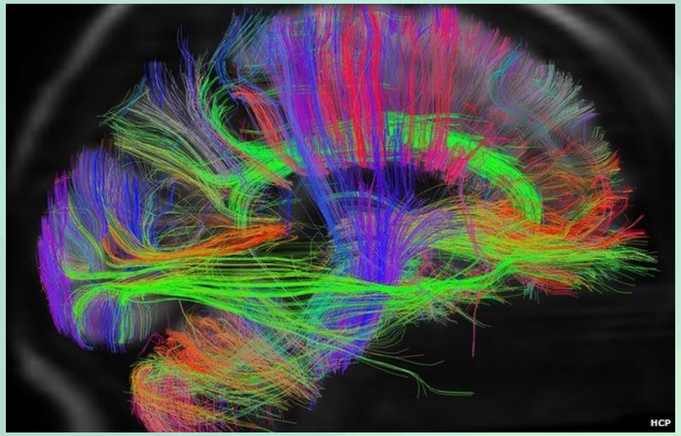


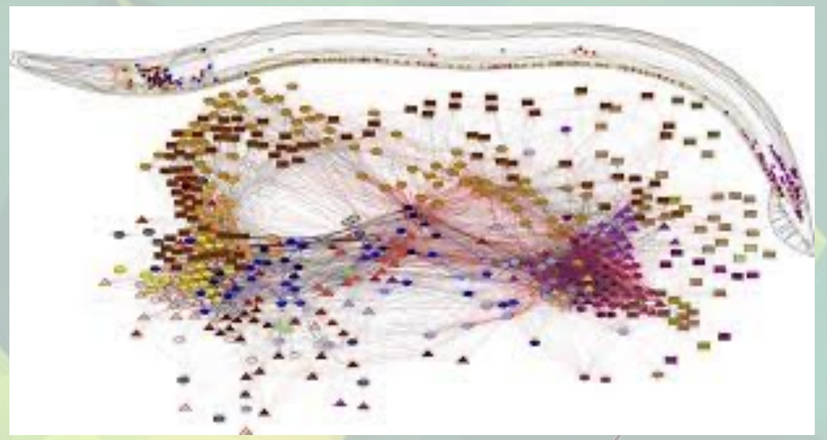
Our brain is complex

100,000.000.000 neurons

7000 synapses per neuron (10^{15})

CAENORHABDITIS ELEGANS



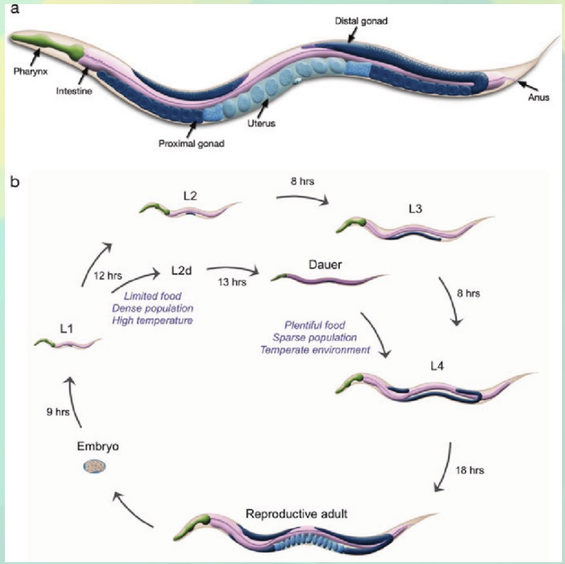


Our brain is complex

100,000.000.000 neurons

7000 synapses per neuron (10^{15})

Expresses the 95% of the genes



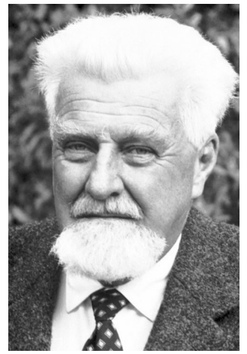
A powerful model for studying memory (much simpler brain)

