# *Molecular and Cellular Bases of Behaviour*


## *Juan Lerma*

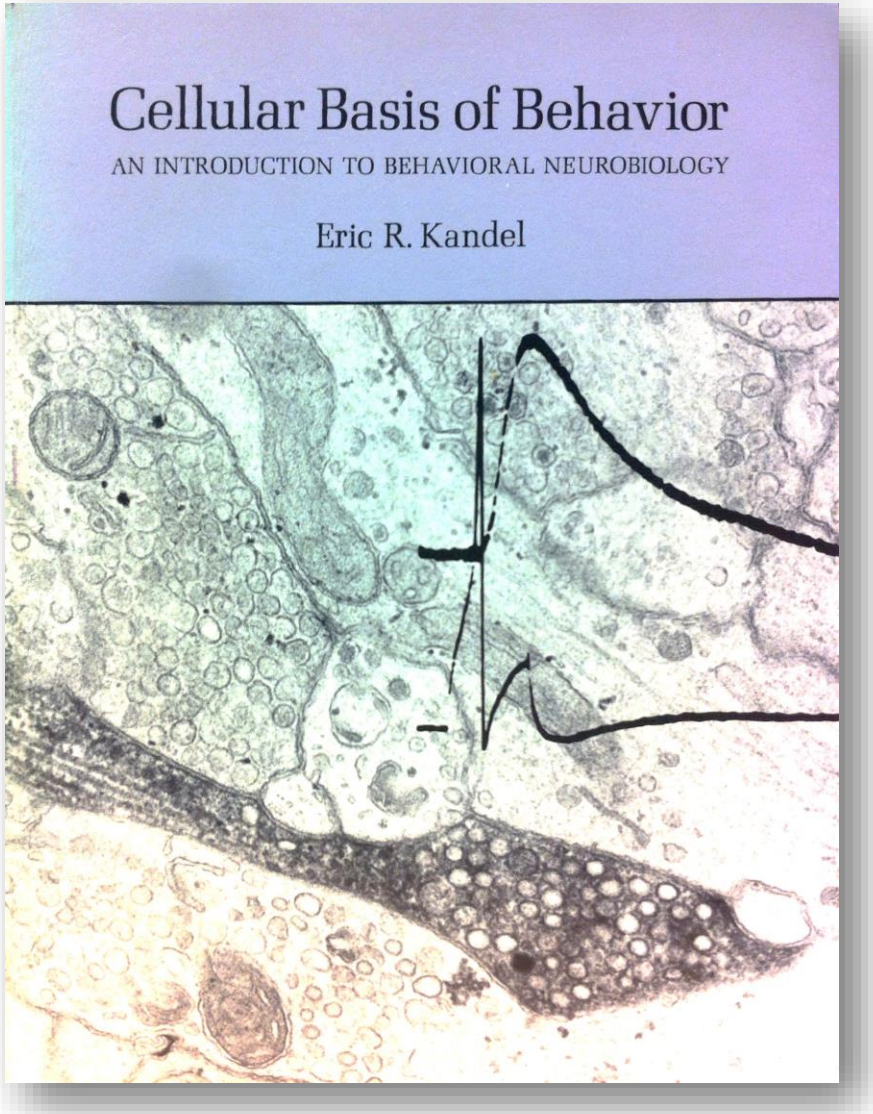
INSTITUTO DE NEUROCIENCIAS

San Juan de Alicante, Spain

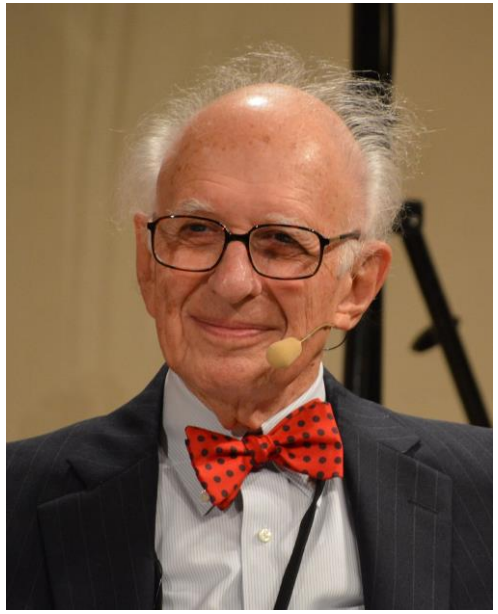
Email: jlerma@umh.es
Twitter: @JuanLerma1


UlaanBaattor, 24th September 2018

# Understanding behaviour: a human's dream




1967



Eric Kandel, Nobel Prize Winner 2000

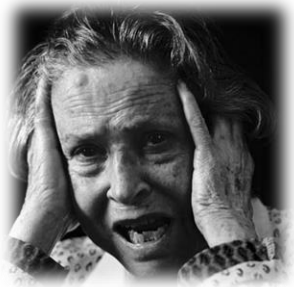
Aplysia californica

INSTITUTO DE NEUROCIENCIAS

# 80.000.000.000 of neurons

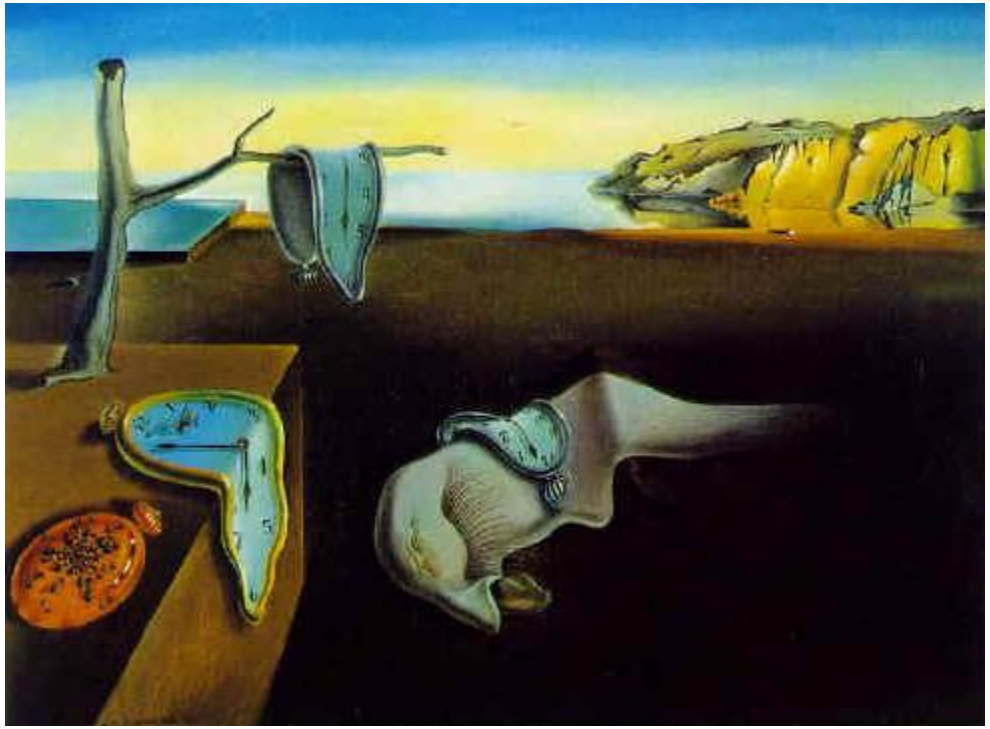
# The cost (in billion €PPP 2010) of the disorders of the brain in Europe*

| | |
|---|---|
| mood disorders | €113,40 |
| dementia | €105,20 |
| psychotic disorders: | €93,90 |
| anxiety disorders | €74,40 |
| addiction | €65,70 |
| stroke | €64,10 |
| headache | €43,50 |
| mental retardation | €43,30 |
| sleep disorders | €35,40 |
| traumatic brain injury | €33,00 |
| personality disorders | €27,30 |
| child/adolescent disorders | €21,30 |
| multiple sclerosis | €14,60 |
| Parkinson's disease | €13,90 |
| epilepsy | €13,80 |
| brain tumor | €5,20 |
| eating disorders | €0,80 |
| **Total** | **€768,80** |



*EU-27+Iceland, Norway and Switzerland

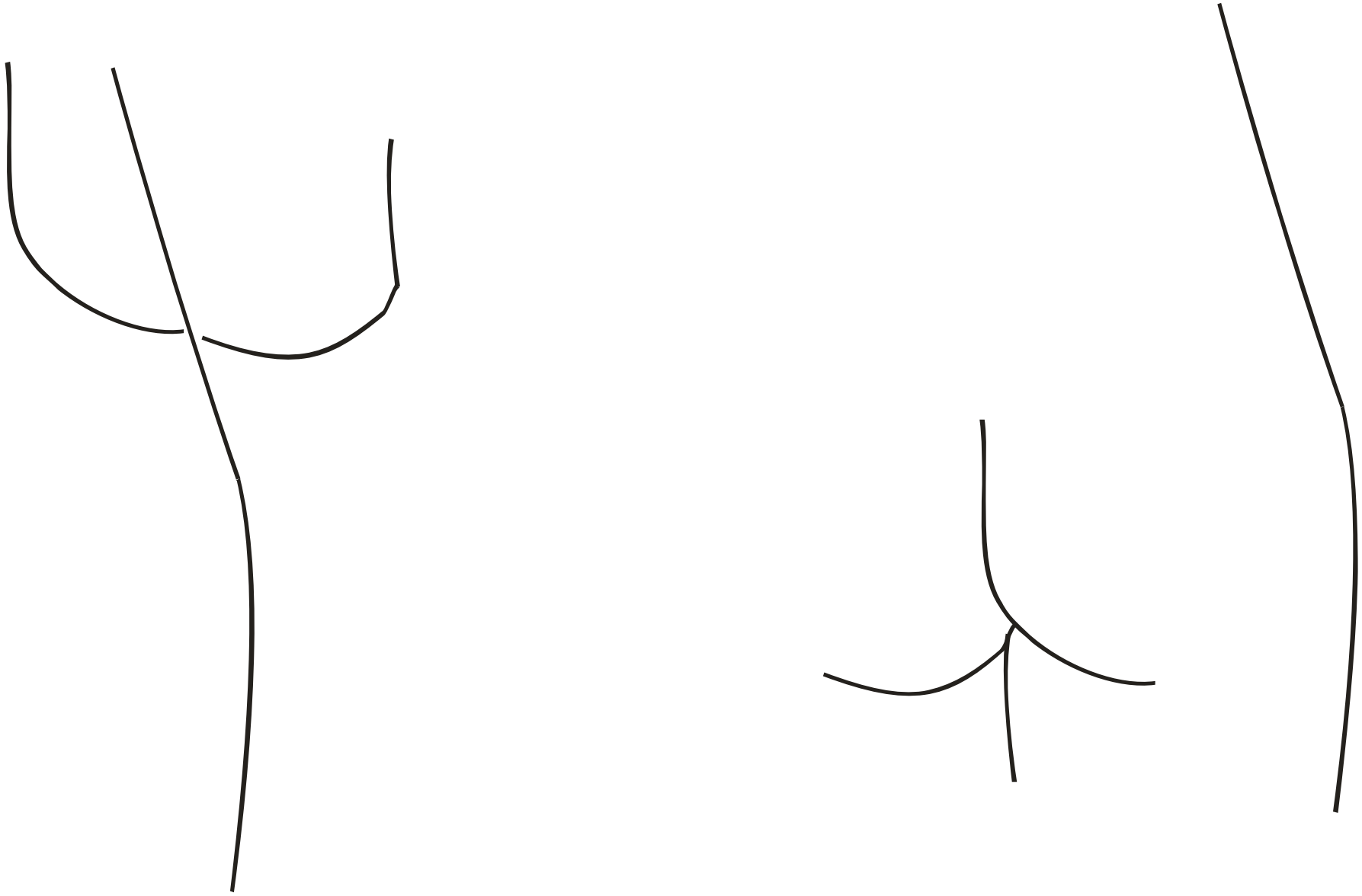
CDBE2010 study group; European Brain Council. Eur J Neurol. 19:155-62. 2012 .



Every 7 seconds, someone develops dementia

By 2020, an estimated 1.5 million people will die each year by suicide

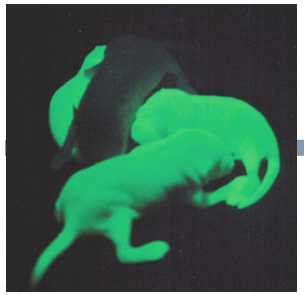
# *Seeing is a creative process…*



Courtesy of Dr. Luis Martínez-Otero, IN

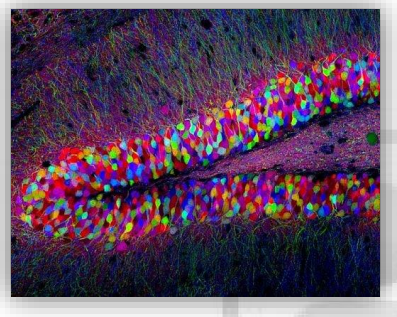
Adapted from a drawing by Pablo Picasso

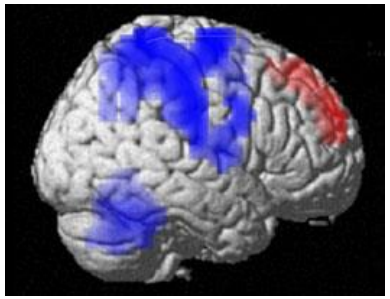
# The Neuroscientific Challenges of XXI Century

**Genetic level** — **Molecular and cellular level** — **In vivo**  → **Organ**

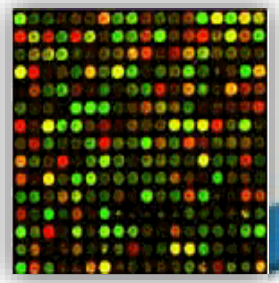
Behaviour & Genetics

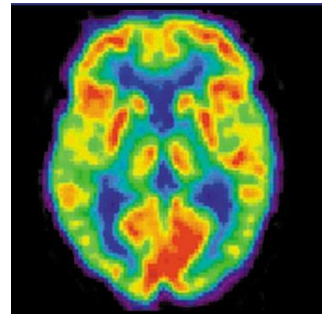
Specific Receptors as pharmacological targets





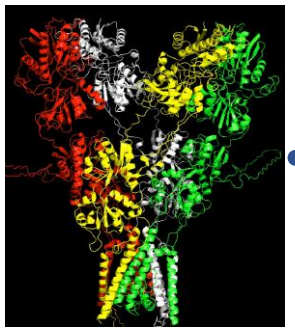
Mutations
Variabilities
Epigenetics



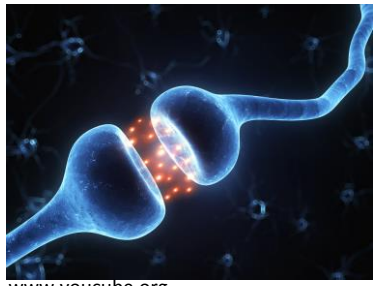


Antisocial behaviours
Addictive behaviours
Educational systems (learning optimisation)
Civil and penal responsibility

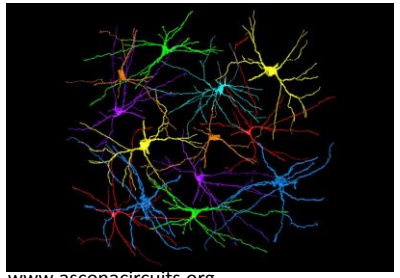
# Levels of Organization in the Brain


Oregon Health and Science University.

