Interazione tra microglia e neuroni: ruolo nella sensibilità allo stress e nel trattamento della depressione

Laura Maggi

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MAJOR DEPRESSION

a huge health, societal, economic problem

- lifetime prevalence is **10% worldwide**, higher in western countries

- suicide is the 3rd cause of death in the 15-24 years age group

- **leading cause of years lost owing to disability worldwide** and the third overall contributor to the worldwide burden of disease (projected to be the biggest contributor by 2030 according to WHO)

- **Syntoms vary from person to person**
  Loss of interest or pleasure

Antidepressant have incomplete efficacy

30-40% does not show a significant response to antidepressants

The Antidepressant Fluoxetine Restores Plasticity in the Adult Visual Cortex

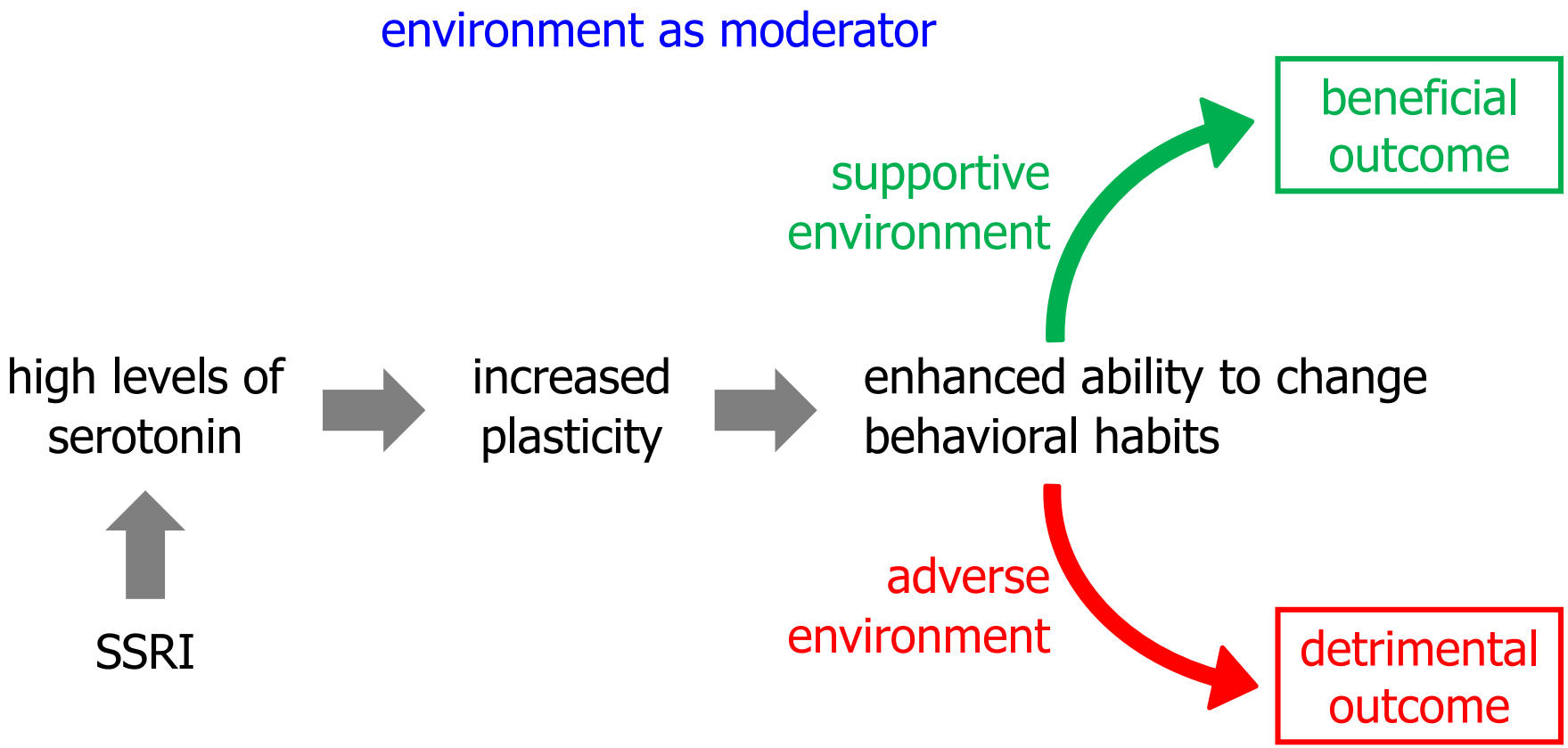
José Fernando Maya Vetencourt,[1*] Alessandro Sale,[1] Alessandro Viegi,[1] Laura Baroncelli,[1] Roberto De Pasquale,[1] Olivia F. O'Leary,[3] Eero Castrén,[3] Lamberto Maffei[1,2]

Science AAAS

www.sciencemag.org SCIENCE VOL 320 18 APRIL 2008

Neuroplasticity – or brain plasticity – is the ability of the brain to modify its connections or re-wire itself as a result of one's experience

UNDIRECTED SUSCEPTIBILITY TO CHANGE hypothesis



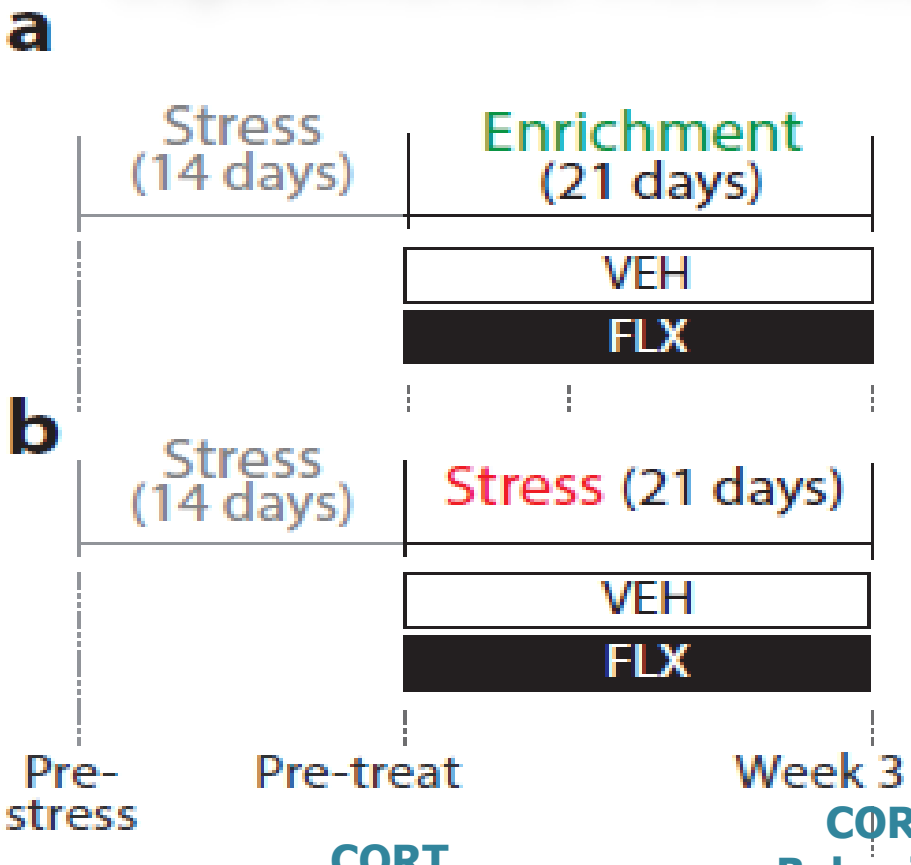
SSRI induce the change
but the environment drives the change

Branchi, Psychoneuroendocrinology, 2011

Fluoxetine increase plasticity

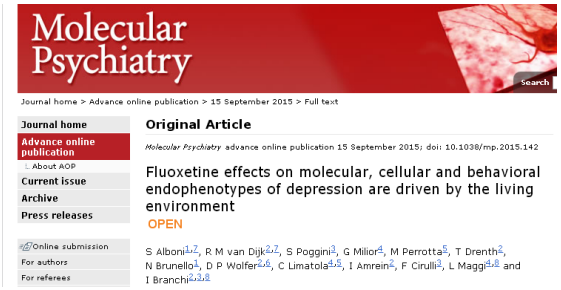
Can the environment influence Fluoxetine effects?

Experimental mouse model *in vivo*



CORT
Behaviour

CORT
Behaviour
Neuroanatomy
Electrophysiology
Molecular marker
Inflamamtory markers
Microglia morphology
Inflamatory markers in microglia



Molecular Psychiatry

Journal home > Advance online publication > 15 September 2015 > Full text

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For referees

Original Article

Molecular Psychiatry advance online publication 15 September 2015; doi: 10.1038/mp.2015.142

Fluoxetine effects on molecular, cellular and behavioral endophenotypes of depression are driven by the living environment

OPEN

S Alboni[1,7], R M van Dijk[2,7], S Poggini[3], G Milior[4], M Perrotta[5], T Drenth[2], N Brunello[1], D P Wolfer[2,6], C Limatola[4,5], I Amrein[2], F Cirulli[3], L Maggi[5,8] and I Branchi[2,1,8]

Effects of fluoxertine, compared to vehicle, in enriched and stressful condition

	Reduction in liking-type anhedonia	Reduction in wanting-type anhedonia	Cognitive bias	Neurogenesis (Ki67)	ERK signaling	CREB signaling	BDNF levels	Reduction in CORT levels	LTP
Enriched condition	↔	↑	↑	↔	↔	↔	↑	↑	↔
Stressful condition	↓	↓	↔	↓	↓	↓	↔	↔	↑

Alboni et al.; submitted

Modello sperimentale ADxE

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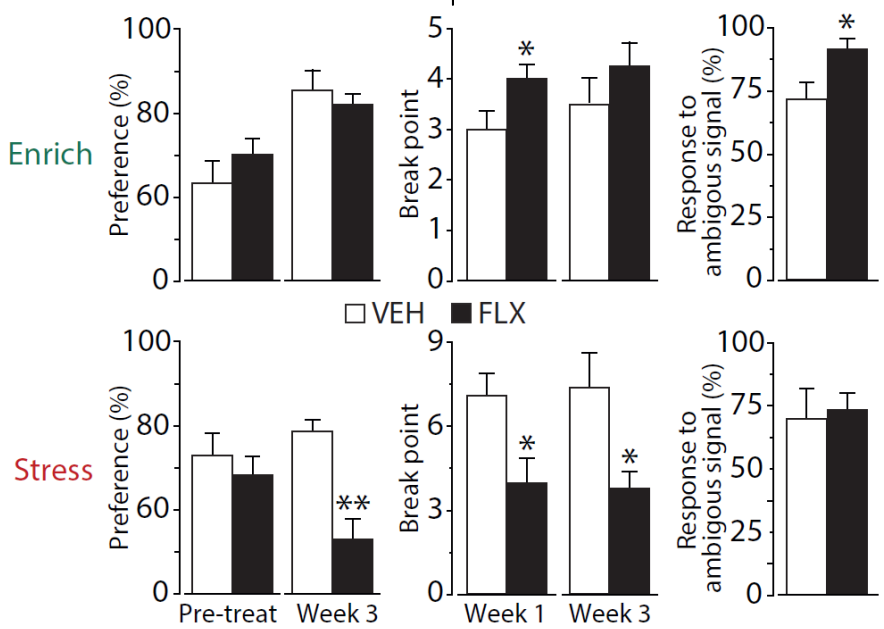

Alboni et al.; submitted

Modello sperimentale ADxE

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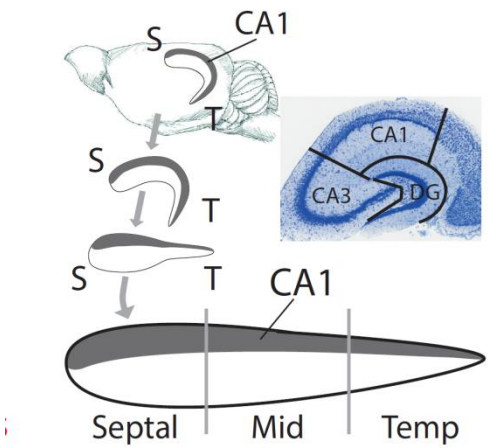

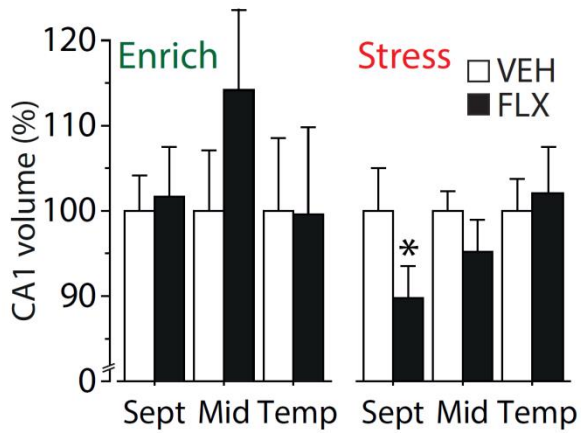

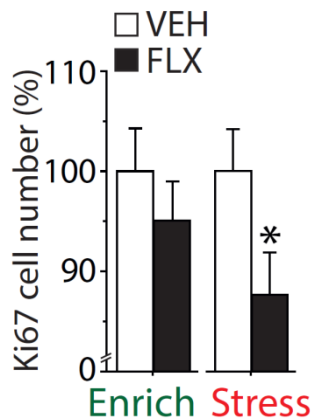

Alboni et al.; submitted

Modello sperimentale ADxE

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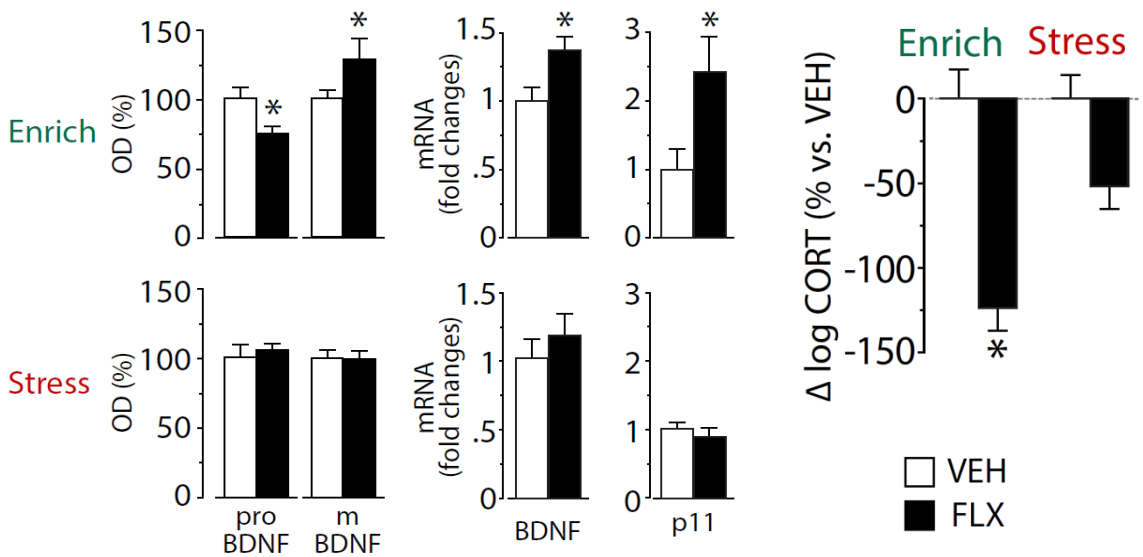


Alboni et al.; submitted

CLINICAL DATA

Article

Evaluation of Outcomes With Citalopram for Depression Using Measurement-Based Care in STAR*D: Implications for Clinical Practice

http://ajp.psychiatryonline.org *Am J Psychiatry 163:1, January 2006*

Soc Psychiatry Psychiatr Epidemiol (2009) 44:272–277 DOI 10.1007/s00127-008-0436-8

ORIGINAL PAPER

Alex Cohen · Stephen E. Gilman · Patricia R. Houck · Katalin Szanto · Charles F. Reynolds III

Socioeconomic status and anxiety as predictors of antidepressant treatment response and suicidal ideation in older adults

Psychosomatic Medicine 67:703–706 (2005)

Cardiovascular Risk Factors May Moderate Pharmacological Treatment Effects in Major Depressive Disorder

Dan V. Iosifescu, MD, Nicoletta Clementi-Craven, MD, Renerio Fraguas, MD, PhD, George I. Papakostas, MD, Timothy Petersen, PhD, Jonathan E. Alpert, MD, Andrew A. Nierenberg, MD, and Maurizio Fava, MD

CONCLUSION 1.

UNDIRECTED SUSCEPTIBILITY TO CHANGE hypothesis

- the effects of SSRI (fluoxetine) treatment depend on the quality of the environment
  + not univocal effect

- neural plasticity is not good per se, but it can be beneficial or detrimental according to the quality of the environment

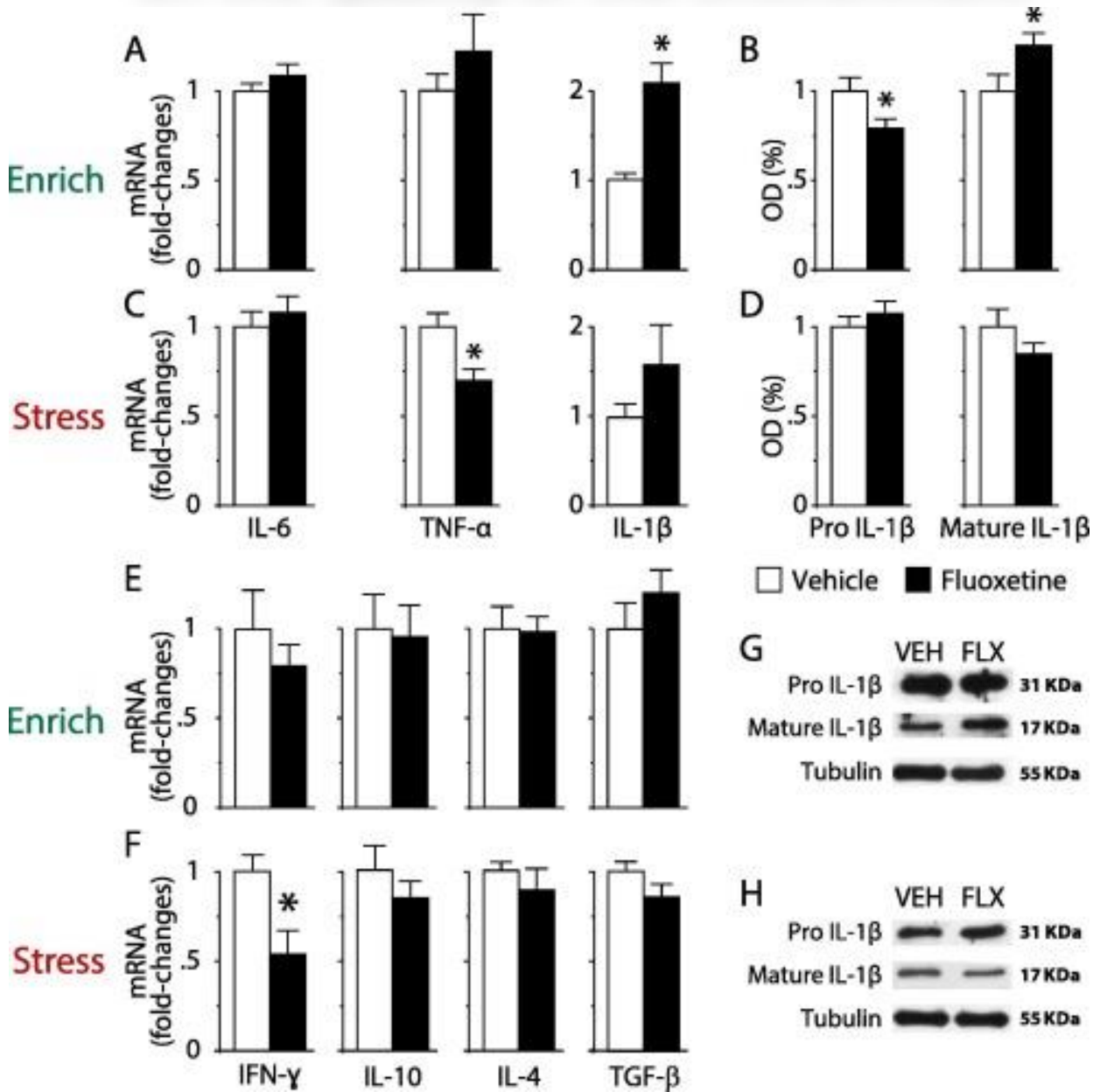
- effects of SSRI on plasticity as a starting point

- If the quality of the environment takes part in determining the outcome of behavioral treatment with fluoxetine.

- If the inflammation has a role in the pathogenesis and in the treatment of depression

Does fluoxetine affect cellular and molecular inflammatory components in an environment dependent manner?

The effect of fluoxetine on inflammation mediators depends on the quality of the environment



Alboni et al. BBI (2016)

the inflammatory response in the CNS is ochestrated by MICROGLIA CELLS

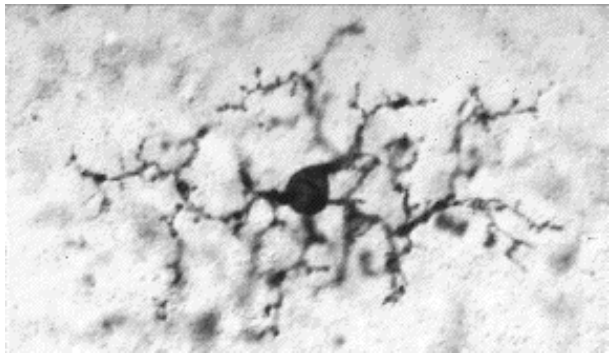
Can fluoxetine affect microglia function?

Microglia background

- resident macrophages of the brain

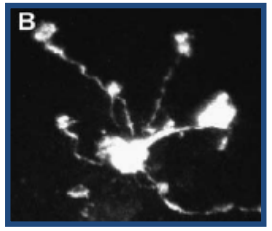
10-20 % of CNS cells; more numerous in gray matter

- **highly influenced by the environment**
- Activated in pathology and experimental insults
- React by **releasing inflammatory/reactive molecules** and/or phagocytosis
- Adopt stimulus dependent phenotype (morphology, transcription, migration, proliferation)
- **Orchestrating inflammatory response in the CNS**



Resting and activated microglial cells

•Resting microglial cells (ramified) monitor brain environment and are activated in case of damage (tissue scanning)



The entire volume of the brain is examined approximately every 4-5 hours!

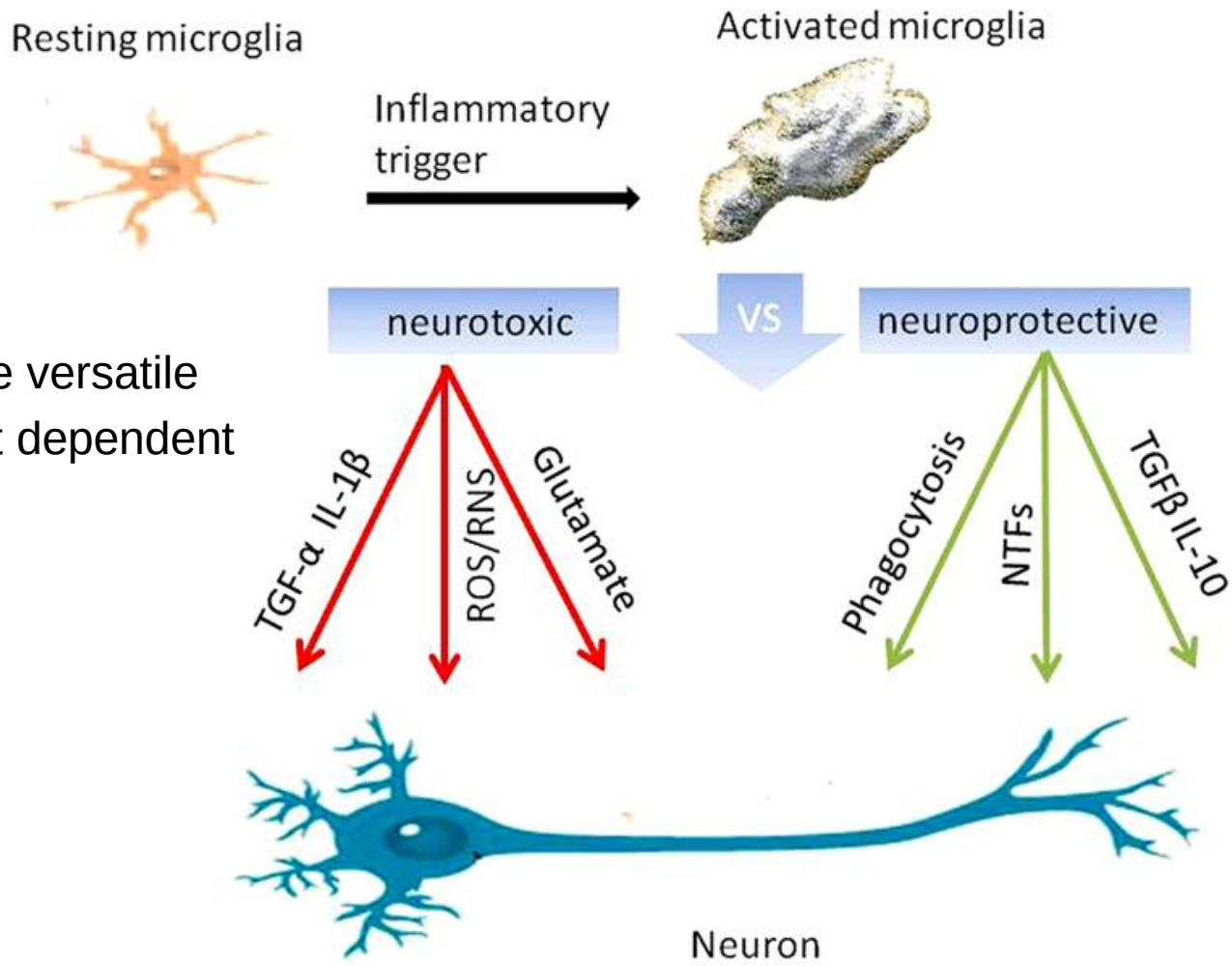
•Activated microglia (ameboid, short processes) migrate to the site of injury, proliferate, release cytokines, have phagocytic activity

More functional states than originally stated based on morphology

•Microglial activation is not an all-or-none process

Neurotoxic and neuroprotective microglia

- Microglial actions are versatile
- Intensity and context dependent
- Competing stimuli
- Instructed behavior



Microglia: sensors of changes in the CNS

New roles for microglia in the healthy brain

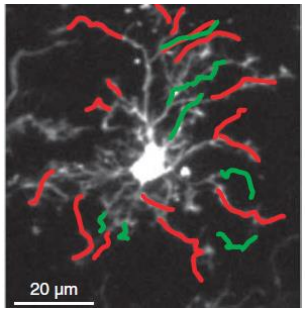
•Release substances affecting neural activity

Vol 438|15 December 2005|doi:10.1038/nature04223

BDNF from microglia causes the shift in neuronal anion gradient underlying neuropathic pain

Jeffrey A. M. Coull[1,2,*], Simon Beggs[3,*], Dominic Boudreau[1], Dominick Boivin[1], Makoto Tsuda[3,4], Kazuhide Inoue[4], Claude Gravel[5,6], Michael W. Salter[3] & Yves De Koninck[1,2,6]

•Contact synapses in the healthy brain



3974 • The Journal of Neuroscience, April 1, 2009 • 29(13):3974–3980

Resting Microglia Directly Monitor the Functional State of Synapses *In Vivo* and Determine the Fate of Ischemic Terminals

Hiroaki Wake,[1,2] Andrew J. Moorhouse,[1,3] Shozo Jinno,[4] Shinichi Kohsaka,[5] and Junichi Nabekura[1,2,6]

•Mediate synaptic pruning and synaptogenesis during development

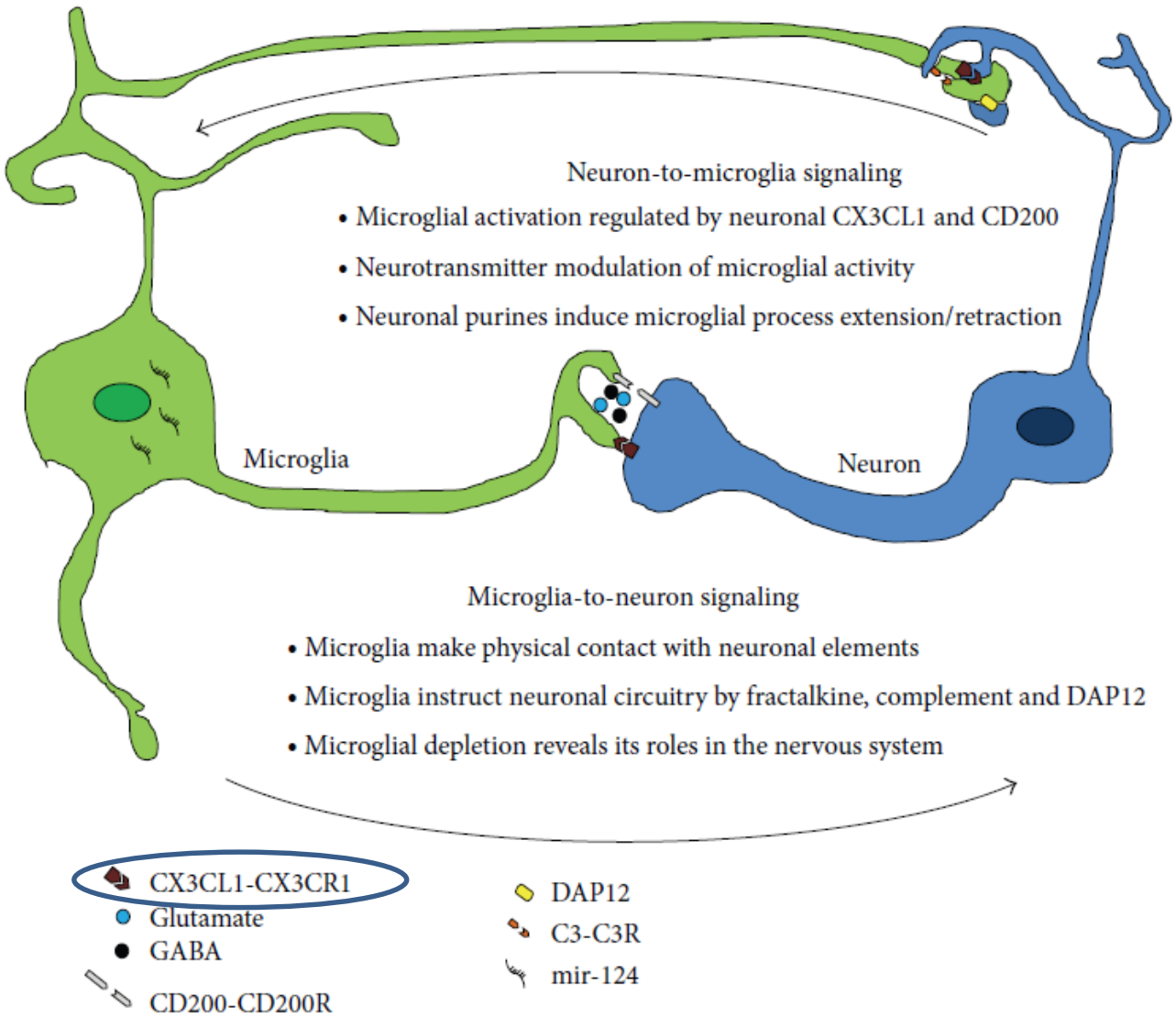
Microglia Sculpt Postnatal Neural Circuits in an Activity and Complement-Dependent Manner

Dorothy P. Schafer,[1] Emily K. Lehrman,[1,5] Amanda G. Kautzman,[1,5] Ryuta Koyama,[1] Alan R. Mardinly,[3] Ryo Yamasaki,[4] Richard M. Ransohoff,[4] Michael E. Greenberg,[3] Ben A. Barres,[2] and Beth Stevens[1,*]

Microglial Interactions with Synapses Are Modulated by Visual Experience

Marie-Ève Tremblay*, Rebecca L. Lowery, Ania K. Majewska*

Bidirectional microglia-neuron communication in the healthy brain



Neuron to microglia

Microglia to Neuron

Microglial Activation

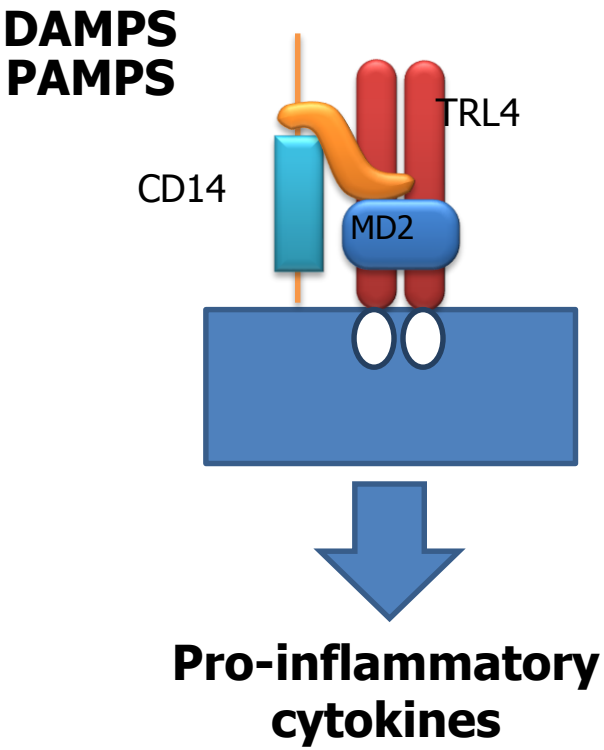
Various bacterial and viral infections and psychological stress can induce direct microglial activation via the release of:

PAMPs
DAMPs (also termed alarmins)

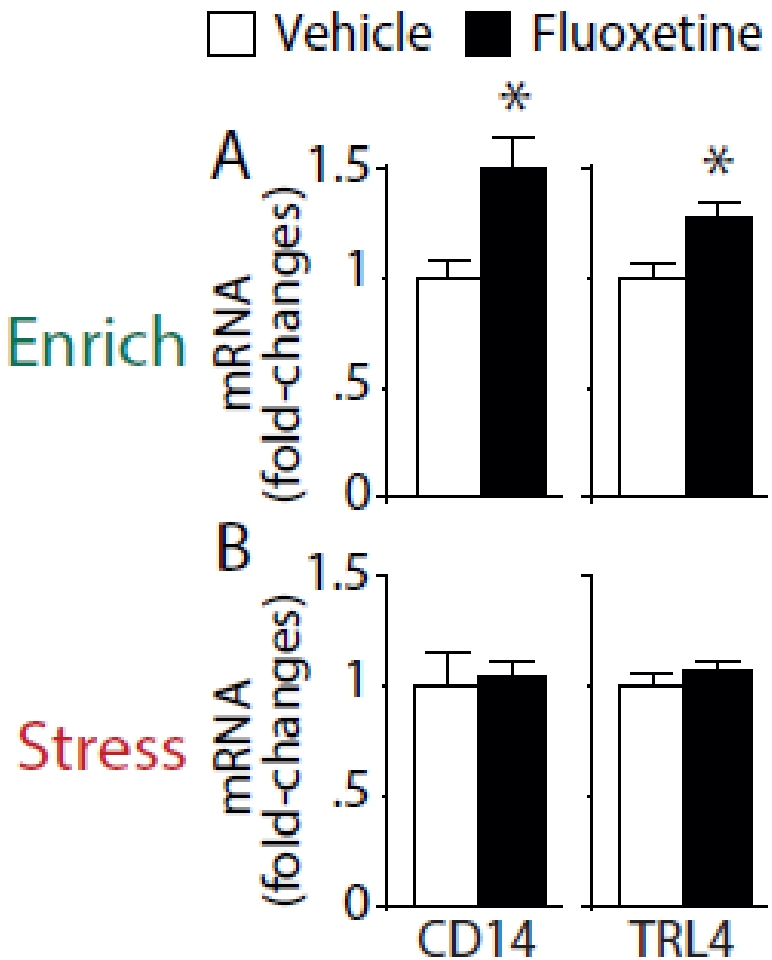
These molecules can signal via microglial Toll-like receptor 4 (TLR4)