302 neurons - 7000 synapses

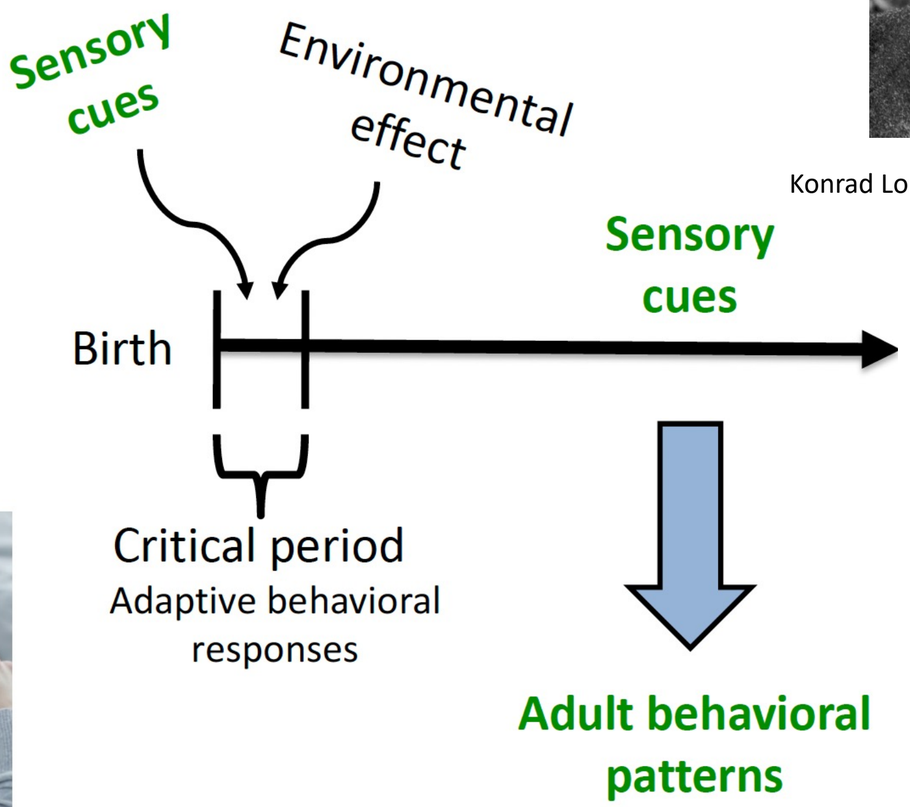
Connectome and short life cycle, which is useful for studying the inheritance.

Many molecular pathways like humans

IMPRINTING: A PHASE-SPECIFIC LONG TERM MEMORY



Konrad Lorenz (Nobel Prize, 1973)



Lorenz,1937; Nevitt et al,1994; Wilson and Sullivan, 1994

INHERITED MEMORY?

Stable inheritance of an acquired behavior in *Caenorhabditis elegans*

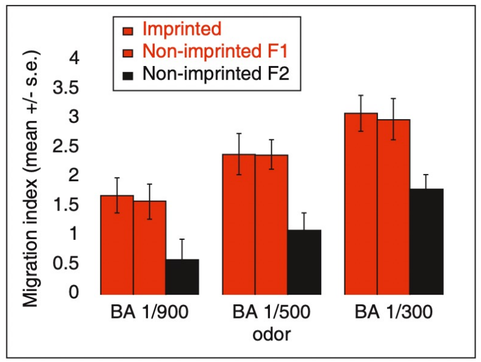
Jean-Jacques Remy

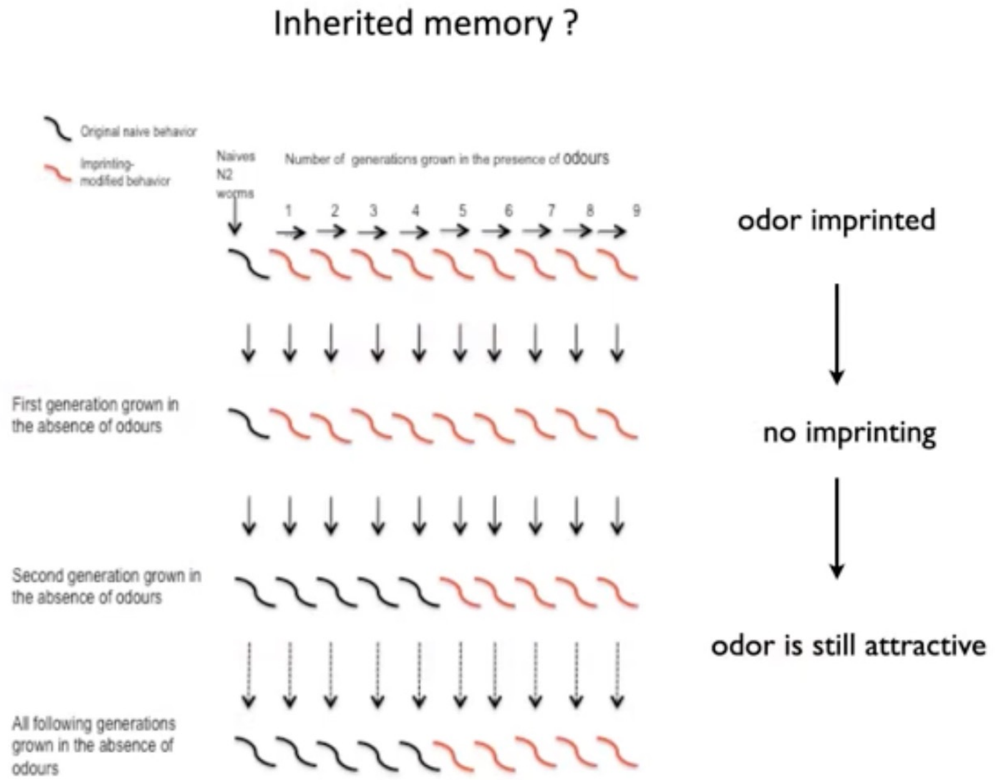
Sensory imprinting produces life-long attachment to environmental features experienced during a critical period of early development. Imprinting of this kind is highly conserved in evolution and is an important form of adaptive behavioral plasticity [1]. The nematode *Caenorhabditis elegans* undergoes such adaptation to new environments through imprinting: attractive odorants, when present during the first larval stage, produce life-long olfactory