Molecules

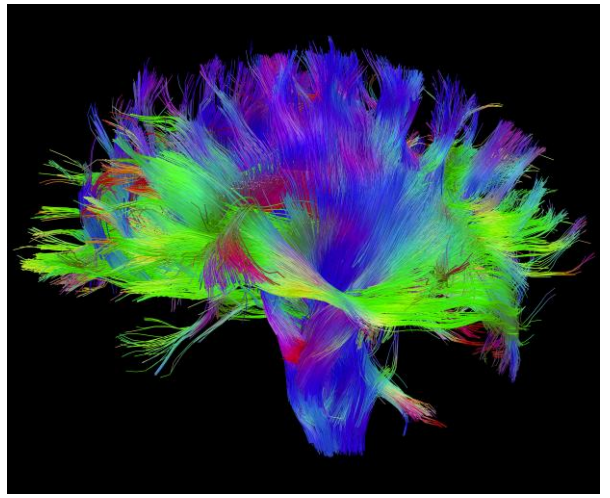

www.youcube.org

Synapses


www.asconacircuits.org

Networks

Systems

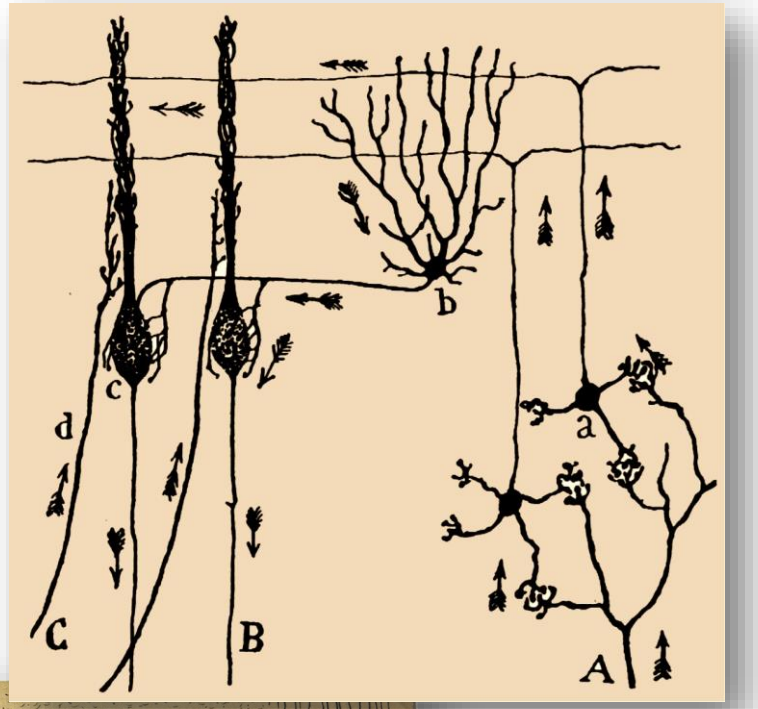

From: Human Connectome Project

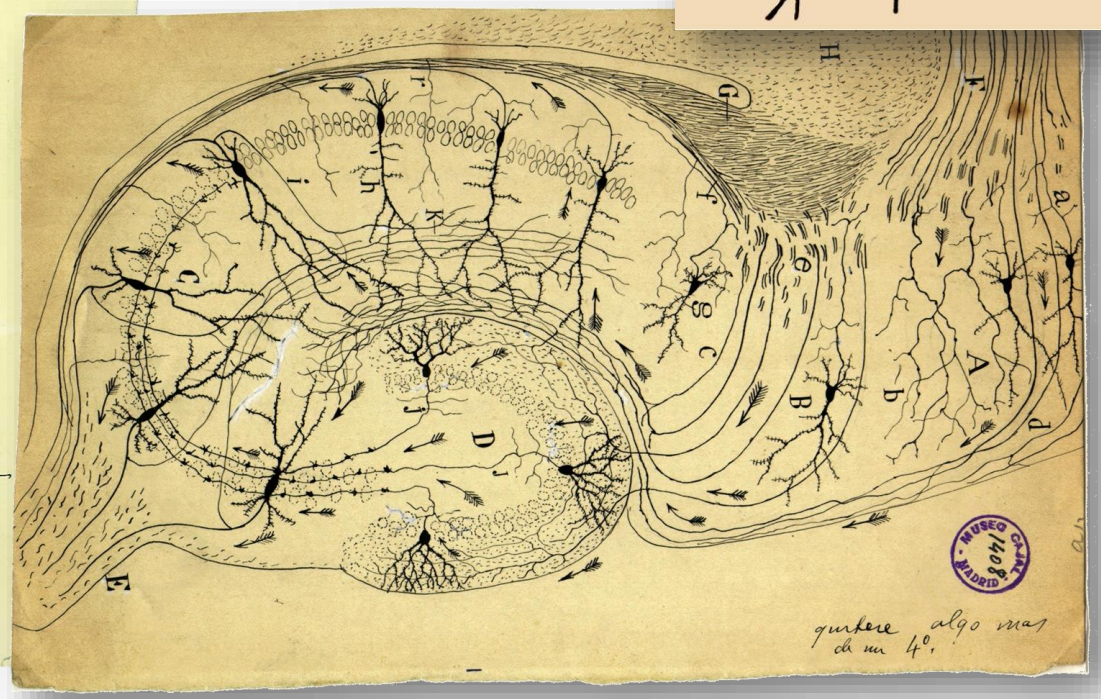
CNS


www.dulops.net/seresvivos

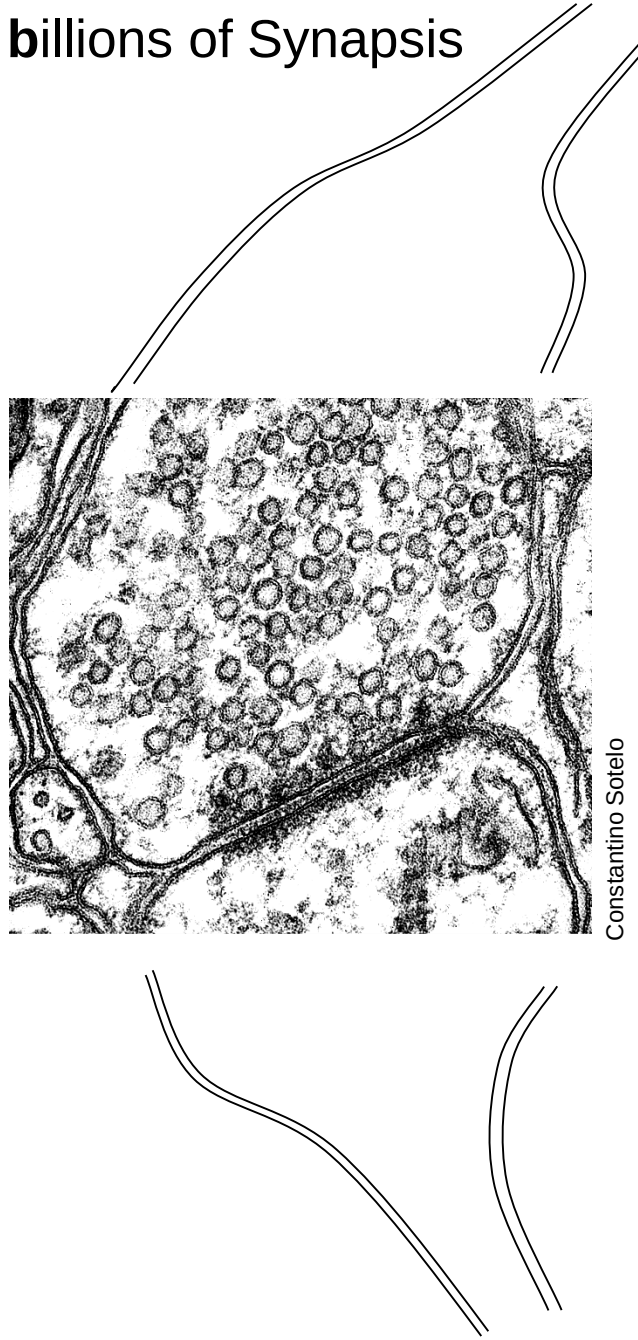
Behaviour

# Some examples through Cajal's drawings

80,000 millions of Neurons
80 **b**illions of Synapsis

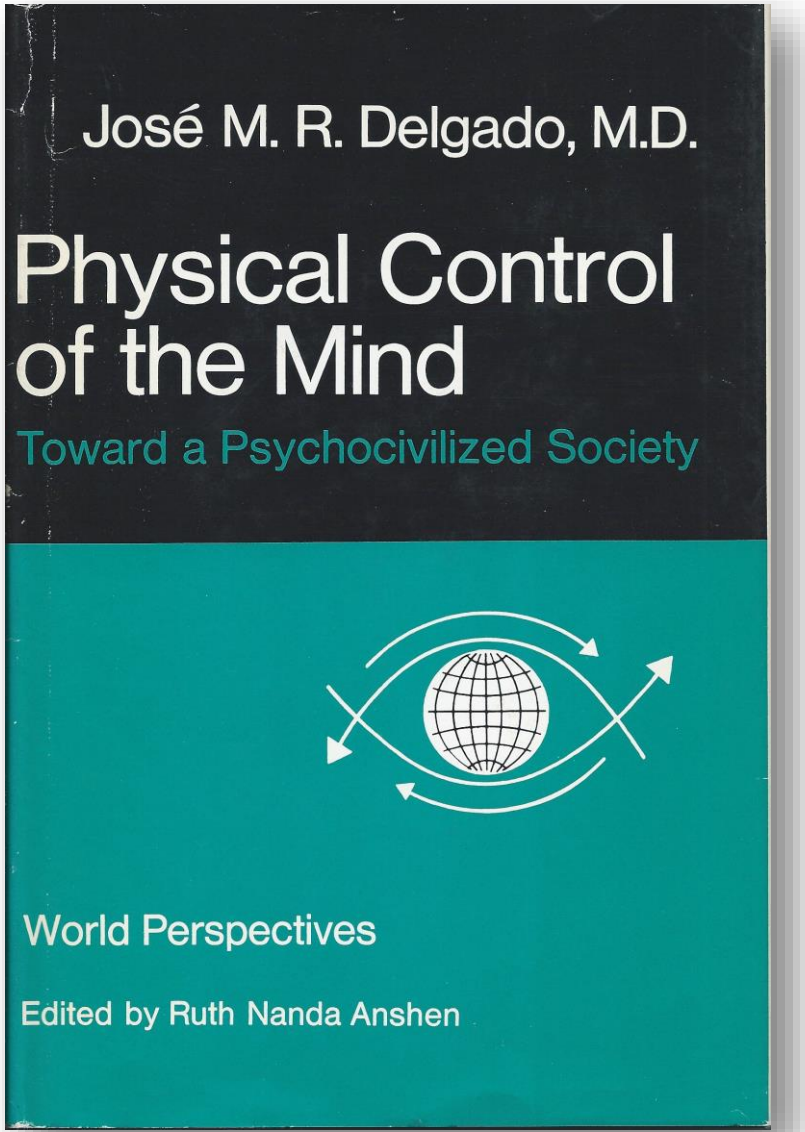


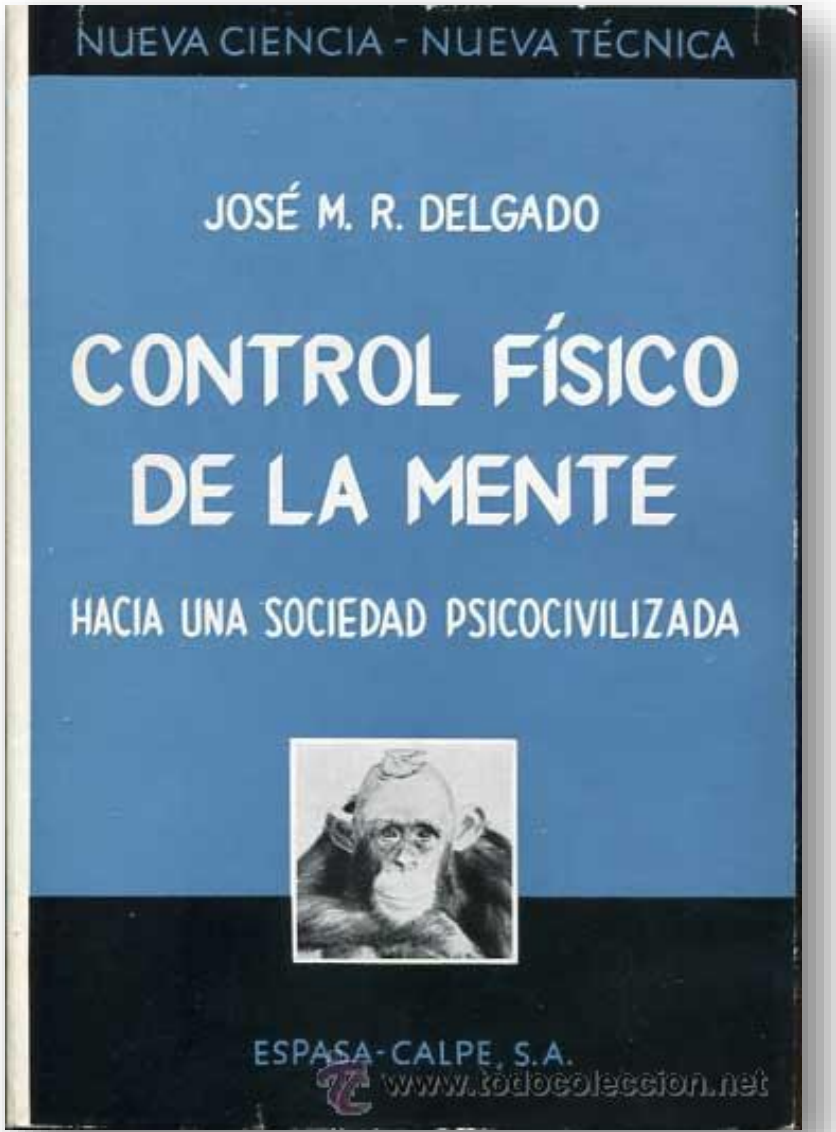
Constantino Sotelo