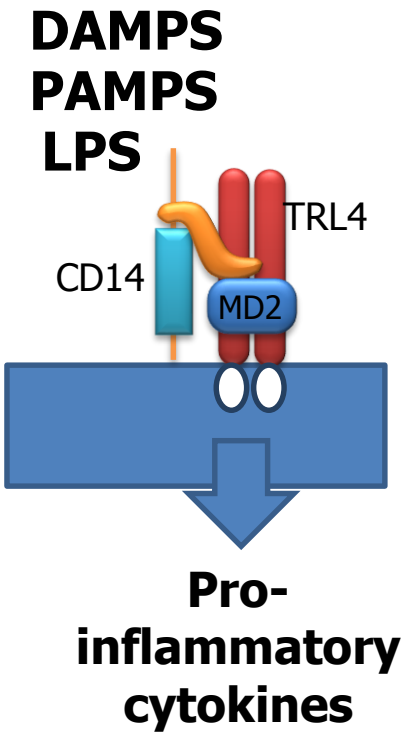
Conserved pathogen-associated molecular patterns (PAMPs)

danger-associated molecular patterns (DAMPs)



Fluoxetine modulates CD14 and TLR4 expression in an environmental dependent manner

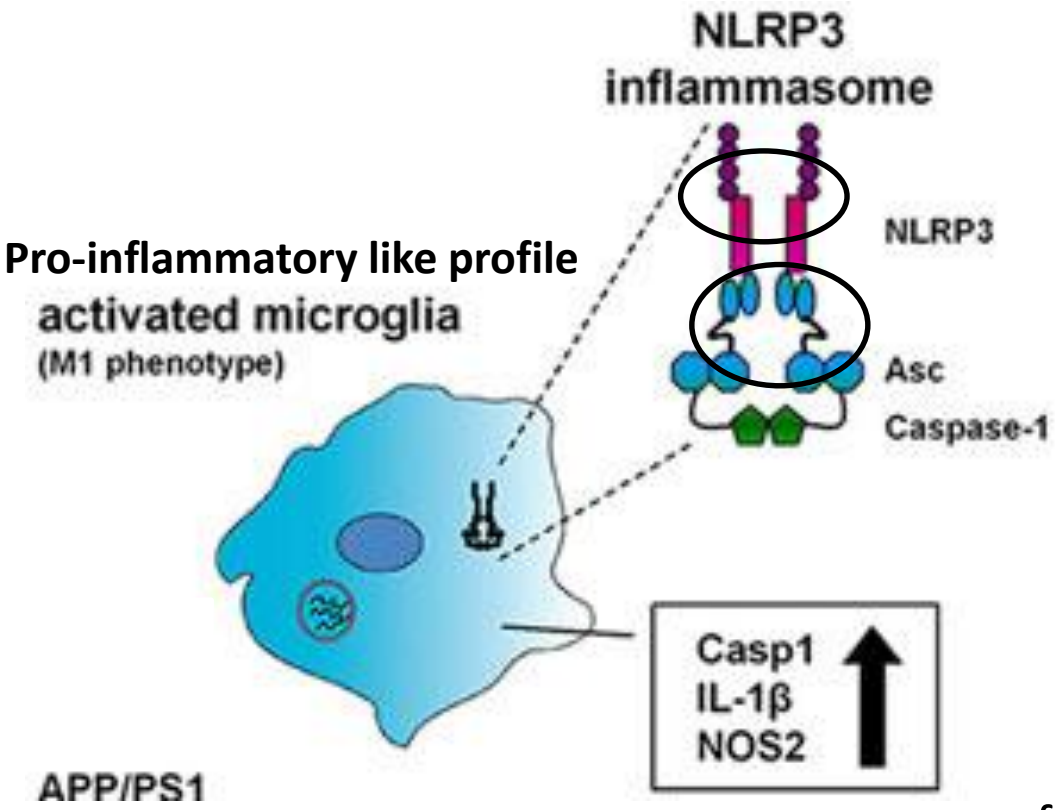




Alboni et al. BBI (2016)

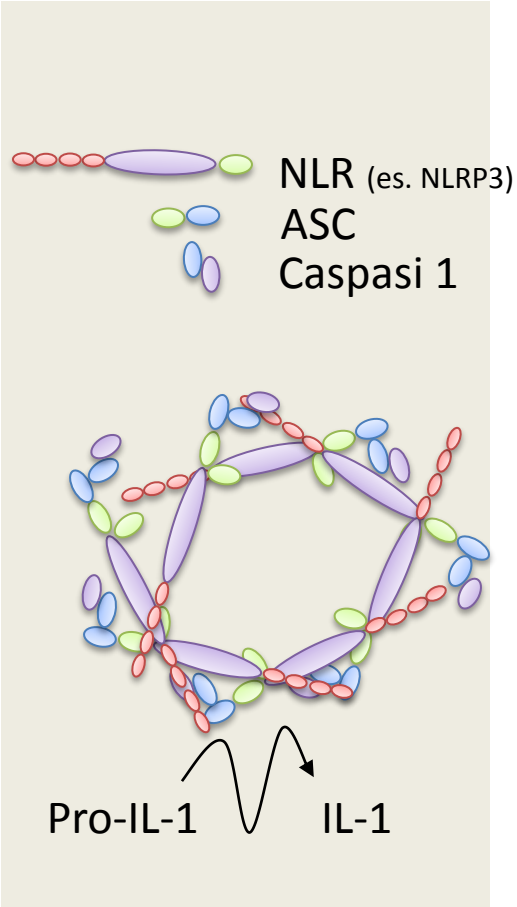
NLRP3 inflammasome

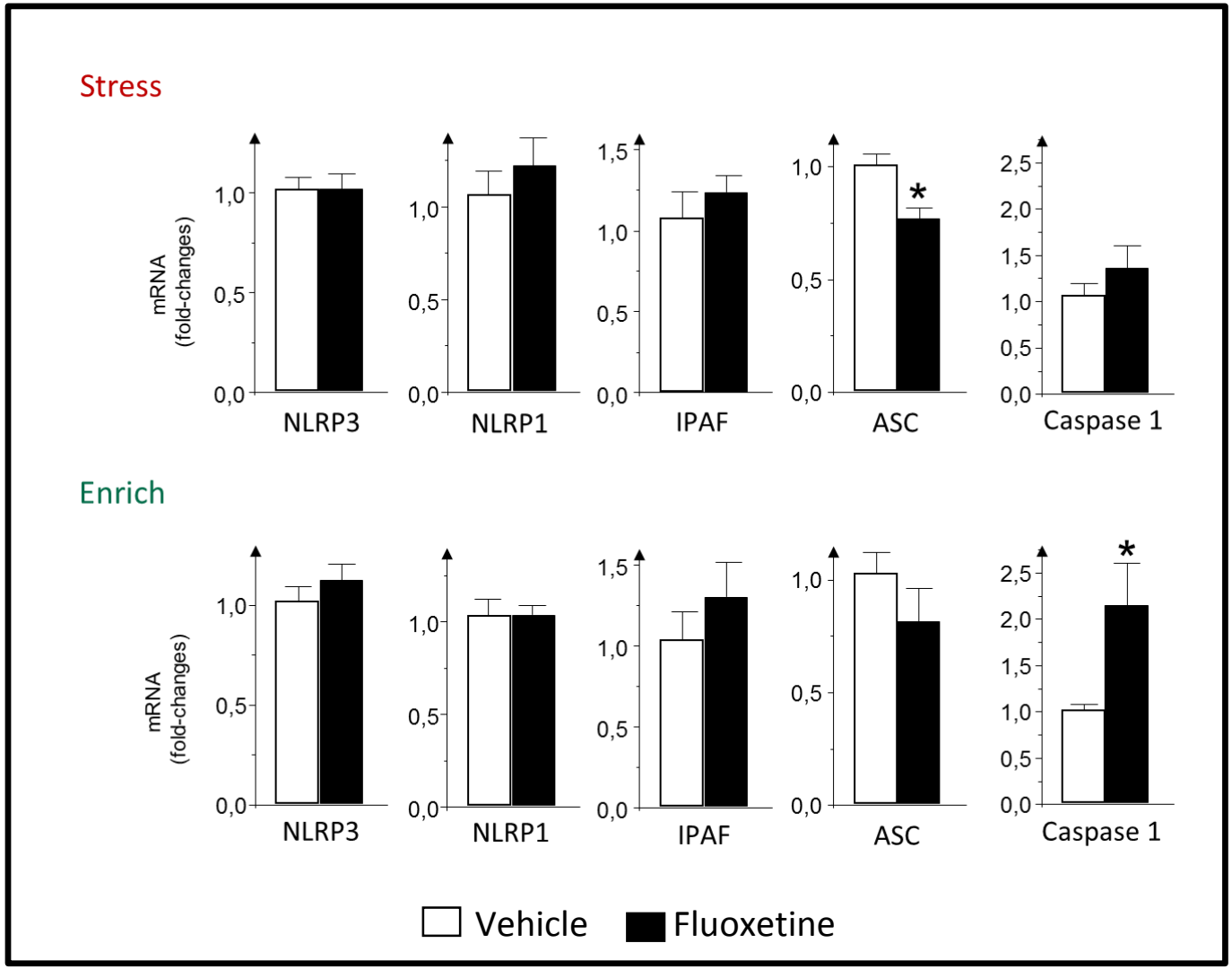
Activation of he inflammasome, a multiprotein oligomer that is a component of the innate immune system, promotes the maturation of the inflammatory cytokines, i.e. Interleukin 1β (IL-1β)



The inflammasome is responsible for the activation of inflammatory processes

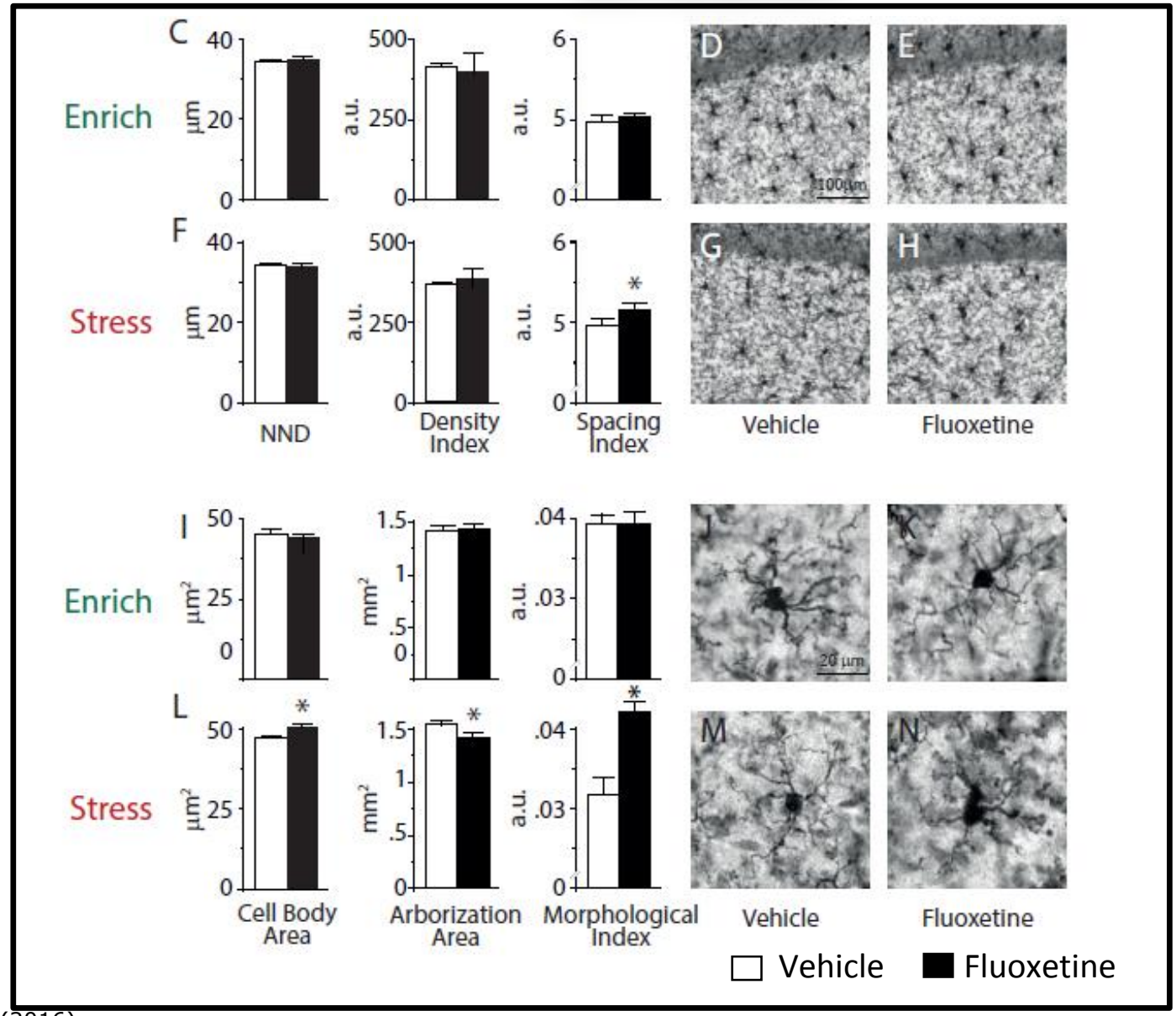
The effect of fluoxetine on inflammosome depends on the quality of the environment





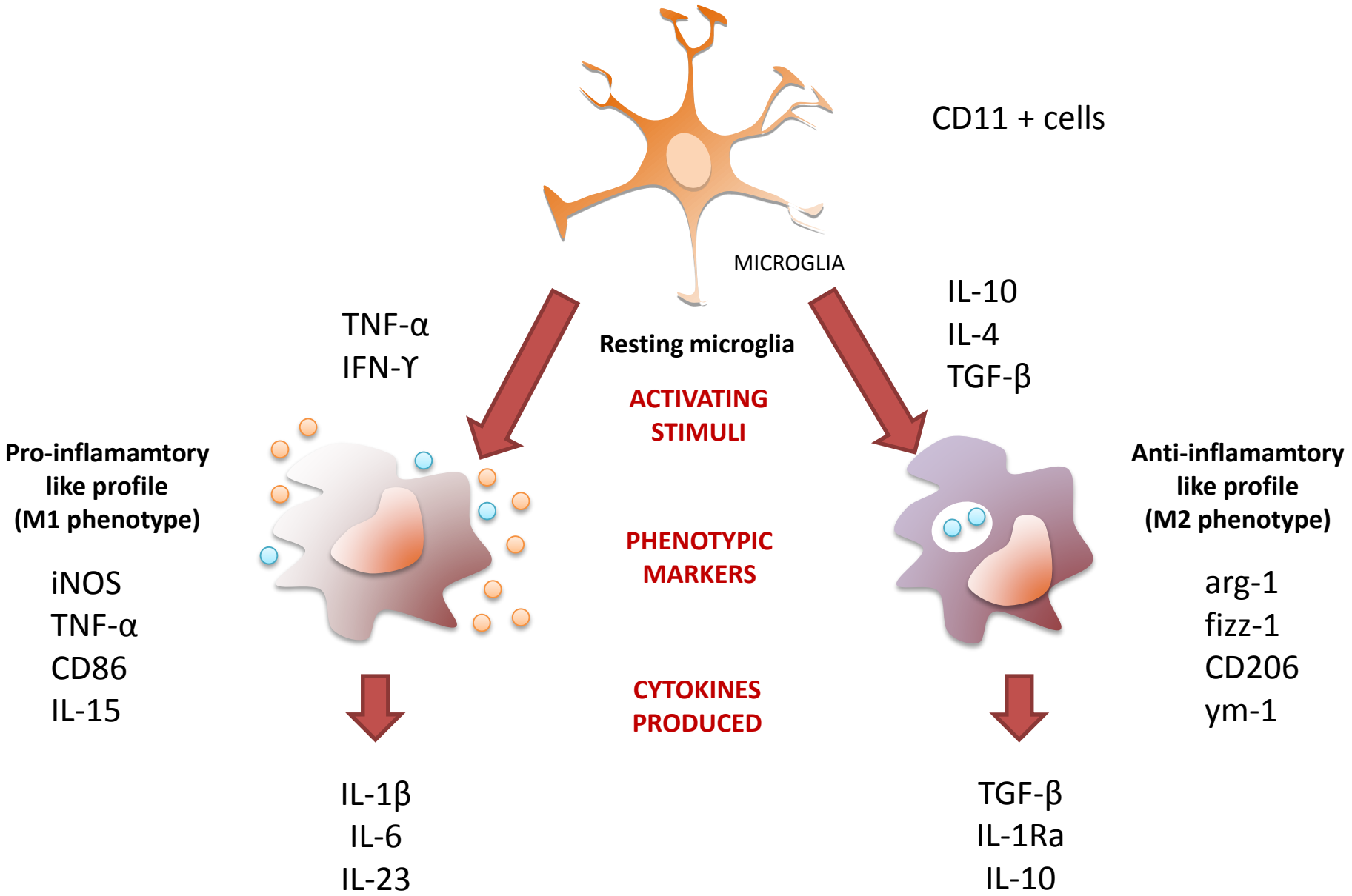
Alboni et al. BBI (2016)

Microglial modulation by fluoxetine upon environmental stimulation

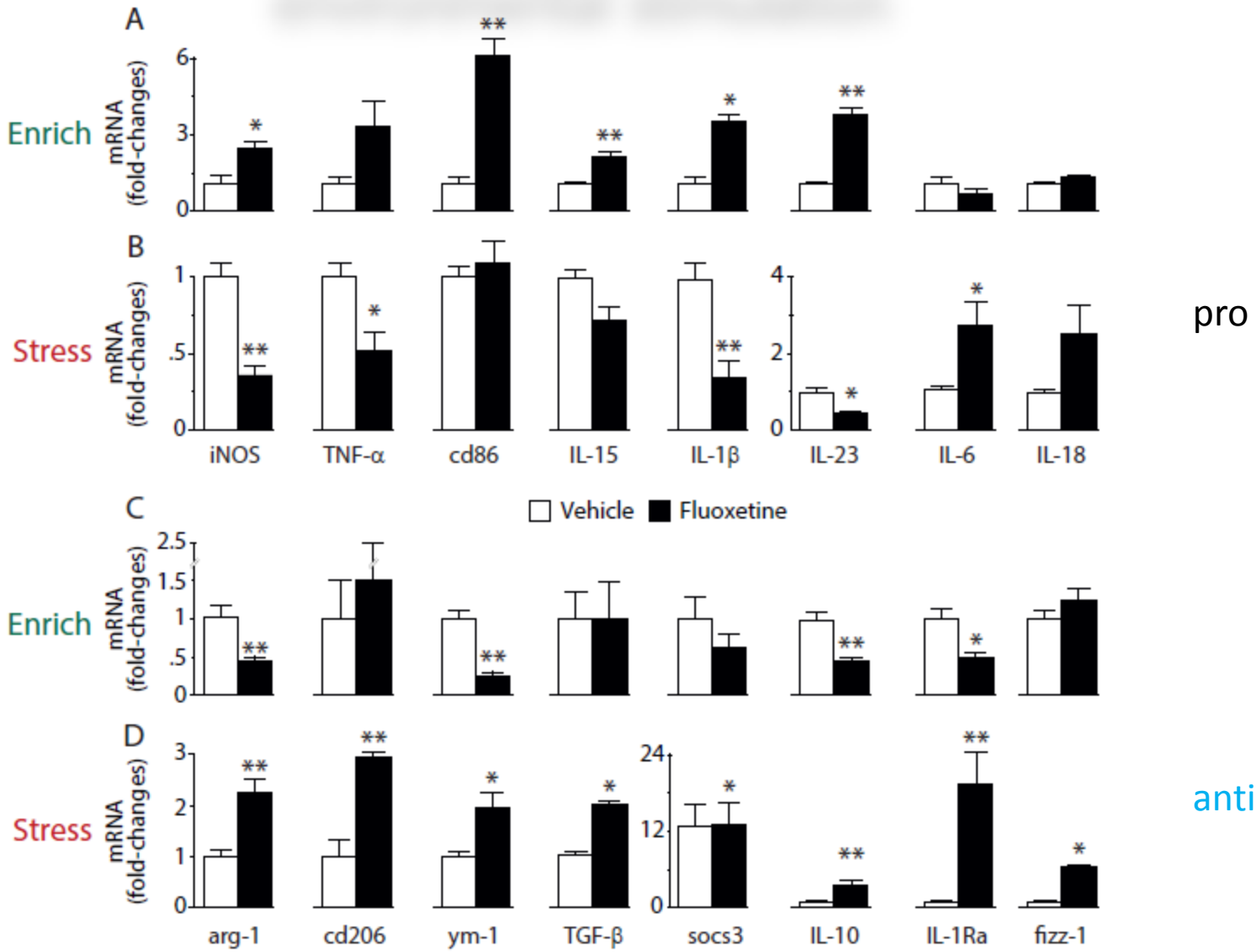


Alboni et al. BBI (2016)

M.E. Tremblay

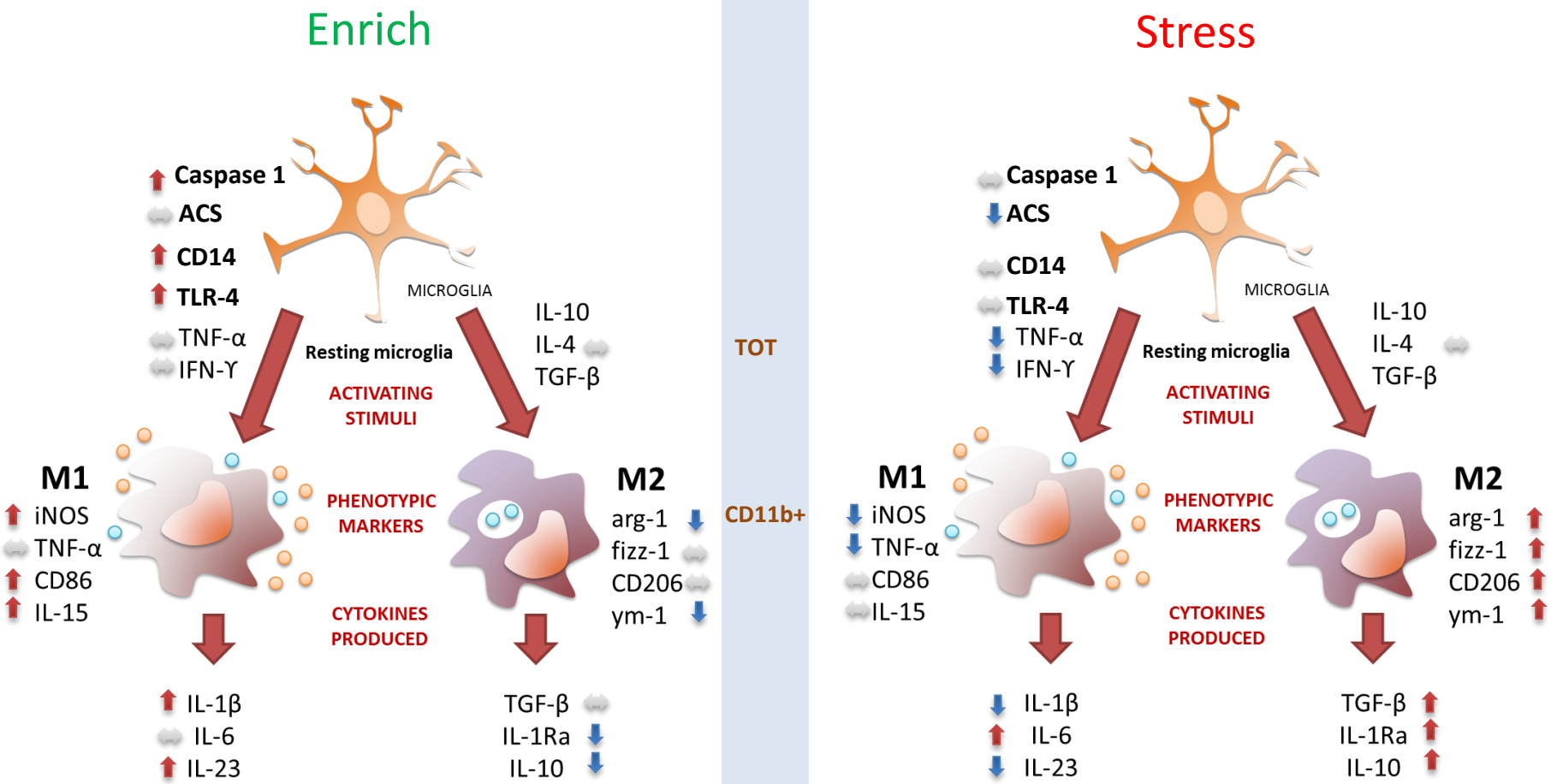

CD11 + cells
MICROGLIA
Resting microglia
ACTIVATING STIMULI
TNF-α
IFN-Υ
IL-10
IL-4
TGF-β
Pro-inflamamtory like profile (M1 phenotype)
iNOS
TNF-α
CD86
IL-15
PHENOTYPIC MARKERS
Anti-inflamamtory like profile (M2 phenotype)
arg-1
fizz-1
CD206
ym-1
CYTOKINES PRODUCED
IL-1β
IL-6
IL-23
TGF-β
IL-1Ra
IL-10

Microglia polarization induced by fluoxetine upon environmental stimulation



Alboni et al. BBI (2016)

Fluoxetine effect depends on environmental stimulation



Overall fluoxetine increase inflammation

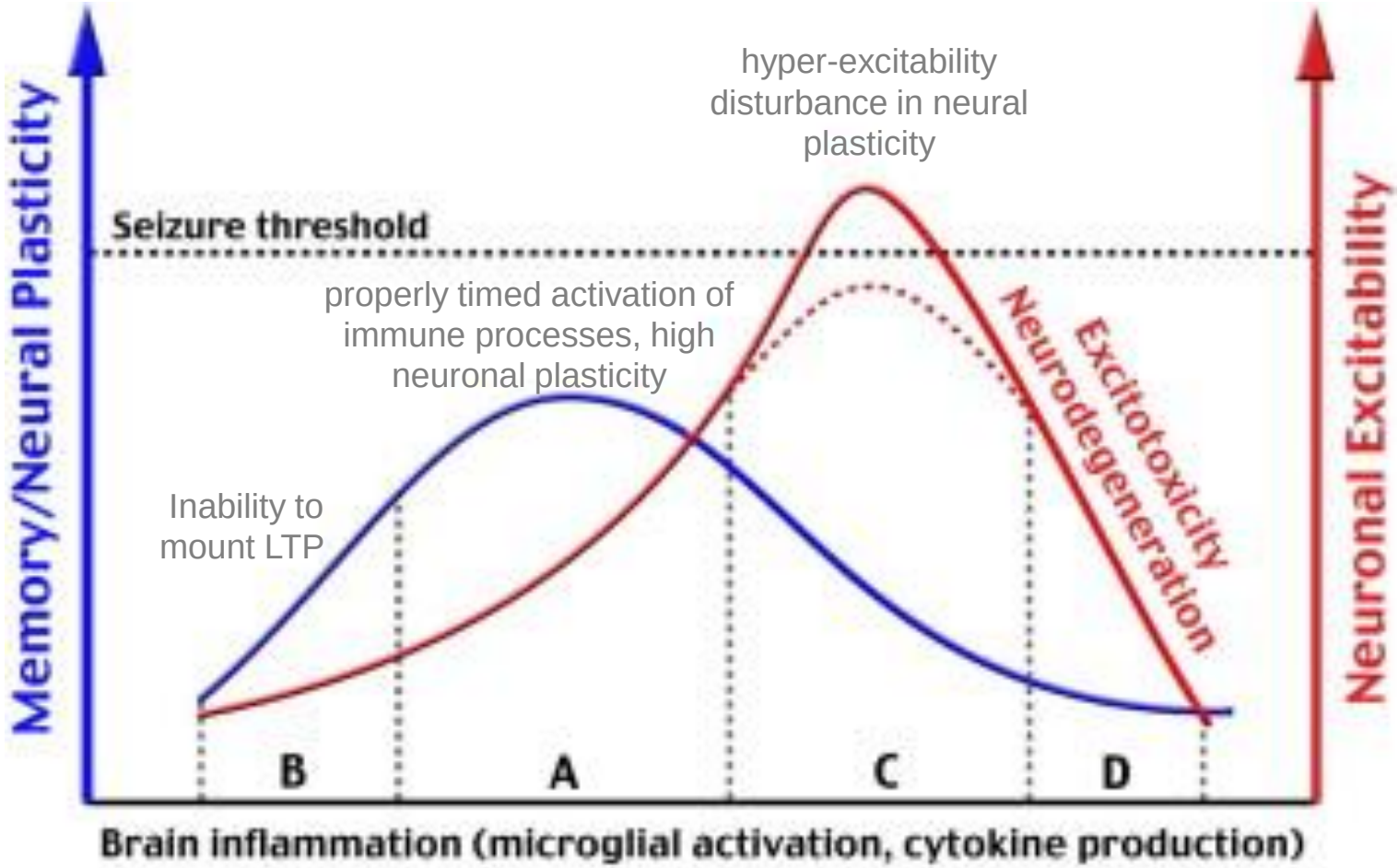
Overall fluoxetine reduce inflammation

CONCLUSION 2.

-fluoxetine administration affects the inflammatory response in a context dependent-manner

It counteracts the influence of the environment: fluoxetine administration, increasing and decreasing inflammatory markers respectively in the enriched and stressful condition, produces an effect opposite to that caused by enrichment and stress per se'

Memory, neural plasticity and neuronal excitability as a function of brain inflammation



Any deviation from the physiological range, either by excessive immune activation or by immune suppression, results in memory and plasticity impairments:

Immune modulation of learning, memory, neural plasticity and neurogenesis
R Yirmiya, I Goshen - Brain, behavior, and immunity, 2011

- If microglia act as a “sensor” of the environment.

- If microglia is relevant in neuronal plasticity processes

What are the consequences of disrupting neuronal-microglia crosstalk on brain plasticity and responsiveness to the environment ?

Fractalkine receptor deficiency impairs microglial and neuronal responsiveness to chronic stress

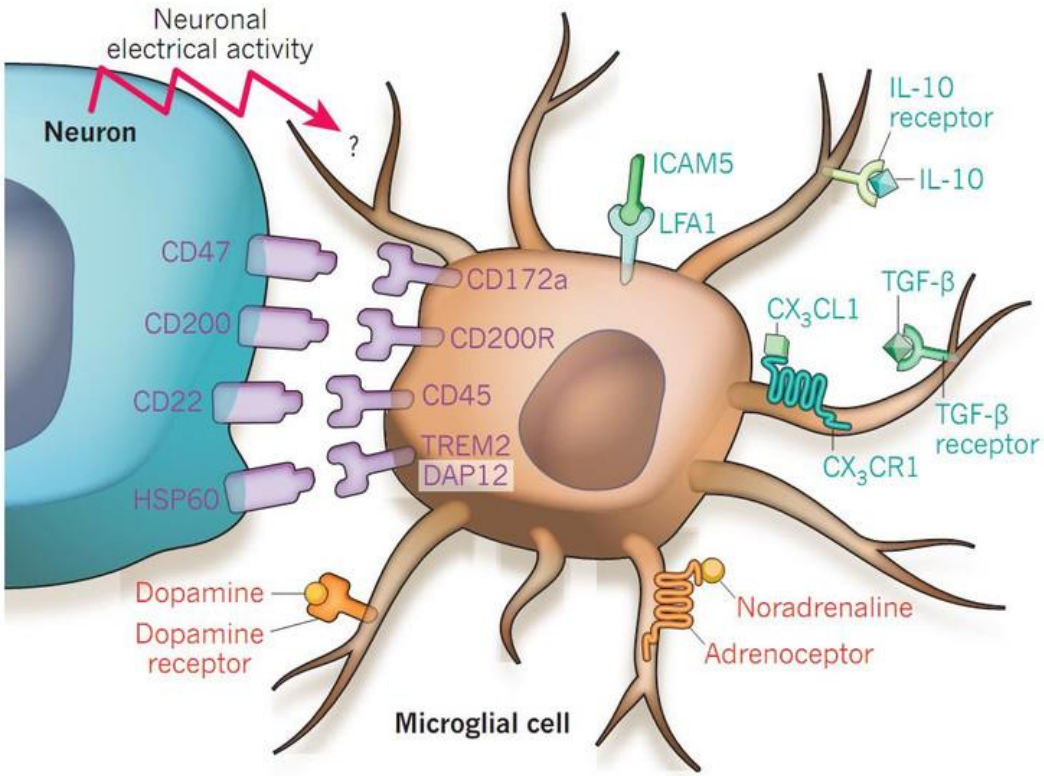
Giampaolo Milior[1]*, Cynthia Lecours[2]*, Louis Samson[2], Kanchan Bisht [2], Silvia Poggini[3], Francesca Pagani[4], Cristina Deflorio[1,5], Clotilde Lauro[1], Silvia Alboni[6], Cristina Limatola[1,7], Igor Branchi[3#], Marie-Eve Tremblay[2#] and Laura Maggi[1#]

Brain, Behavior, and Immunity, 2016-07-01,
Volume 55, Pages 114-125,

Regulation of microglia activation by neurons

Microglial defective models

- CD200-CD200R
- CX3CL1-CX3CR1



Richard M. Ransohoff[1] & Astrid E. Cardona[2]

2010 | VOL 468 | NATURE | 253

Stress condition (3 weeks)

CX_3CR1 ko

wt mice

Behaviour

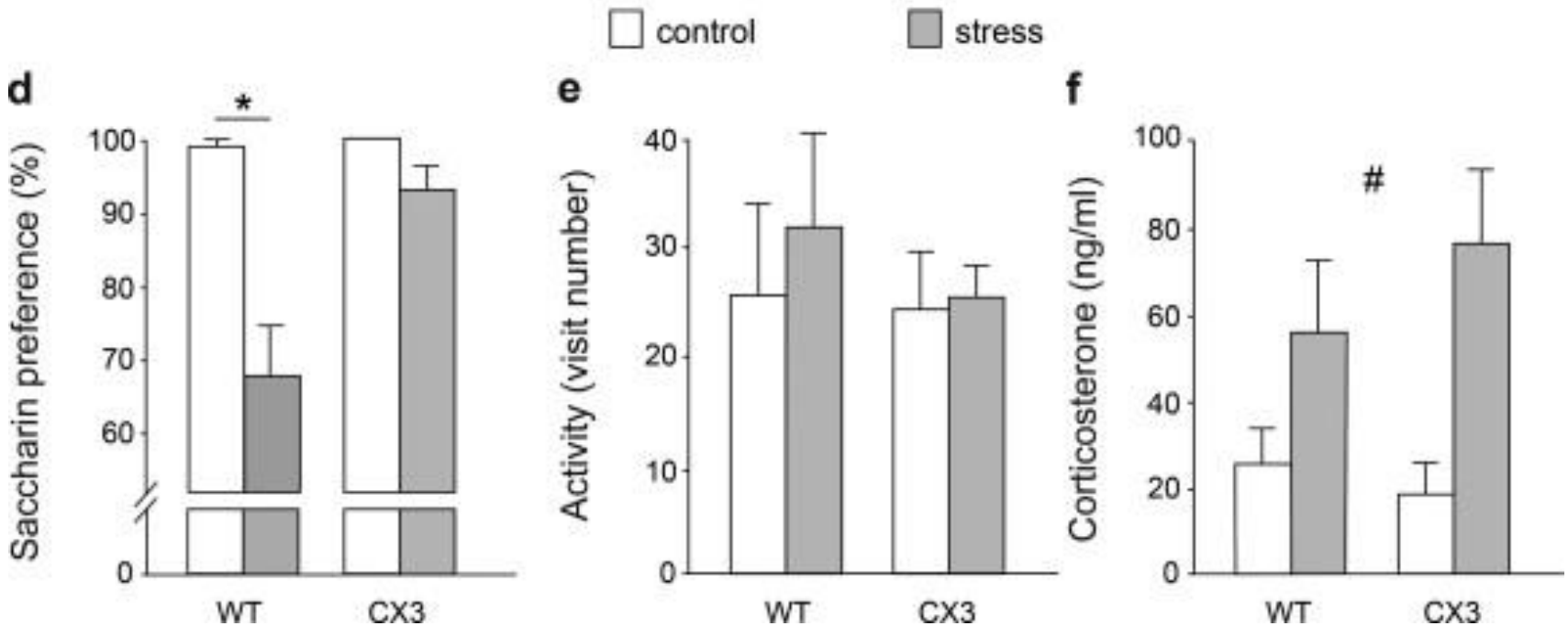
Microglia Morphology

Electrophysioloigy

Responses in WT and CX3 mice exposed to chronic unpredictable stress

Behaviour

ANHEDONIA- Saccharine preference

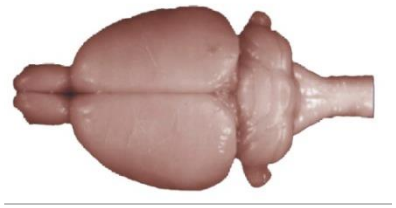


How to measure neuronal plasticity ?