would have an improved attraction to olfactory cues if its parent was imprinted. Intriguingly, this appears to be the case: as shown in Figure 1A, a parental imprint was inherited by F1 worms, but not transmitted to F2 worms.

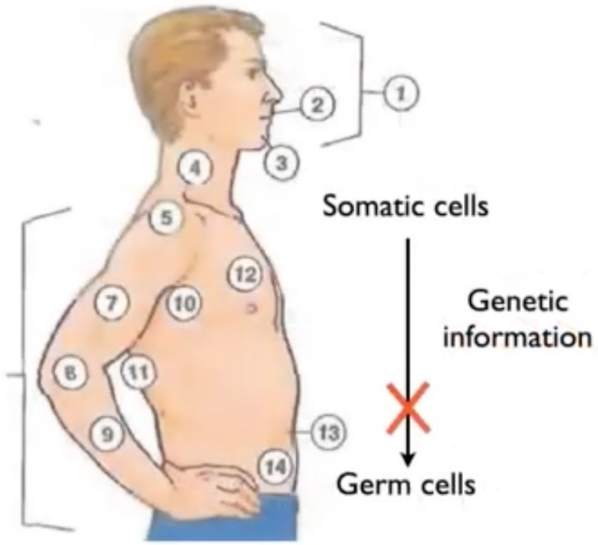
Oliver Hobert and I [2] have previously reported that olfactory imprinting involves at least two classes of neurons, the chemosensory neurons AWC and the interneurons AIY. Imprinting inheritance suggests that neuronal

A





THE ”WEISMANN BARRIER”