**José Manuel Rodríguez-Delgado (right) with Francisco Rubia, Sir John Eccles and Juan Lerma. March, 1984 @ Research Dept, Hospital Ramón y Cajal (Madrid)**

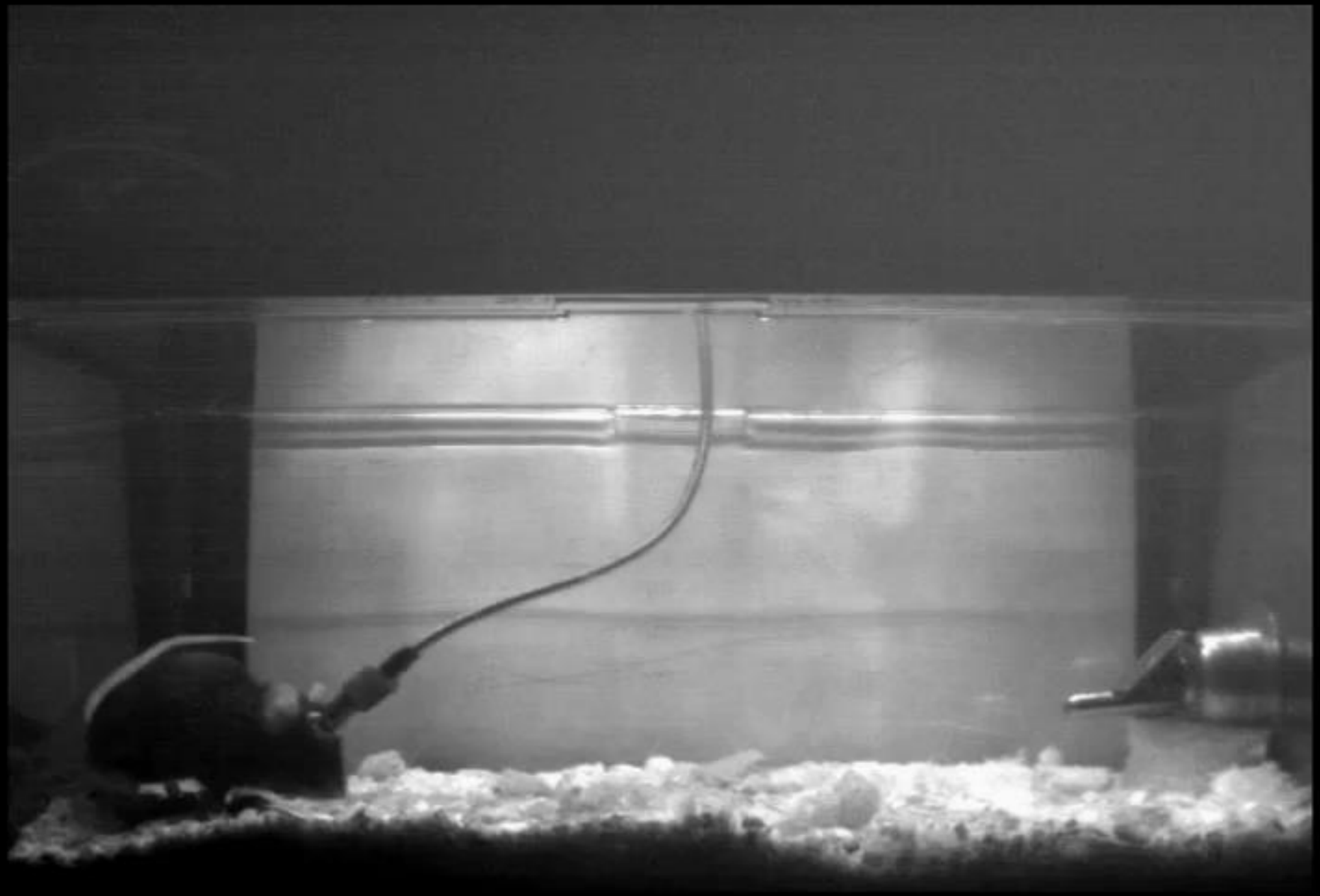
https://youtu.be/pRHkBxb5lFM

https://youtu.be/pRHkBxb5lFM

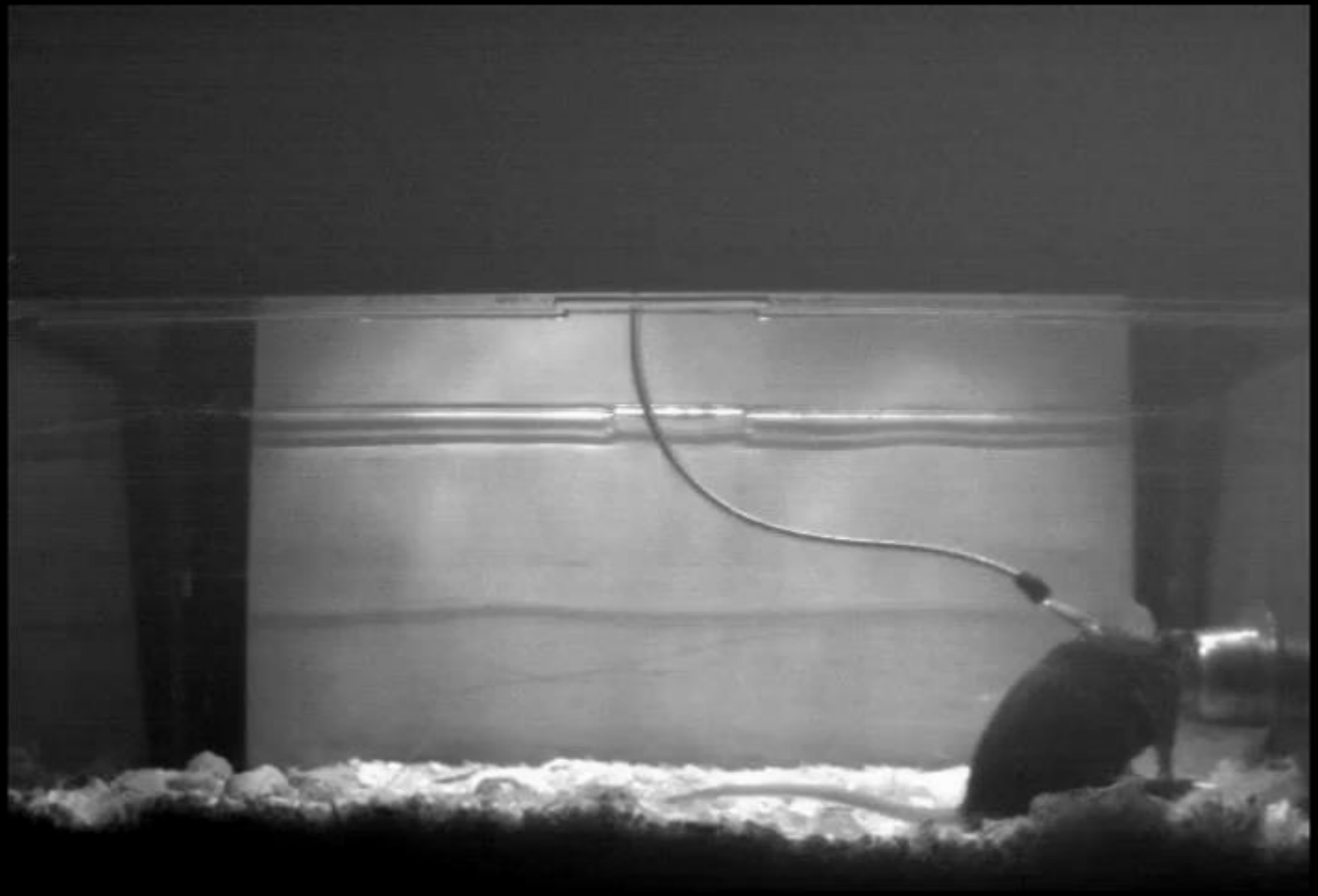

José M. R. Delgado, M.D.
Physical Control of the Mind
Toward a Psychocivilized Society
World Perspectives
Edited by Ruth Nanda Anshen


NUEVA CIENCIA - NUEVA TÉCNICA
JOSÉ M. R. DELGADO
CONTROL FÍSICO DE LA MENTE
HACIA UNA SOCIEDAD PSICOCIVILIZADA
ESPASA-CALPE, S.A.
www.todocoleccion.net