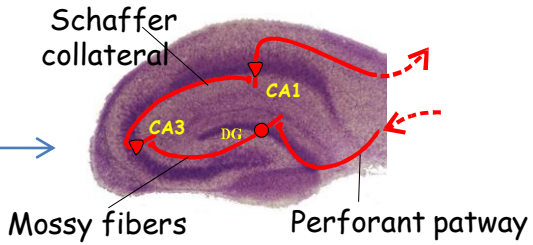
Long-Term Potentiation

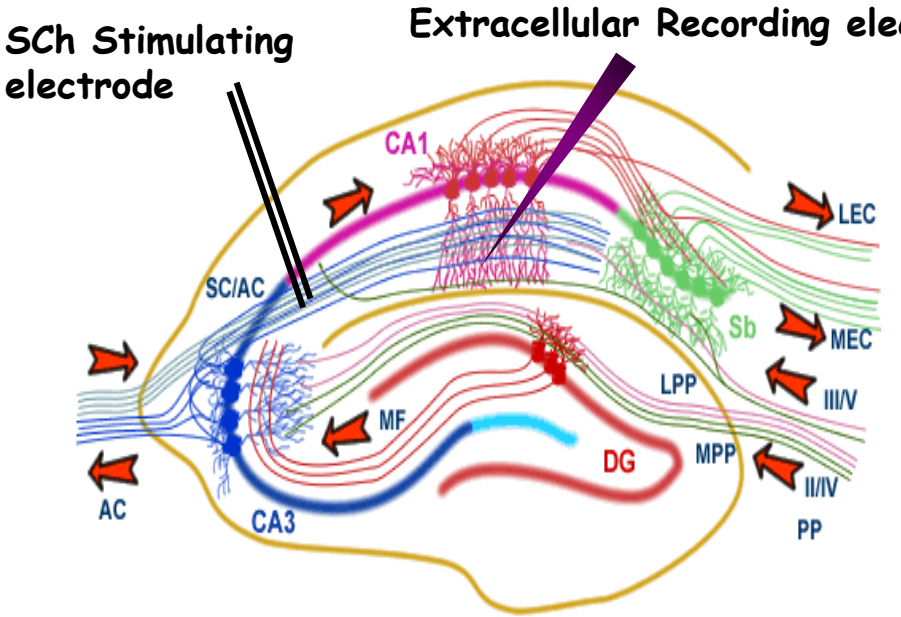
High frequency stimulation of a neuronal circuitry induces an increase in synaptic strenght

Methods



Mouse Hippocampal slices (350 μm)



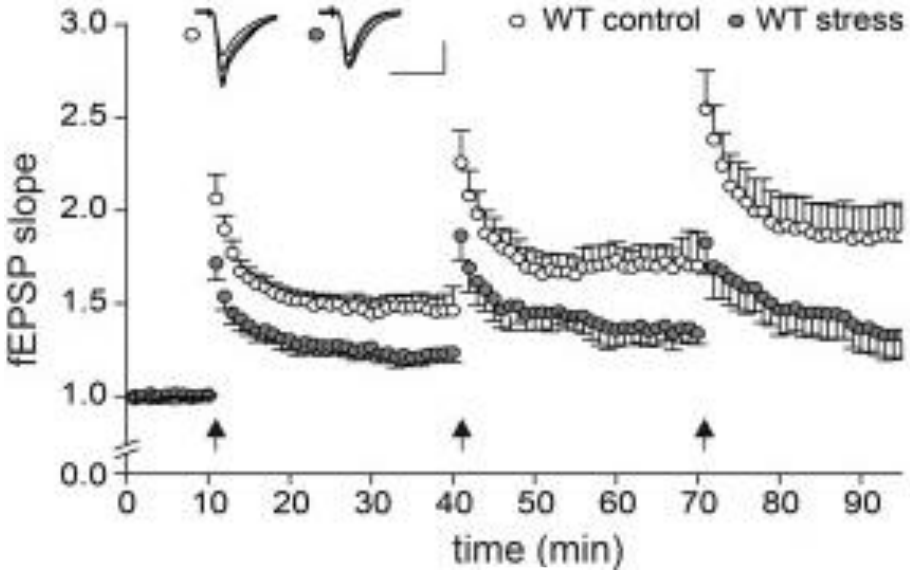


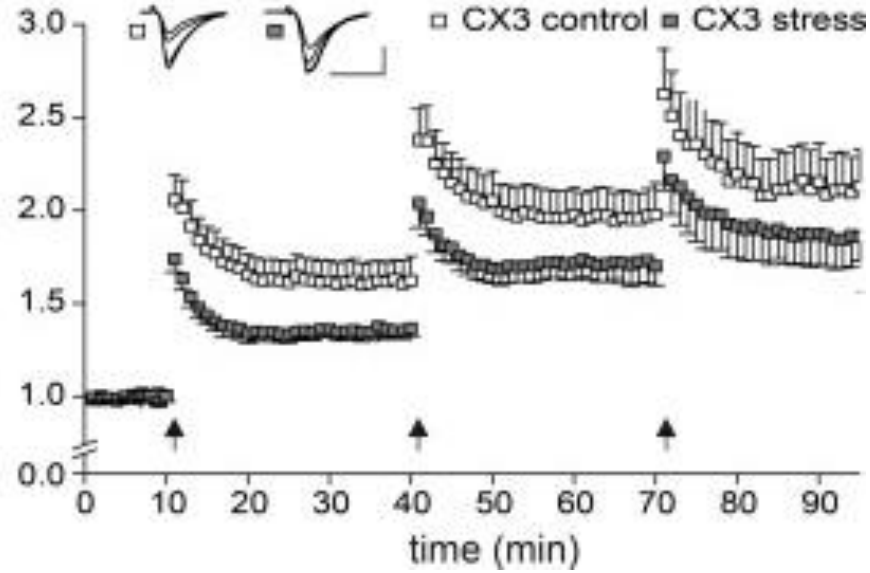
fEPSP

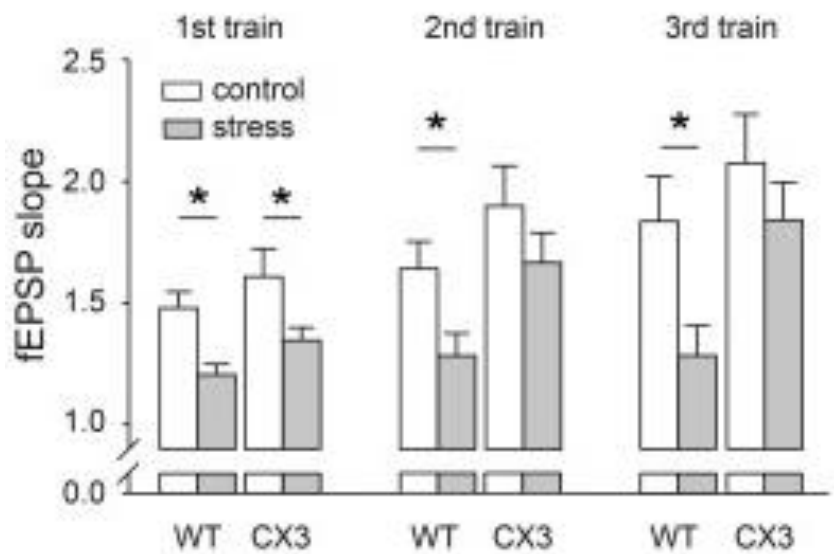
Electrical field potentials (fEPSP)

synaptic plasticity in WT and CX3 mice upon chronic unpredictable stress

Electrophysiology





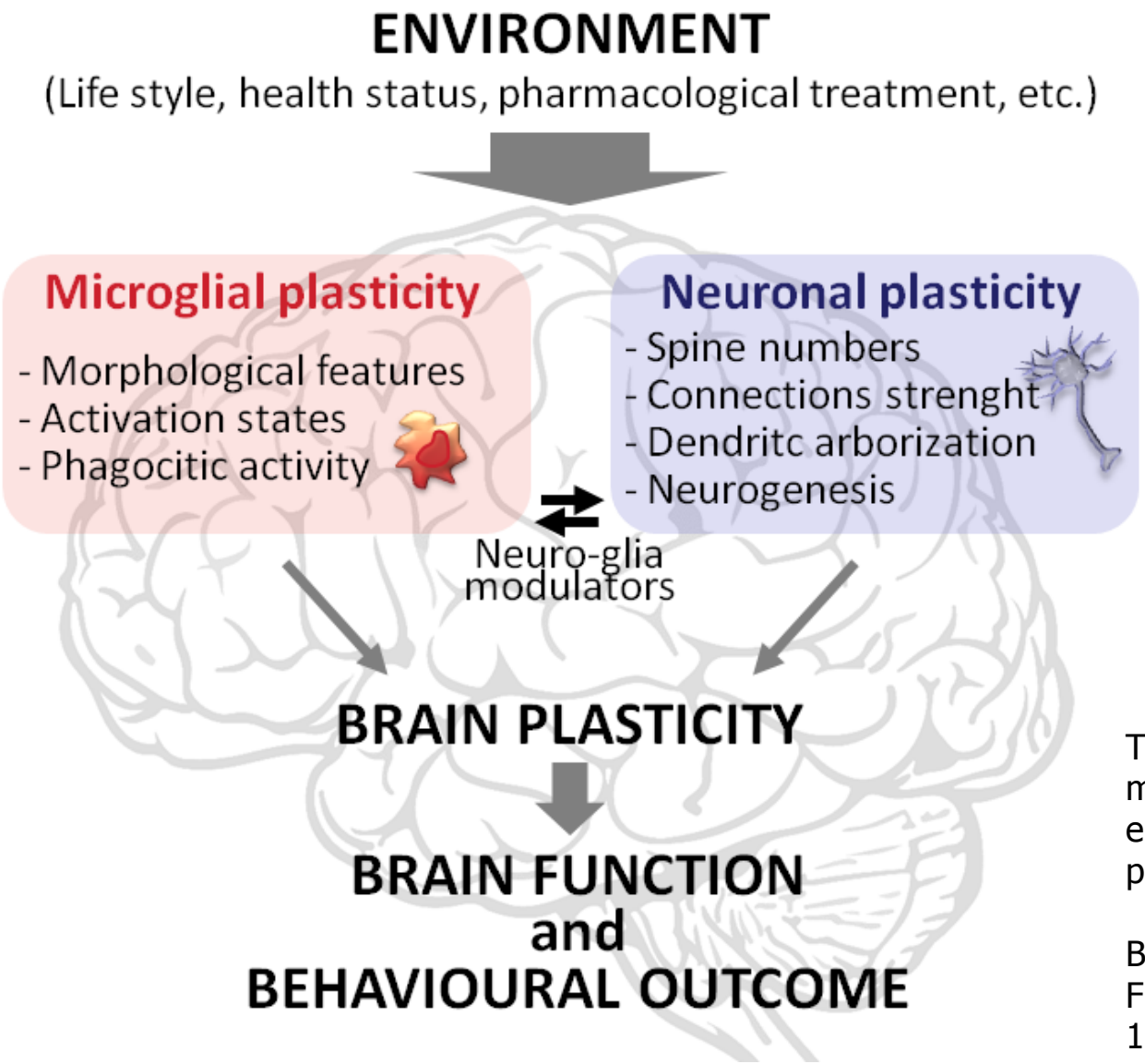


CONCLUSION 3.

-CX3CR1 (-/-) mice are less affected by chronic stress than wild type mice

The absence of FKN/ CX3CR1 signalling makes microglia less responsive to the environment (enriched and stress) consequently affecting neuronal plasticity

Microglia not only actively participates but it is integral part of brain plasticity



The role of microglia in mediating the effect of the environment in brain plasticity and behavior.

Branchi I, Alboni S, Maggi L. Front Cell Neurosci. (2014) 18;8:390

Thank you for the attention

SAPIENZA
UNIVERSITÀ DI ROMA

Physiology and Pharmacology Department

Cristina Limatola

Giampaolo Milior

Maria Scianni

Flavia Trettel

Clotilde Lauro

Francesca Pagani

Cristina DeFlorio

Fabrizio Eusebi

Collaborations

ISTITVTO SVPERIORE DI SANITÀ

Istituto Superiore di Sanità

Igor Branchi

Ivana D'Andrea

Silvia Poggini

University of Modena and Reggio Emilia

Silvia Alboni

Nicoletta Brunello

Centre de recherche du CHU de Québec

Marie-Eve Tremblay

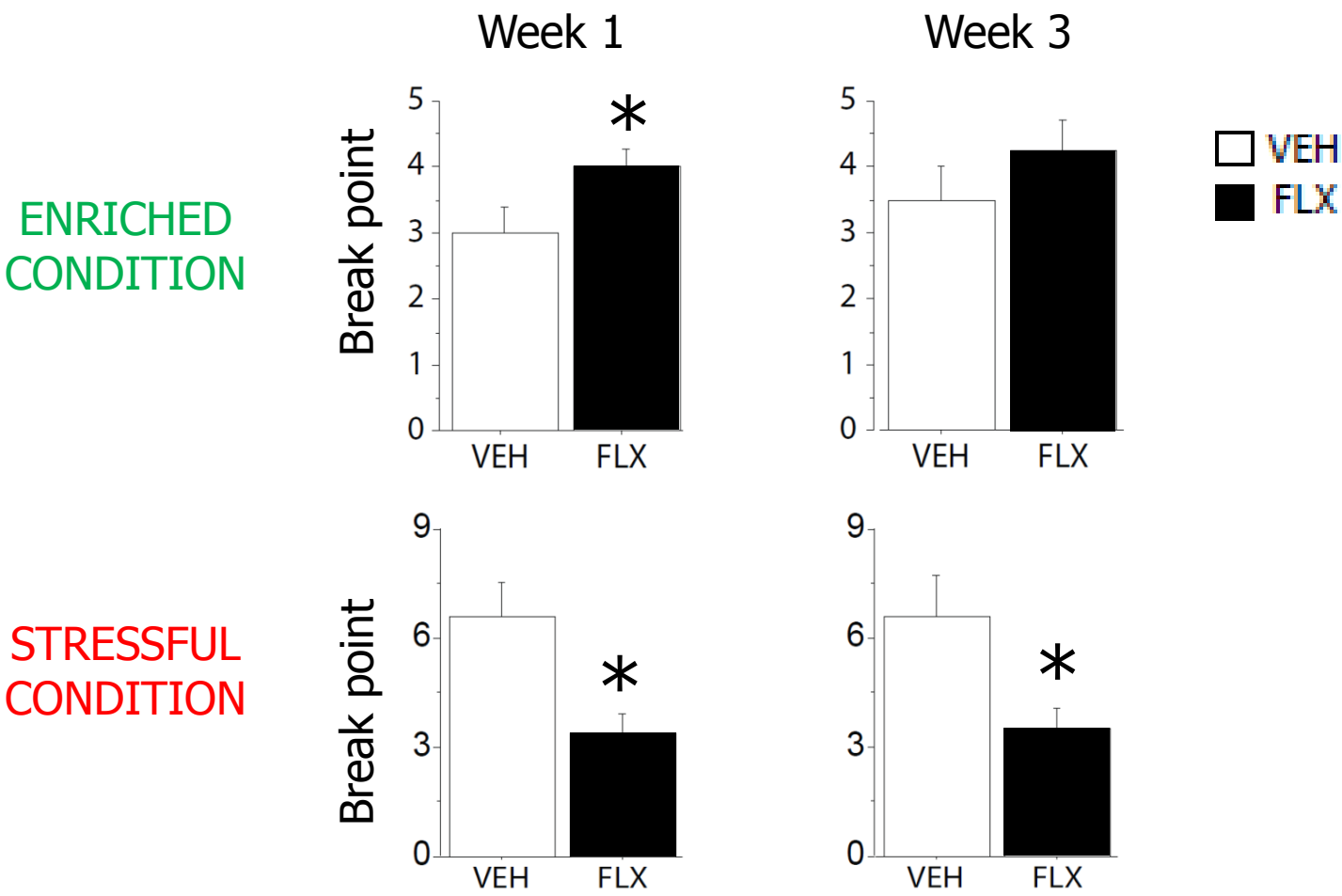
Louis Samson[b],

Kanchan Bisht

Behavioural characterization

TESTING ANHEDONIA: PROGRESSIVE RATIO

do you simply like or really want it?

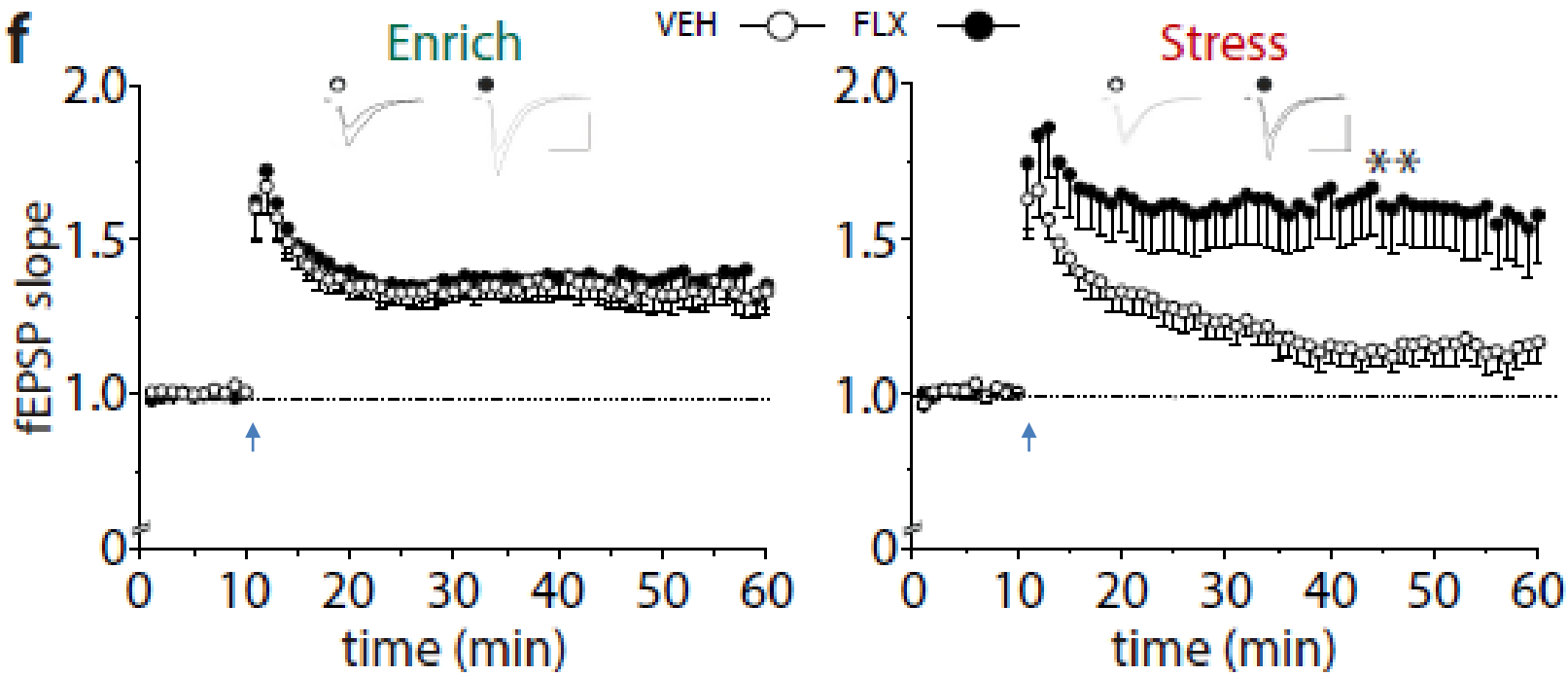


Progressive Ratio reinforcement schedules utilize a multiplicative increase in the number of responses (i.e. nosepokes) required to dispense a unit of reinforcer (i.e. saccharin)

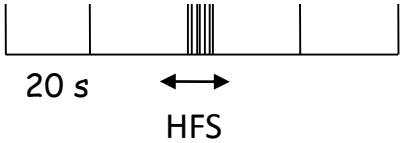
Alboni et al. Molecular Psychiatry (2015).

Electrophysiology

Long term plasticity (LTP) is affeted by the fluoxetine in a environmental dependent manner



Protocol of LTP induction



1 x100 Hz train
HFS

Alboni et al. Molecular Psychiatry (2015)

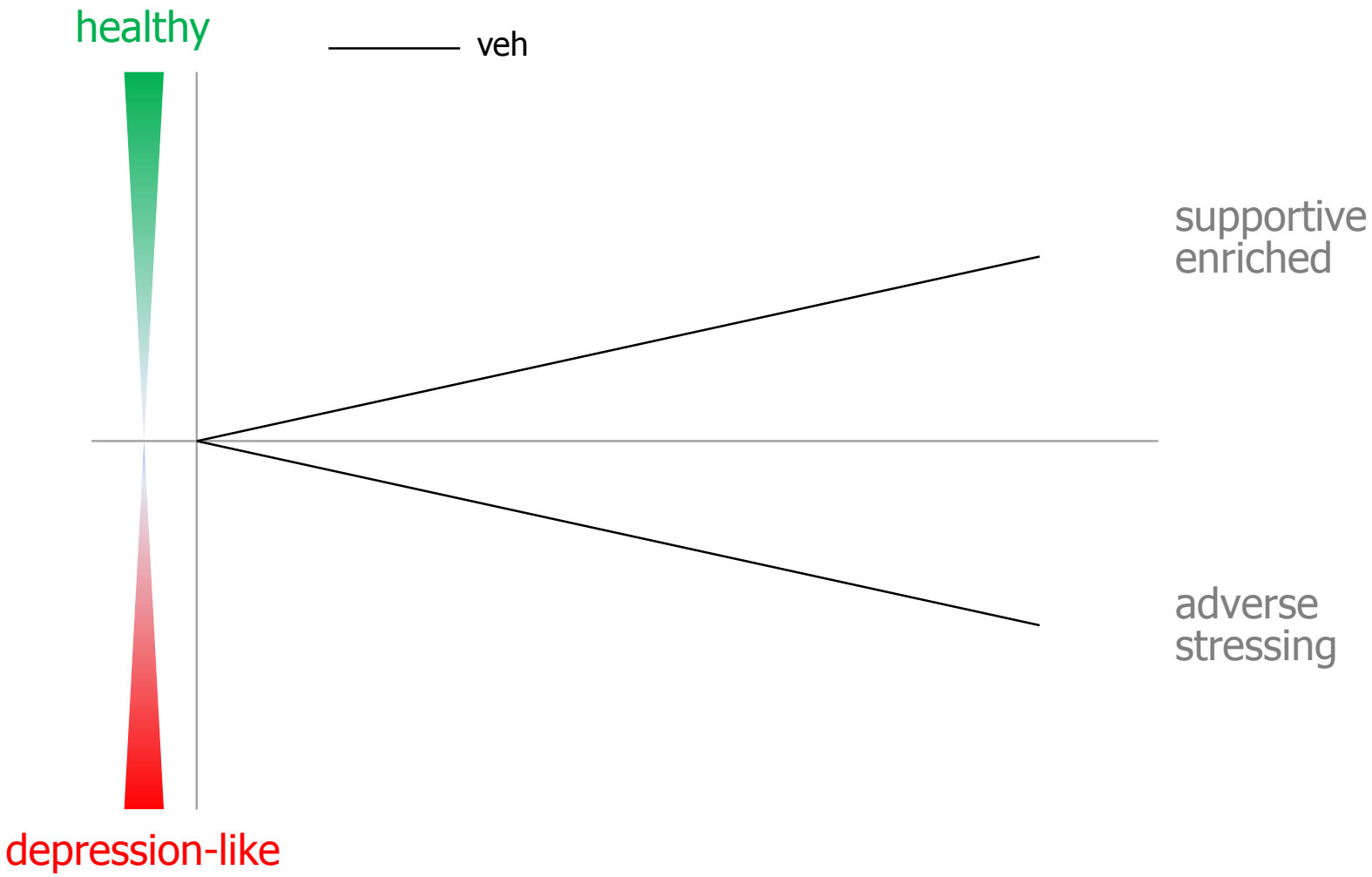
- fine

testing and validating the

undirected susceptibility to change hypothesis in mice

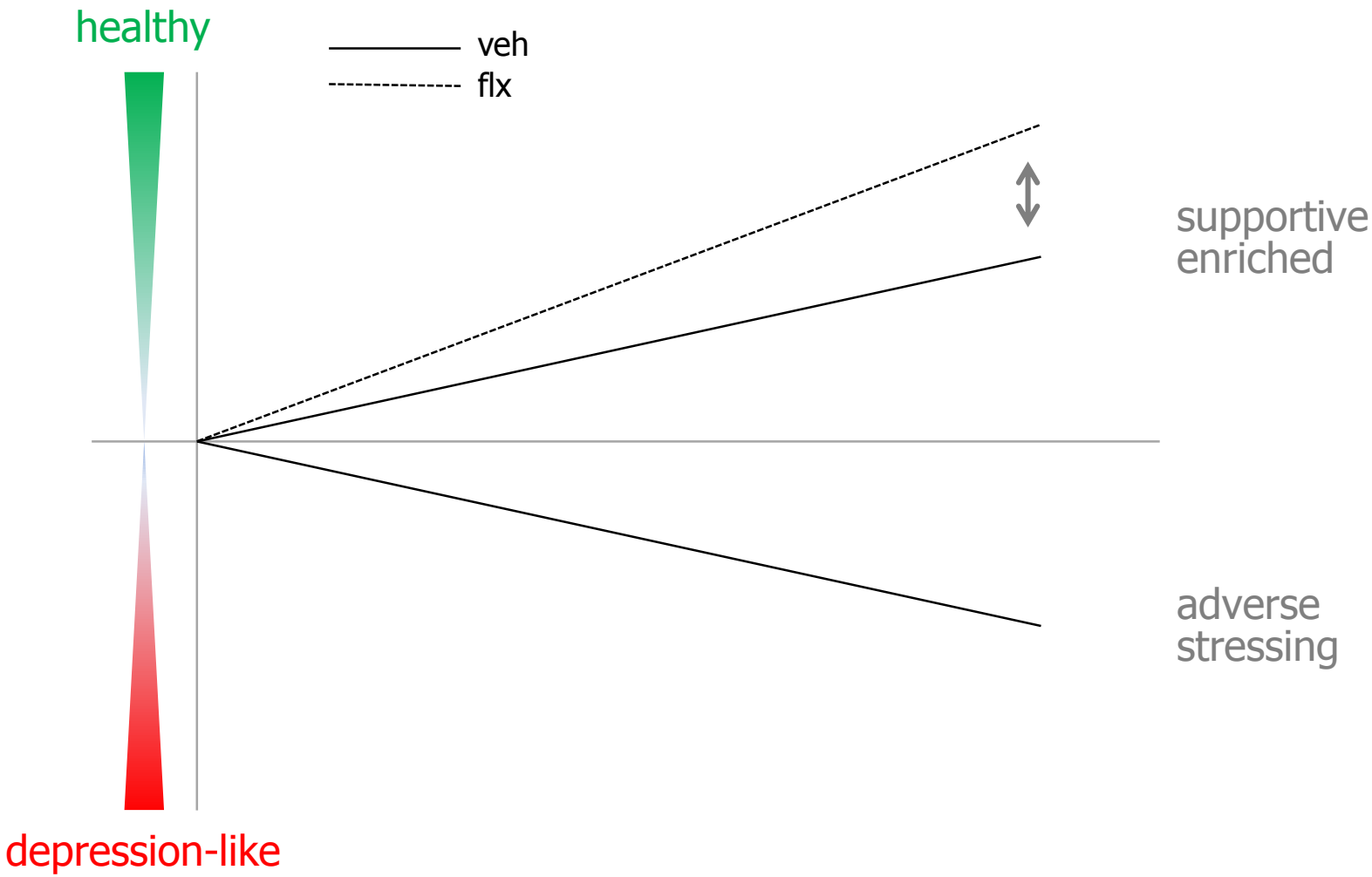
testing and validating the

undirected susceptibility to change hypothesis in mice



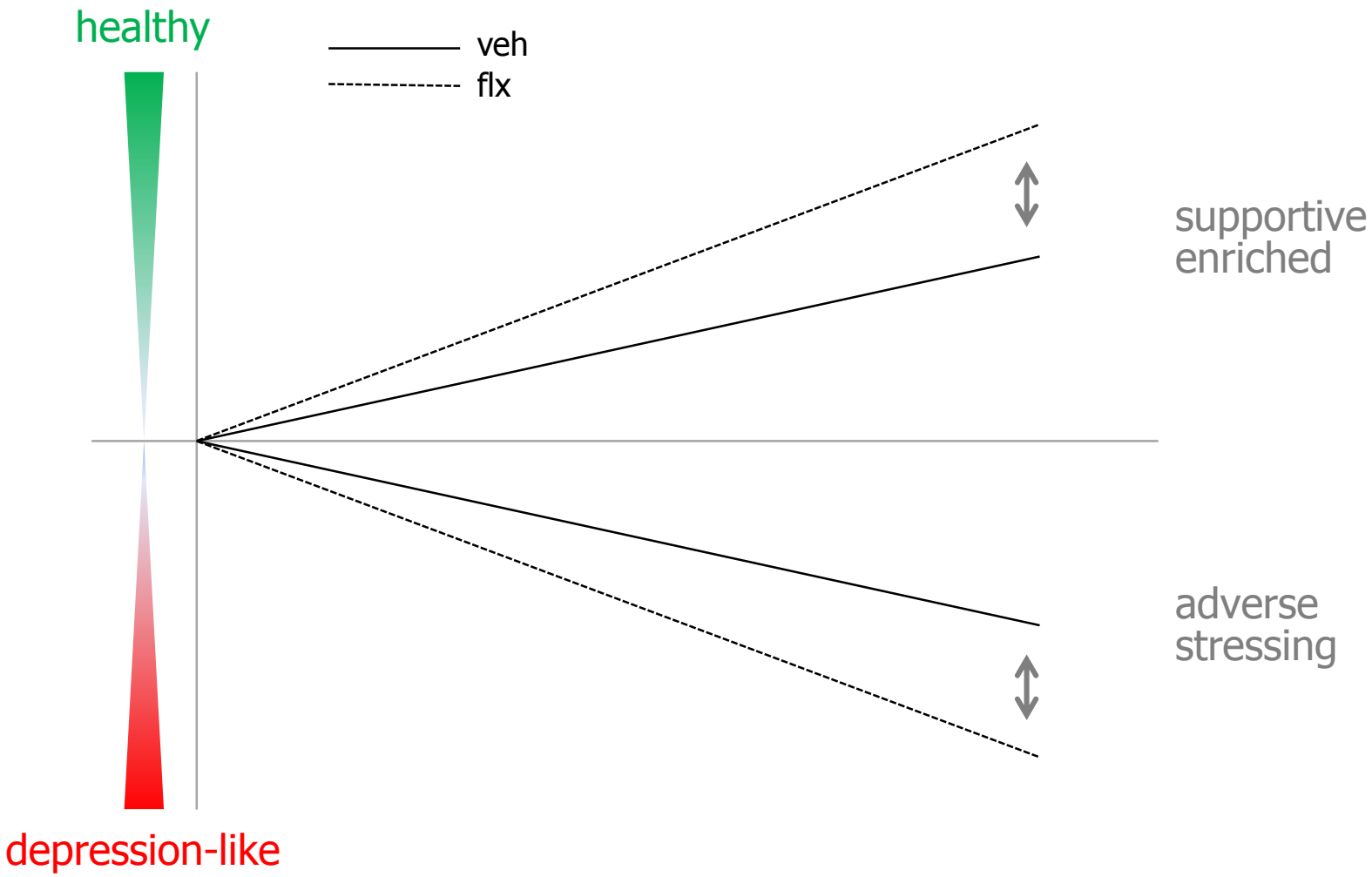
testing and validating the

undirected susceptibility to change hypothesis in mice



testing and validating the

undirected susceptibility to change hypothesis in mice



Enriched condition (3 weeks)