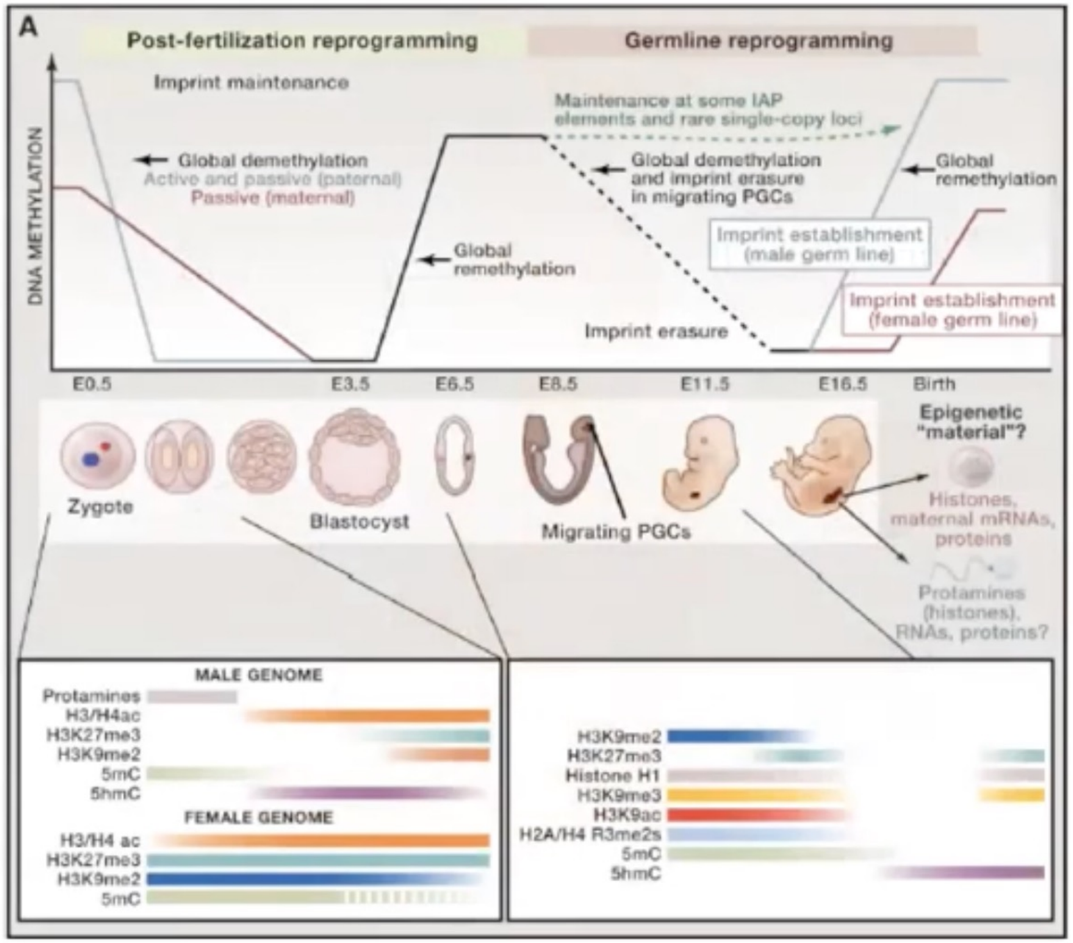


August Weismann
1834-1914

Genetic information cannot pass from the soma to the germ line

(The “Weismann Barrier”)

EPIGENETIC REPROGRAMMING



August Weismann
1834-1914

E. Heard and R. Martienssen, *Cell* 2014

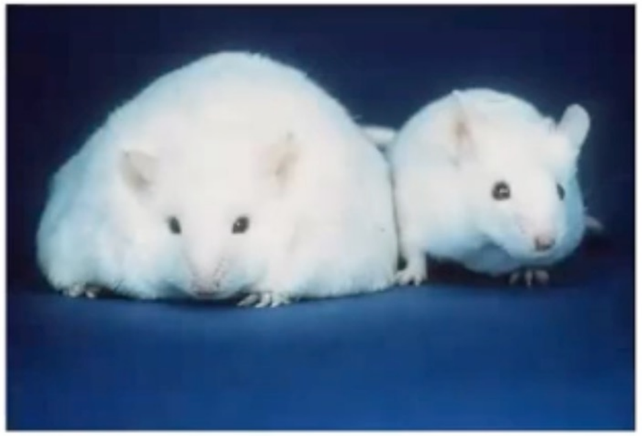
CAN THE PARENTS' DIETARY STATE TRANSMITE TRANSGENERATIONALLY?

"The fathers have eaten sour grapes, and the children's teeth are set on edge."

The Dutch Famine ("Hungerwinter")

(Painter et al. 2008)

Inherited effects of high-fat diet



(Massiera et al. 2010)

International Journal of *Molecular Sciences*

MDPI

Article

Maternal Resveratrol Supplementation Prevents Cognitive Decline in Senescent Mice Offspring

Vanesa Izquierdo [1], Verónica Palomera-Ávalos [1,2], Sergio López-Ruiz [1], Anna-Maria Canudas [1], Mercè Pallàs [1,*] and Christian Griñán-Ferré [1]

[1] Department of Pharmacology and Therapeutic Chemistry. Institut de Neurociències—University of Barcelona, Avda. Joan XXIII, 27. 08028 Barcelona, Spain; vanesa_izquierdo@hotmail.com (V.I.); Vpalomera@hotmail.com (V.P.-Á.); sergio.slr3@gmail.com (S.L.-R.); canudas@ub.edu (A.-M.C.); christian.grinan@ub.edu (C.G.-F.)
[2] Department of Cellular and Molecular Biology, University Center of Biological and Agricultural Sciences, University of Guadalajara, km 15.5 Guadalajara-Nogales highway, C.P. 45110 Zapopan, Jalisco, Mexico
* Correspondence: pallas@ub.edu; Tel.: +34-934024531