1969

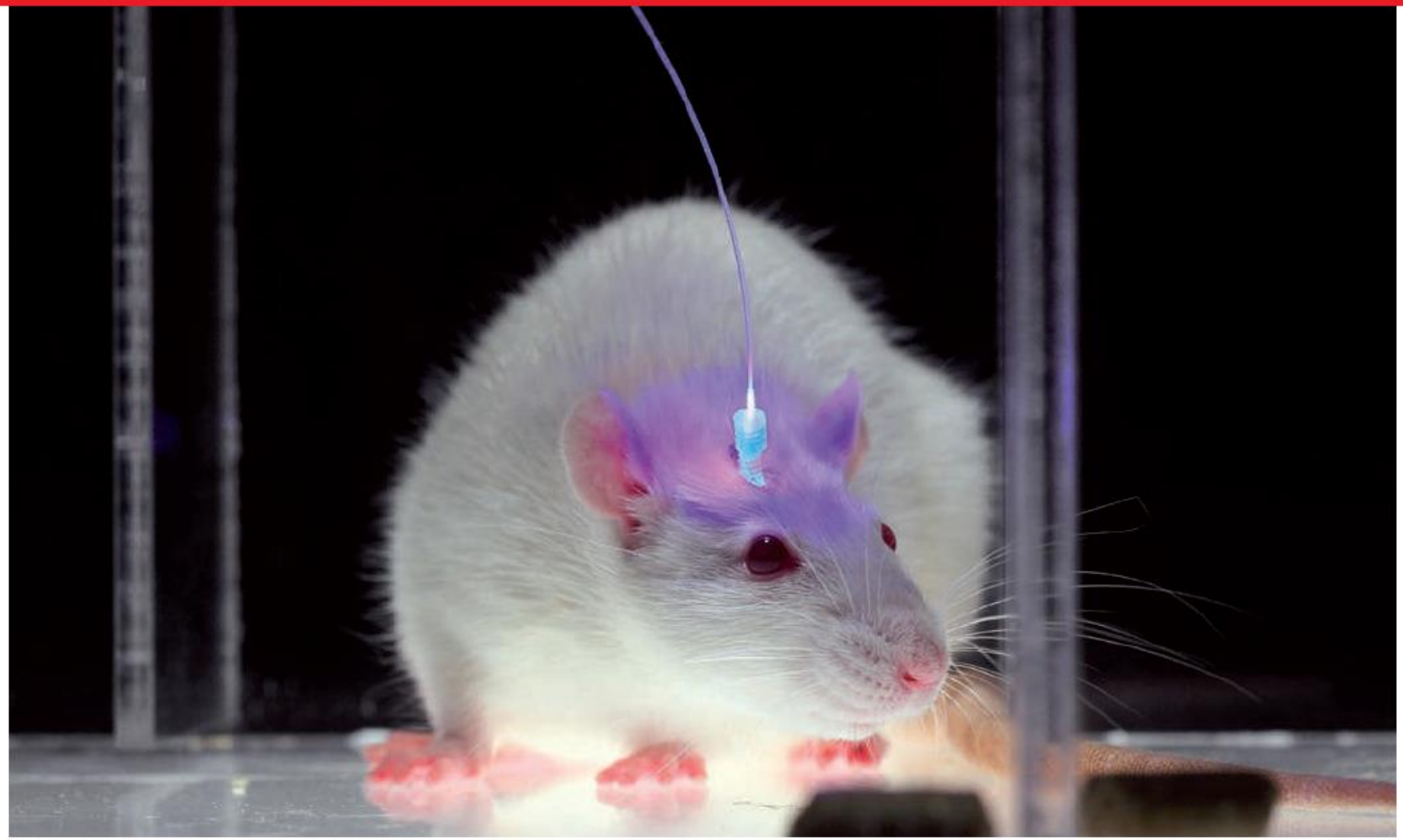


Lin et al., **Nature** 470, 221-226, 2011



Lin et al., **Nature** 470, 221-226, 2011

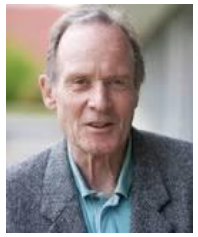
NATURE|Vol 465|6 May 2010



# ILLUMINATING THE BRAIN

# Channelrhodopsins (ChRs)
# Ion Channels from Green Algae that Can Be Activated by Light

Ernst Bamberg



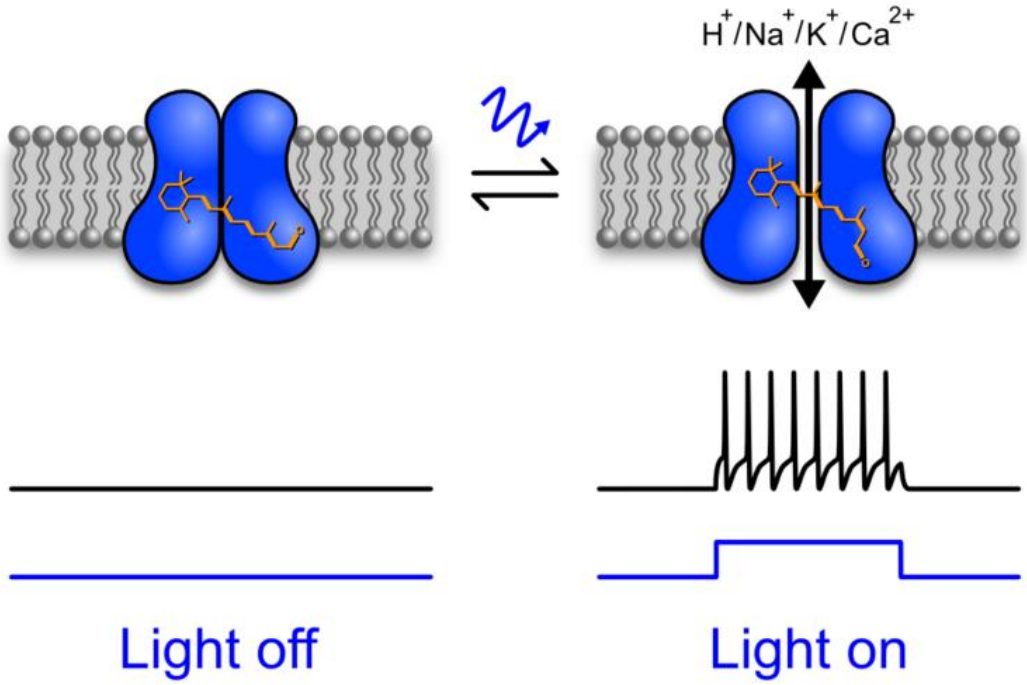
Georg Nagel

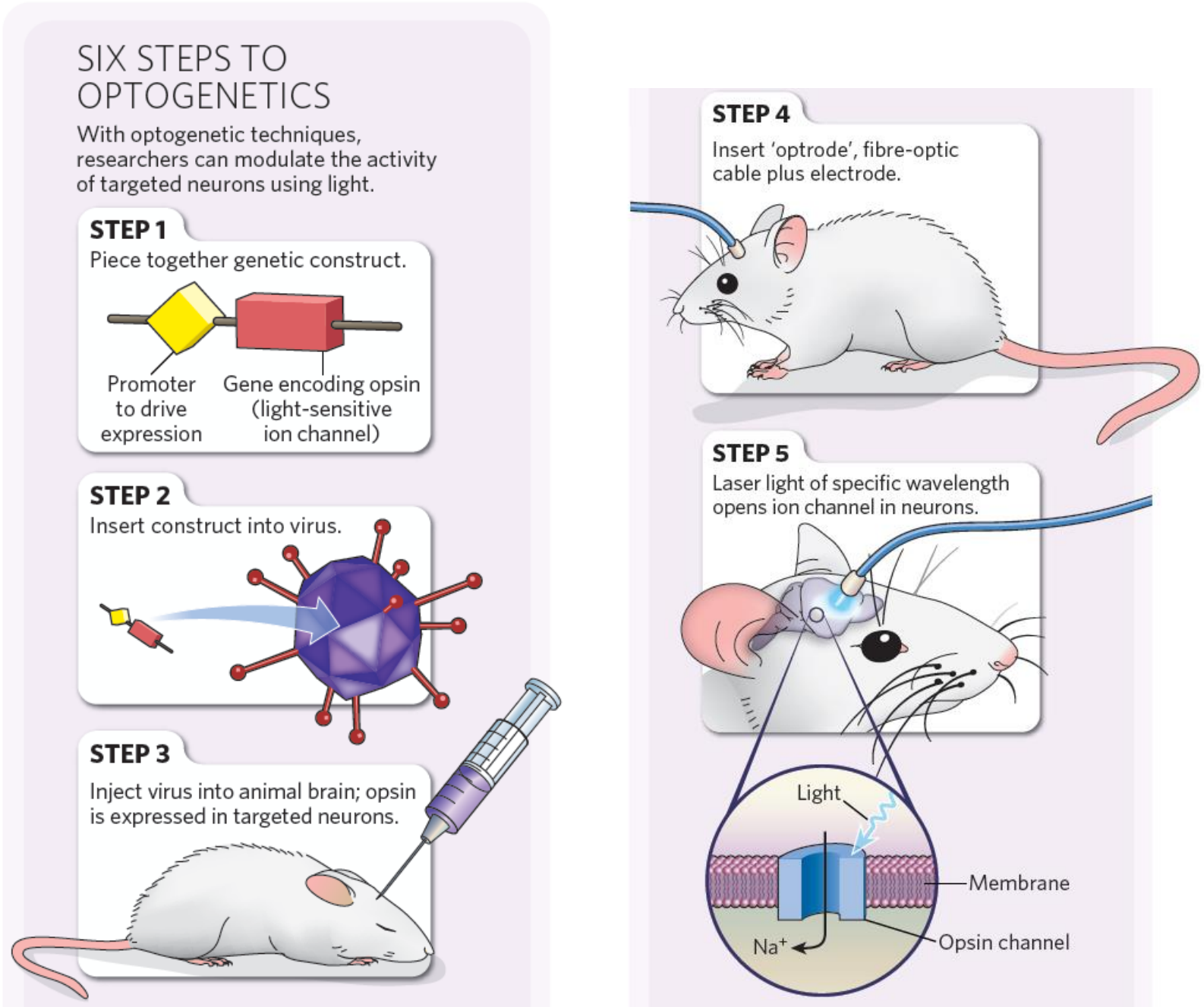
Peter Hegemann

Karl Deisseroth

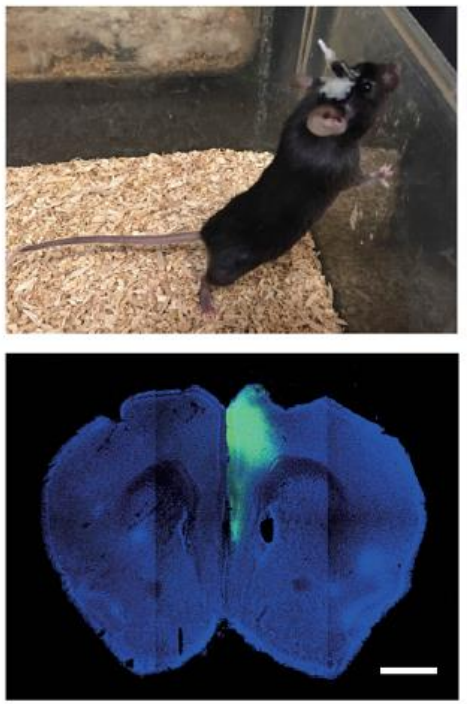
Ed Boyden

Feng Zhang

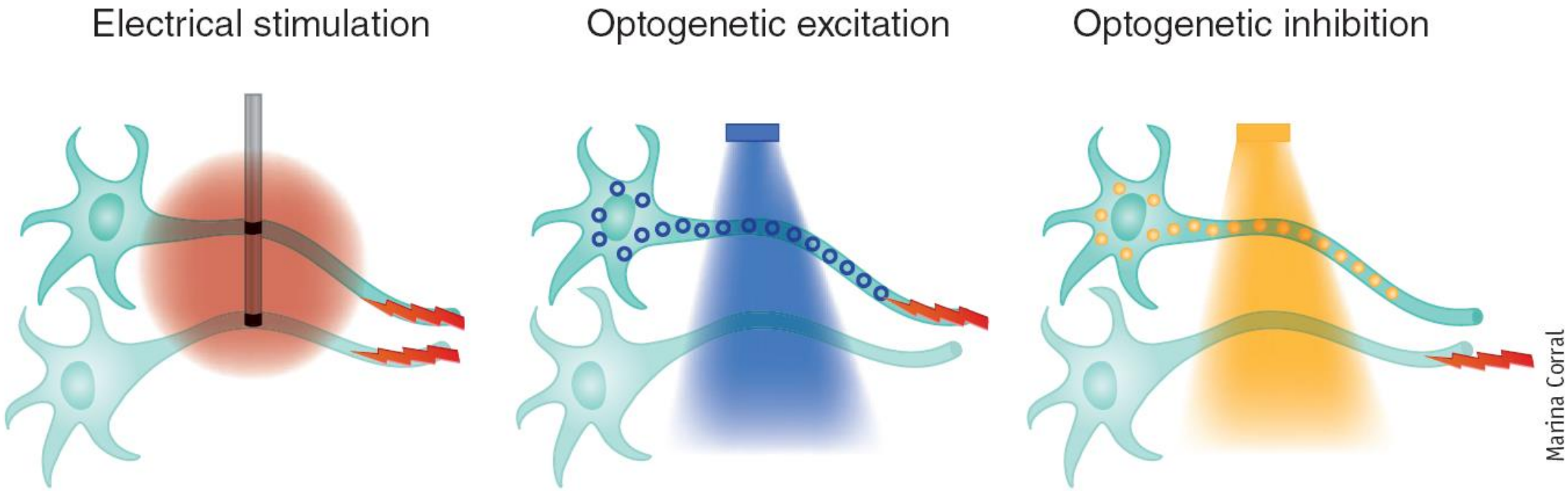





Buchen, Nature 2010

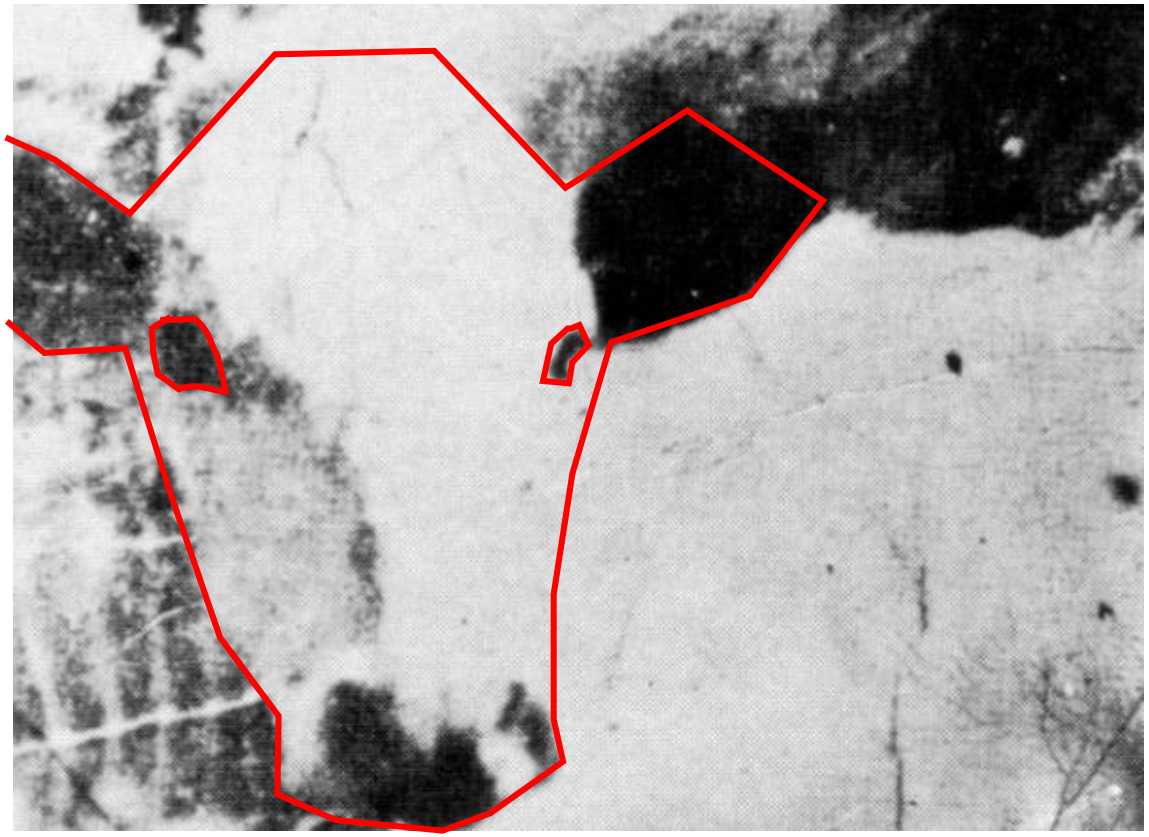


Park et al., Nat Neurosci 2017




Deisseroth, Nature Methods, 2011

Lin et al., **Nature** 470, 221-226, 2011



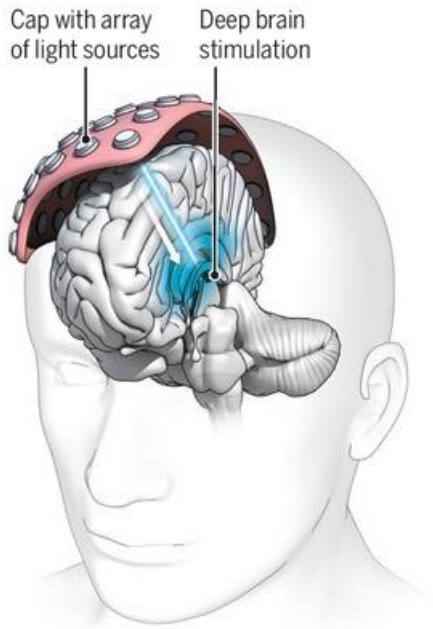
Chen *et al.*, *Science* **359**, 679–684 (2018) 9 February 2018

# Near-infrared deep brain stimulation via upconversion nanoparticle–mediated optogenetics

Shuo Chen,[1]* Adam Z. Weitemier,[1] Xiao Zeng,[2] Linmeng He,[1] Xiyu Wang,[1] Yanqiu Tao,[1] Arthur J. Y. Huang,[1] Yuki Hashimotodani,[3] Masanobu Kano,[3,4] Hirohide Iwasaki,[5] Laxmi Kumar Parajuli,[5] Shigeo Okabe,[5] Daniel B. Loong Teh,[6] Angelo H. All,[7] Iku Tsutsui-Kimura,[8] Kenji F. Tanaka,[8] Xiaogang Liu,[2,9]* Thomas J. McHugh[1,10]*

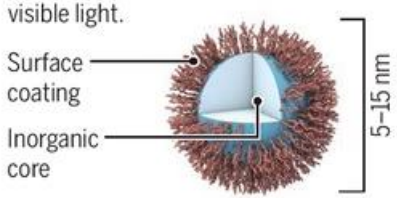
## Activating neurons with light

With technological advances, it might be possible to optically stimulate neurons deep in the human brain. This could aid treatment of patients with Parkinson's disease.