$CX_3CR1^{GFP/GFP}$ mice

wt mice

Behaviour

Electrophysioloigy

Immunoistochemistry

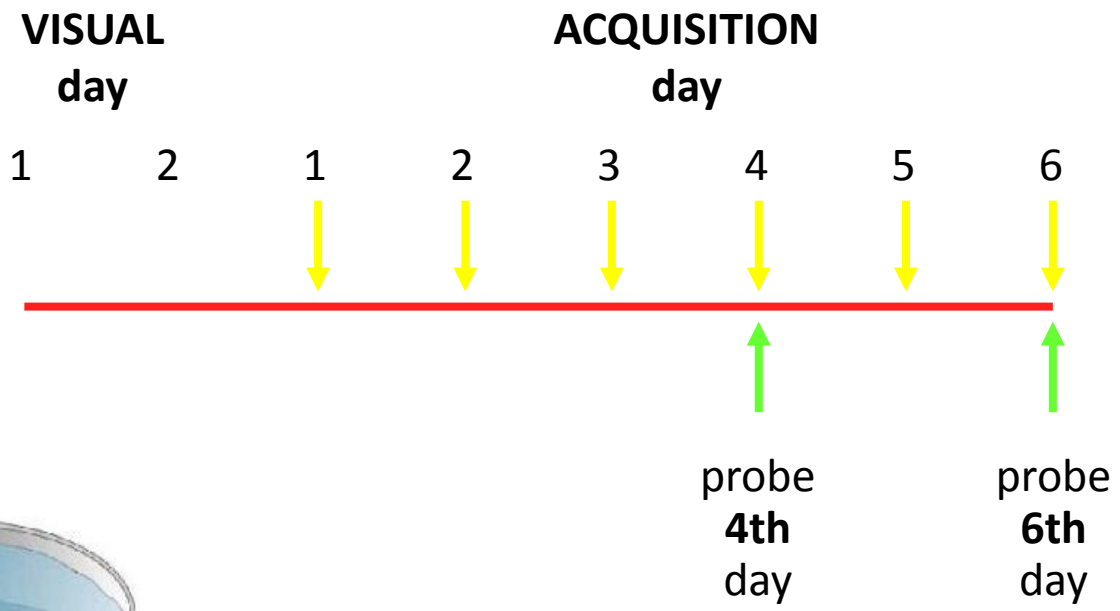
Behaviour

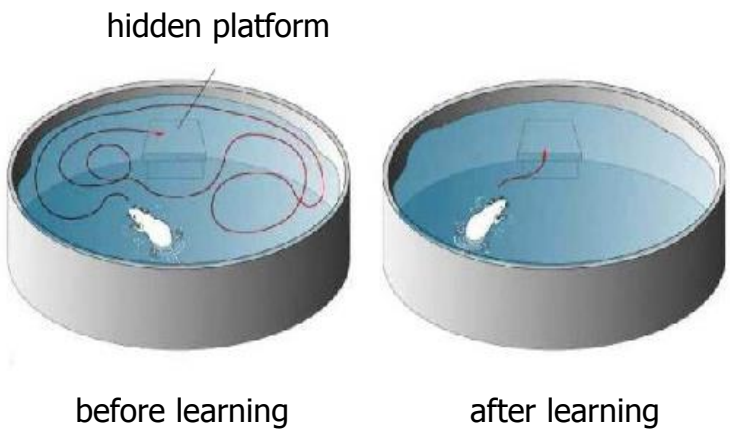
WATER MAZE TEST

1- visual

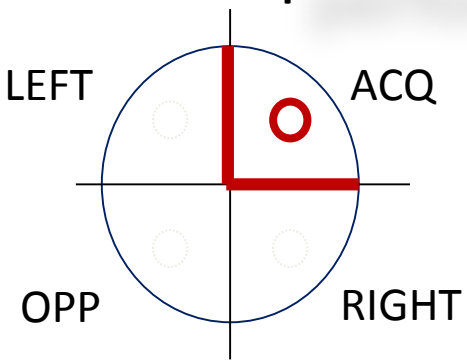
2 - acquisition

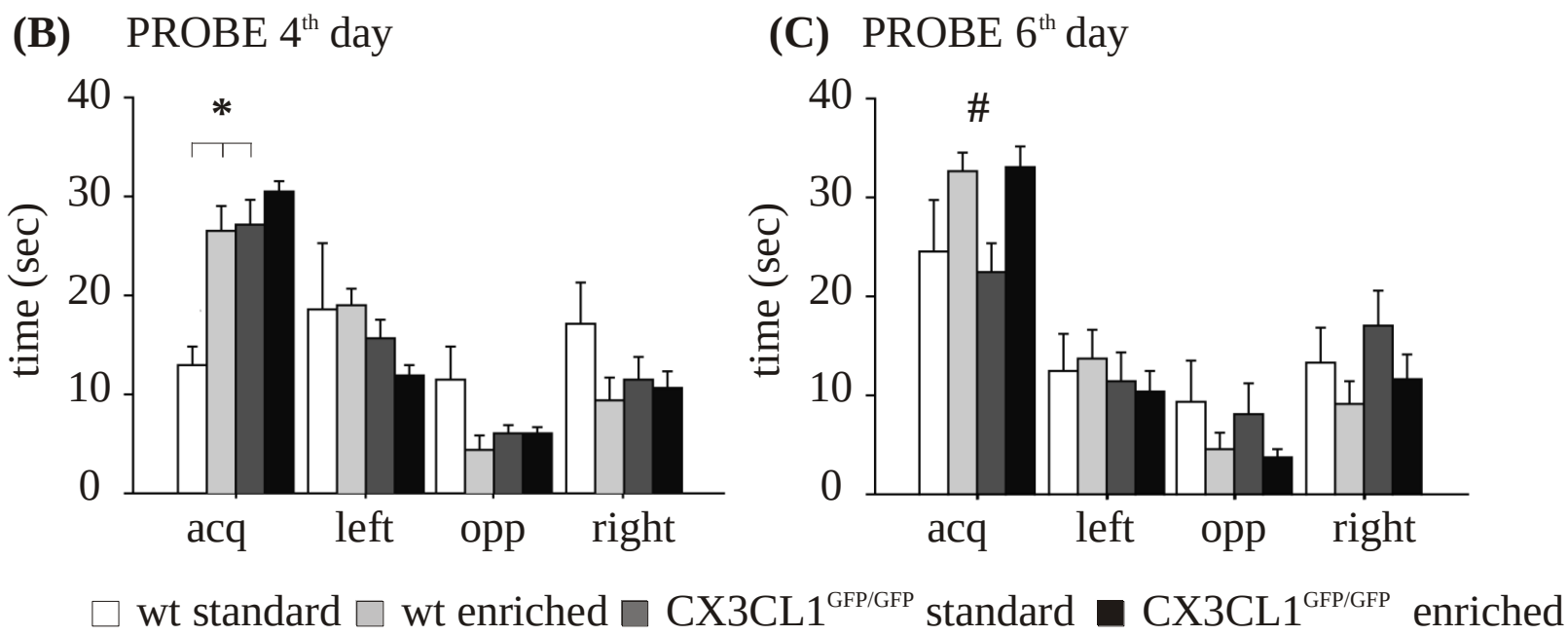
3 - probe





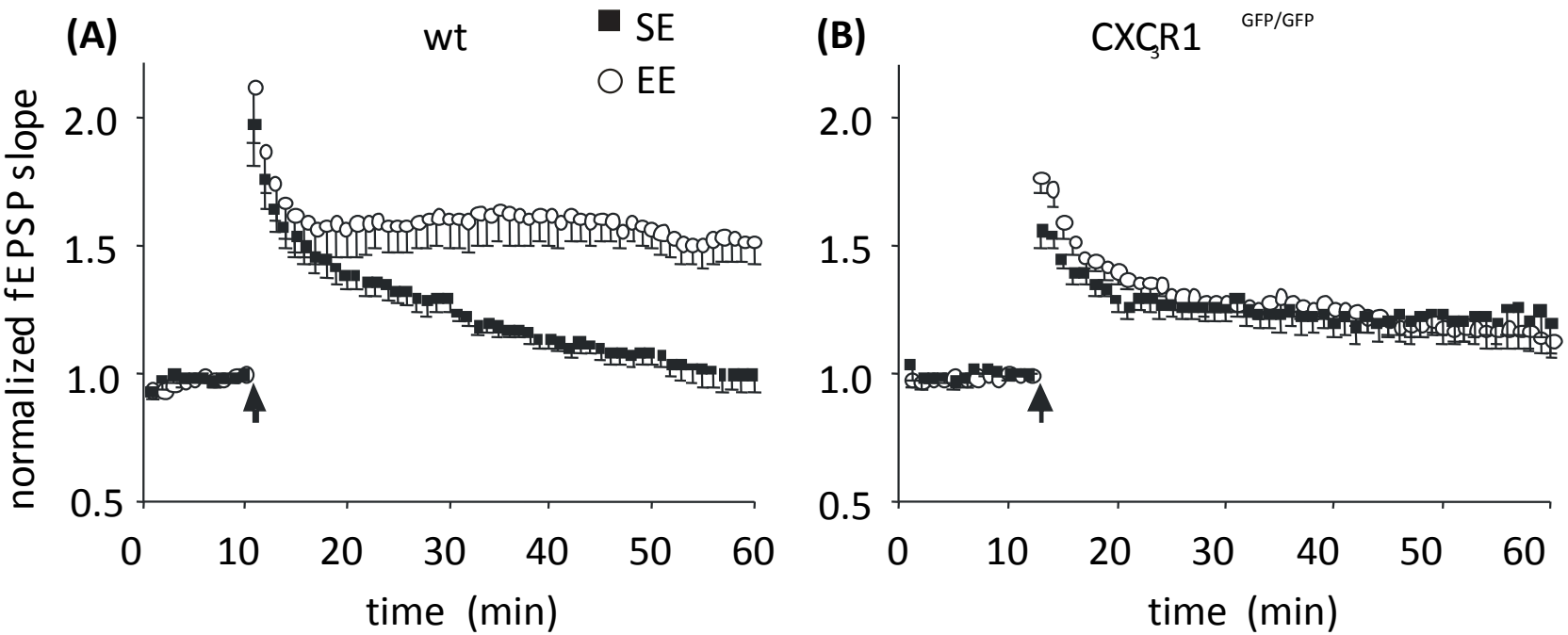
$CX_3CR1^{GFP/GFP}$ mice learned faster than *wt* mice and their performance was not affected by the EE





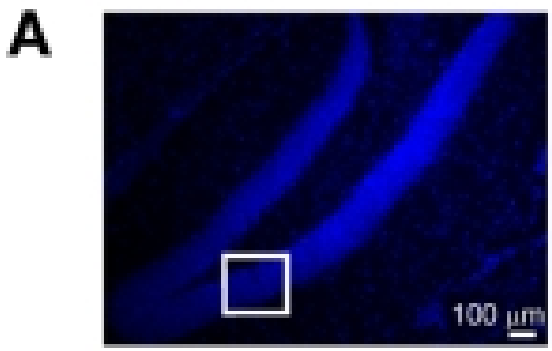
Electrophysiology

The absence of CX_3CR1 increases hippocampal LTP but abolish the effect of EE



EE enhances neurogenesis in the DG of both wt and $CX_3CR1^{GFP/GFP}$ mice

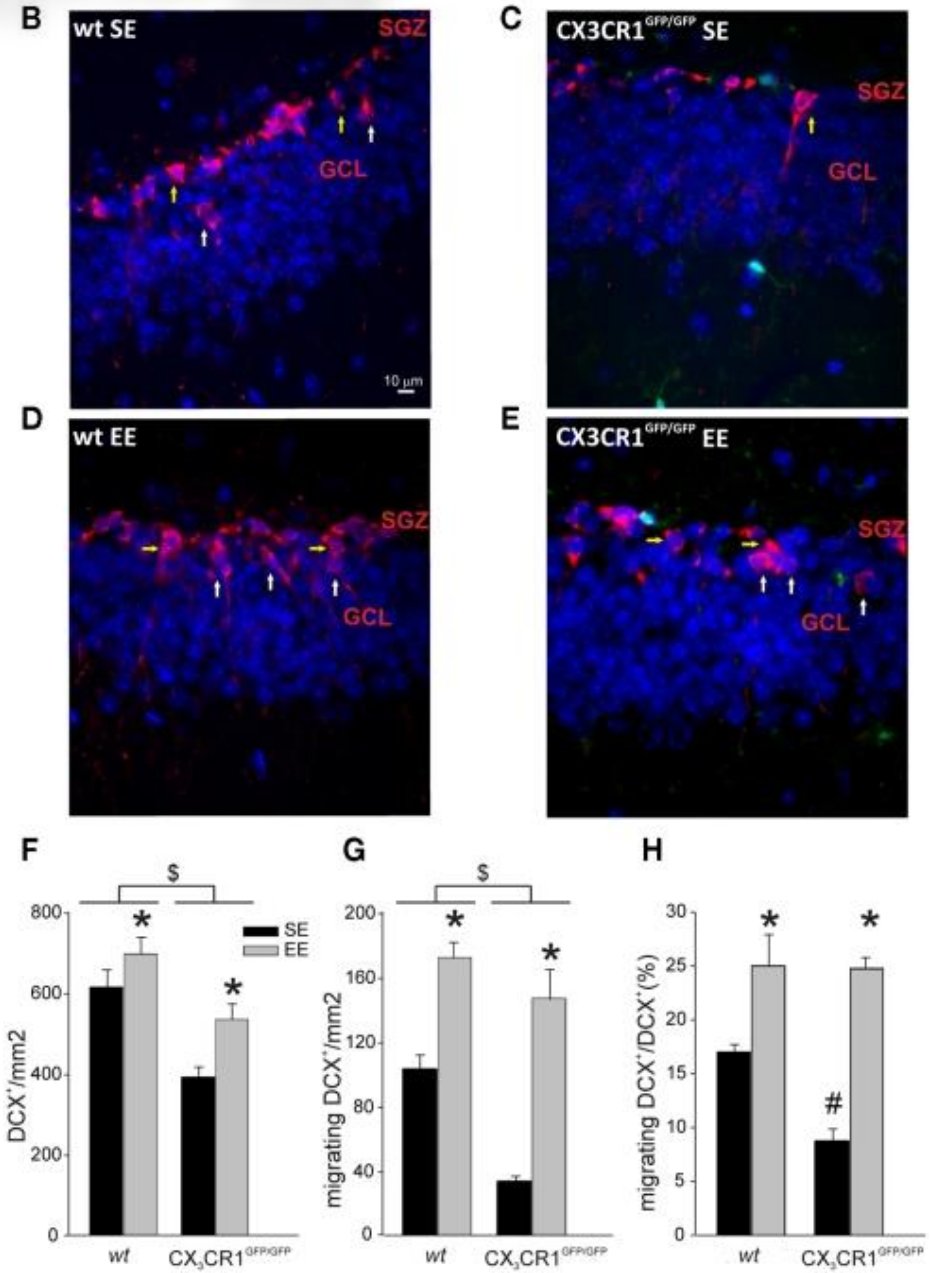
Immunoistochemistry



Blu-Hoechst

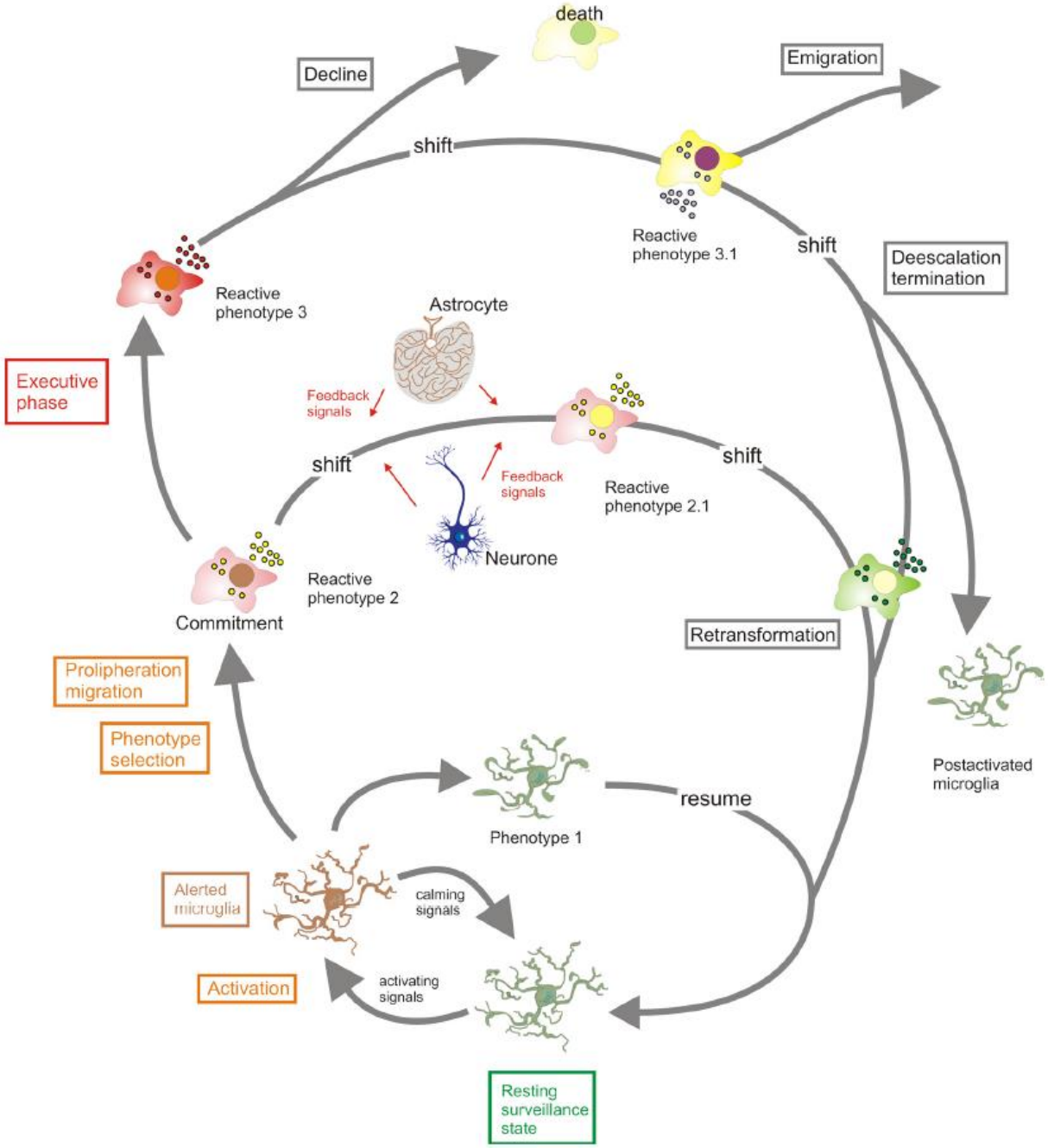
Green-GFP, microglia

red-DCX



Microglial phenotypes

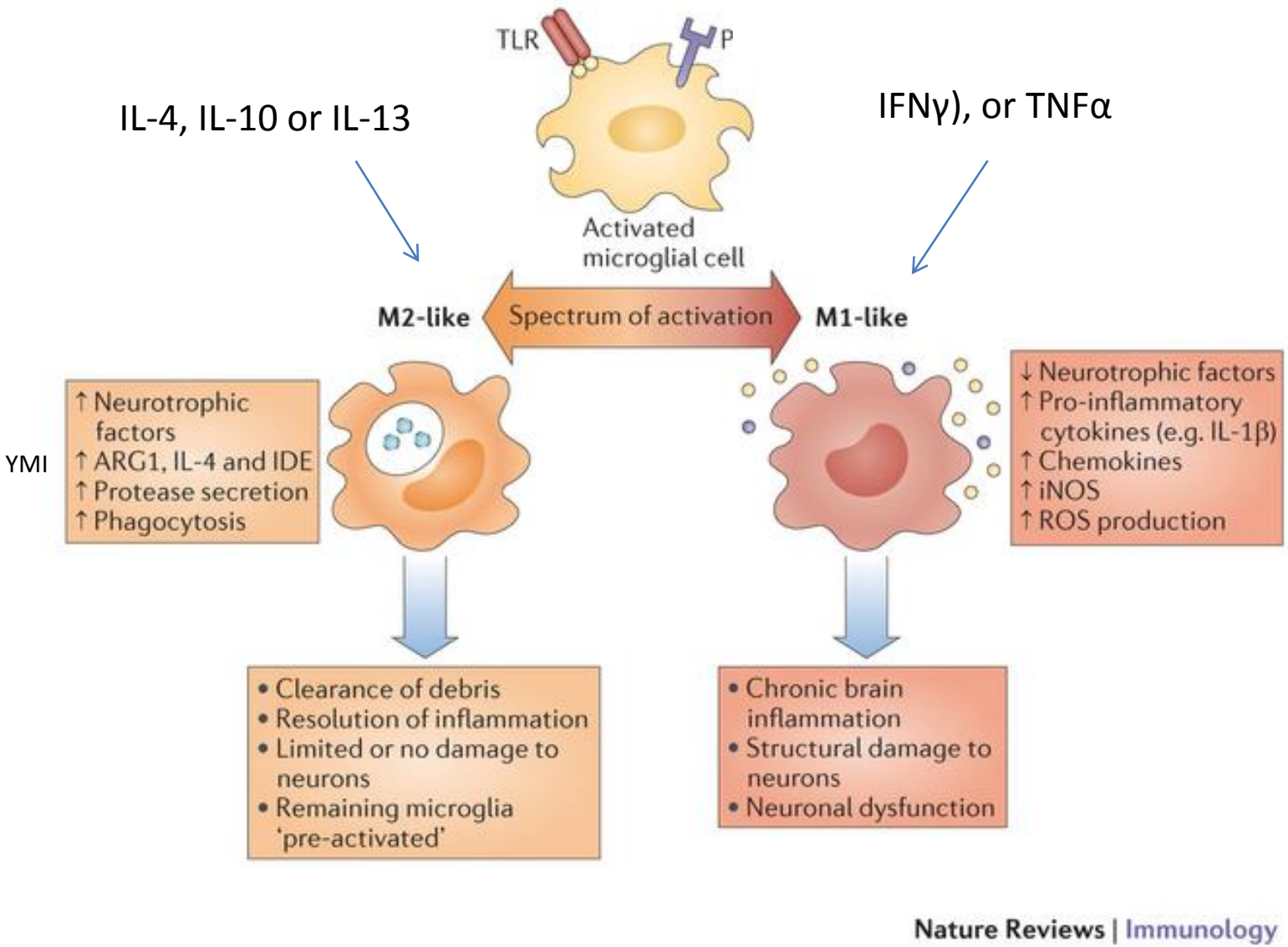
- The concept that activation of microglia occurs along a linear range, has been discarded



Uwe-Karsten Hanisch[1] & Helmut Kettenmann[2]

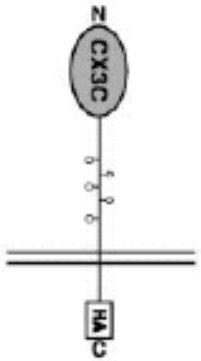
NATURE NEUROSCIENCE VOLUME 10 | NUMBER 11 | NOVEMBER 2007

Microglia Phenotypes



Microglia likely behave similarly to macrophages

Fractalkine/CX_3CL1



10488 • The Journal of Neuroscience, October 11, 2006 • 26(41):10488–10498

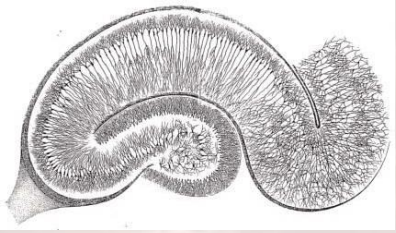
Development/Plasticity/Repair

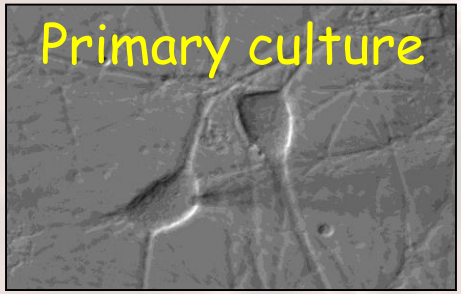
Chemokine Fractalkine/CX_3CL1 Negatively Modulates Active Glutamatergic Synapses in Rat Hippocampal Neurons

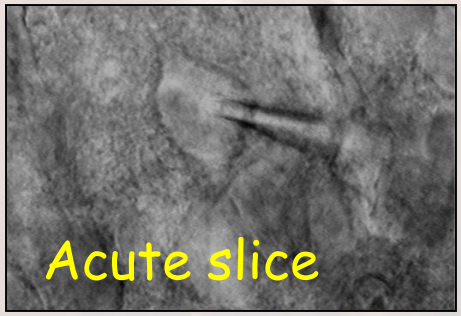
Davide Ragozzino,[1,2]* Silvia Di Angelantonio,[1]* Flavia Trettel,[1] Cristina Bertollini,[1] Laura Maggi,[1] Cornelius Gross,[3] Israel F. Charo,[4] Cristina Limatola,[1,2] and Fabrizio Eusebi[1,2]

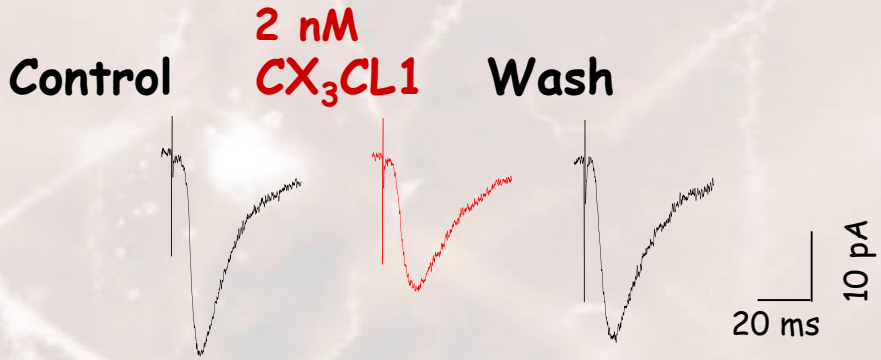
[1]Istituto Pasteur-Fondazione Cenci Bolognetti and Dipartimento di Fisiologia Umana e Farmacologia, Università La Sapienza, Centro di Eccellenza BEMM, 00185 Roma, Italy, [2]Neuromed, 86077 Pozzilli, Italy, [3]European Molecular Biology Laboratory, Mouse Biology Unit, 00016 Monterotondo, Italy, and [4]Gladstone Institute of Cardiovascular Disease, San Francisco, California 94141

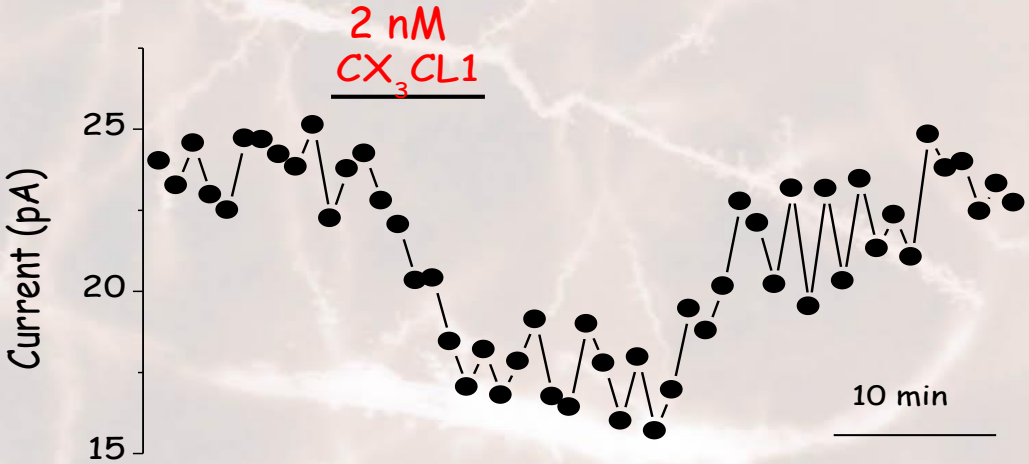
CX_3CL1 reduces glutamatergic synaptic currents



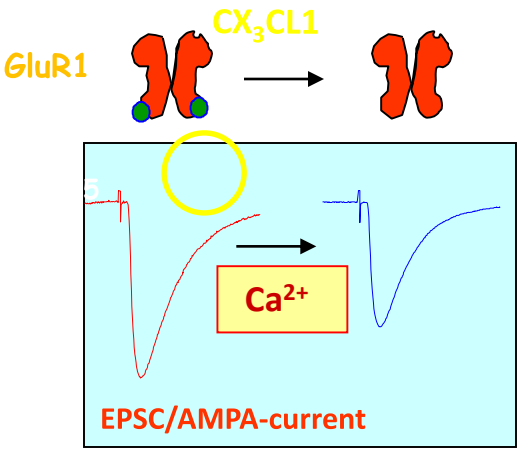


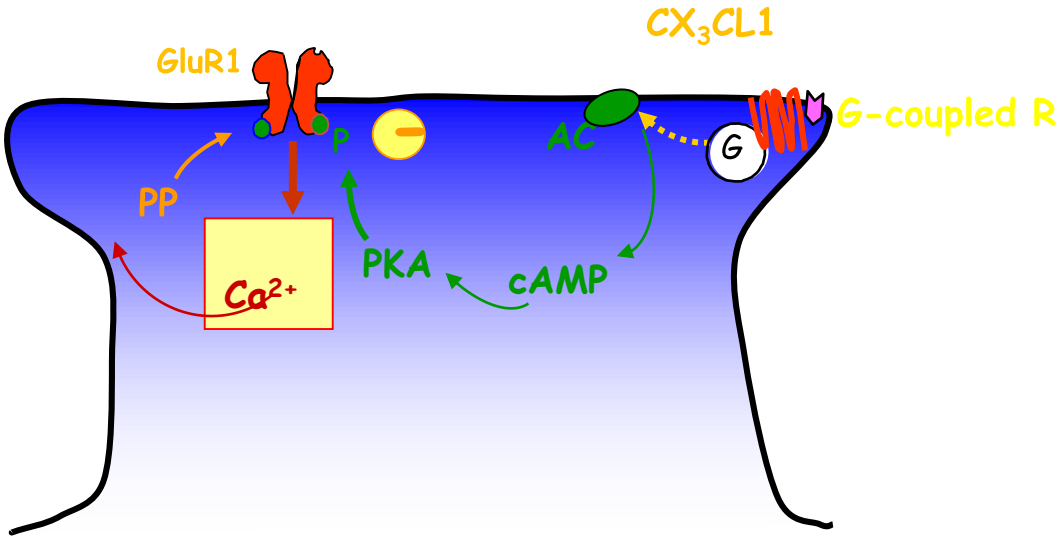




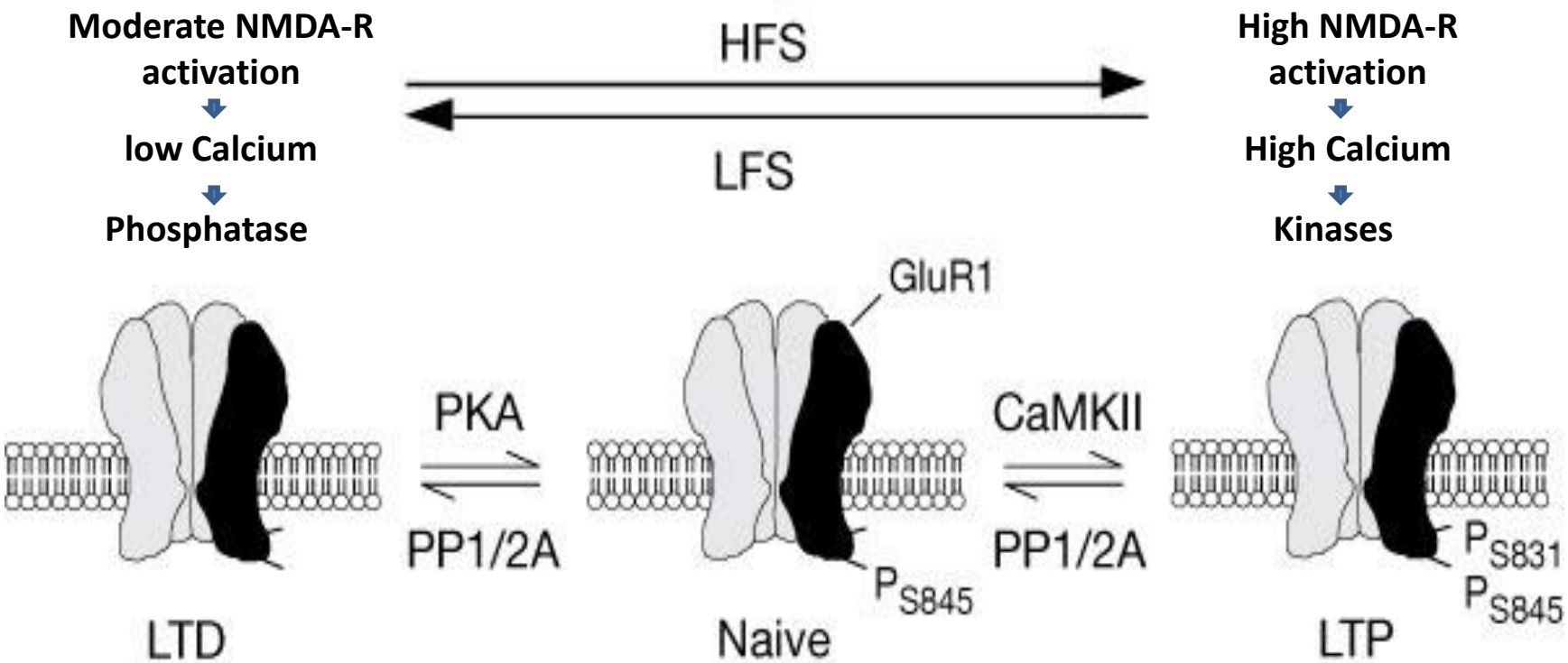


Our model

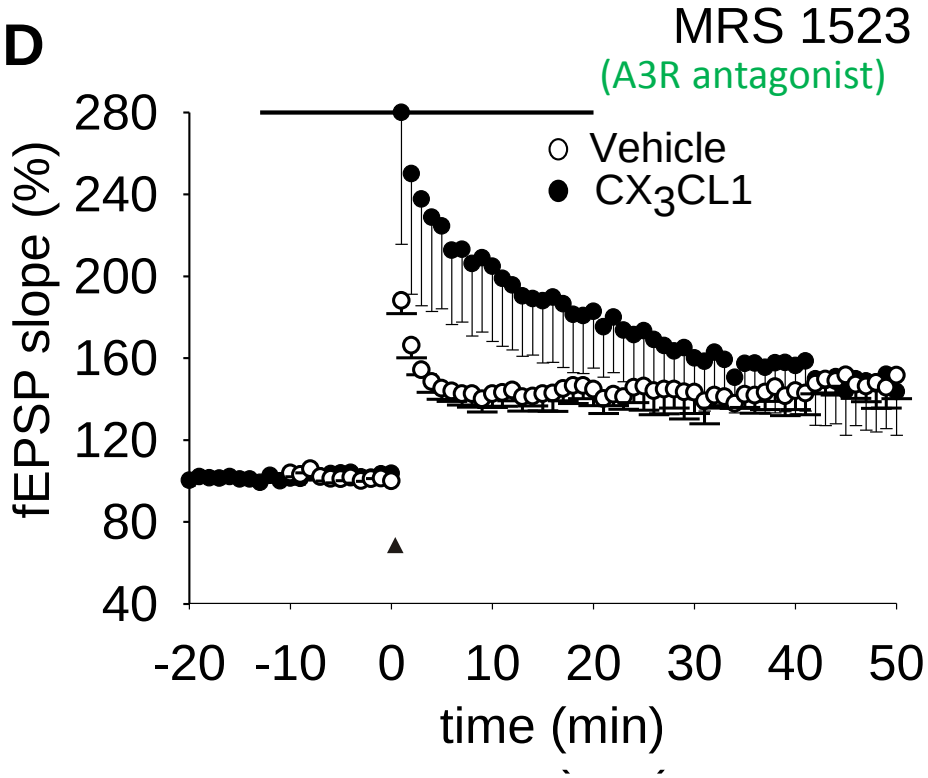

GluR1
CX3CL1
Ca2+
EPSC/AMPA-current


GluR1
CX3CL1
G-coupled R
P
AC
G
PP
Ca2+
PKA
cAMP

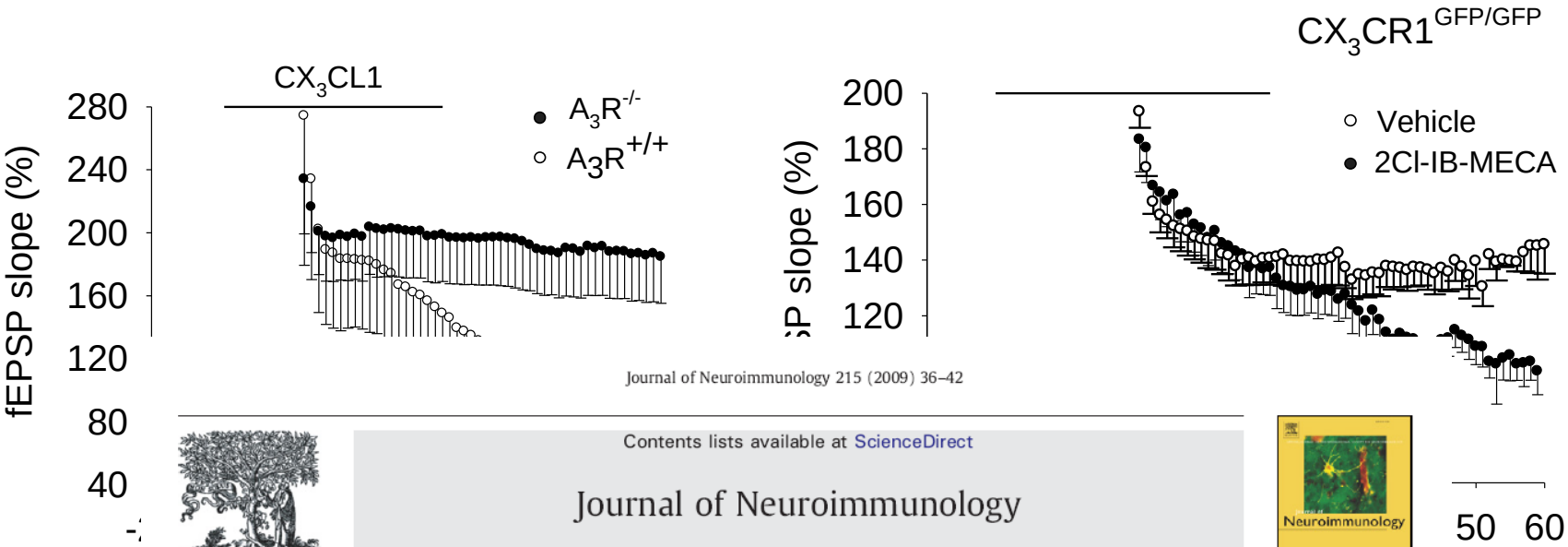
Synaptic plasticity in the hippocampus requires a balance of protein kinase and phosphatase activities



Adenosine receptors are involved in CX_3CL1 action



CX_3CL1-induced effect on LTP are mediated through A_3R



Journal of Neuroimmunology 215 (2009) 36–42

Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

LTP impairment by fractalkine/CX_3CL1 in mouse hippocampus is mediated through the activity of adenosine receptor type 3 (A_3R)

Laura Maggi [a], Flavia Trettel [a], Maria Scianni [a], Cristina Bertollini [a], Fabrizio Eusebi [a,b], Bertil B. Fredholm [c], Cristina Limatola [a,b,*]

[a] Istituto Pasteur-Fondazione Cenci Bolognetti & Dipartimento di Fisiologia e Farmacologia, Centro di Eccellenza BEMM, Università di Roma "Sapienza", Piazzale A. Moro 5, I00185 Roma, Italy
[b] Neuromed I.R.C.C.S., Via Atinese 18, I-86077 Pozzilli, Italy
[c] Department of Physiology and Pharmacology, Karolinska Institutet, S-171 77 Stockolm, Sweden.