Received: 7 February 2019; Accepted: 26 February 2019; Published: 6 March 2019

check for updates

International Journal of *Molecular Sciences*

MDPI

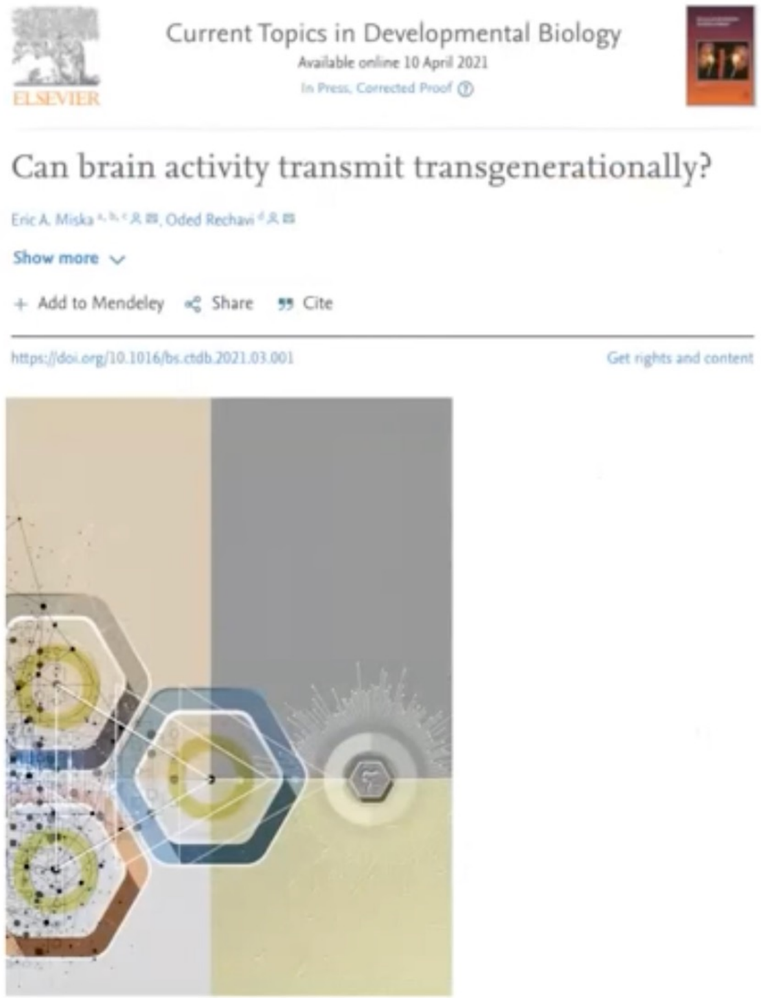
Article

Resveratrol Supplementation Attenuates Cognitive and Molecular Alterations under Maternal High-Fat Diet Intake: Epigenetic Inheritance over Generations

Vanesa Izquierdo [1], Verónica Palomera-Ávalos [2], Mercè Pallàs [1] and Christian Griñán-Ferré [1,*]

[1] Department of Pharmacology and Therapeutic Chemistry, Institut de Neurociències—Universitat de Barcelona, Avda. Joan XXIII, 27, 08028 Barcelona, Spain; vanessa_izquierdo@hotmail.com (V.I.); pallas@ub.edu (M.P.)
[2] Department of Cellular and Molecular Biology, University Center of Biological and Agricultural Sciences, University of Guadalajara, km 15.5 Guadalajara-Nogales Highway, 45110 Zapopan, Jalisco, Mexico; vpalomera@hotmail.com
* Correspondence: christian.grinan@ub.edu; Tel.: +34-93-402-4526

CAN NEURONAL MEMORIES TRANSFER BETWEEN GENERATIONS?



Current Topics in Developmental Biology
Available online 10 April 2021
In Press, Corrected Proof

Can brain activity transmit transgenerationally?