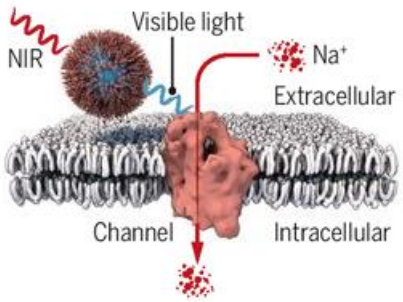

**Upconverting nanoparticles**

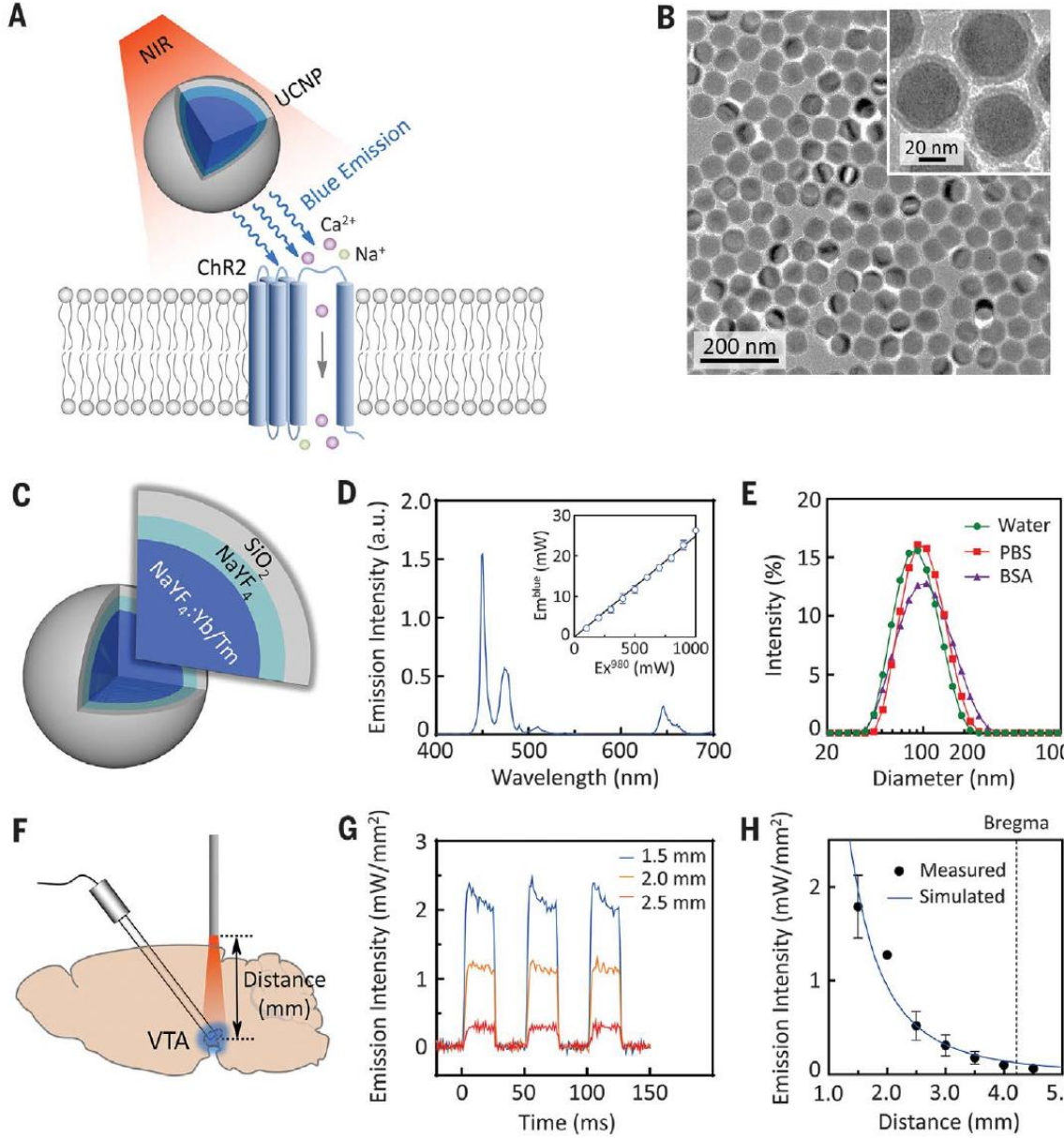
Inorganic nanoparticles with organic surface capping can convert NIR into visible light.




**Light-sensitive neurons**

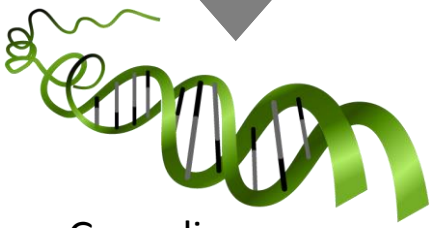
Light-gated ion channels are opened by visible light emitted upon NIR excitation of upconverting nanoparticles.



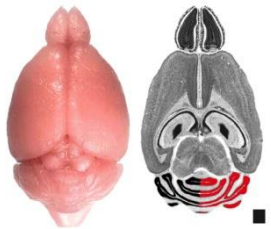



# The Promise of Molecular Medicine

Human brain disease

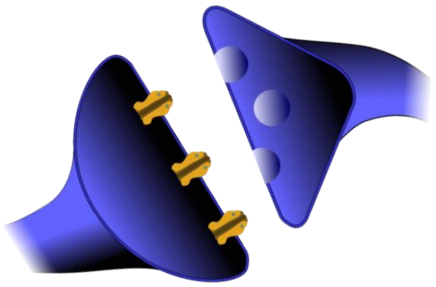


Gene discovery

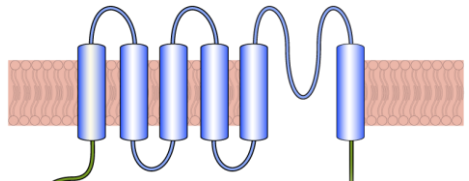


Mouse disease model

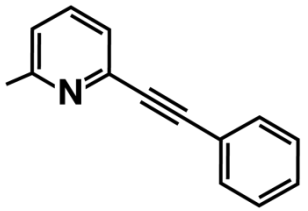
**Basic neuroscience**



Disease pathophysiology



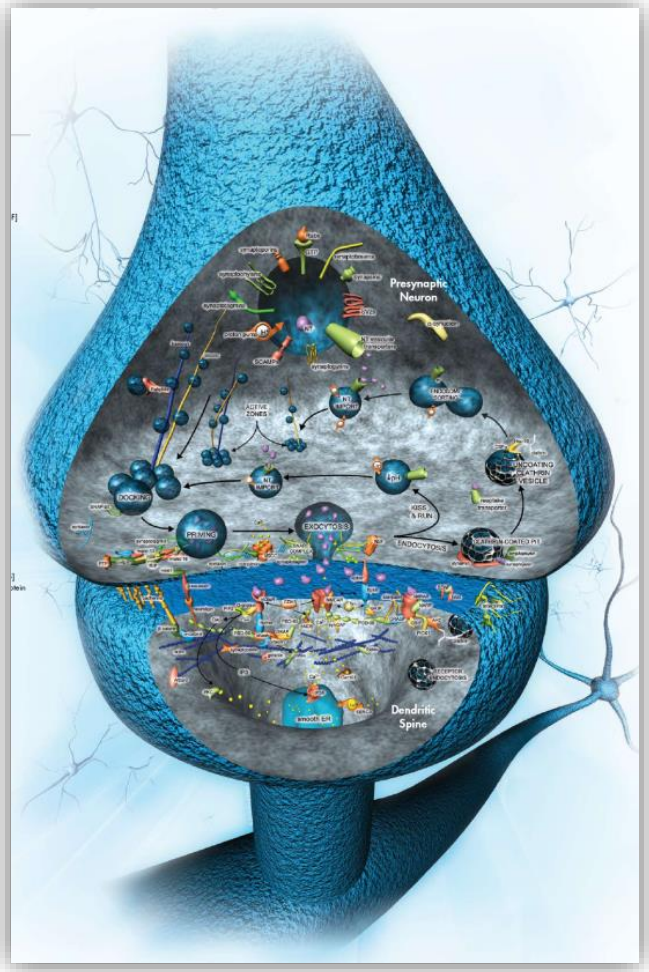
Target ID & drug development

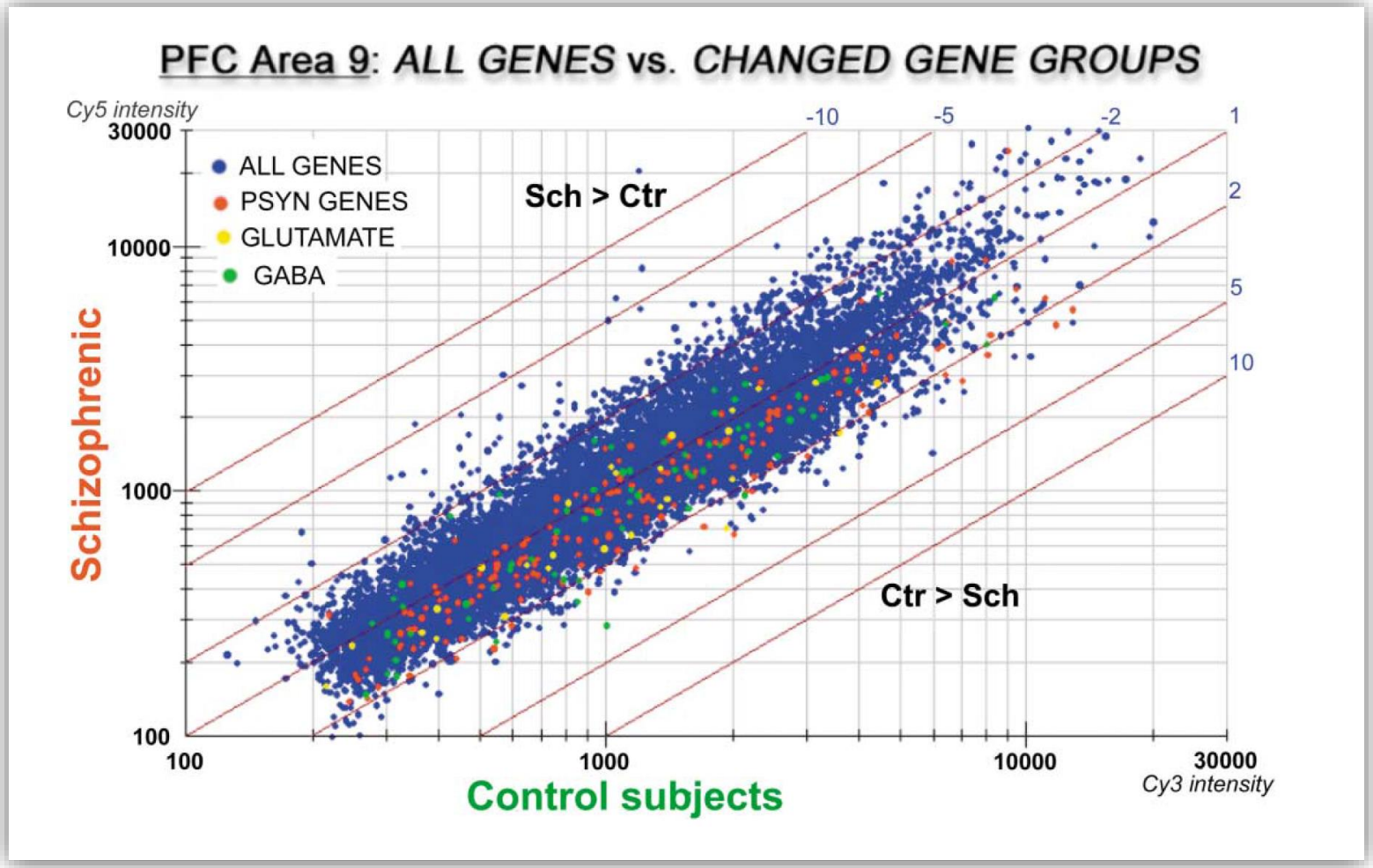



Novel therapeutics

Modified from Mark Bear

# Synaptic Hypothesis of Schizophrenia




Frankle, Lerma and Laruelle, (2003). *Neuron* 39: 205-216

*Human Molecular Genetics, 2012, Vol. 21, No. 15* **3513–3523**
*doi:10.1093/hmg/dds164*
*Advance Access published on April 27, 2012*