Mice lacking CX3CR1 present:

These evidences suggest that microglia-driven CX_3CL1/CX_3CR1 signaling play a role in plasticity processes and it is involved in hippocampal plasticity enhancement observed after environmental stimulation

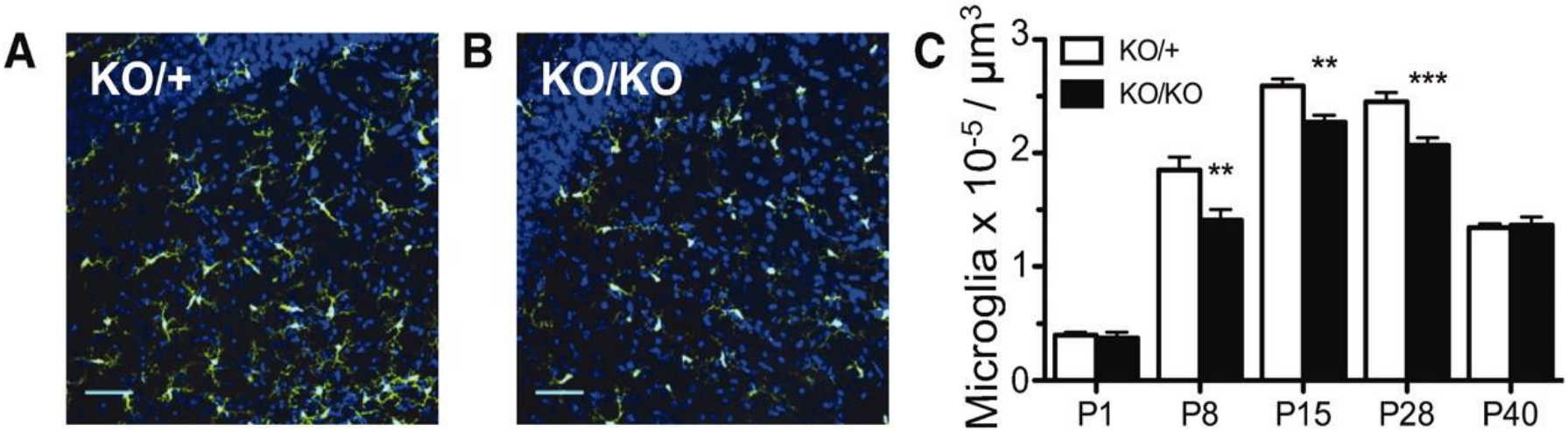
How microglia cells can influence plasticity processes?

Working hypothesis

development

adult

1. Role of CX_3CL1/CX_3CR1 signaling during development



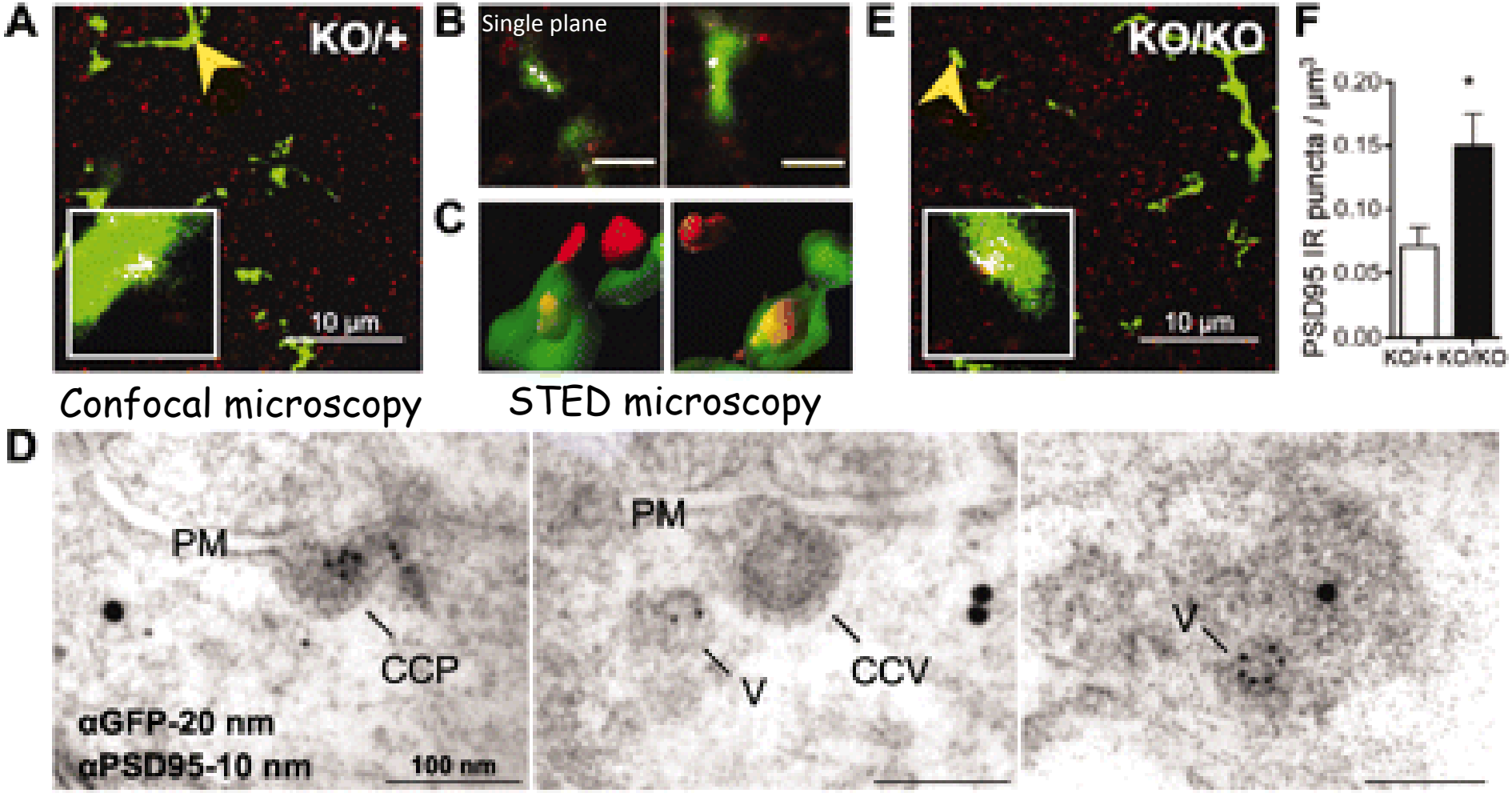
Science
AAAS

Synaptic Pruning by Microglia Is Necessary for Normal Brain Development
Rosa C. Paolicelli, *et al.*
Science **333**, 1456 (2011);
DOI: 10.1126/science.1202529

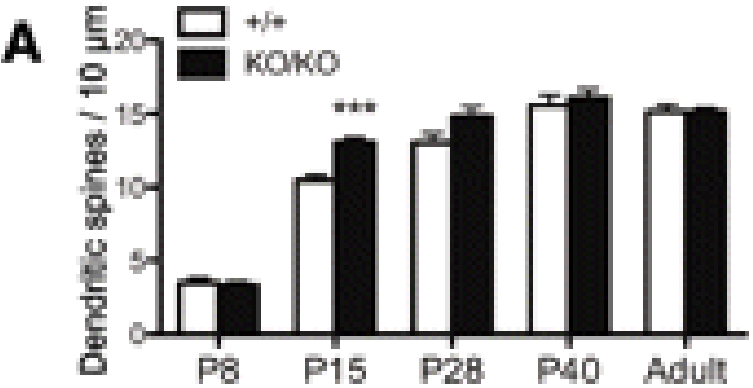
Engulfment of synaptic material by microglia

PSD95 red (

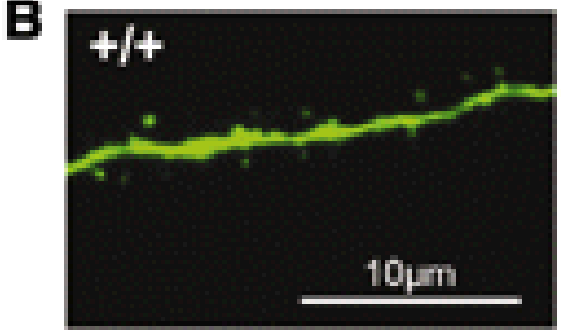
CA1 stratum radiatum, P15



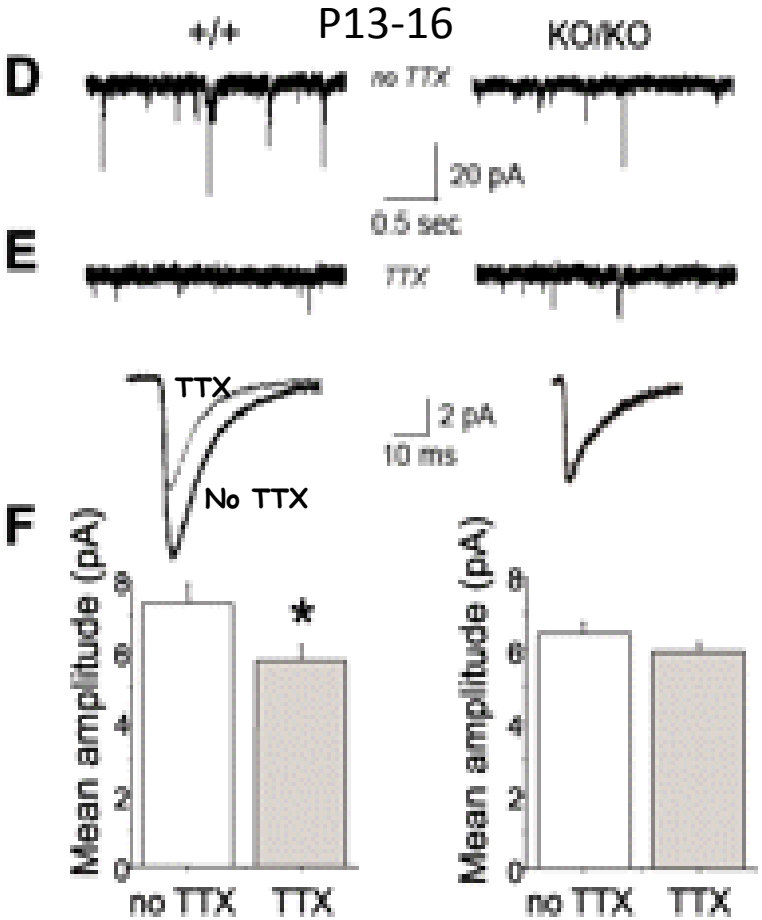
Increased dendritic spines in *Cx3cr1*^{KO} mice

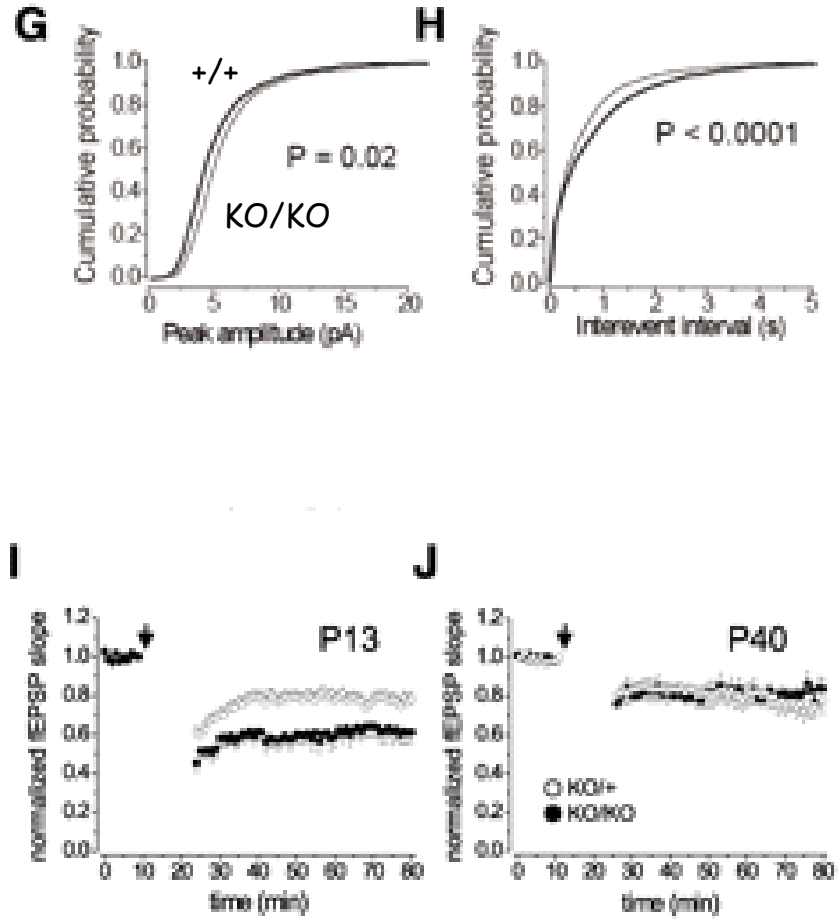


apical secondary dendrites



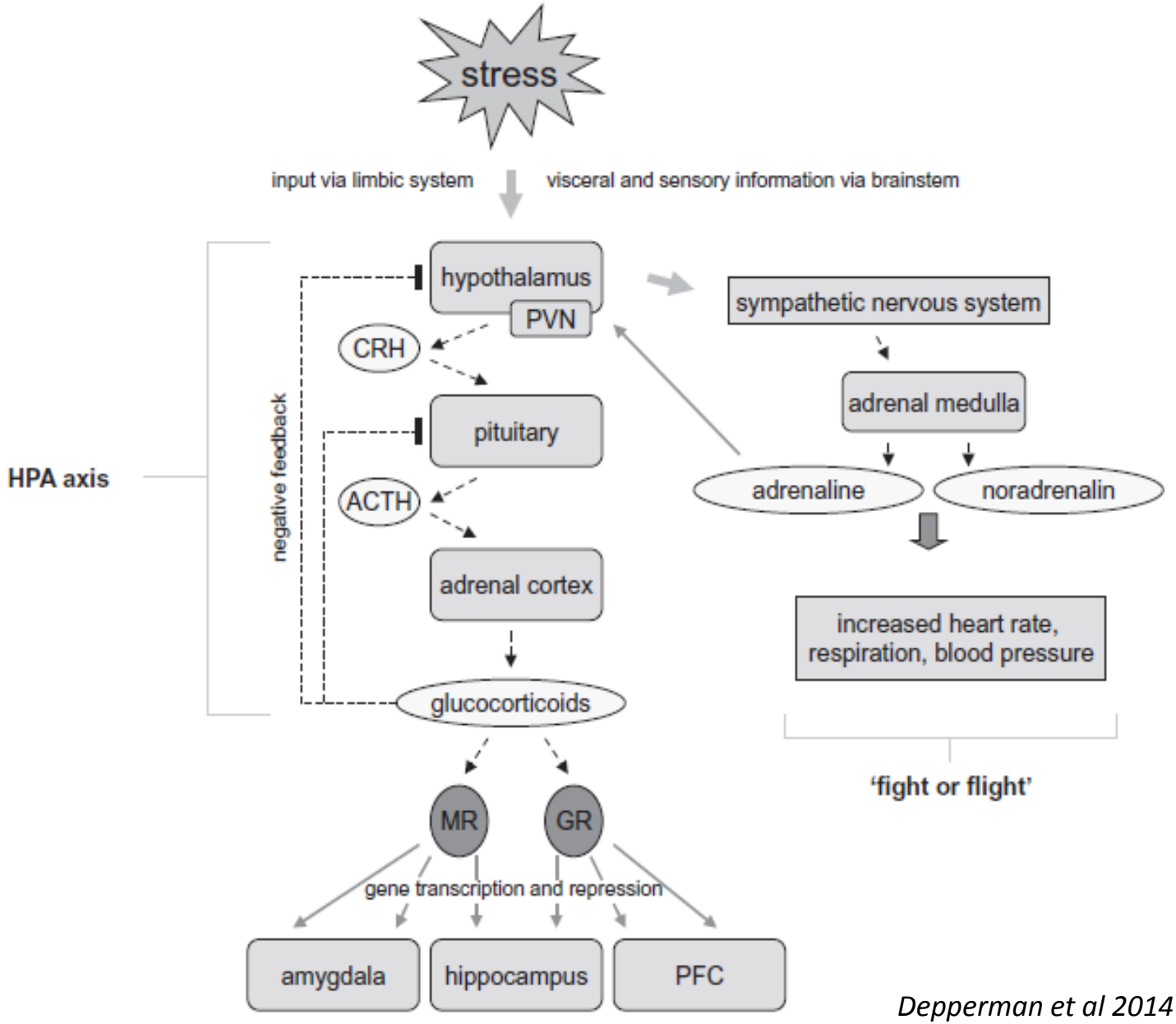
Increased immature synapses in *Cx3cr1*^{KO} mice





3. Conclusions

Stress response

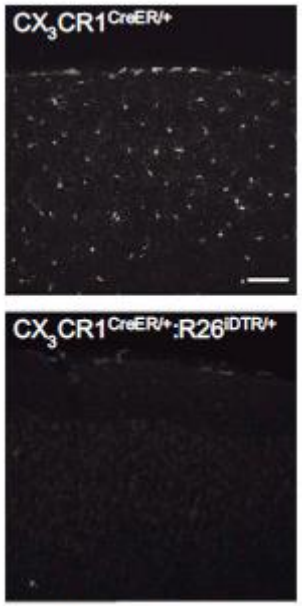


Depperman et al 2014

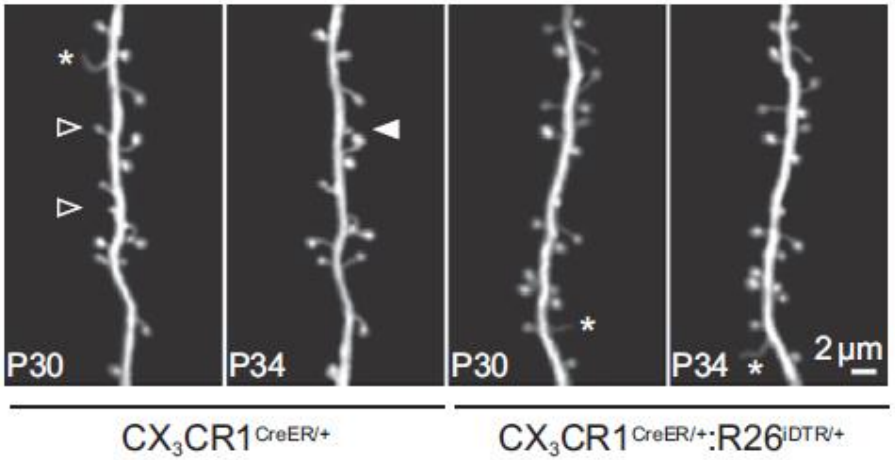
Microglia in the adult brain: plasticity

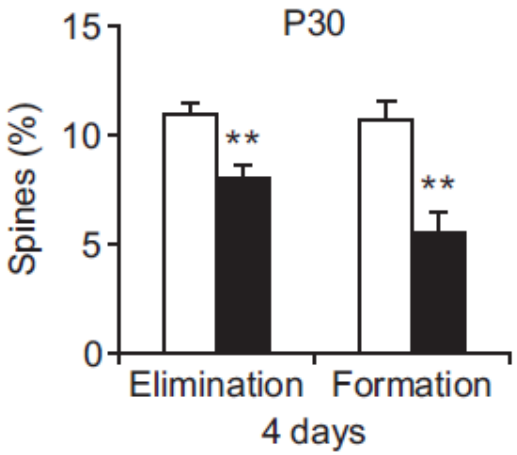
Mice genetically modified in order to deplete microglia in the adult

Microglia-depleted mice:



Motor Cortex





- showed deficits in hippocampal-dependent learning and motor learning.
- had reductions in the elimination and the formation of spines induced by motor learning

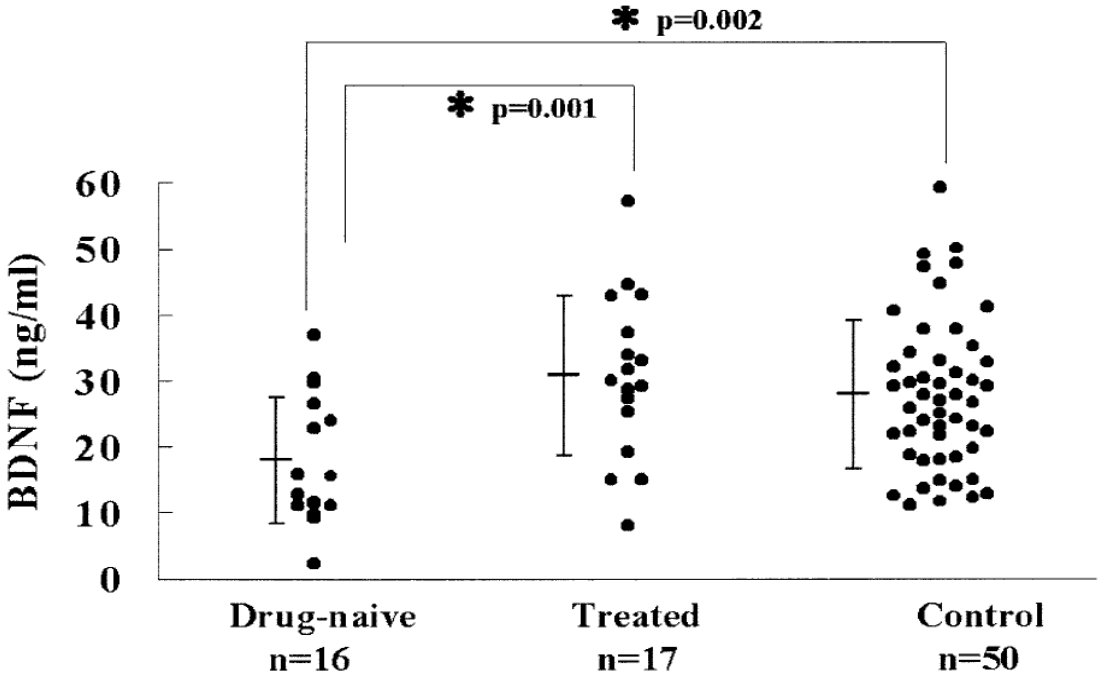
Microglia Promote Learning-Dependent Synapse Formation through Brain-Derived Neurotrophic Factor

Christopher N. Parkhurst,[1] Guang Yang,[2] Ipe Ninan,[3] Jeffrey N. Savas,[4] John R. Yates III,[4] Juan J. Lafaille,[5] Barbara L. Hempstead,[6] Dan R. Littman,[5,7] and Wen-Biao Gan[1,*]

Cell 155, 1596–1609, 2013

Brain Derived Neurotrophic Factor

A decrease of BDNF levels is associated with depression



Shimizu et al. 2003

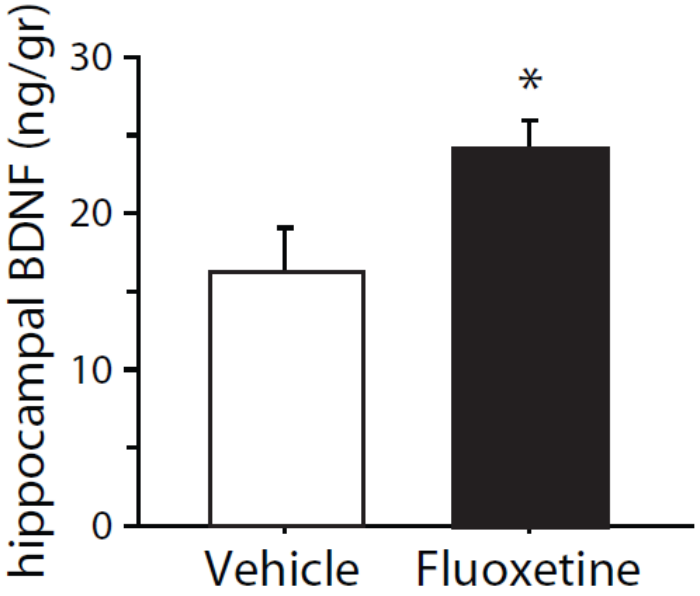
Scatter plot of serum brain-derived neurotrophic factor (BDNF) concentrations in antidepressant-naive, -treated, and control groups. Serum levels of BDNF in the drug-naive group (*n* = 16; 17.6 ± 9.6 ng/mL; mean ± SD) were significantly decreased compared with those of the treated group (*n* = 17; 30.6 ± 12.3 ng/mL; mean ± SD; *p* _ .001) or the control group (*n* = 50; 27.7 ± 11.4 ng/mL; mean ± SD; *p* < .002).

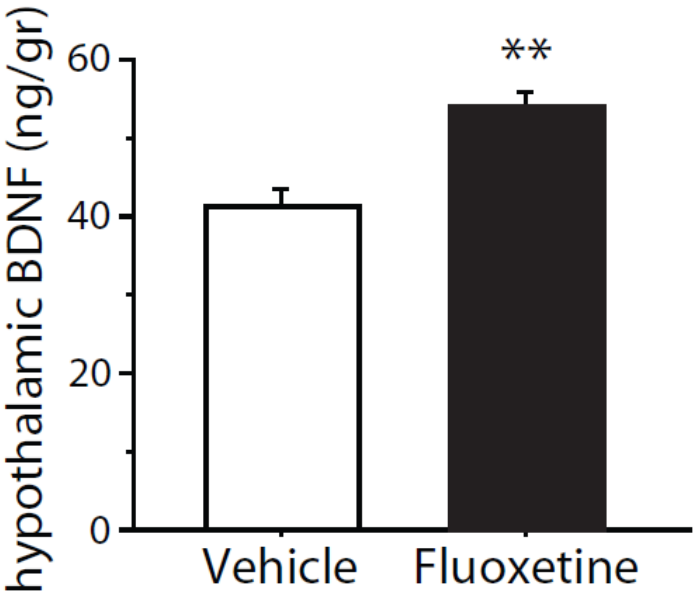
testing and validating the

undirected susceptibility to change hypothesis in mice

experiment 1: enriched condition

Brain Derived Neurotrophic Factor





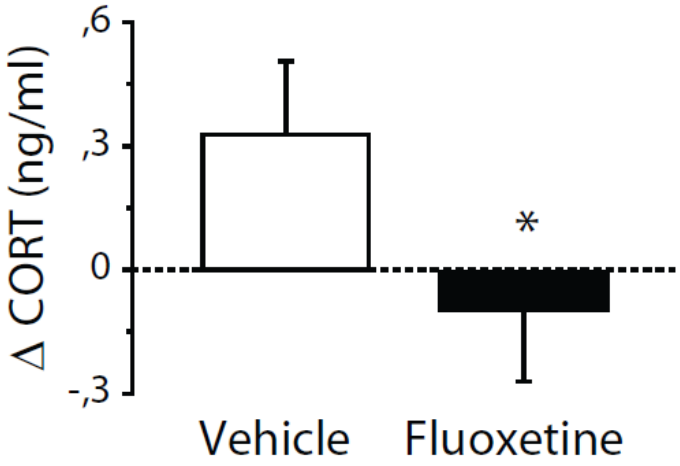
Branchi et al., PLoS one, 2013

testing and validating the

undirected susceptibility to change hypothesis in mice

experiment 1: enriched condition

CORTICOSTERONE

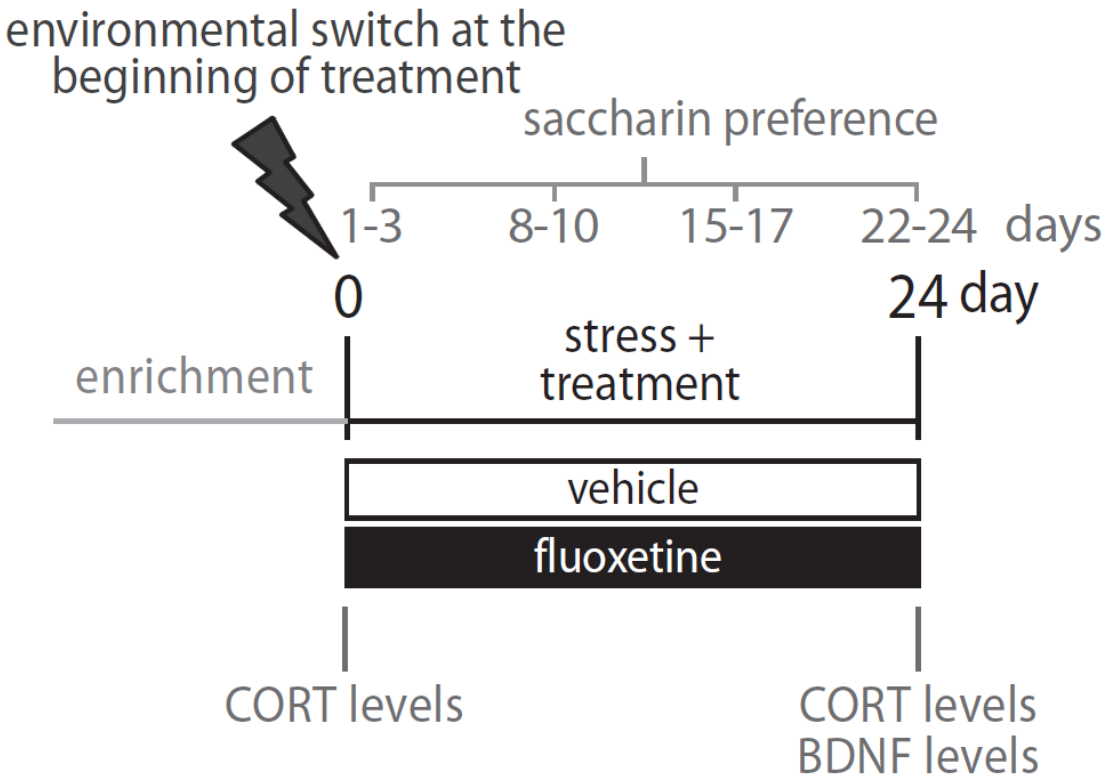


Branchi et al., PLoS one, 2013

testing and validating the

undirected susceptibility to change hypothesis in mice

experiment 2: adverse condition



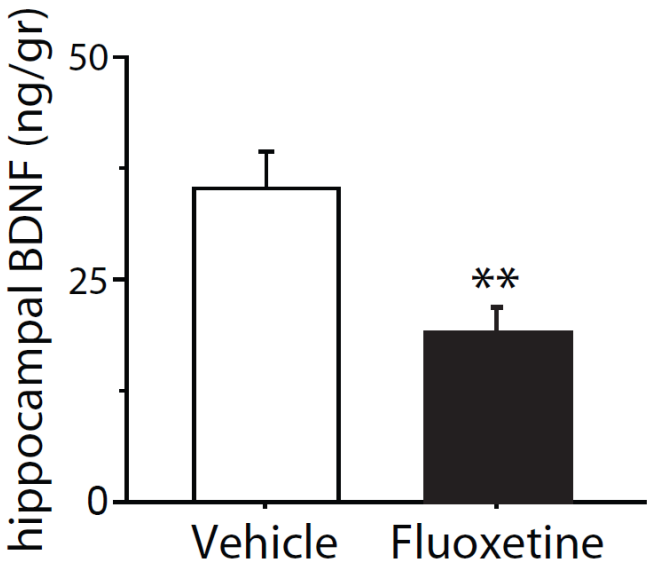
Branchi et al., PLoS one, 2013

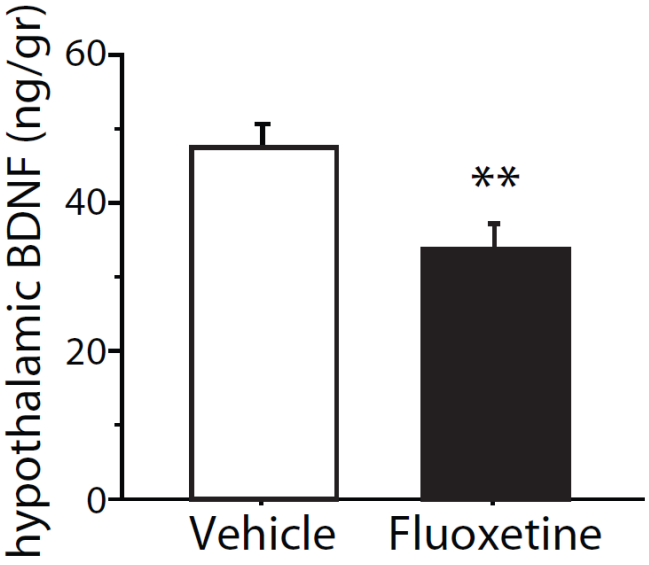
testing and validating the

undirected susceptibility to change hypothesis in mice

experiment 2: adverse condition

Brain Derived Neurotrophic Factor





Branchi et al., PLoS one, 2013

testing and validating the

undirected susceptibility to change hypothesis in mice

experiment 2: adverse condition

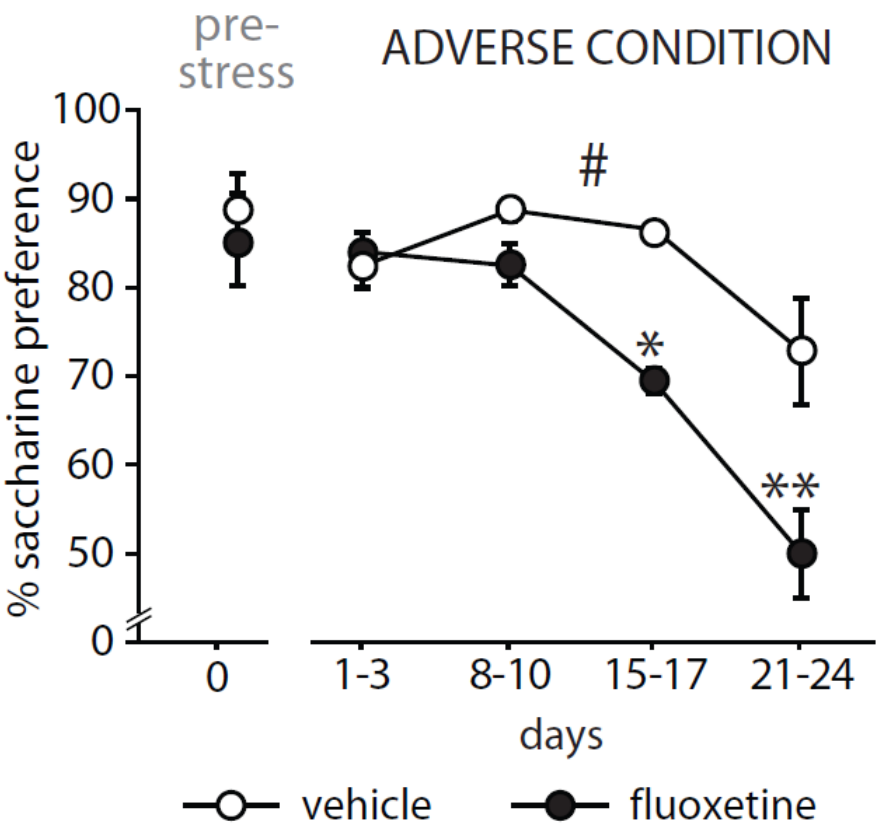
Branchi et al., PLoS one, 2013

testing and validating the

undirected susceptibility to change hypothesis in mice

experiment 2: adverse condition

ANHEDONIA



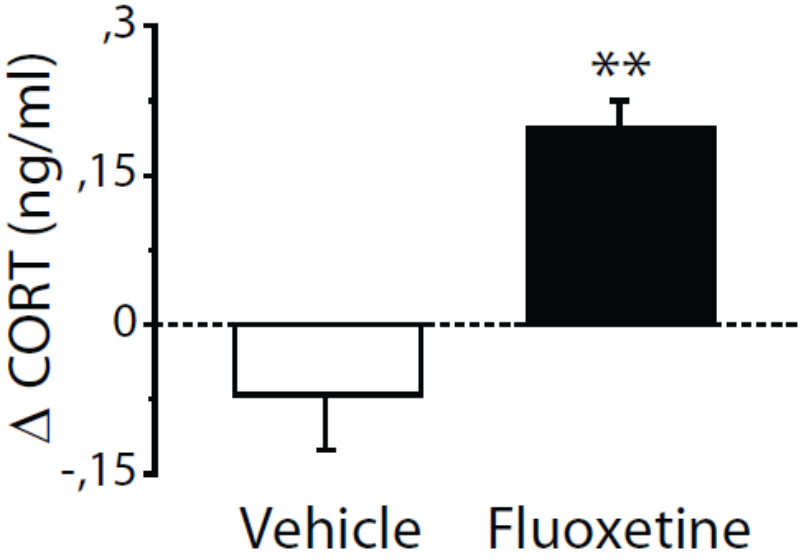
Branchi et al., PLoS one, 2013

testing and validating the

undirected susceptibility to change hypothesis in mice

experiment 2: adverse condition

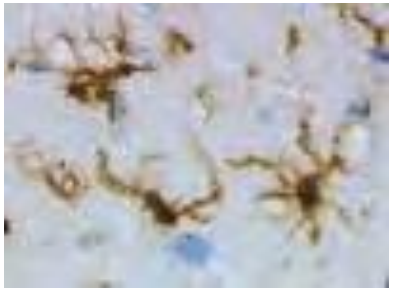
CORTICOSTERONE



Branchi et al., PLoS one, 2013

Brain cells

- Microglia



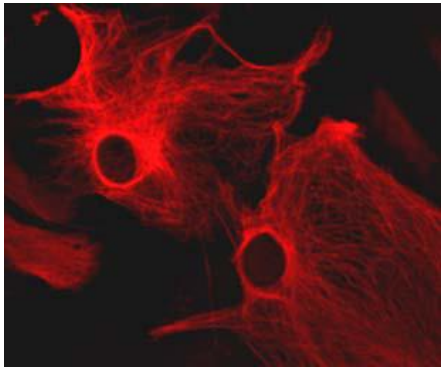
- Macroglia

Astrocytes

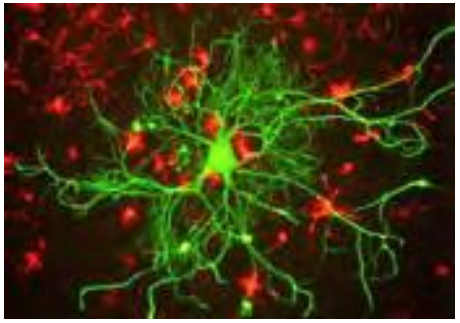
Ependymal cells / radial cells

Oligodendrocytes (Schwann cells)