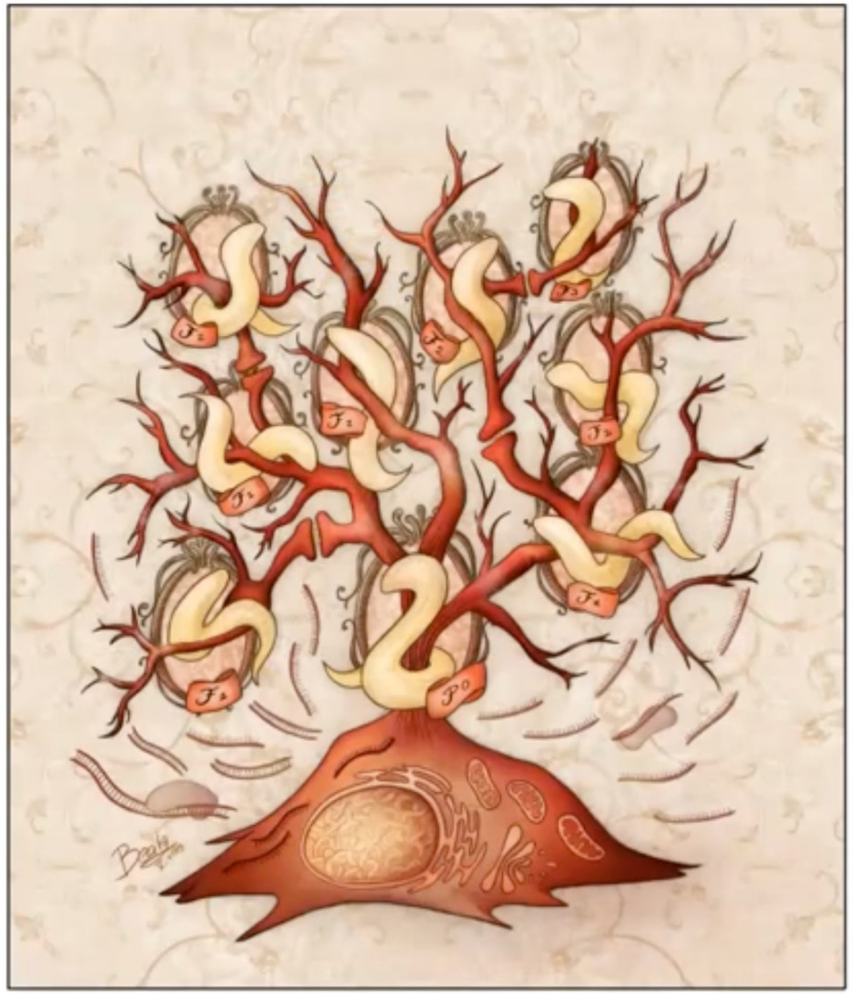
Eric A. Miska, Oded Rechavi

Show more

Add to Mendeley Share Cite

https://doi.org/10.1016/bs.ctdb.2021.03.001

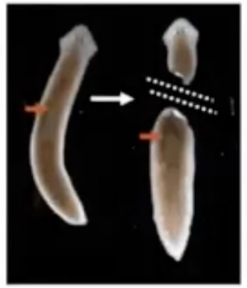
Get rights and content



CAN MEMORIES TRANSFER BETWEEN INDIVIDUALS?

James V. McConnell

Decapitated Worms Regrow Heads with Memories Still Inside



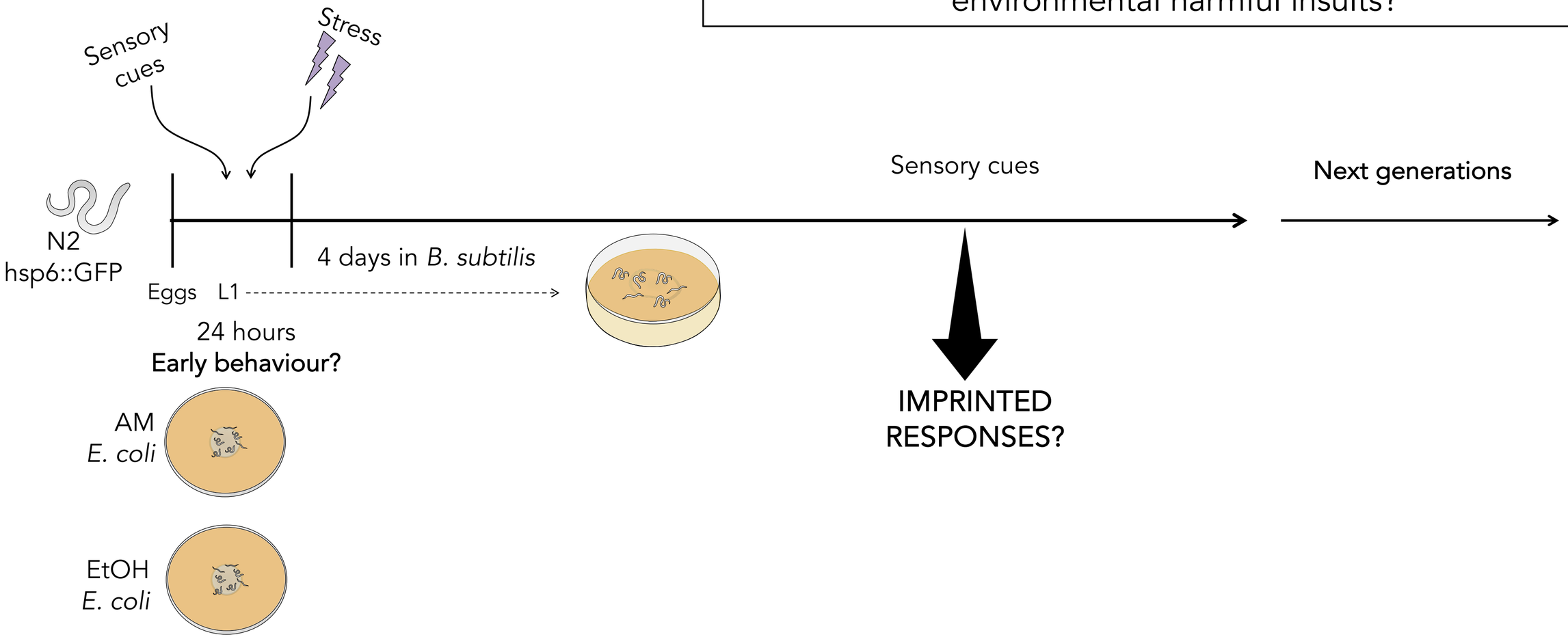
How good are you at remembering something you learned two weeks earlier? What if during the intervening 14 days, your head was removed? One flatworm isn't bothered by this scenario. After growing back its entire head and brain, it picks off pretty much where it left off.