# Evaluation of copy number variations reveals novel candidate genes in autism spectrum disorder-associated pathways

**Anthony J. Griswold[1,†], Deqiong Ma[1,2,†], Holly N. Cukier[1,†], Laura D. Nations[1], Mike A. Schmidt[1,2], Ren-Hua Chung[1,2], James M. Jaworski[1], Daria Salyakina[1], Ioanna Konidari[1], Patrice L. Whitehead[1], Harry H. Wright[3], Ruth K. Abramson[3], Scott M. Williams[4], Ramkumar Menon[5], Eden R. Martin[1,2], Jonathan L. Haines[4], John R. Gilbert[1,2], Michael L. Cuccaro[1,2] and Margaret A. Pericak-Vance[1,2,*]**

**Table 5.** Case-unique CNVs in ASD candidate genes

| Position (hg 18) | Cytoband | Genes | CNV type | Inheritance | Family | Affected siblings with CNV[a] | Unaffected siblings with CNV[b] |
|---|---|---|---|---|---|---|---|
| Chr2:184744259–186437079 | 2q32.1 | *FLJ44048,FSIP2,ZNF804A* | Duplication | Paternal | 7678 | 2/2 | 0/0 |
| chr2:119642873–119882278 | 2q14.2 | *C2orf76,DBI,STEAP3* | Duplication | *De novo* | 17113 | 1/1 | 0/0 |
| chr2:230078358–230181261 | 2q36.3 | *DNER* | Duplication | Paternal | 17171 | 1/1 | 0/1 |
| chr3:10823410–10943172 | 3p25.3 | *SLC6A11* | Deletion | Paternal | 7804 | 2/2 | 0/0 |
| chr6:101260386–102979782 | 6q16.3 | *ASCC3,GRIK2* | Deletion | Maternal | 17182 | 2/2 | 0/0 |
| chr7:51155279–51263037 | 7p12.1 | *COBL* | Deletion | Maternal | 39391 | 1/1 | 1/3[c] |
| chr10:87754758–87839034 | 10q23.1 | *GRID1* | Deletion | Paternal | 37276 | 1/1 | 1/1 |
| chr11:118685526–121040148 | 11q23.3–q24.1 | *ARHGEF12,C1QTNF5,GRIK4,MCAM, MFRP,OAF,POU2F3,PVRL1,RNF26, SC5DL,SORL1,TBCEL,TECTATHY1, TMEM136, TRIM29,USP2* | Duplication | *De novo* | 37341 | 1/1 | 0/1 |
| chr12:10248041–10332152 | 12p13.2 | *GABARAPL1* | Deletion | Paternal | 37240 | 1/1 | 1/1 |
| chr12:13753741–13788728 | 12p13.1 | *GRIN2B* | Deletion | Maternal | 7614 | 1/1 | 0/0 |
| chr14:78373505–78506223 | 14q24.3–q31.1 | *NRXN3* | Deletion | Maternal | 7484 | 1/1 | 1/2 |
| chr15:26849239–28157206 | 15q13.1–q13.2 | *APBA2,KIAA0574,NDNL2,TJP1* | Deletion | Maternal | 17630 | 2/2 | 0/1 |
| | | | | Maternal | 7486 | 1/1 | 0/2 |
| chr16:6866262–7042998 | 16p13.2 | *A2BP1* | Deletion | Paternal | 7636 | 2/2 | 0/0 |
| | | | | Paternal | 7851 | 1/1 | 0/0 |
| | | | | Paternal | 17855 | 1/1 | 1/1 |
| | | | | Maternal | 37350 | 1/1 | 1/1[d] |
| chr22:31499975–31930759 | 22q12.3 | *SYN3,TIMP3* | Duplication | Paternal | 39377 | 1/1 | 0/0 |
| chrX:146676441–146930522 | Xq27.3–q28 | *ASFMR1,FMR1,FMR1NB* | Deletion | Maternal | 18072 | 2/2 | 0/0 |

[a]Number of affected siblings in the family with the CNV/total affected siblings.
[b]Number of unaffected siblings in the family with the CNV/total unaffected siblings.
[c]Unaffected with CNV has speech delay.
[d]Unaffected with CNV has a questionable autism diagnosis.

Cellular/Molecular

The Journal of Neuroscience, October 7, 2015 • 35(40):13619–13628 • 13619

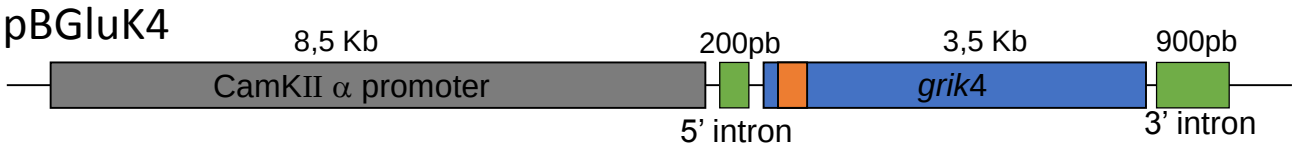
# Increased Dosage of High-Affinity Kainate Receptor Gene *grik4* Alters Synaptic Transmission and Reproduces Autism Spectrum Disorders Features

M. Isabel Aller, Valeria Pecoraro, Ana V. Paternain, Santiago Canals, and Juan Lerma

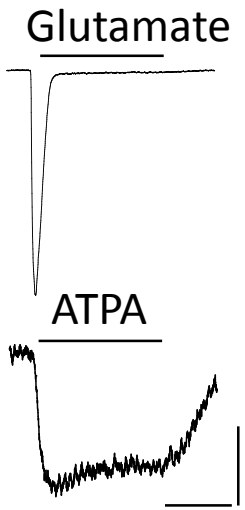
Instituto de Neurociencias, Consejo Superior de Investigaciones Científicas, Universidad Miguel Hernández de Elche, 03550 San Juan de Alicante, Spain