NG-2 cells



- Neurons



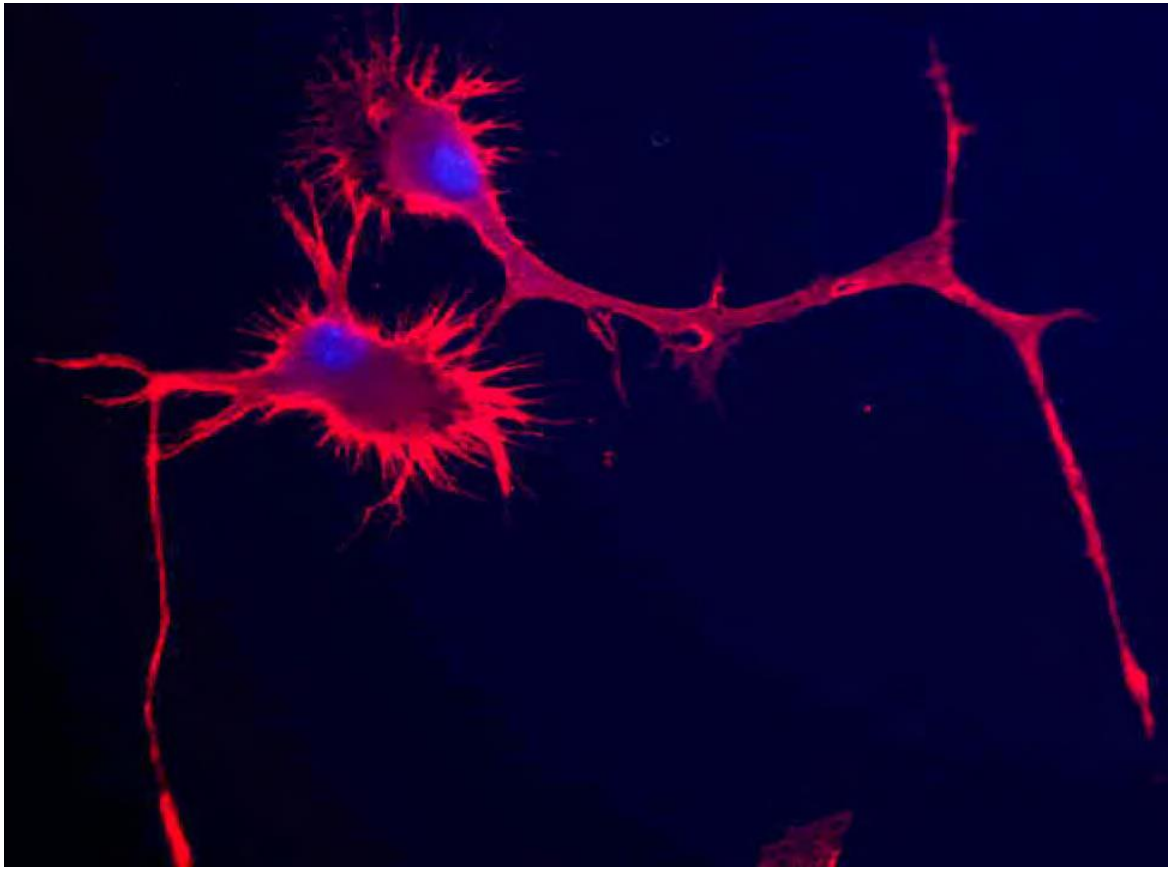
Glia — more than just brain glue

Allen and Barres

NATURE|Vol 457|5 February 2009

- How do glia differ from neurons?
- **Are all glia the same?**
- Where do they originate from?
- What is known about the evolution of glia?
- **So what exactly do glia do?**
- **What is the specific function of microglia?**
- Do any types of glia receive direct neuronal input ?
- **What is the role of glia in brain development?**
- **How do they contribute to the formation of neural networks?**
- **Do glia play a part in disease?**

Types of glia: microglia



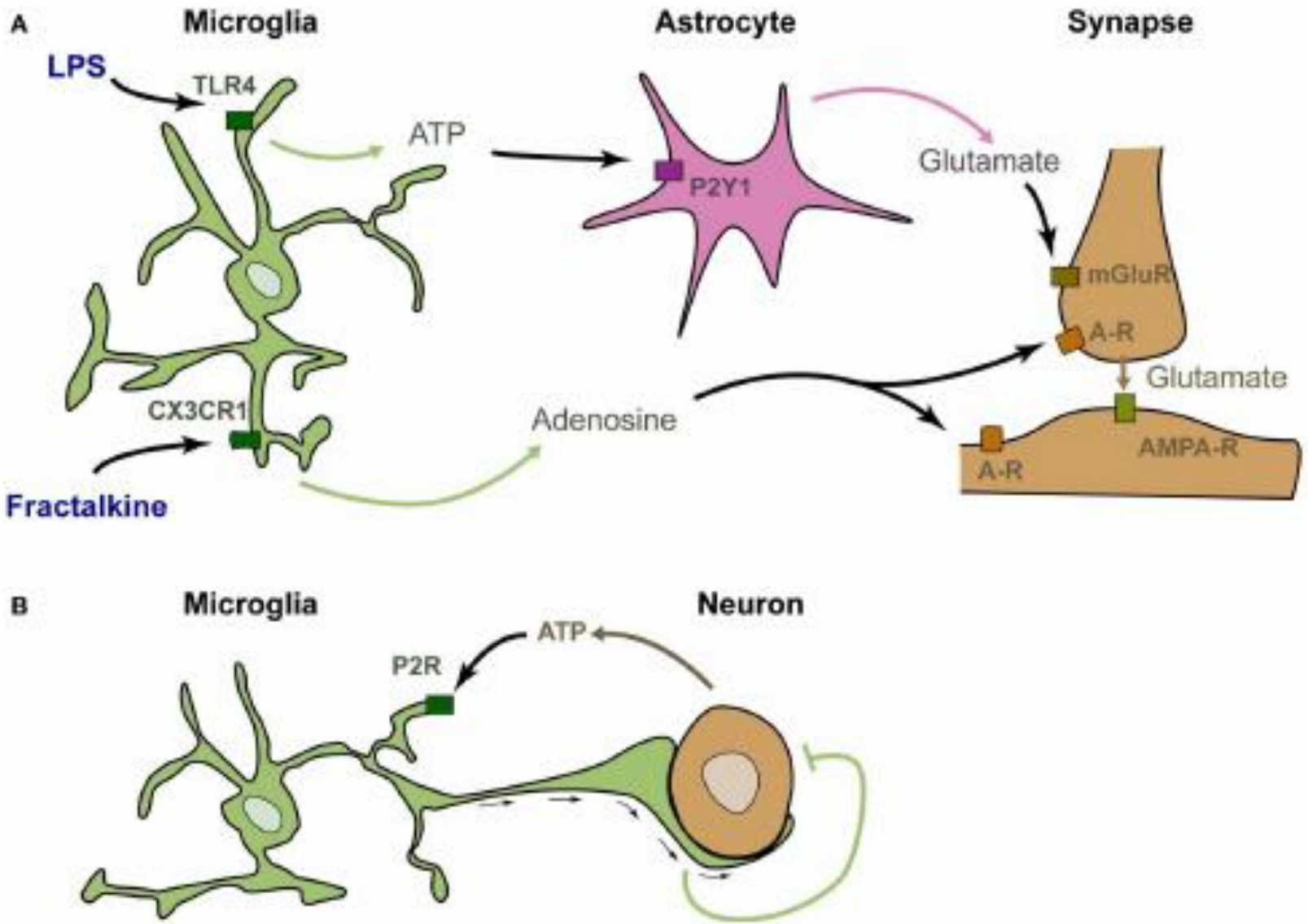
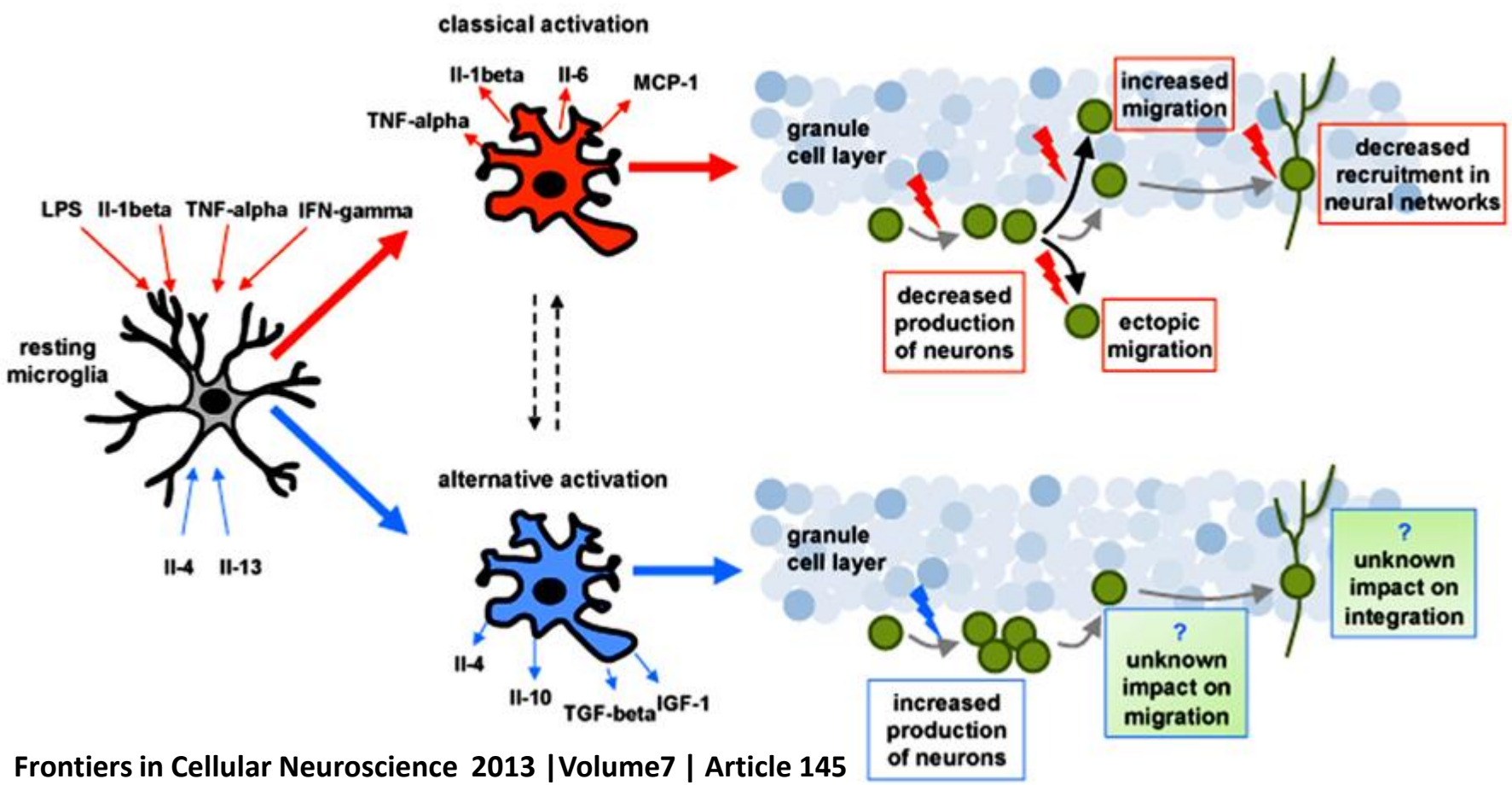


FIGURE 1 | Microglia are genuine partners of synaptic transmission. **(A)** In acute rodent brain slices, stimulation of microglia by LPS induces the rapid release of ATP, which recruits astrocytes. Upon purinergic stimulation, astrocytes release glutamate, inducing a mGluR-dependent release of presynaptic glutamate (Pascual et al., 2012). Stimulation of microglia by fractalkine induces the release of adenosine, which decreases neuronal activity (Meucci et al., 1998; Ragozzino et al., 2006; Piccinin et al., 2010). **(B)** In zebrafish larva, active neurons release the ATP that attracts microglial bulbous processes. These processes decrease neuronal activity by an as yet unknown mechanism (Li et al., 2012).

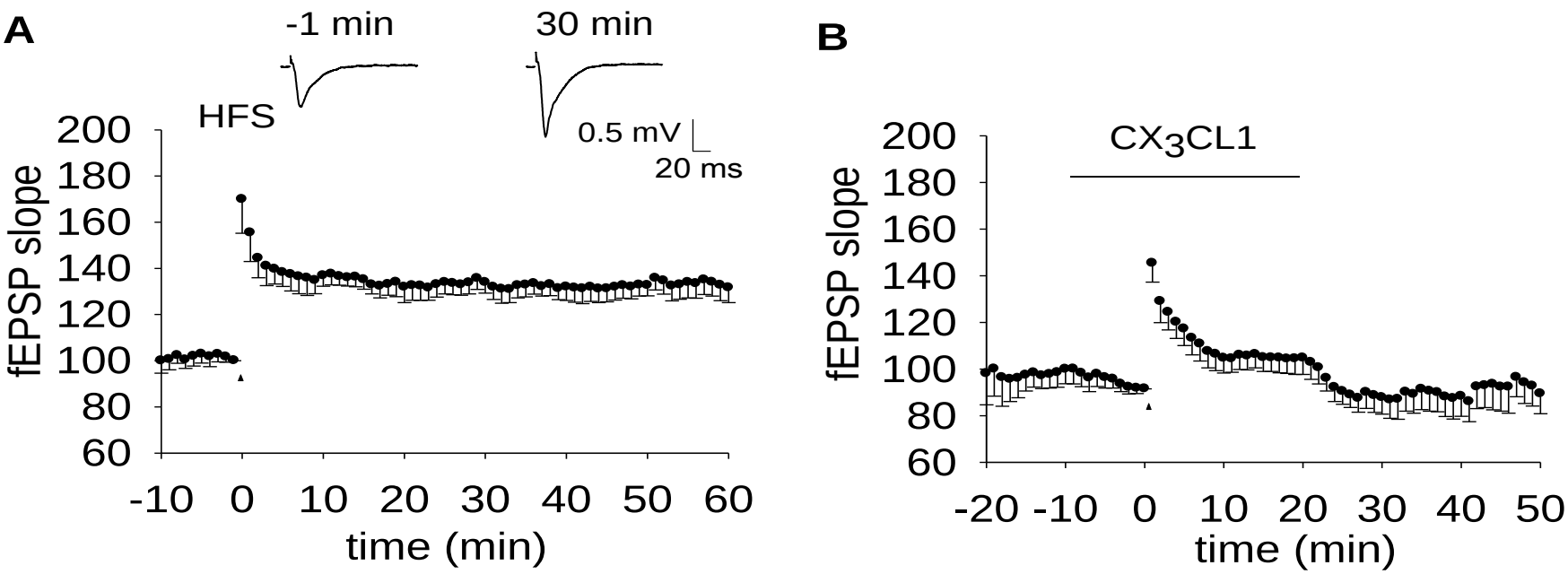
Microglia in the adult brain: neurogenesis

- microglial activation impacts the production, migration and recruitment of new neurons



Frontiers in Cellular Neuroscience 2013 |Volume7 | Article 145

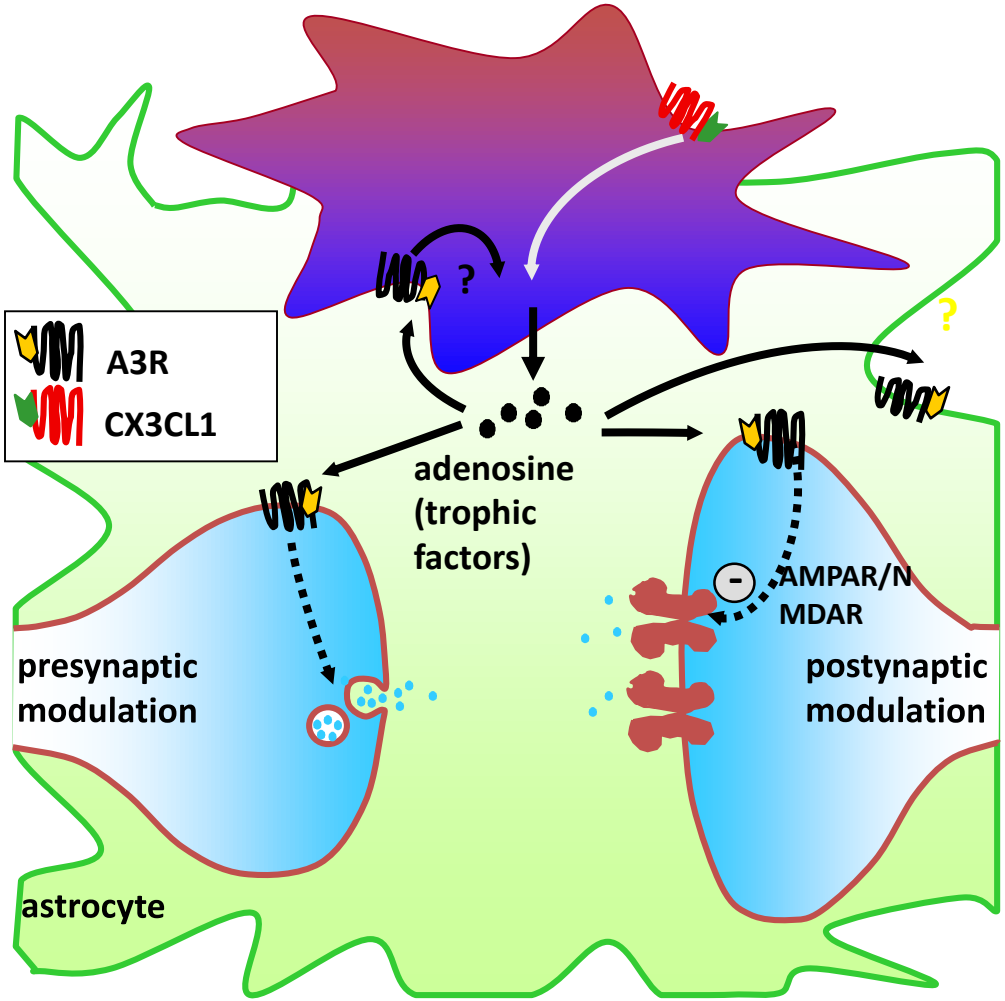
CX_3CL1 impairs hippocampal LTP expression



LTP impairment by fractalkine/CX3CL1 in mouse hippocampus is mediated through the activity of adenosine receptor type 3 (A3R).

Maggi L, Trettel F, Scianni M, Bertollini C, **Eusebi** F, Fredholm BB, Limatola C. J Neuroimmunol. 2009 Oct 30;215(1-2):36-42.

Our model



Adenosine receptors, in particular AR3, are involved in CX_3CL1 action

Psychoneuroendocrinology (2011) **36**, 339—351

available at www.sciencedirect.com

journal homepage: www.elsevier.com/locate/psyneuen

The double edged sword of neural plasticity: Increasing serotonin levels leads to both greater vulnerability to depression and improved capacity to recover

Igor Branchi *

Section of Behavioural Neurosciences, Department of Cell Biology and Neurosciences, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy

Received 16 June 2010; received in revised form 27 August 2010; accepted 29 August 2010

Association of Anxiety-Related Traits with a Polymorphism in the Serotonin Transporter Gene Regulatory Region

Klaus-Peter Lesch,* Dietmar Bengel, Armin Heils, Sue Z. Sabol, Benjamin D. Greenberg, Susanne Petri, Jonathan Benjamin, Clemens R. Müller, Dean H. Hamer, Dennis L. Murphy

SCIENCE • VOL. 274 • 29 NOVEMBER 1996

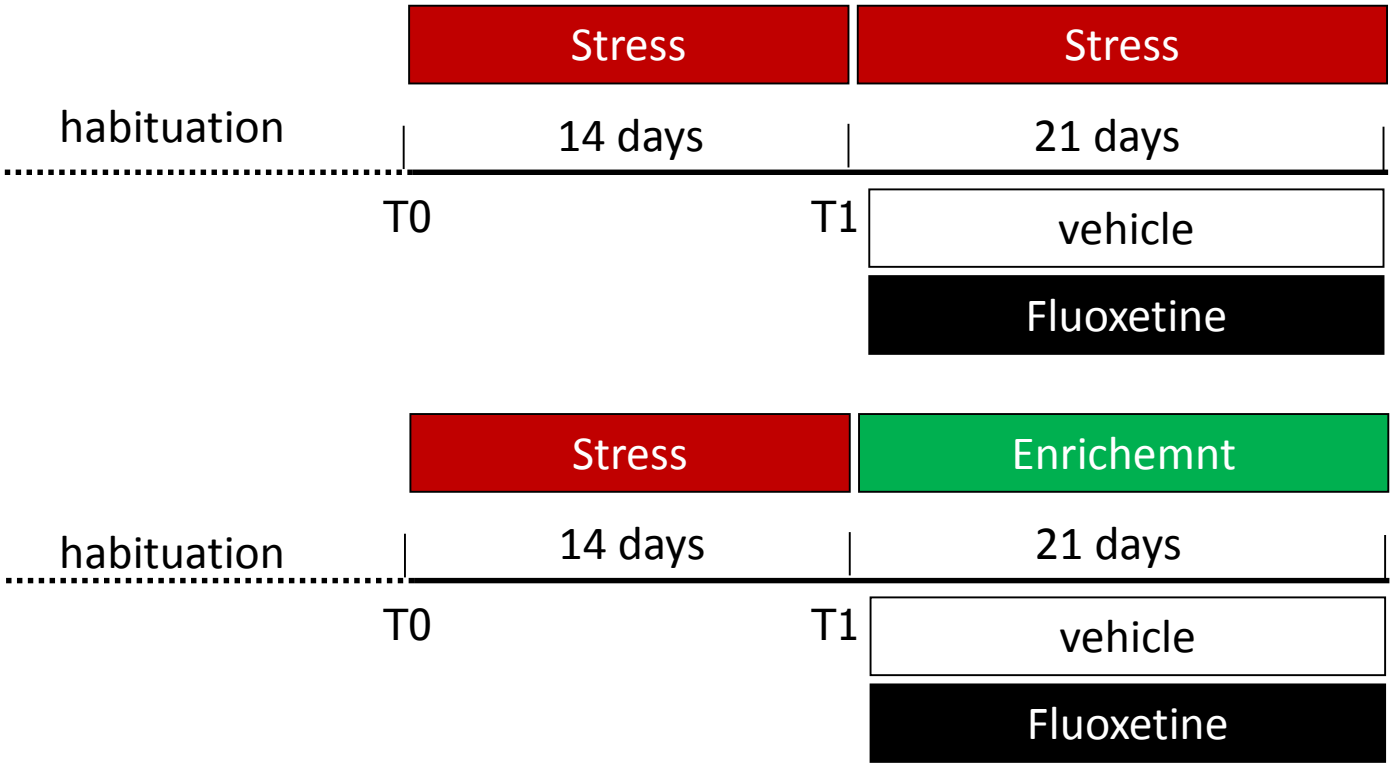
Influence of Life Stress on Depression: Moderation by a Polymorphism in the 5-HTT Gene

Avshalom Caspi,[1,2] Karen Sugden,[1] Terrie E. Moffitt,[1,2*] Alan Taylor,[1] Ian W. Craig,[1] HonaLee Harrington,[2] Joseph McClay,[1] Jonathan Mill,[1] Judy Martin,[3] Antony Braithwaite,[4] Richie Poulton[3]

18 JULY 2003 VOL 301 SCIENCE www.sciencemag.org

Science
AAAS

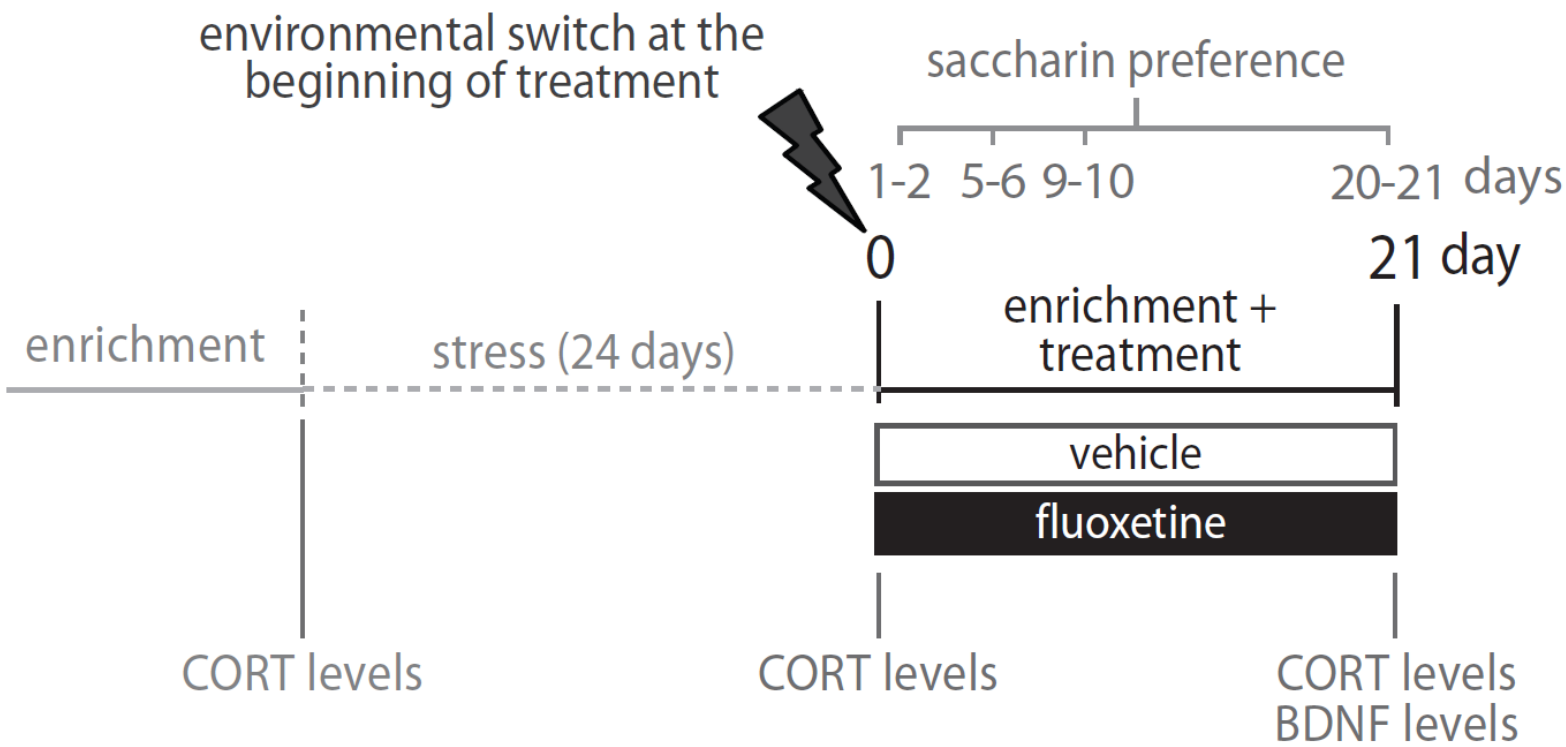
Experimental mouse model *in vivo*



testing and validating the

undirected susceptibility to change hypothesis in mice

experiment 1: enriched condition



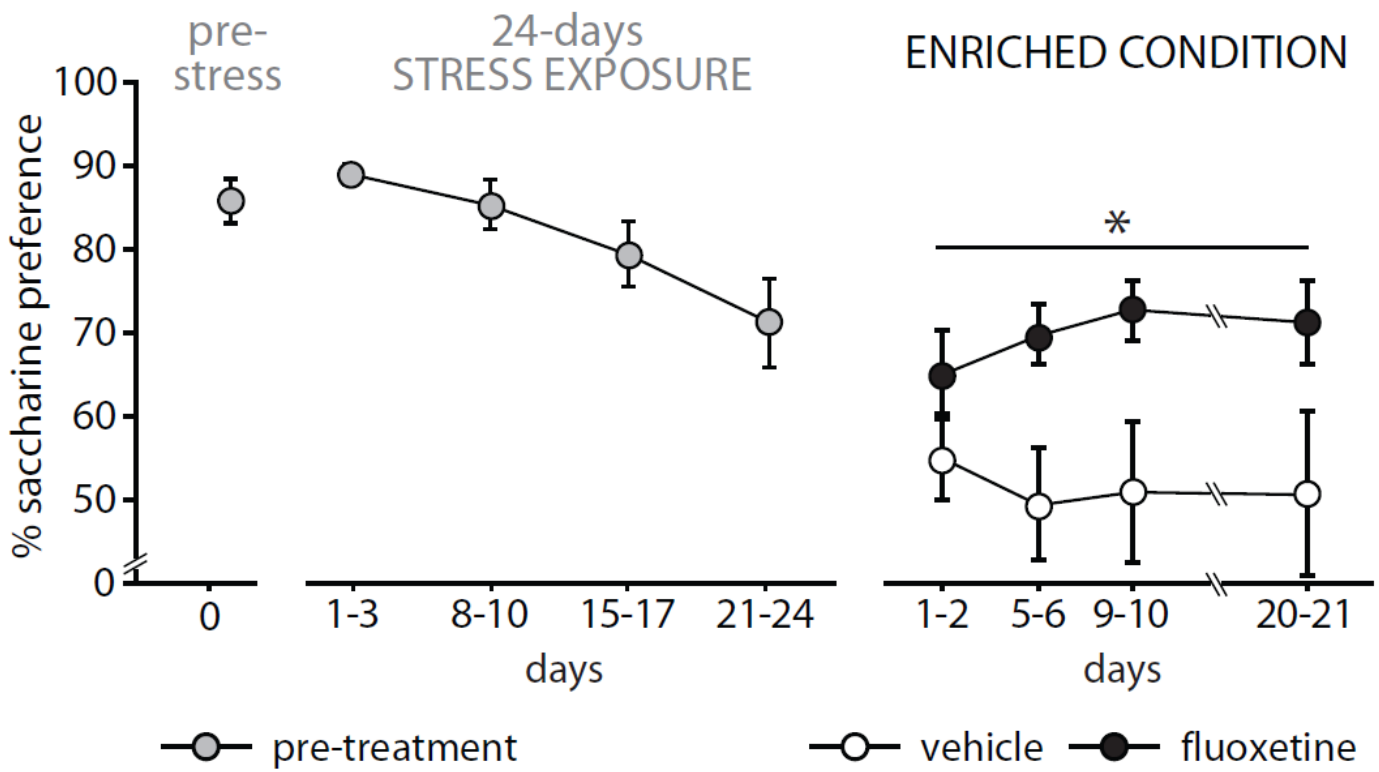
Branchi et al., PLoS one, 2013

testing and validating the

undirected susceptibility to change model in mice

experiment 1: enriched condition

ANHEDONIA



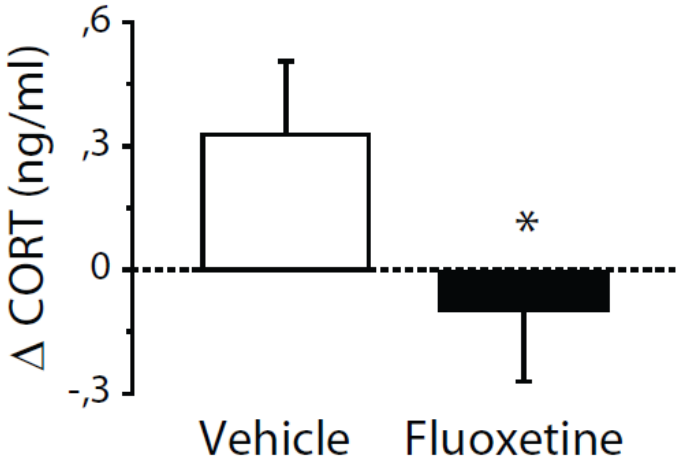
Branchi et al., PLoS one, 2013

testing and validating the

undirected susceptibility to change hypothesis in mice

experiment 1: enriched condition

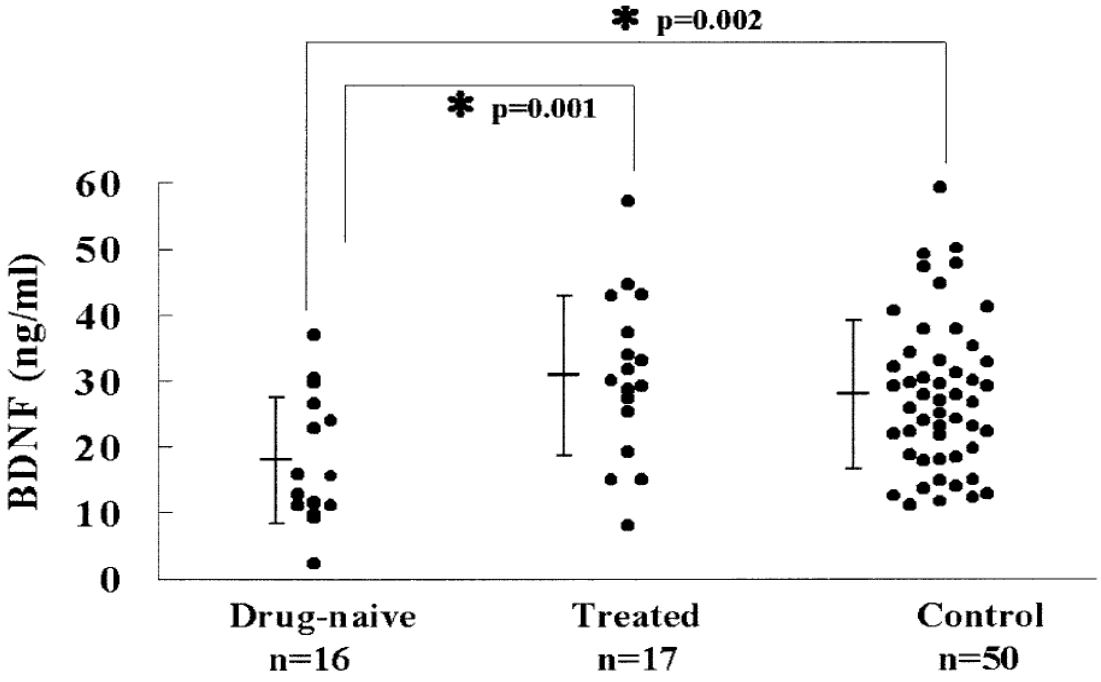
CORTICOSTERONE



Branchi et al., PLoS one, 2013

Brain Derived Neurotrophic Factor

A decrease of BDNF levels is associated with depression



Shimizu et al. 2003

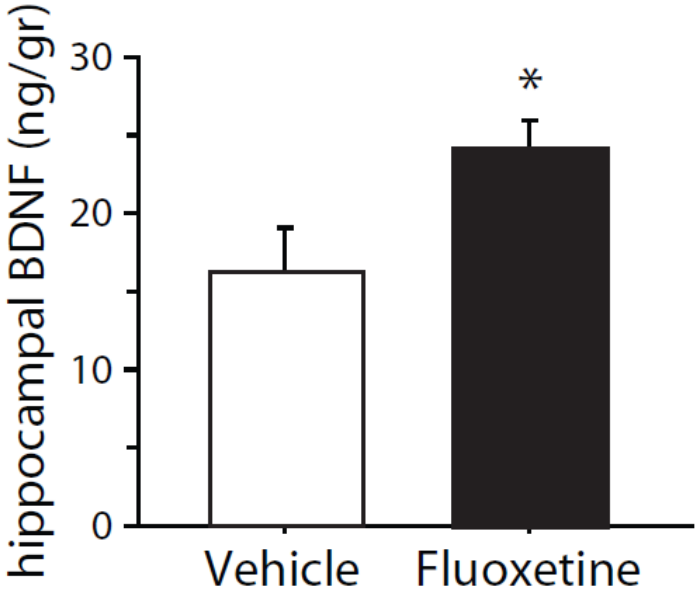
Scatter plot of serum brain-derived neurotrophic factor (BDNF) concentrations in antidepressant-naive, -treated, and control groups. Serum levels of BDNF in the drug-naive group (*n* = 16; 17.6 ± 9.6 ng/mL; mean ± SD) were significantly decreased compared with those of the treated group (*n* = 17; 30.6 ± 12.3 ng/mL; mean ± SD; *p* _ .001) or the control group (*n* = 50; 27.7 ± 11.4 ng/mL; mean ± SD; *p* < .002).