EXPERIMENTAL PARADIGM

Imprinting: a phase-specific long-term memory

Design experiment

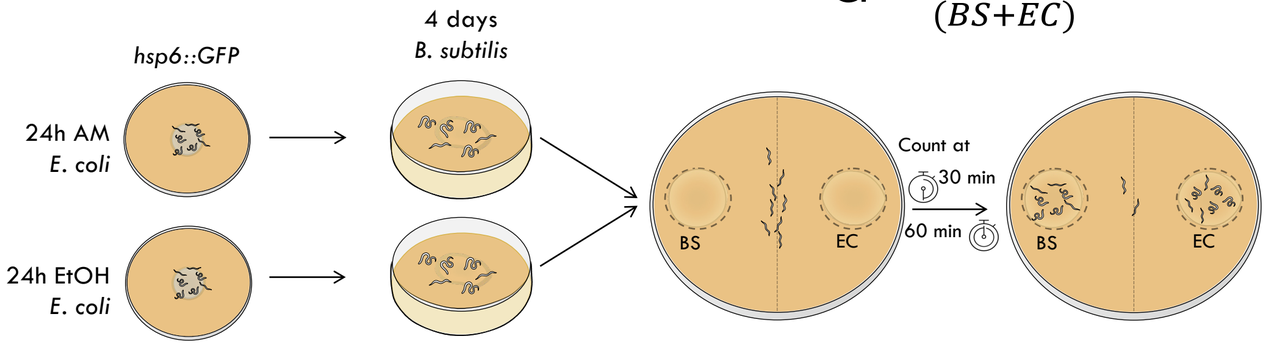
Does **set-25** play an important role in **long-term memory** after environmental harmful insults?