## Generation of over-expressing GluK4 mice in the forebrain

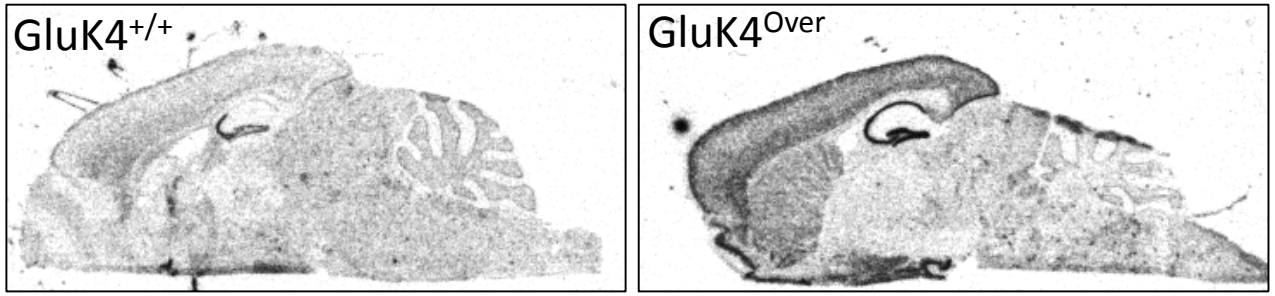
A



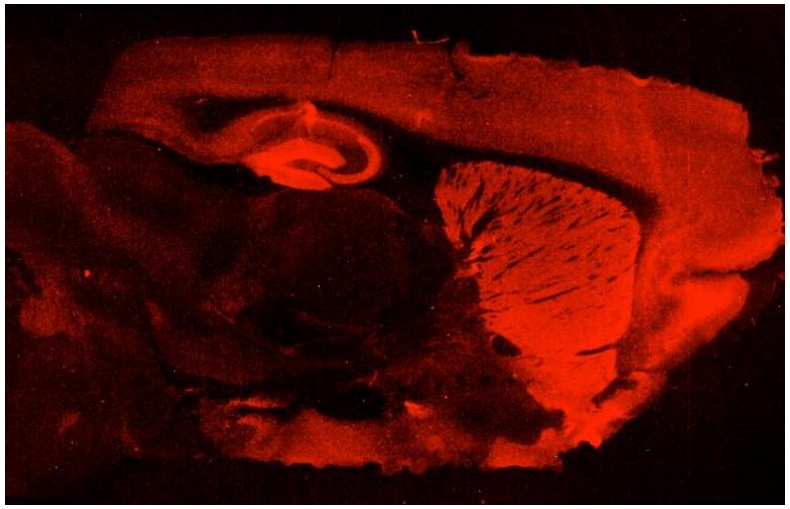

B



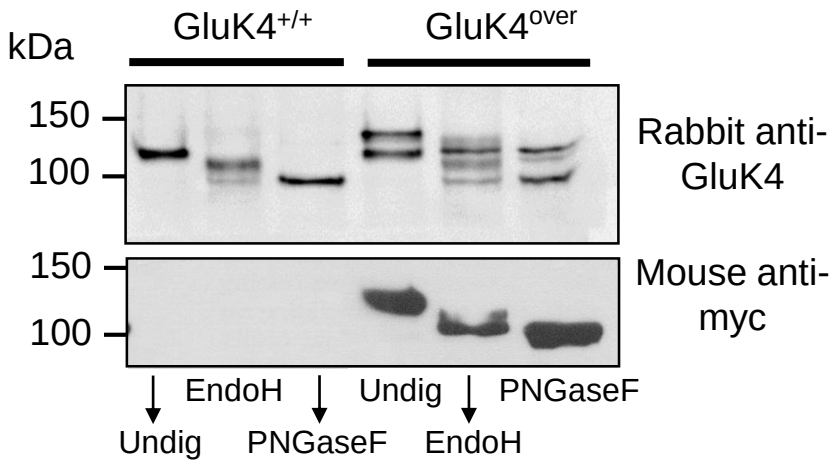

C

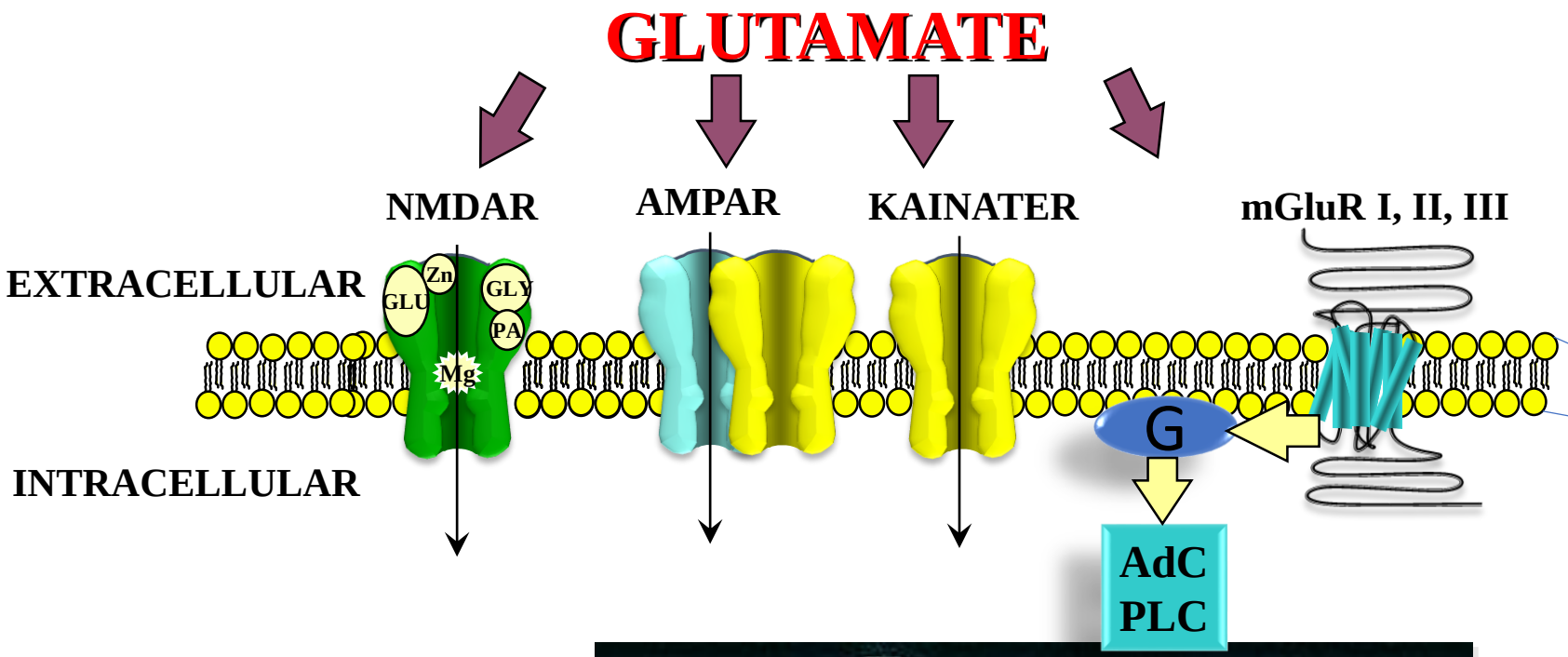


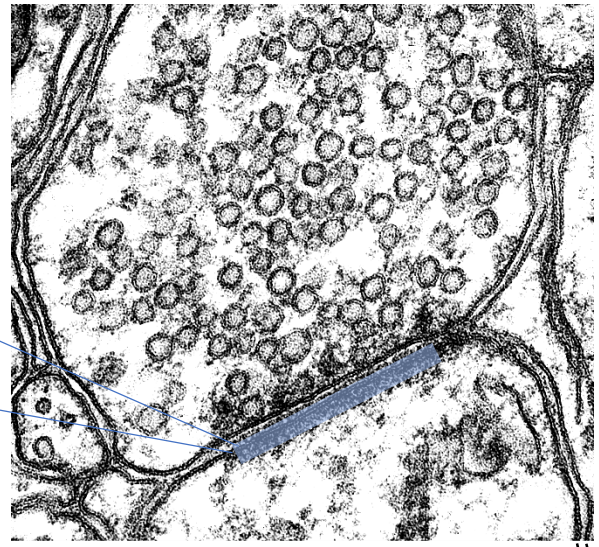

D



E

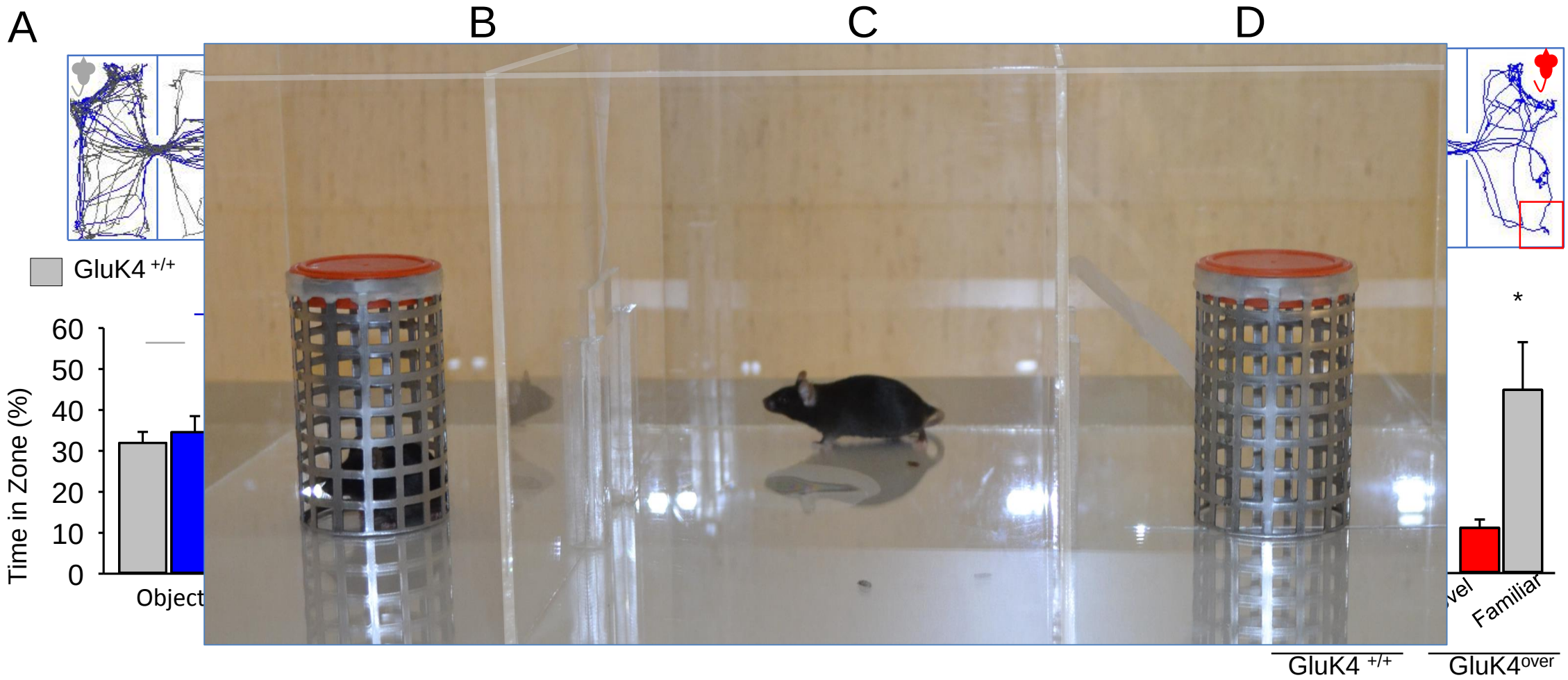




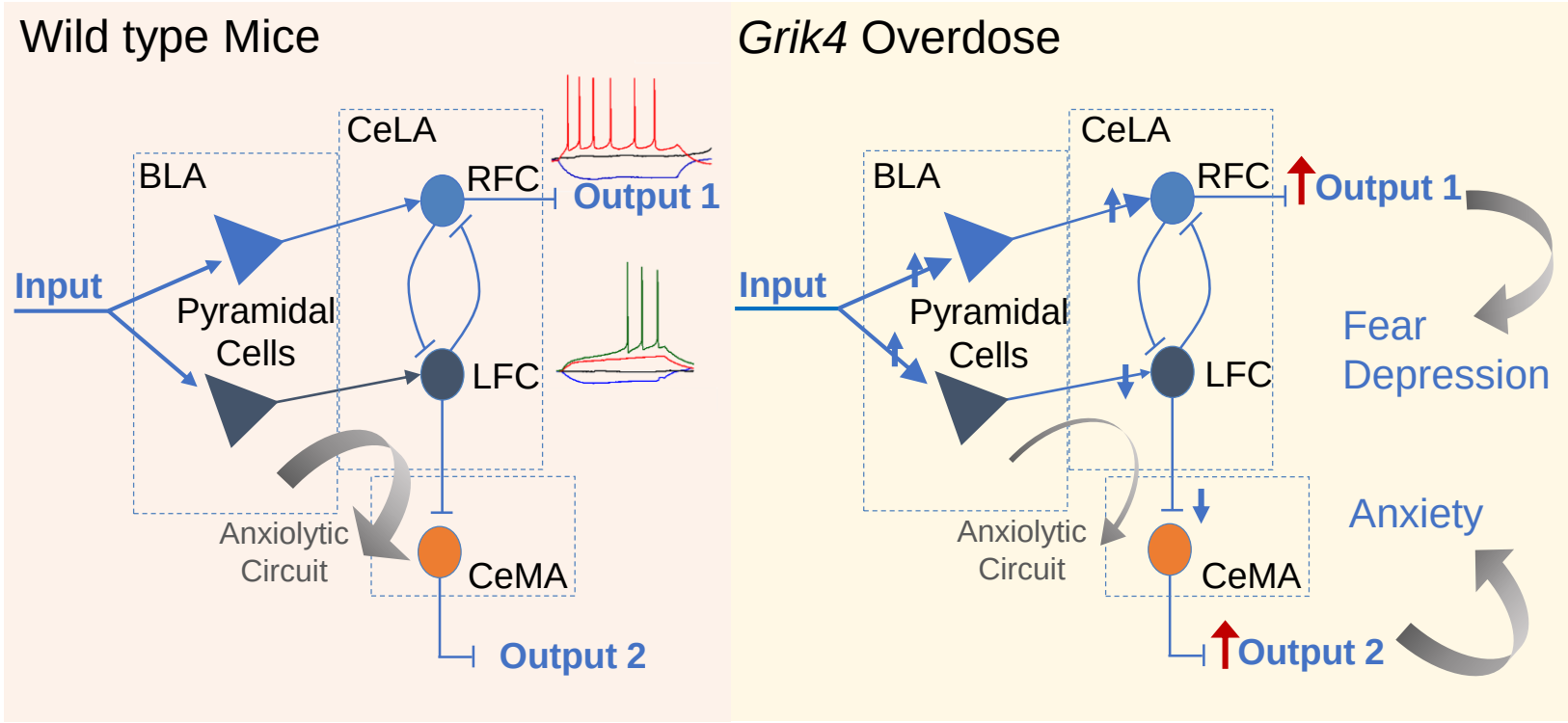



Constantino Sotelo

# Assessing roles of *GRIK4* on social interaction



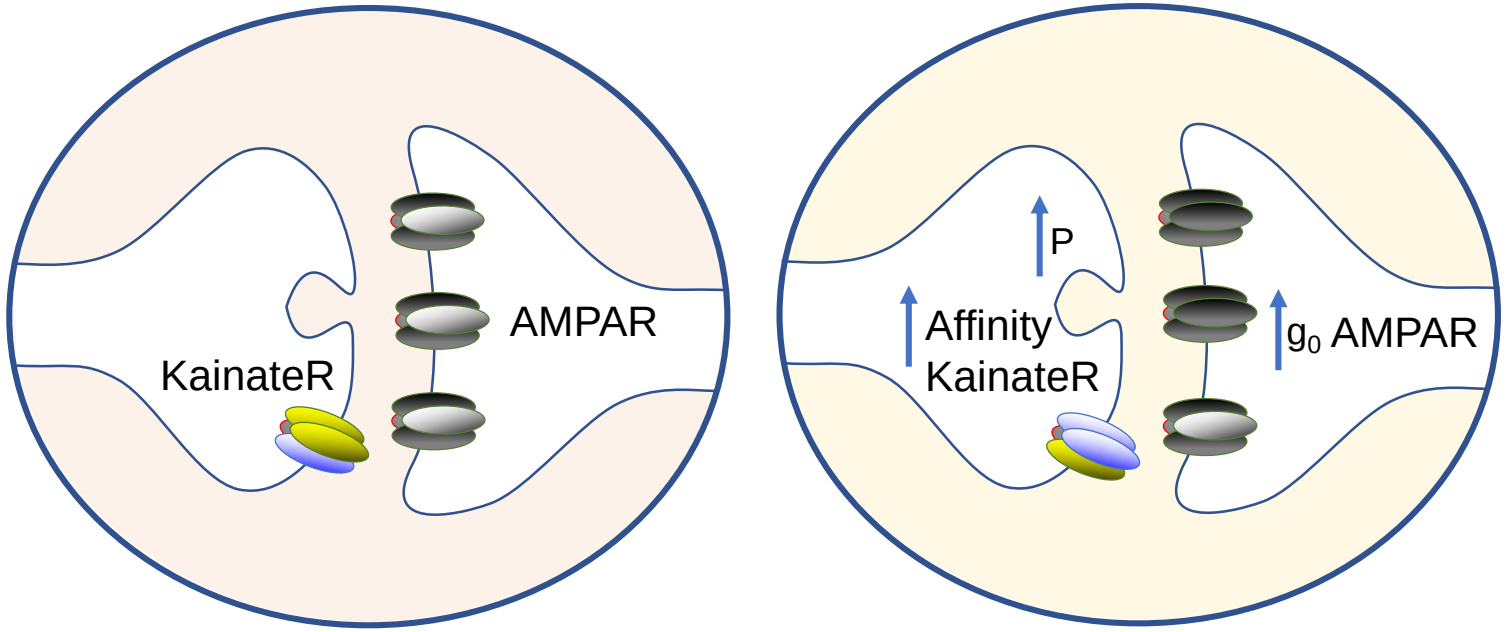

Aller et al., **J. Neurosci.** 35, 2015




Kainate Receptors

GluK4

GluK1-3

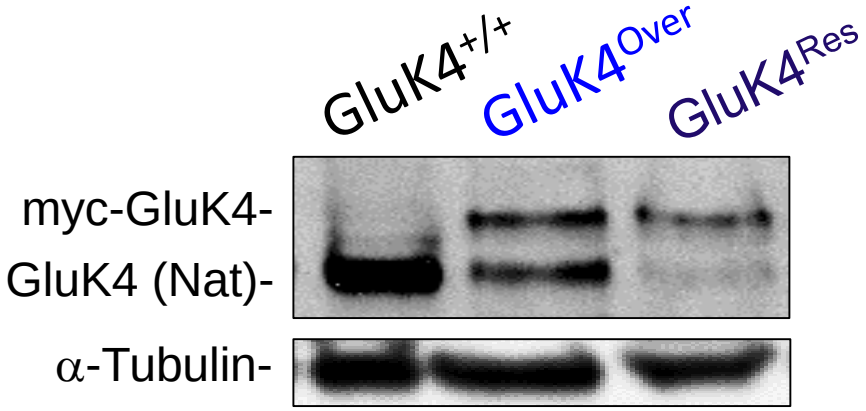



AMPA Receptors

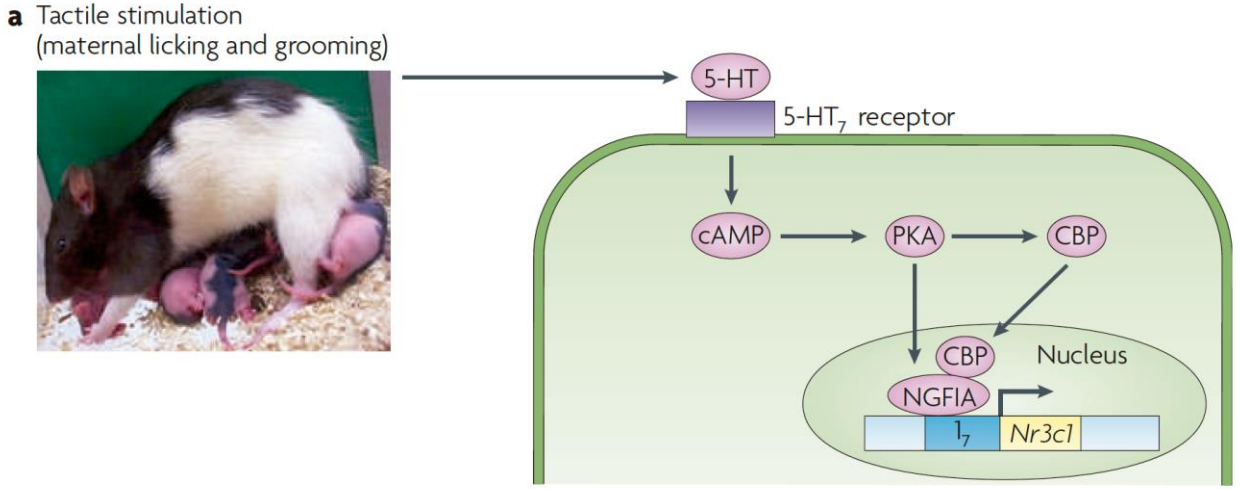
GluA1,3,4

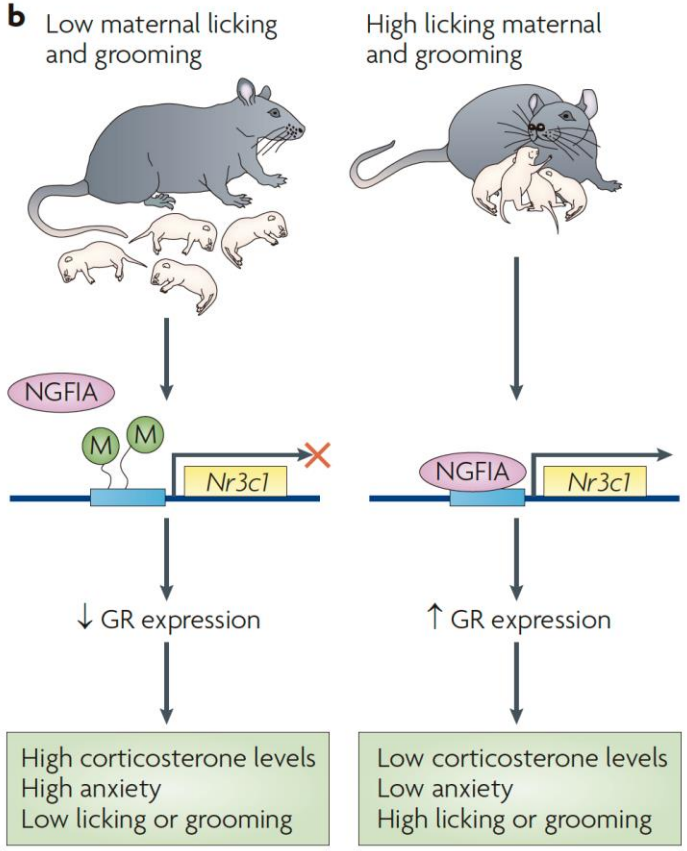
GluA2

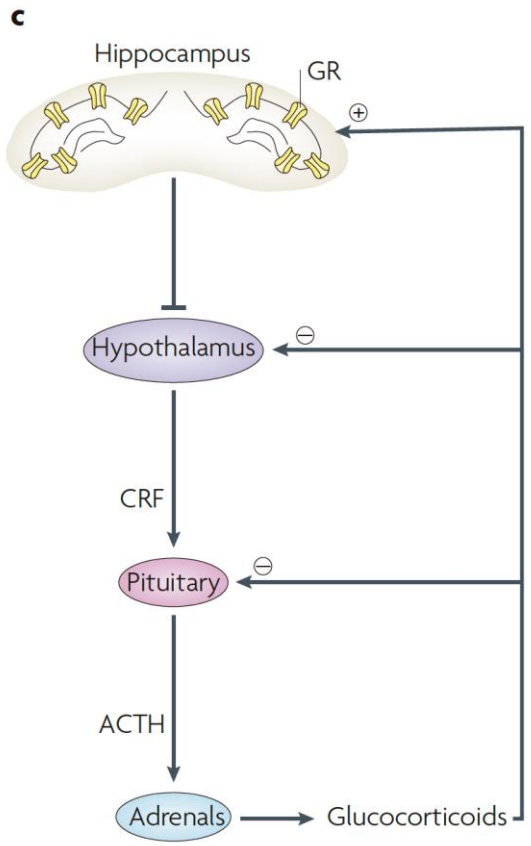
# Can we rescue normal behaviour by normalizing *GriK4* gene doses?




Arora et al., **Cell Rep**, 2018



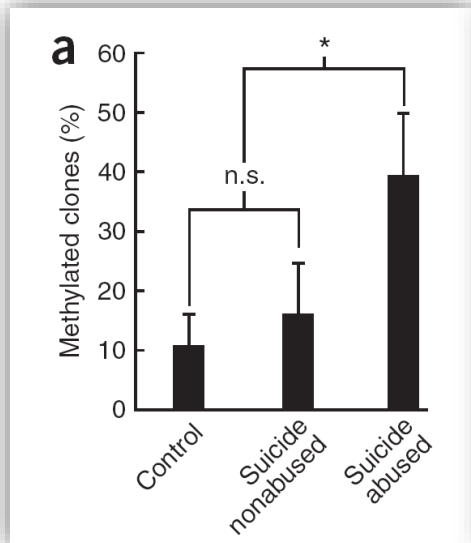



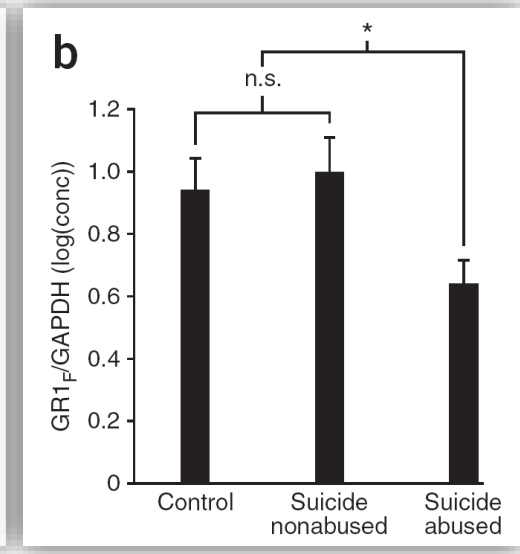

## Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse

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] & Michael J Meaney[1,2,5]

Maternal care influences hypothalamic-pituitary-adrenal (HPA) function in the rat through epigenetic programming of glucocorticoid receptor expression. In humans, childhood abuse alters HPA stress responses and increases the risk of suicide. We examined epigenetic differences in a neuron-specific glucocorticoid receptor (*NR3C1*) promoter between postmortem hippocampus obtained from suicide victims with a history of childhood abuse and those from either suicide victims with no childhood abuse or controls. We found decreased levels of glucocorticoid receptor mRNA, as well as mRNA transcripts bearing the glucocorticoid receptor $1_F$ splice variant and increased cytosine methylation of an *NR3C1* promoter. Patch-methylated *NR3C1* promoter constructs that mimicked the methylation state in samples from abused suicide victims showed decreased NGFI-A transcription factor binding and NGFI-A–inducible gene transcription. These findings translate previous results from rat to humans and suggest a common effect of parental care on the epigenetic regulation of hippocampal glucocorticoid receptor expression.