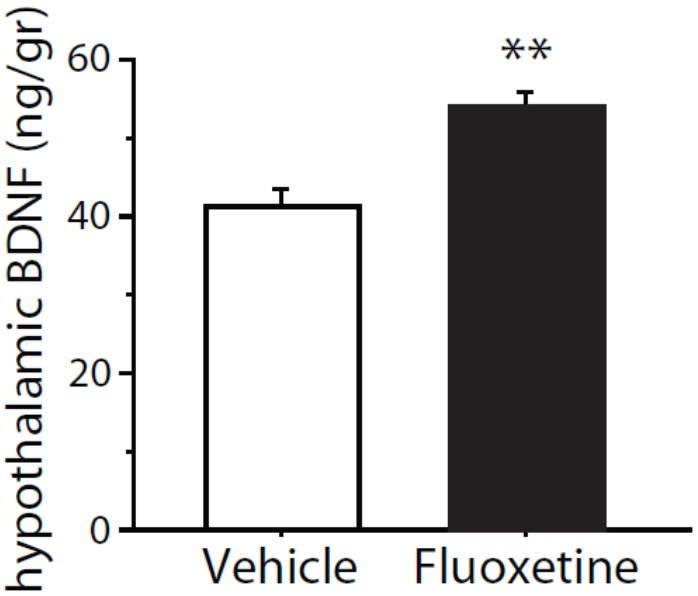
testing and validating the

undirected susceptibility to change hypothesis in mice

experiment 1: enriched condition

Brain Derived Neurotrophic Factor



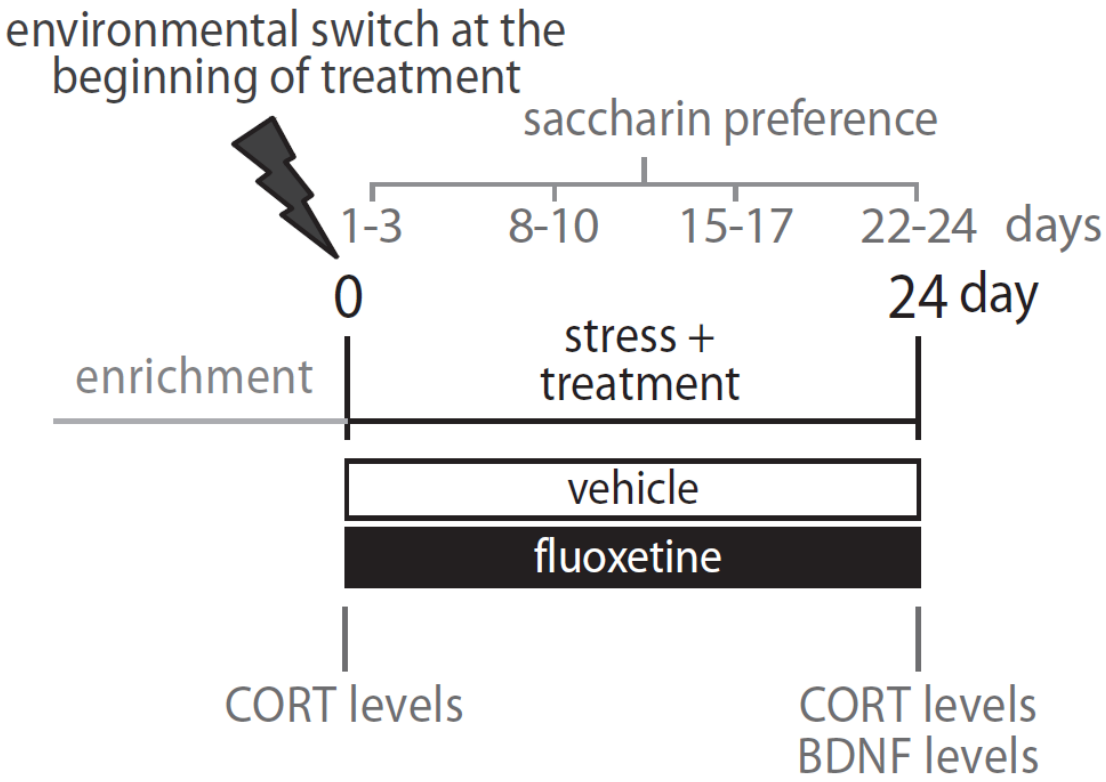


Branchi et al., PLoS one, 2013

testing and validating the

undirected susceptibility to change hypothesis in mice

experiment 2: adverse condition



Branchi et al., PLoS one, 2013

testing and validating the

undirected susceptibility to change hypothesis in mice

experiment 2: adverse condition

Branchi et al., PLoS one, 2013

testing and validating the

undirected susceptibility to change hypothesis in mice

experiment 2: adverse condition

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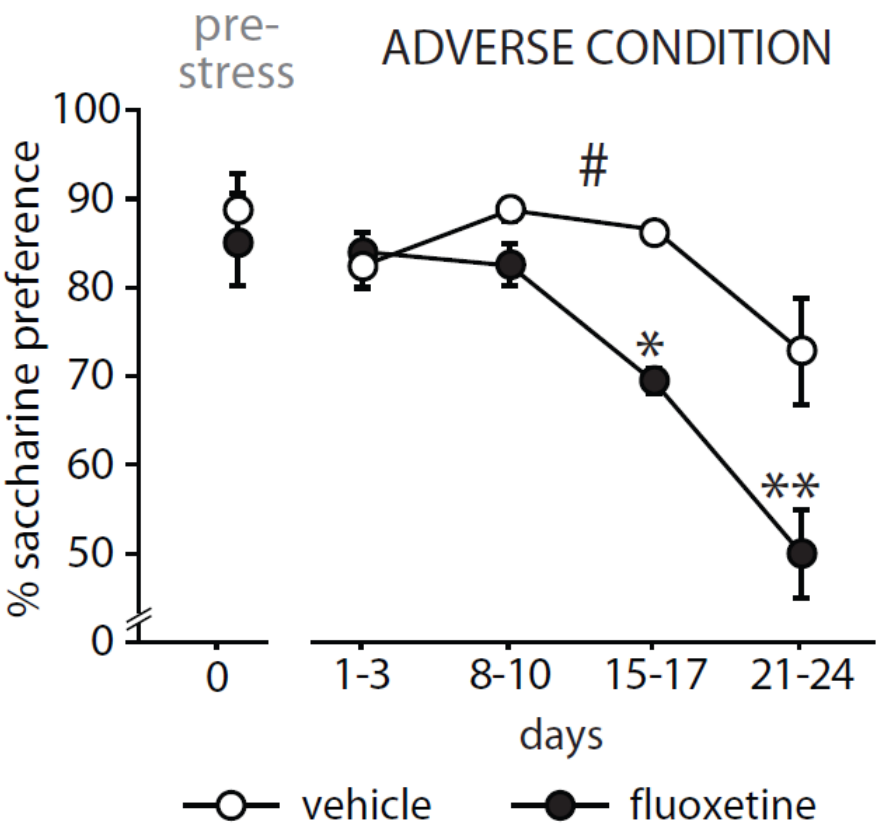


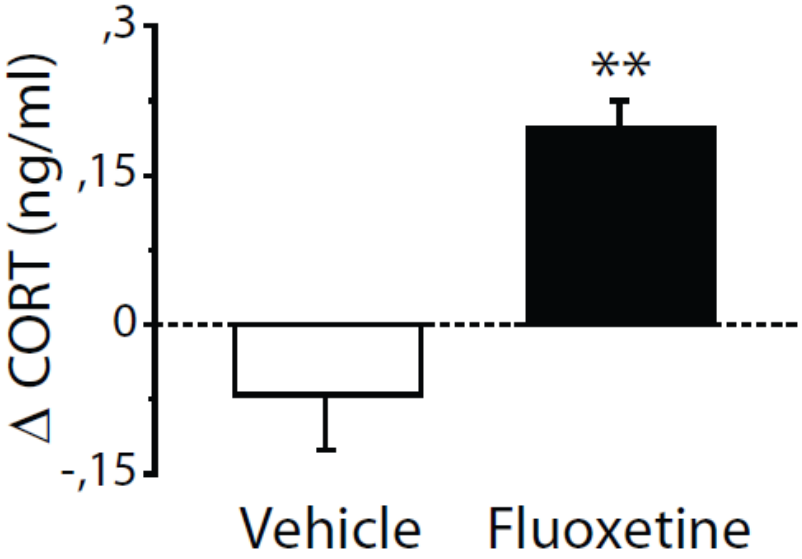
Branchi et al., PLoS one, 2013

testing and validating the

undirected susceptibility to change hypothesis in mice

experiment 2: adverse condition

CORTICOSTERONE



Branchi et al., PLoS one, 2013

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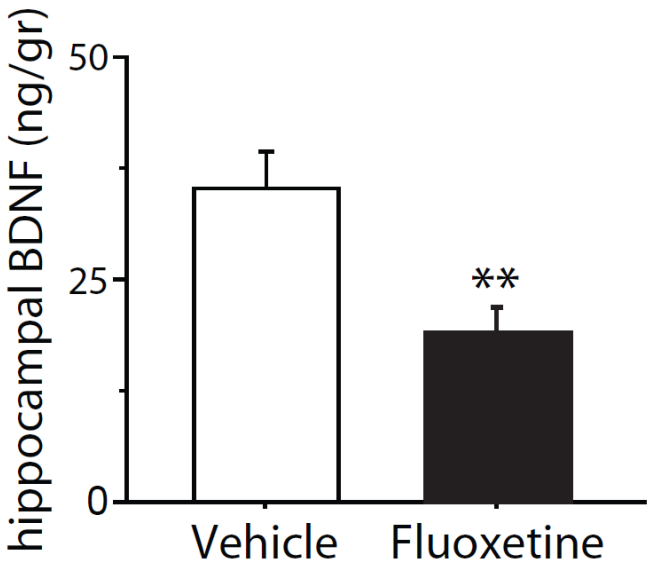
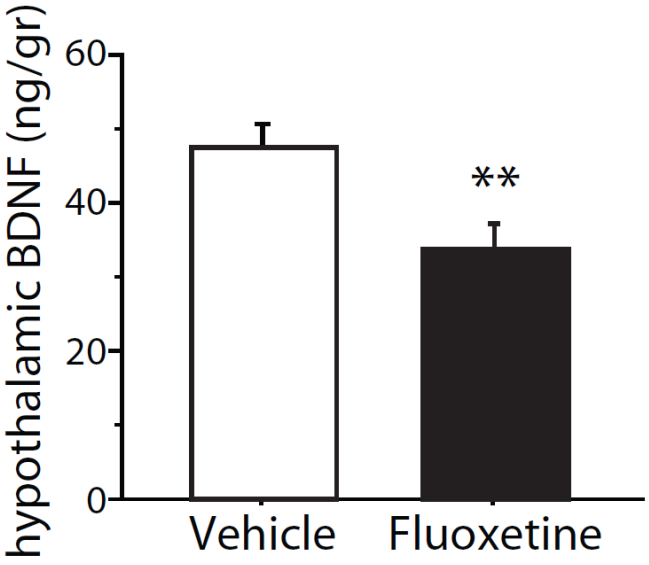
experiment 2: adverse condition

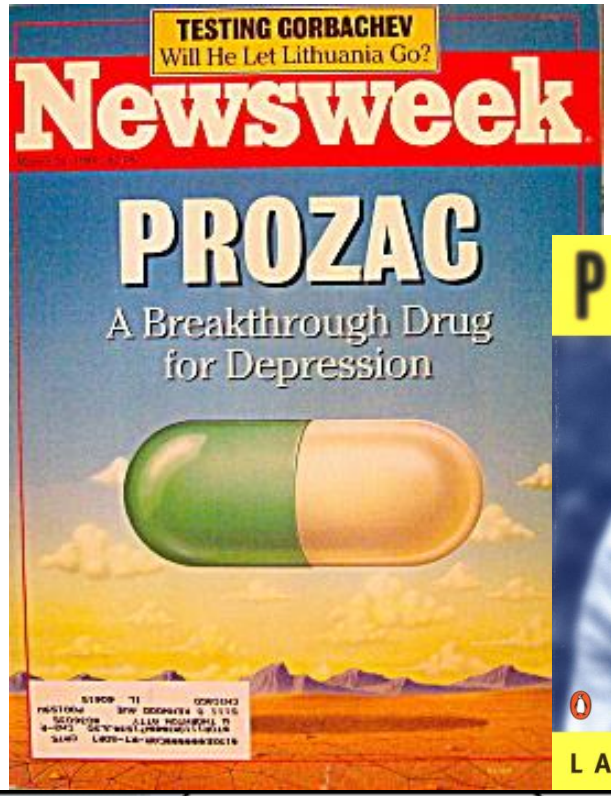
Brain Derived Neurotrophic Factor

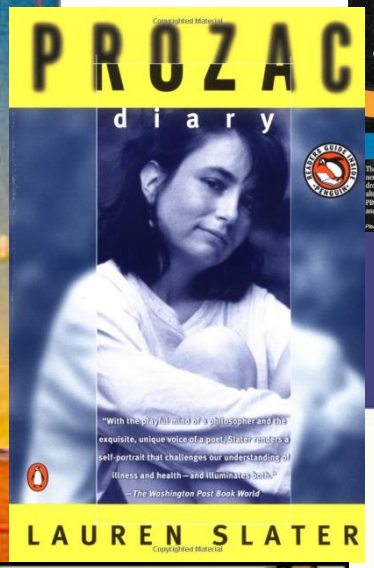


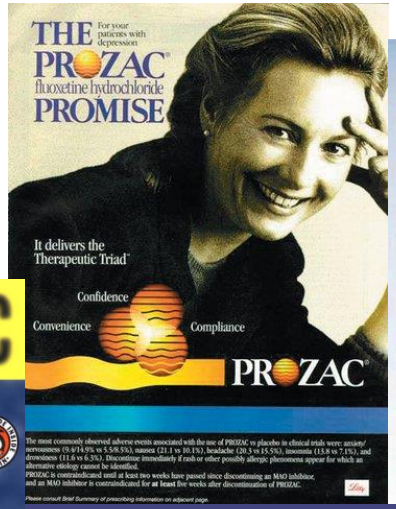


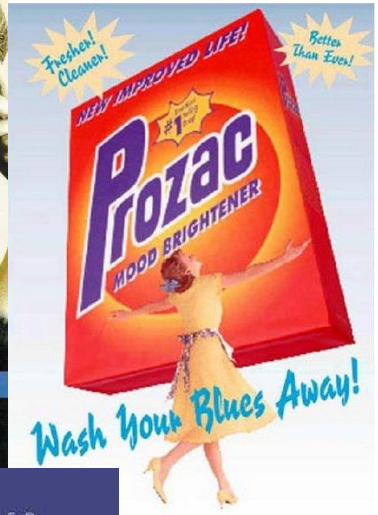
Branchi et al., PLoS one, 2013

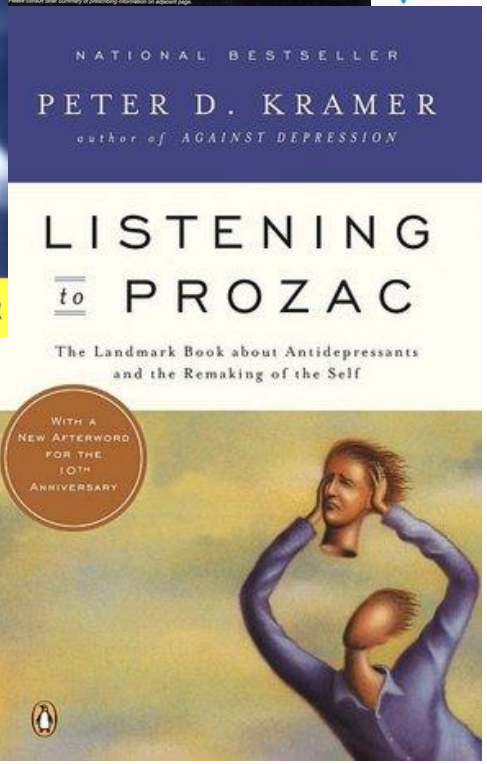
Huge success of antidepressants in 1980s-1990s

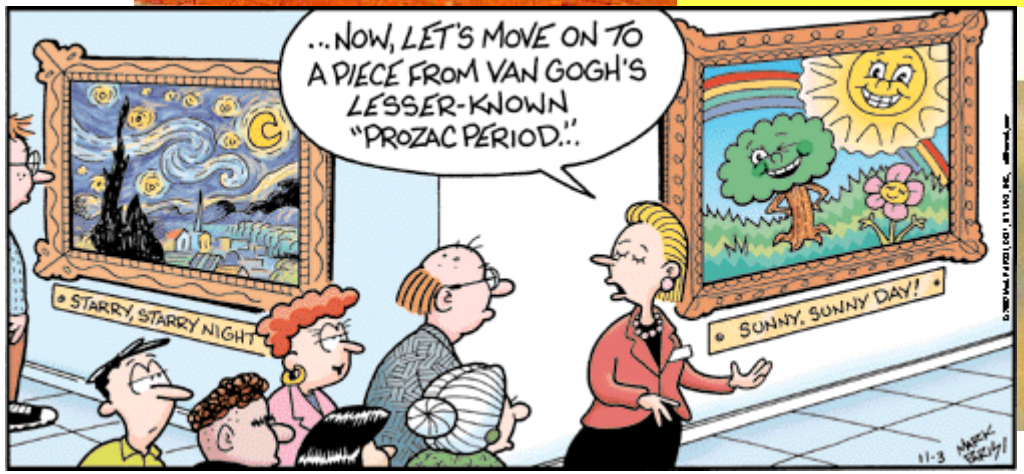








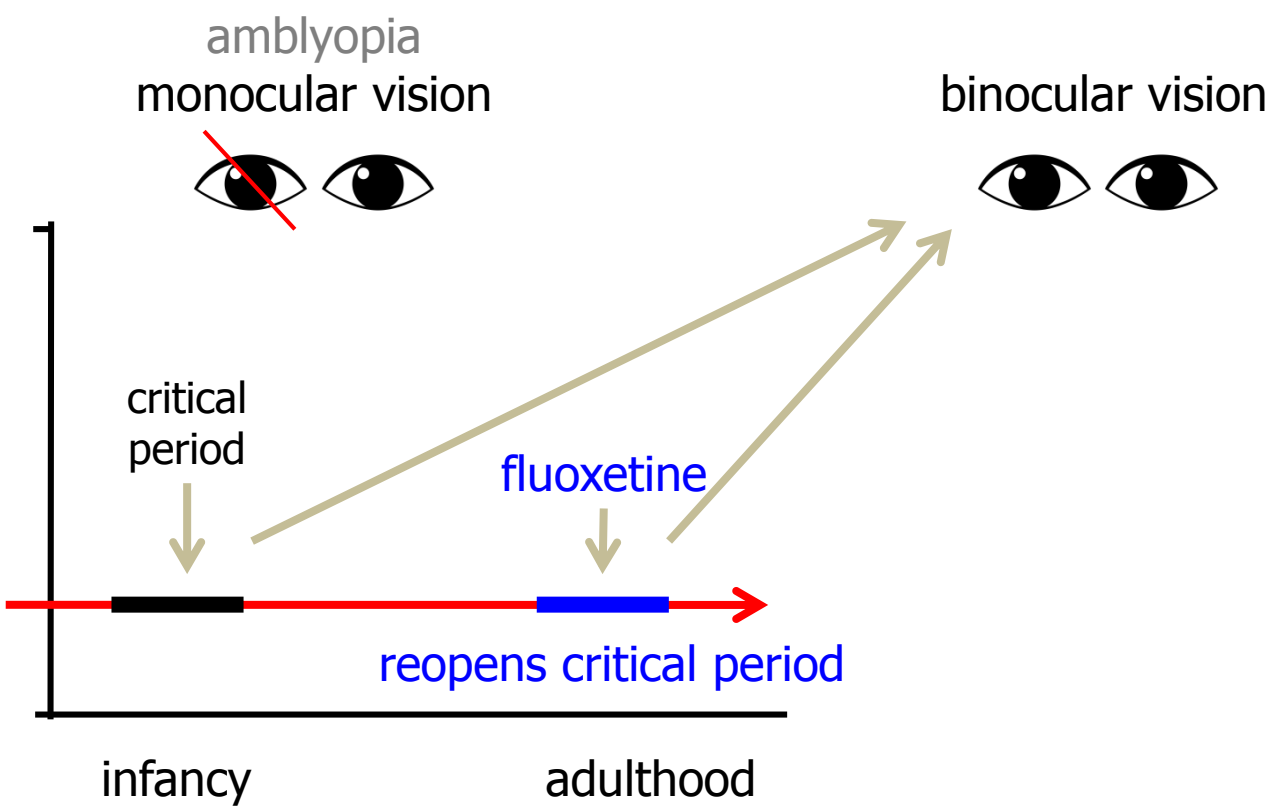




The Antidepressant Fluoxetine Restores Plasticity in the Adult Visual Cortex

José Fernando Maya Vetencourt,[1*] Alessandro Sale,[1] Alessandro Viegi,[1] Laura Baroncelli,[1]
Roberto De Pasquale,[1] Olivia F. O'Leary,[3] Eero Castrén,[3] Lamberto Maffei[1,2]

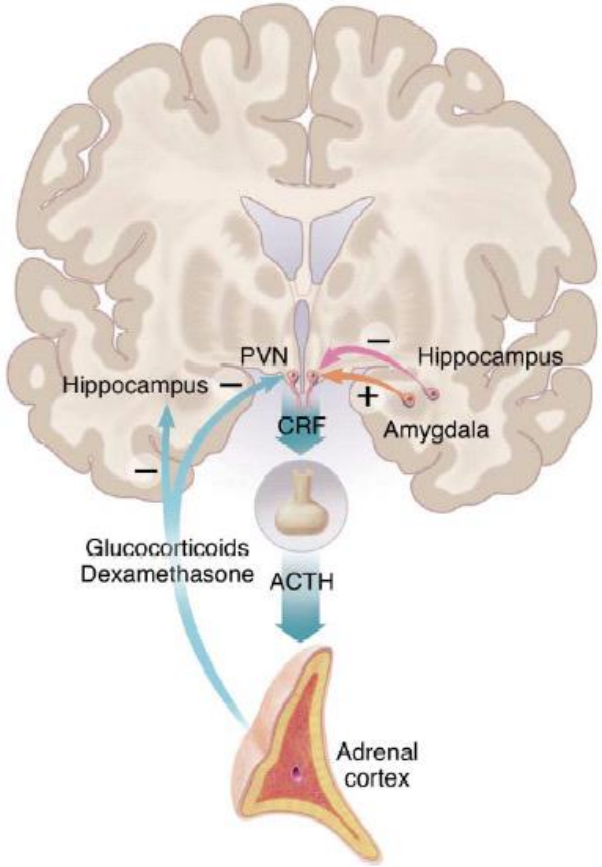
www.sciencemag.org SCIENCE VOL 320 18 APRIL 2008

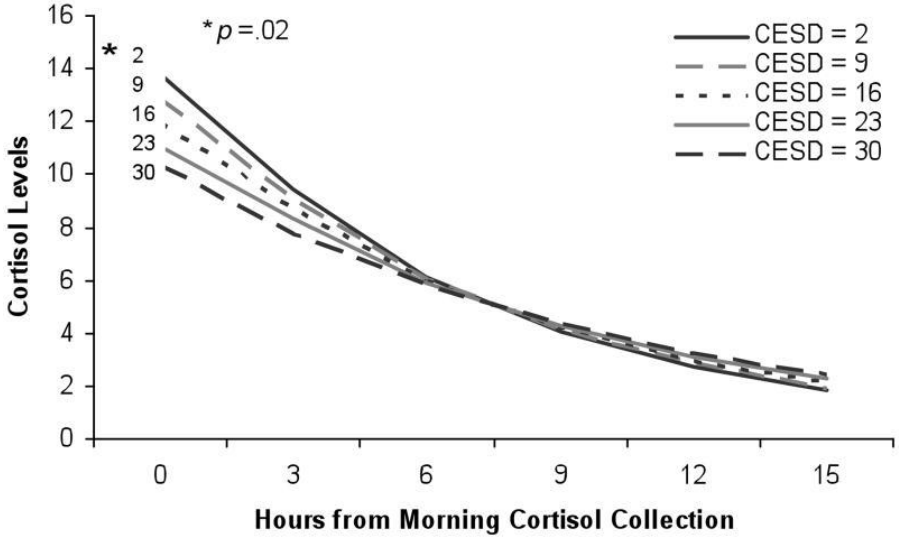


high serotonin levels favor change

HYPOTHALAMIC–PITUITARY–ADRENAL AXIS

Depression has been associated to alterations of hypothalamic-pituitary-adrenal (HPA) axis activity



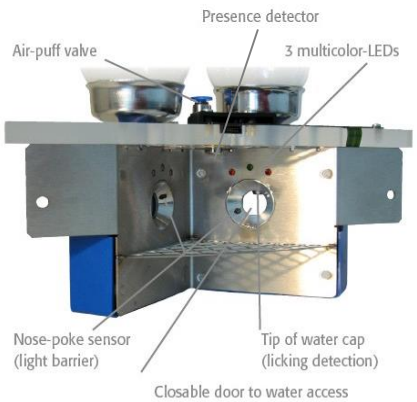


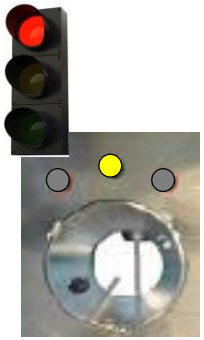
Graded association of depression and the diurnal slope of cortisol after adjustment for all covariates. The interaction of CES-D by time is significant (p<.05) using the continuous version of the CES-D.

Nestler et al, 2002

Knight et al, 2010

COGNITIVE BIAS:
optimistic or pessimistic



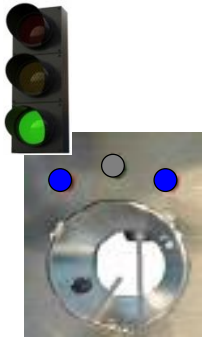


do not go

nosepoke

↓

punishment
- air puff
- no access to water



go

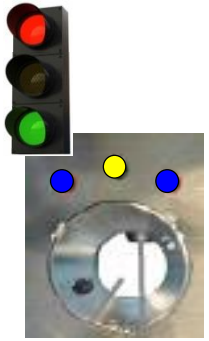
nosepoke

↓

reward
- access to water

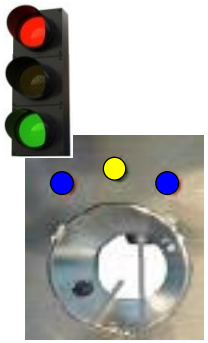
after discrimination has been learned

1 out of 20



ambiguous

COGNITIVE BIAS:
optimistic or pessimistic



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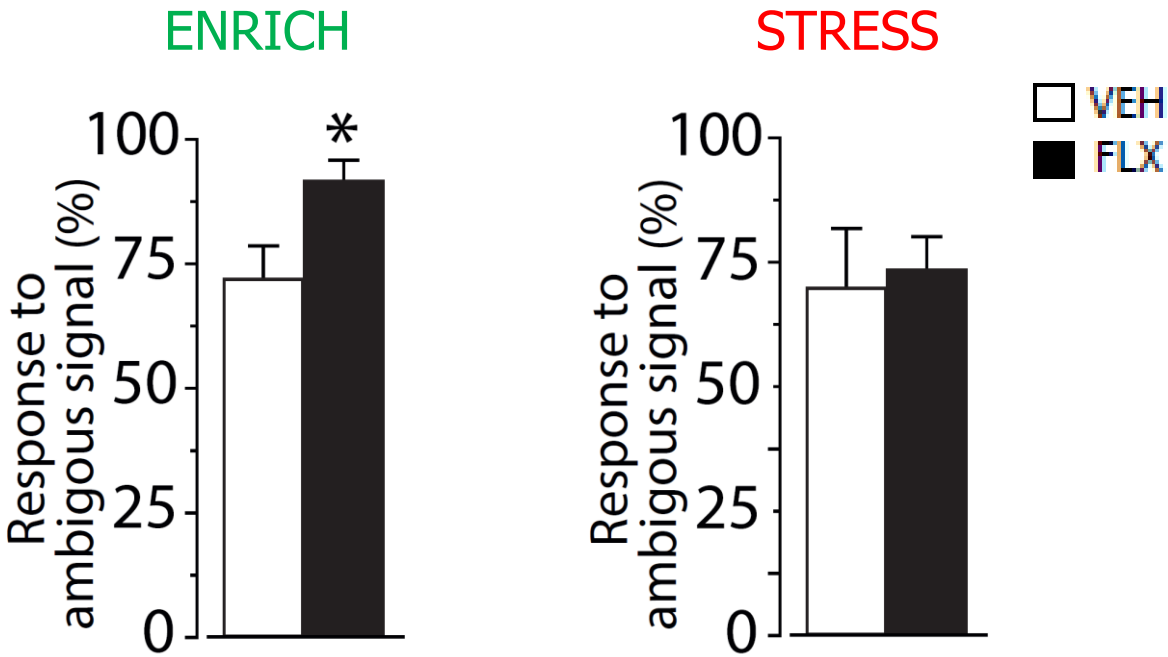


Alboni et al., Molecular Psychiatry, *2015*

Stress-Induced Microglial Activation

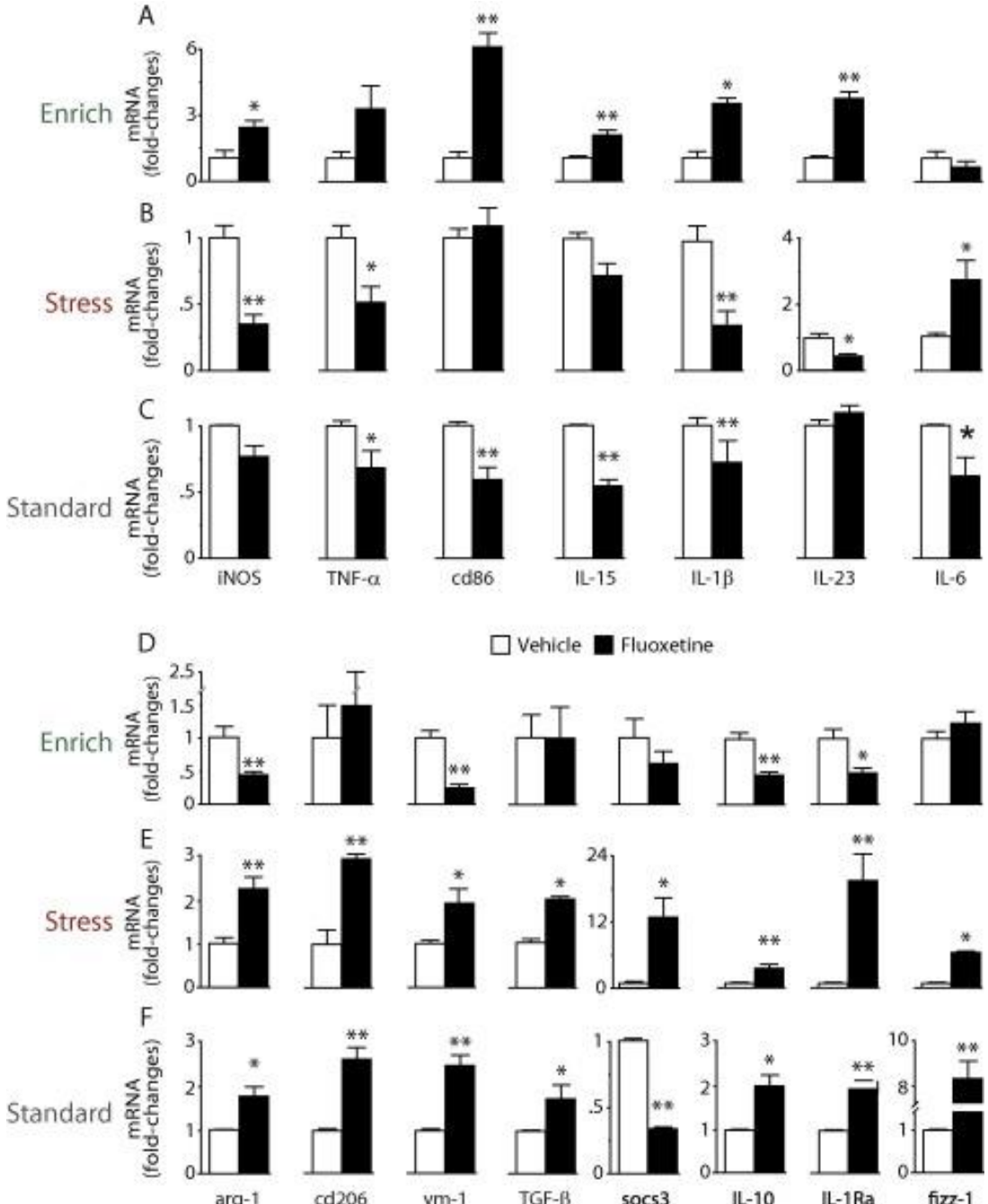
psychological stress can induce direct microglial activation via the release of danger-associated molecular patterns DAMPs (also termed alarmins) within the brain. These molecules can signal via microglial Toll-like receptor 4 (TLR4) and translate psychological danger signals into stress- and depression-associated microglial alterations

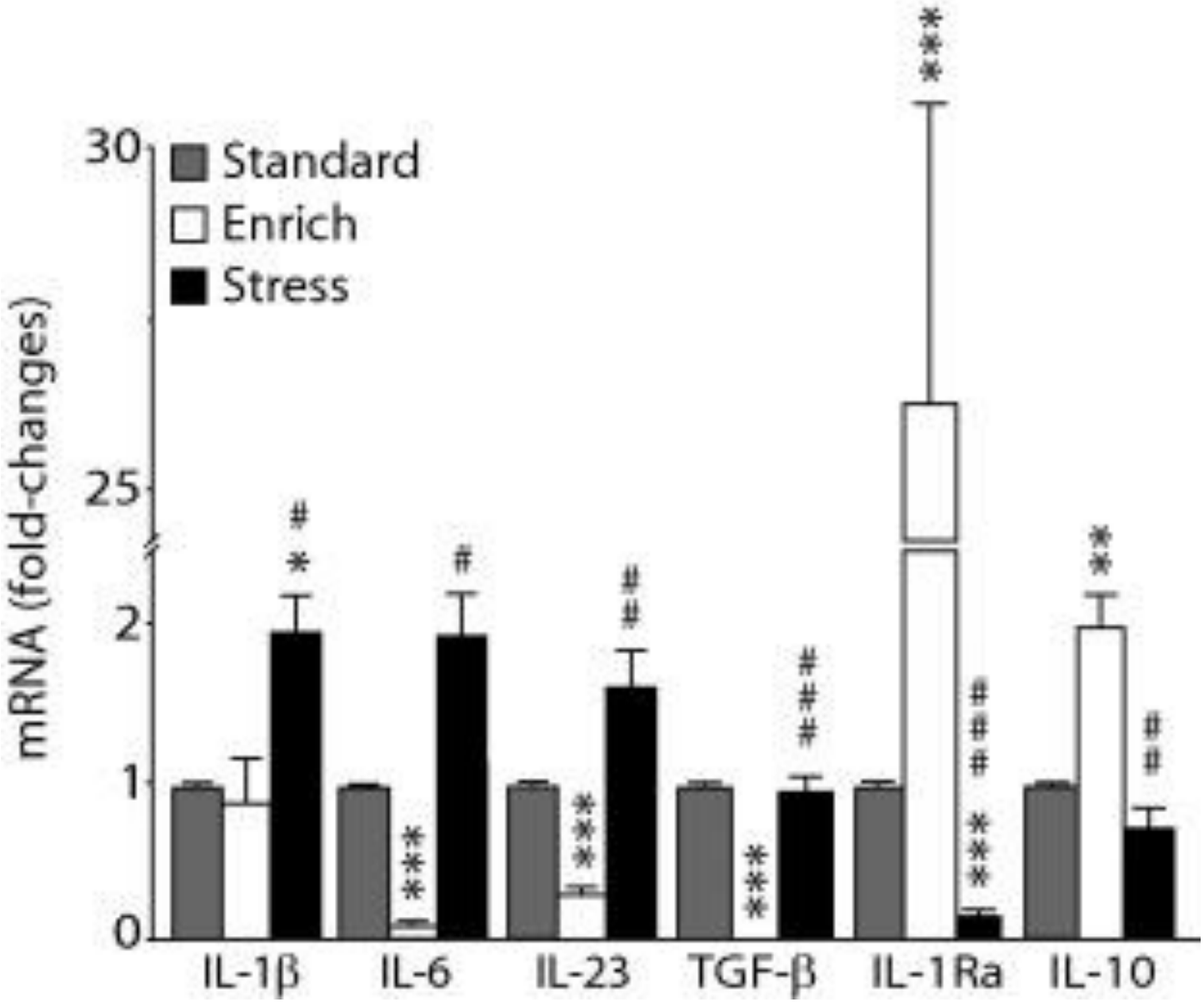
DAMP → TLR4 → microglia activation- → matrix metalloprotease 9
microglia activation- → chemokine release

IL-1 plays an important role in the development of depression
mice with genetically impaired IL-1 signaling display no chronic stress-induced microglial activation, depression, or anxiety

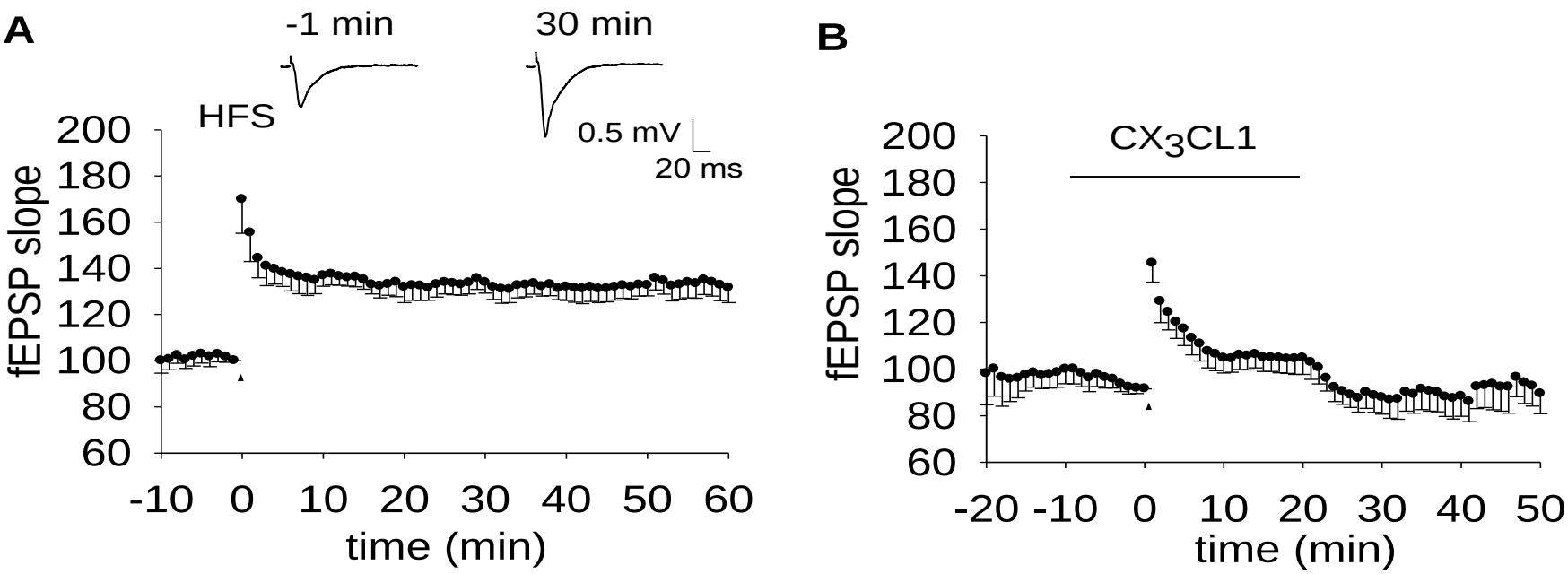
I. Goshen, R. Yirmiya
Interleukin-1 (IL-1): a central regulator of stress responses
Front. Neuroendocrinol., 30 (2009), pp. 30–45

DAMPS: Damage-associated molecular pattern molecules; **PAMPs:** Pathogen-associated molecular pattern molecules.