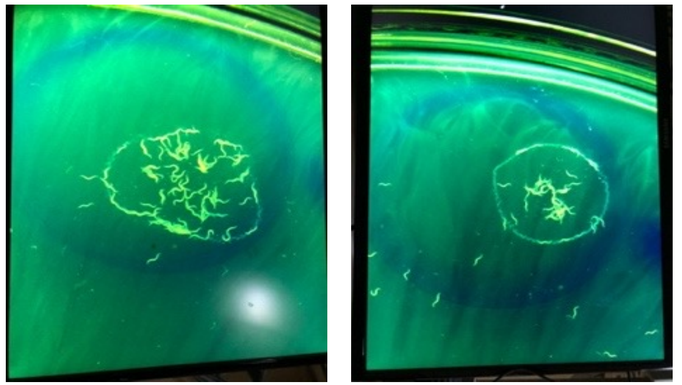


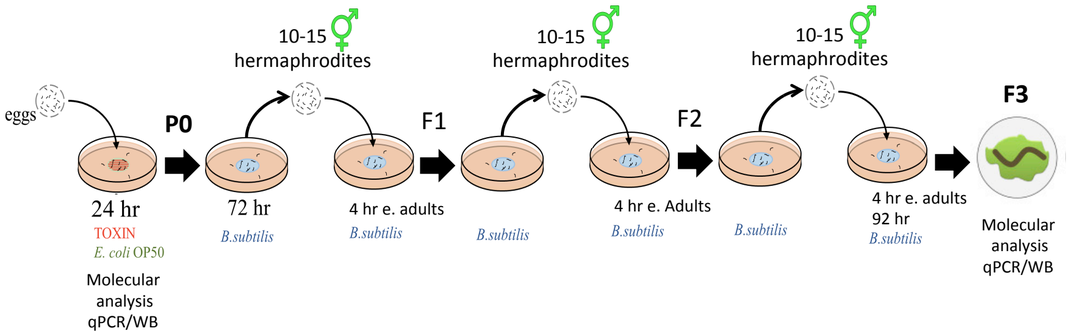
EPIGENETIC INHERITANCE

Olfactory food choice

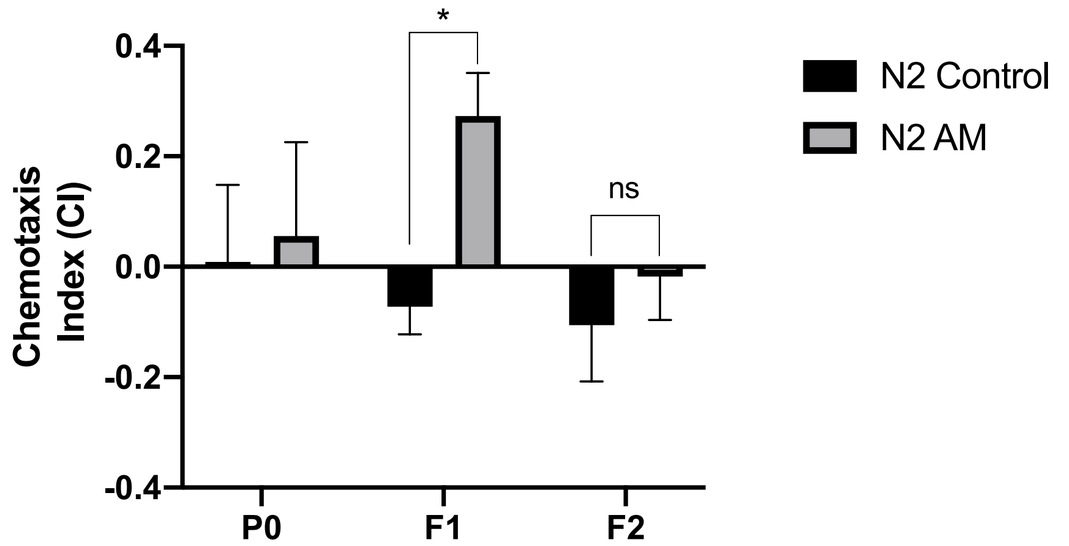
$$CI = \frac{(BS - EC)}{(BS + EC)}$$







Intergenerational epigenetic inheritance after 1 imprinting with AM



Unpublished resuts

One-way ANOVA with Tukey post hoc analysis: *p<0.05; **p<0.01; ***p<0.001;****p<0.0001

Conclusions

- GMFB activation mediates the neuroprotection by G9a inhibition.

- Early life toxic stress exposure induced molecular and behavioural changes across generations in *C. elegans* after 1 exposure, through chemotaxis assay and stimulates the expression of the hsp-6 enzyme a toxin- specific cytoprotective.

- Several methyltransferases play an important role in the long-term memory after imprinting intervention

Dra Mercè Pallàs
Dr Christian Griñán Ferré
Dra Anna M. Canudas
Dr Daniel Ortuño
Dra Celia Gonzalez
Dr Csaba Sötti
Dr Santiago Vázquez
Dra Carmen Escolano
Dr Diego Muñoz

Dra Coral Sanfeliu
Dra Perla Kalimany
Dra Gemma Navarro
Aina Bellver-Sanchis
Júlia Companys
Júlia Jarne-Ferrer
Alba Irisarri
Bhanwar Singh

Thank you

TAKE HOME MESSAGE

Our work reports a new finding that pharmacological inhibition of G9a might be a promising target for AD therapy, promoting neuroprotection through reduction of its repressive chromatin marks as well as it take part in the epigenetic inheritance memory process.

CTQ2015-66030/R
SAF2016-77703-C-R