342 VOLUME 12 | NUMBER 3 | MARCH 2009 NATURE NEUROSCIENCE




cf. Hackman et al. Nat Rev Neurosci. 2010

*Science* **359**, 1395–1399 (2018) 23 March 2018

# Early life experience drives structural variation of neural genomes in mice

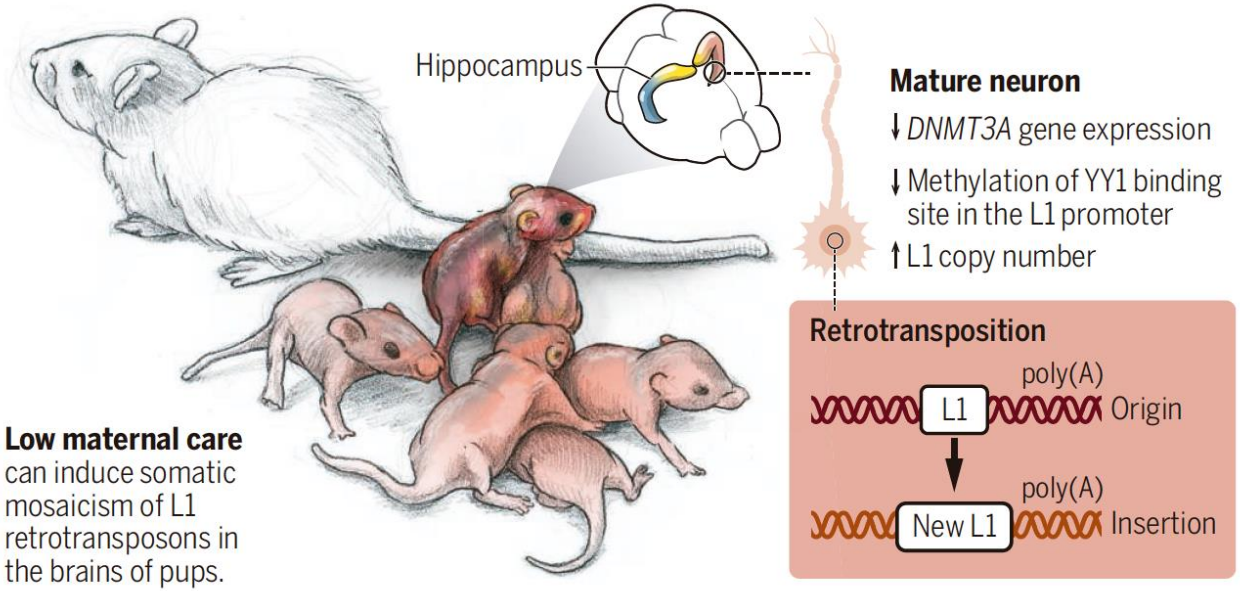
**Tracy A. Bedrosian,* Carolina Quayle, Nicole Novaresi, Fred. H. Gage***

The brain is a genomic mosaic owing to somatic mutations that arise throughout development. Mobile genetic elements, including retrotransposons, are one source of somatic mosaicism in the brain. Retrotransposition may represent a form of plasticity in response to experience. Here, we use droplet digital polymerase chain reaction to show that natural variations in maternal care mediate the mobilization of long interspersed nuclear element–1 (LINE-1 or L1) retrotransposons in the hippocampus of the mouse brain. Increasing the amount of maternal care blocks the accumulation of L1. Maternal care also alters DNA methylation at YY1 binding sites implicated in L1 activation and affects expression of the de novo methyltransferase DNMT3a. Our observations indicate that early life experience drives somatic variation in the genome via L1 retrotransposons.

http://driving-fear-program.com/treat-anxiety-disorder/

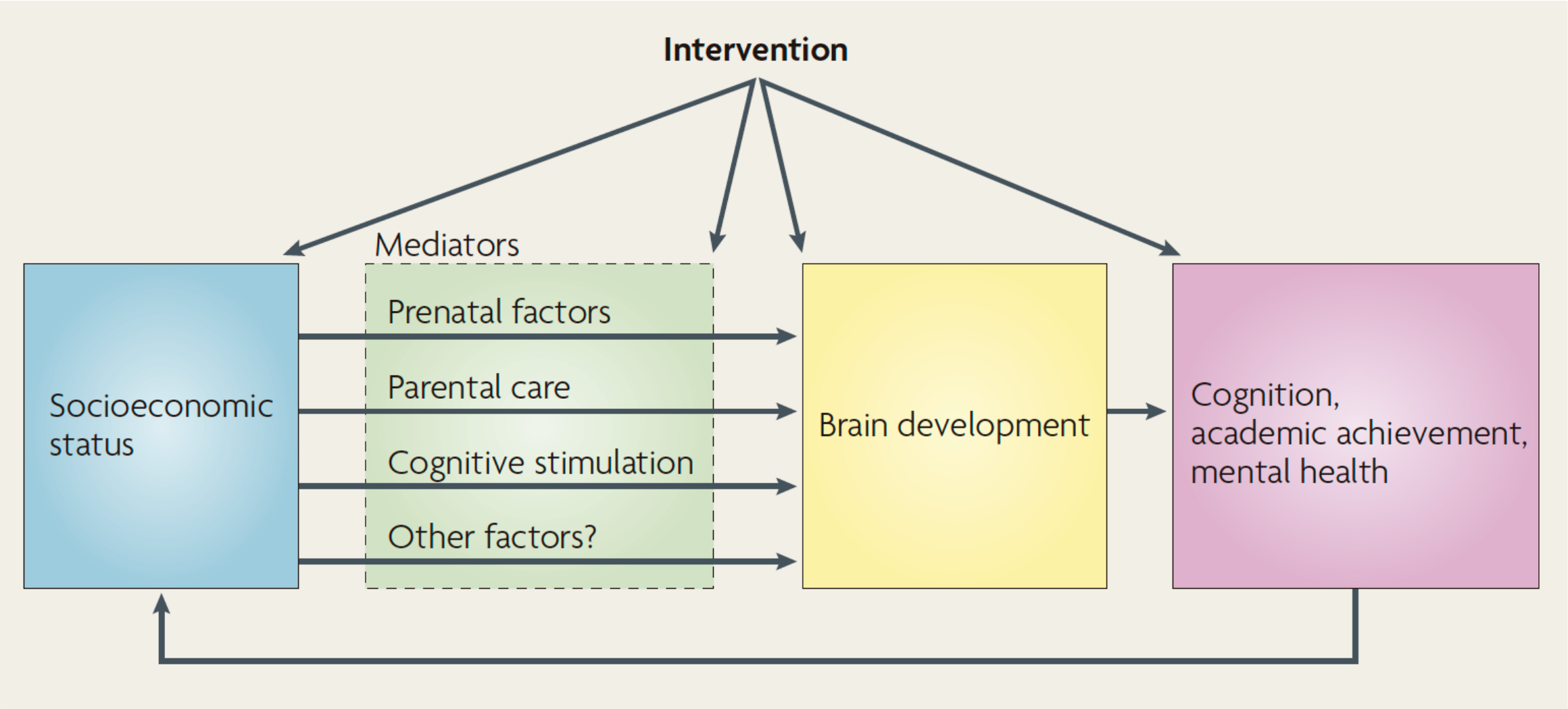
## Maternal care alters genomic structure

Early life experiences such as maternal care affect DNA sequence in neurons of the hippocampus via L1 retrotransposition. The accumulation of L1 retrotransposons in the hippocampus of rodent pups reared with low maternal care might contribute to higher anxiety-like behavior in adulthood.




**Low maternal care** can induce somatic mosaicism of L1 retrotransposons in the brains of pups.

# Socioeconomic Status Has Effects on Cognition, Academic Achievement and Mental Health




cf. Hackman et al. Nat Rev Neurosci. 2010