A
Enrich
mRNA (fold-changes)
B
Stress
C
Standard
iNOS
TNF-α
cd86
IL-15
IL-1β
IL-23
IL-6
Vehicle
Fluoxetine
D
E
F
arg-1
cd206
ym-1
TGF-β
socs3
IL-10
IL-1Ra
fizz-1


Standard
Enrich
Stress
mRNA (fold-changes)
30
25
2
1
0
IL-1β
IL-6
IL-23
TGF-β
IL-1Ra
IL-10

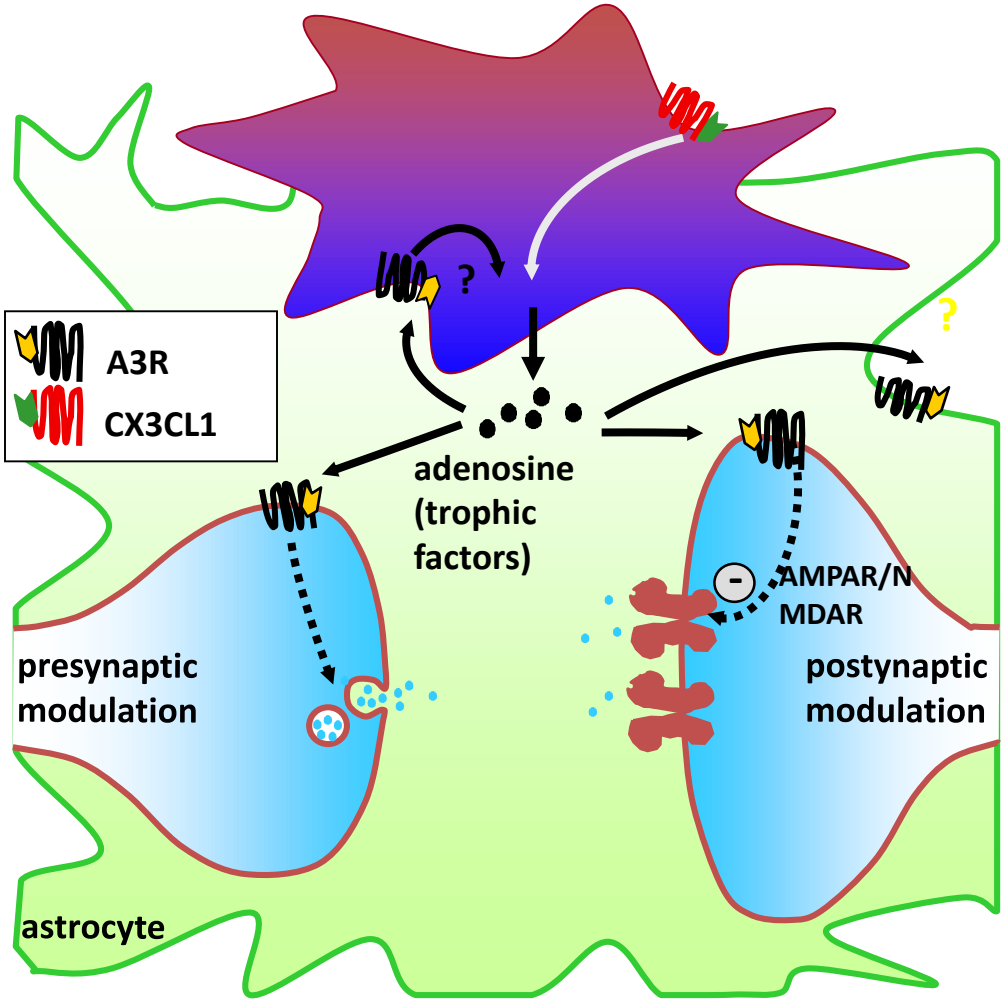
Cx_3CL1 impairs hippocampal LTP expression



LTP impairment by fractalkine/CX3CL1 in mouse hippocampus is mediated through the activity of adenosine receptor type 3 (A3R).

Maggi L, Trettel F, Scianni M, Bertollini C, **Eusebi** F, Fredholm BB, Limatola C. J Neuroimmunol. 2009 Oct 30;215(1-2):36-42.

Our model



Adenosine receptors, in particular AR3, are involved in CX_3CL1 action

...but antidepressants go on being prescribed

The New York Review of Books

'The Illusions of Psychiatry': An Exchange

John Oldham, Daniel Carlat, Richard Friedman, and Andrew Nierenberg, reply by Marcia Angell

EBMH Notebook

Do antidepressants work? A commentary on "Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration" by Kirsch *et al*

R H McAllister-Williams

August 2008 Vol 11 No 3

EBMH

BMJ Group

Evidence-Based Mental Health

The New York Times

SundayReview | The Opinion Pages

OPINION

In Defense of Antidepressants

By PETER D. KRAMER
Published: July 9, 2011

PROVIDENCE, R.I.

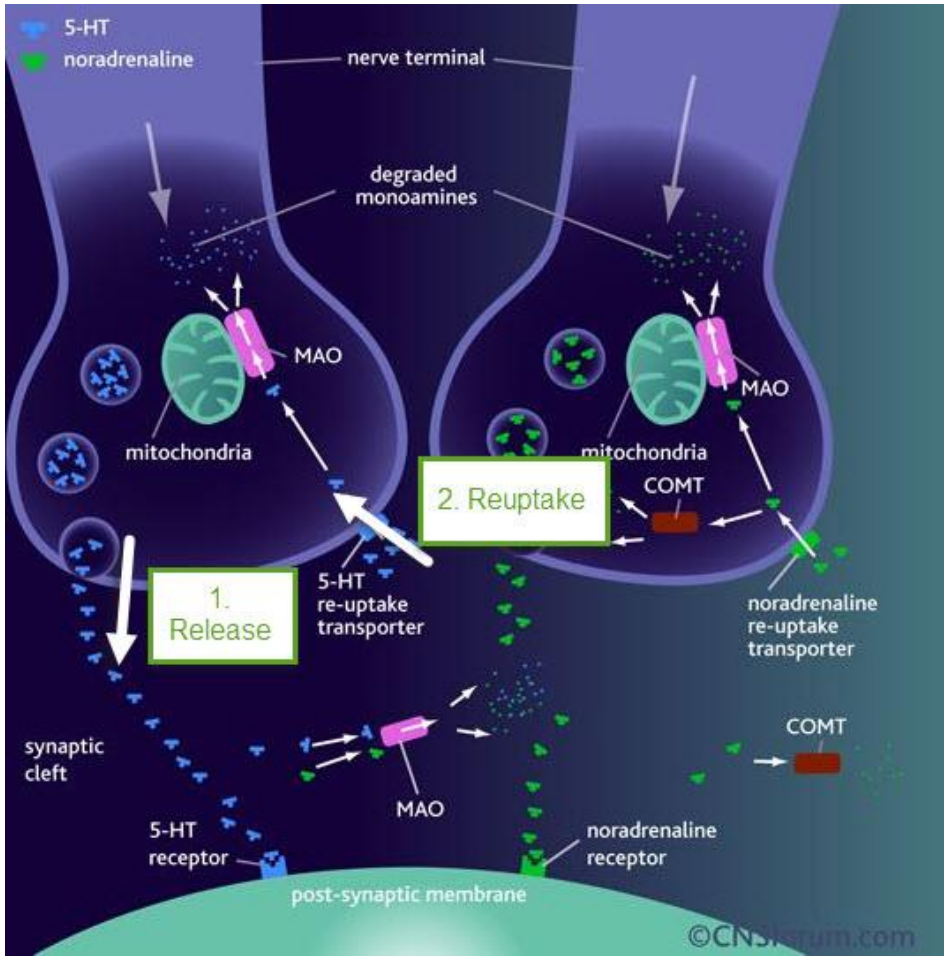
Enlarge This Image

IN terms of perception, these are hard times for antidepressants. A number of articles have suggested that the drugs are no more effective than placebos.

Last month brought an especially high-profile debunking. In an essay in The New York Review of Books, Marcia Angell, former editor in chief

Prof Lewis Wolpert
Editor-in-Chief
Journal of Theoretical Biology

Selective serotonin reuptake inhibitors SSRI (Fluoxetine)- are antidepressant drug prescribed for the treatment of major depression associated with mood disorders.



The Aim of an Antidepressant is to stabilize and normalize the neurotransmitters in our brain. Neurotransmitters such as serotonin, dopamine and norepinephrine play a role in regulating our mood.

The Role of Microglial Activation in Illness-Associated Depression

Evidence for microglia involvement:

- Various bacterial and viral infections are associated with a range of depressive symptoms. They induce microglial activation and the secretion of proinflammatory cytokines

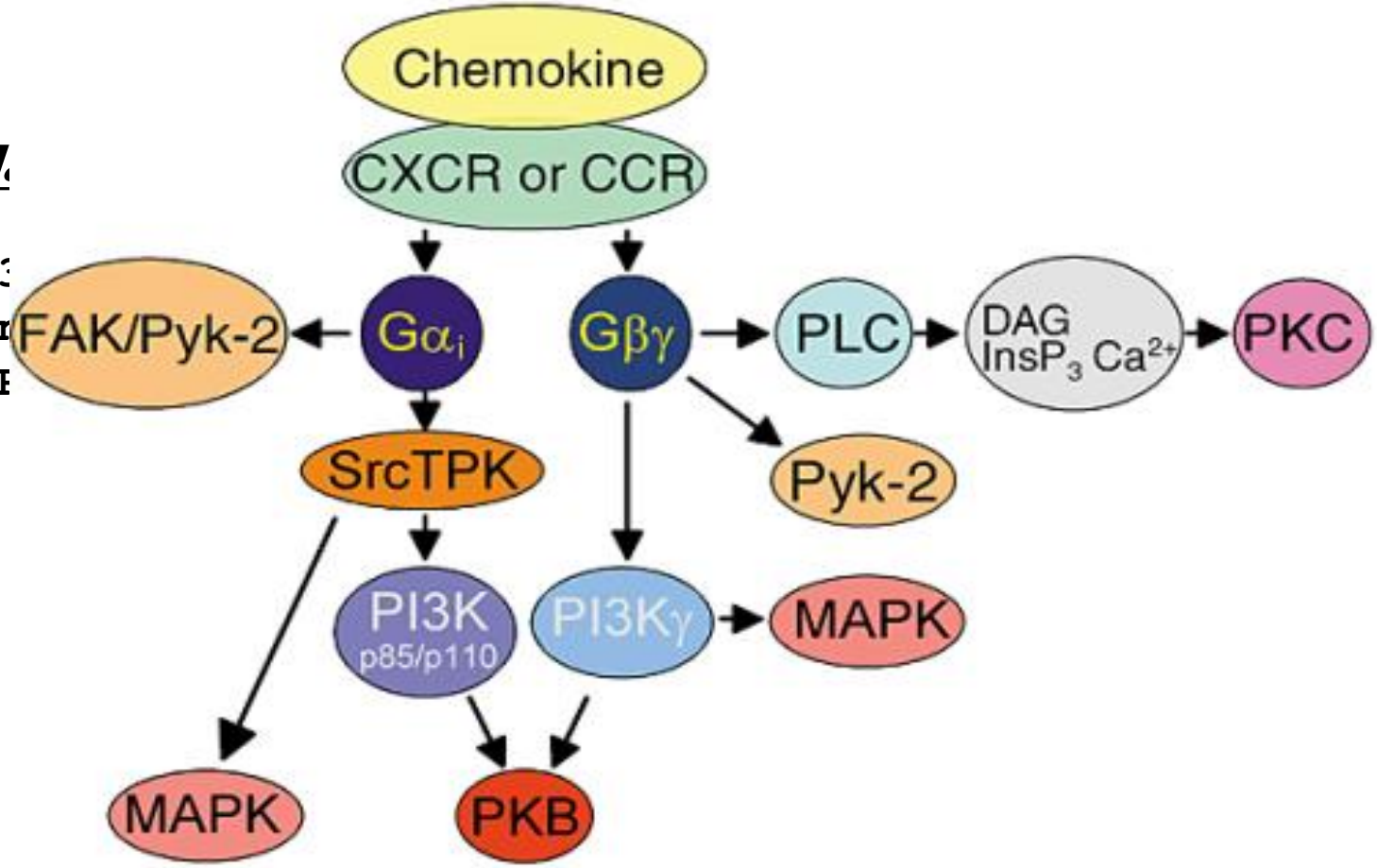
- Experimental administration of immune challenges that are known to activate microglia (e.g., LPS or Salmonella) induces depressive symptoms, whose severity is highly correlated with elevated blood levels of inflammatory cytokines

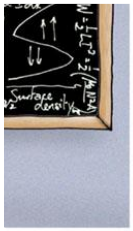
Chemokines

-

Cl ***es***

CX3 L1
nor #
ELR #
4C
6C
C:





ple

J Neuroimmunol. 2009 Oct 30;215(1-2):36-42.

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Maggi L[1], Trettel F, Scianni M, Bertollini C, Eusebi F, Fredholm BB, Limatola C.

Adverse Stresss

Various physiological, psychological and behavioral reactions to so-called 'stressors' such as an environmental condition or a stimulus

- Stress is often described as a feeling of being overwhelmed, worried or run-down

- Stress can affect people of all ages, genders and circumstances and can lead to both physical and psychological health issues

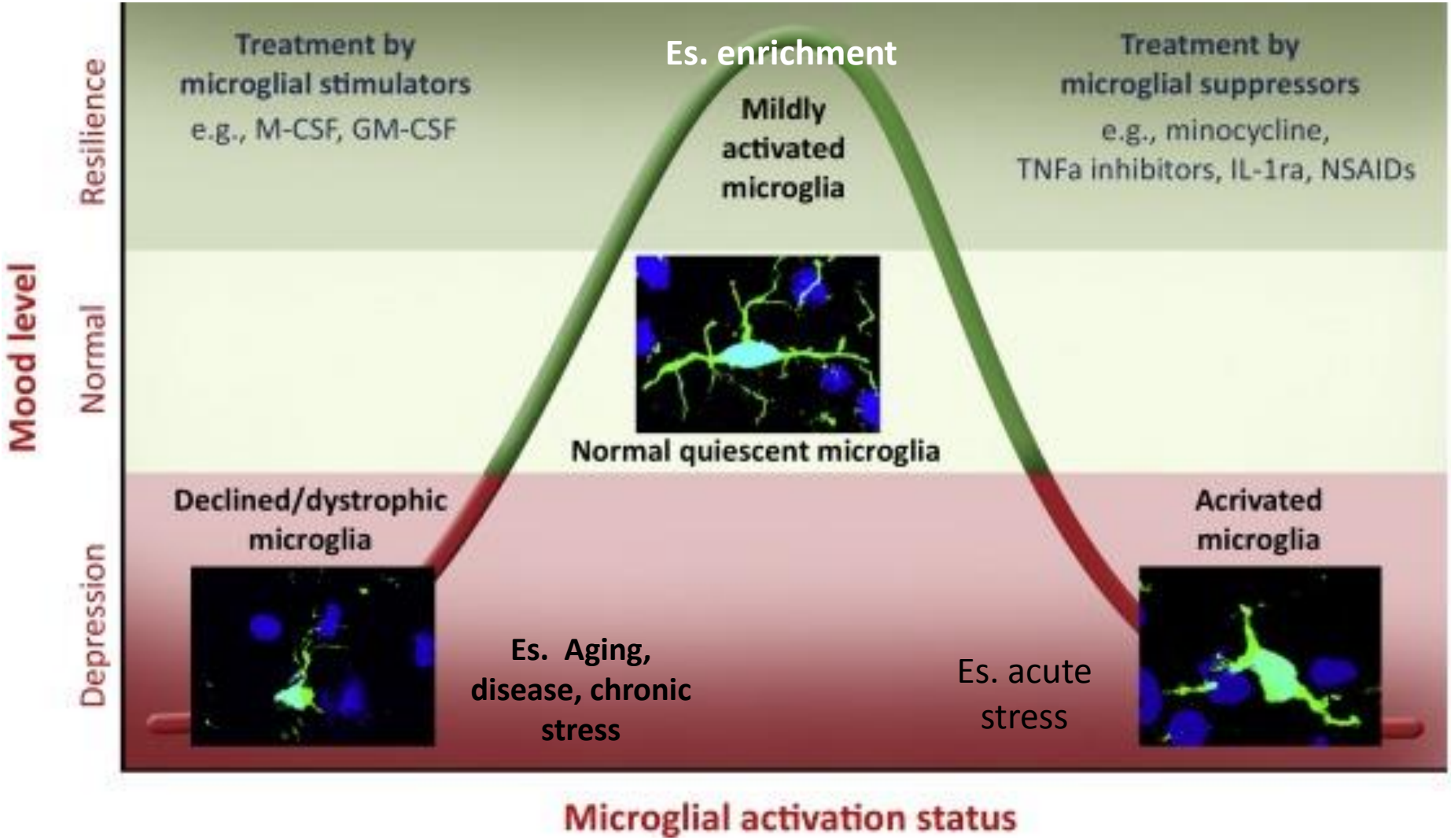
…in the brain

- Stress has a well-established influence on brain structure, function, and behavior *(Radley et al 2011)*

- Optimal stress level facilitates long-term memory and stimulates cognitive performance by promoting consolidation but….

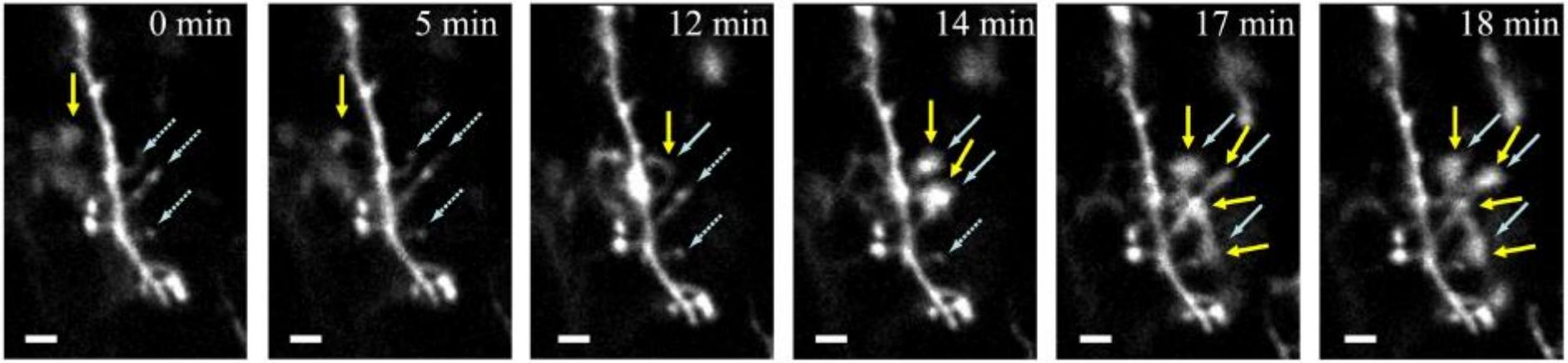
- Exposure to extreme, traumatic or chronic stress, on the contrary, can lead to cognitive impairments, neuroinflammation and psychopathological disorders such as anxiety disorders, depression and posttraumatic stress disorder. *(de Kloet et al., 2005; Finsterwald and Alberini, 2014).*

Deviations From Microglial Homeostasis Induce Depression



Yirmiya R et al. *Trends Neurosci.* 2015

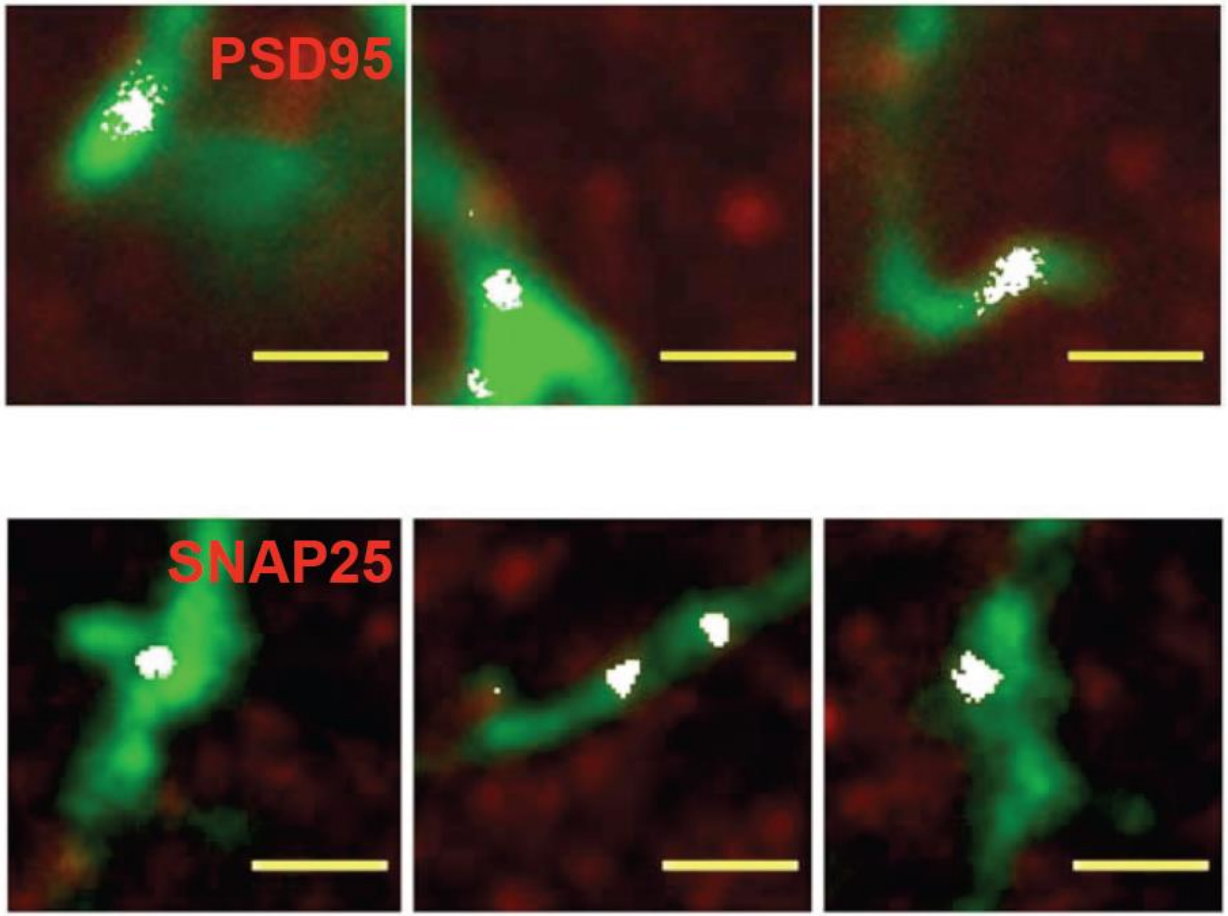
Microglial processes contact synapses in the healthy brain



Resting microglial processes make brief (5 min) contacts with neuronal synapses (1|hour)

•Reduced in frequency by reductions in neuronal activity

Micoglial processes engulf synaptic material



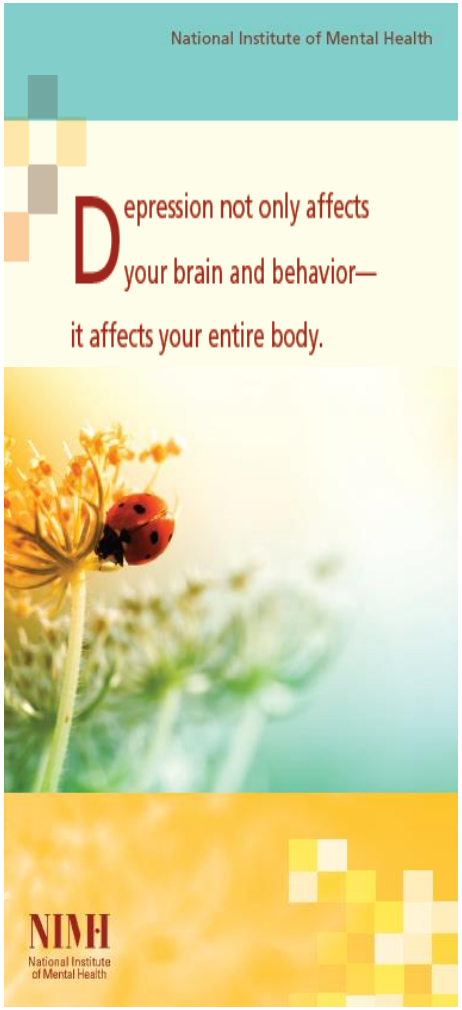
Microglia are dynamic sensors during activity-dependent synaptic remodeling and may be actively engulfing synapses destined for elimination

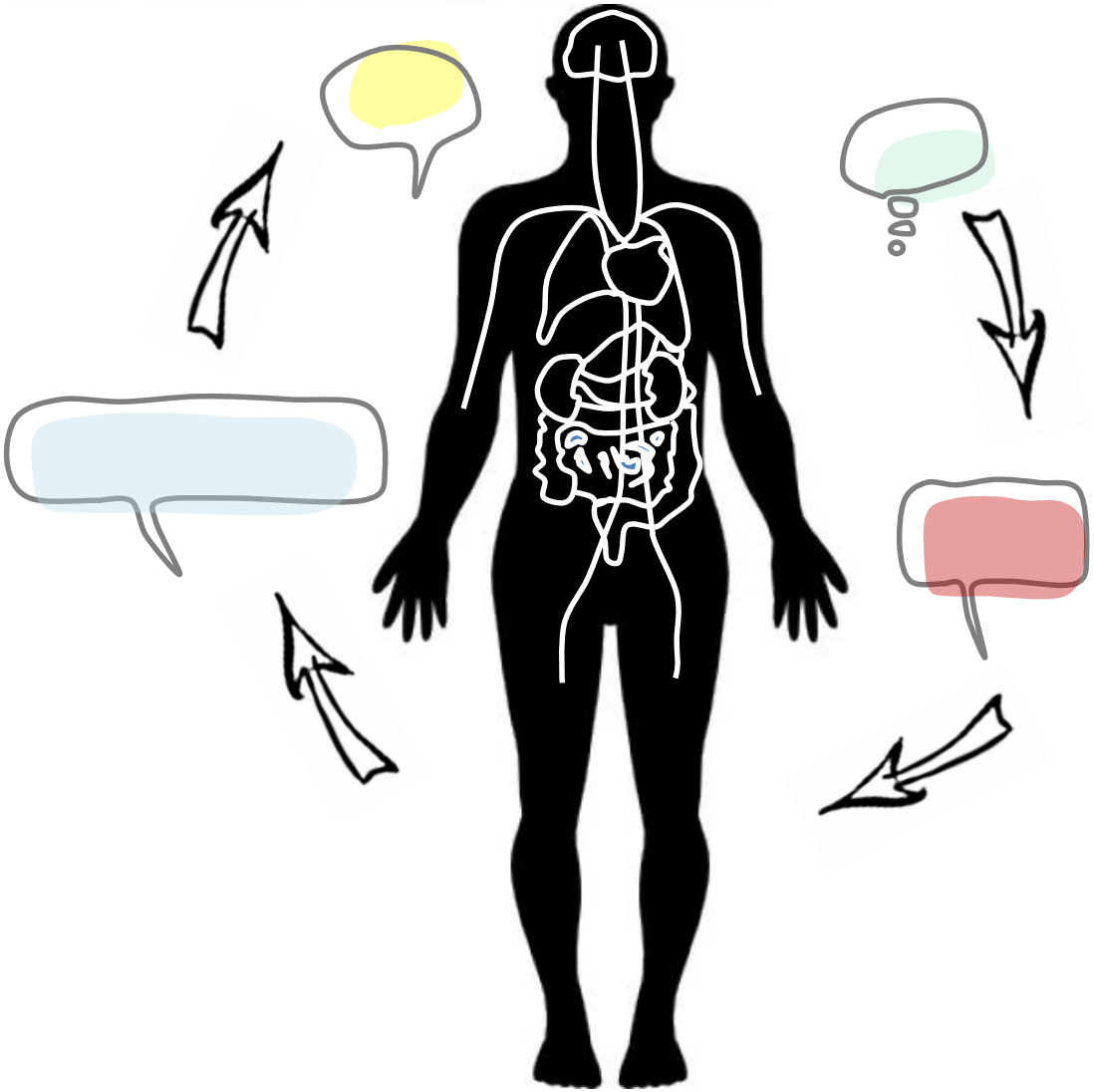
Science **333**, 1456 (2011)

Synaptic Pruning by Microglia Is Necessary for Normal Brain Development

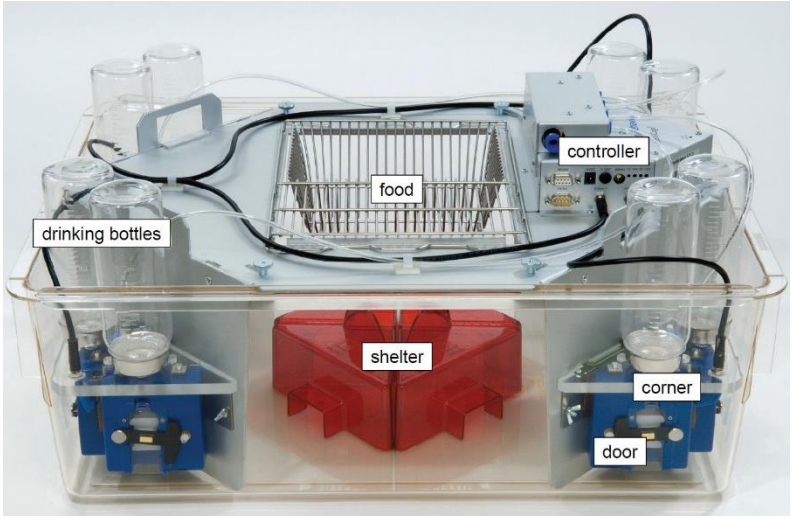
Rosa C. Paolicelli,[1] Giulia Bolasco,[1] Francesca Pagani,[2] Laura Maggi,[2] Maria Scianni,[2] Patrizia Panzanelli,[3] Maurizio Giustetto,[3,4] Tiago Alves Ferreira,[1] Eva Guiducci,[1] Laura Dumas,[1] Davide Ragozzino,[2] Cornelius T. Gross[1]*

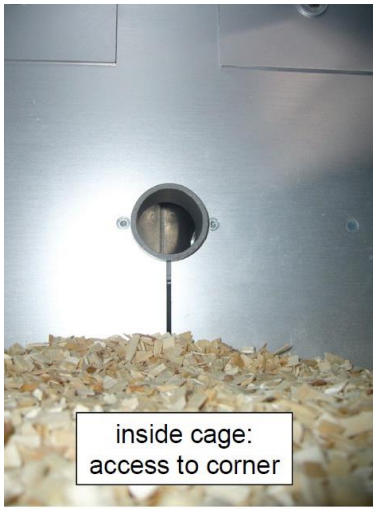
Depression is a total body disease

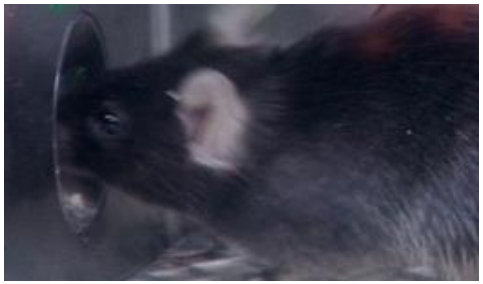




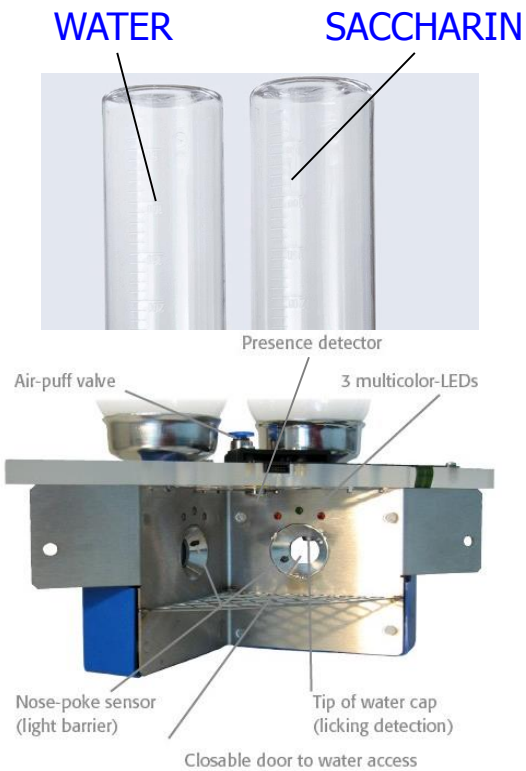
INTELLICAGE







nosepoke

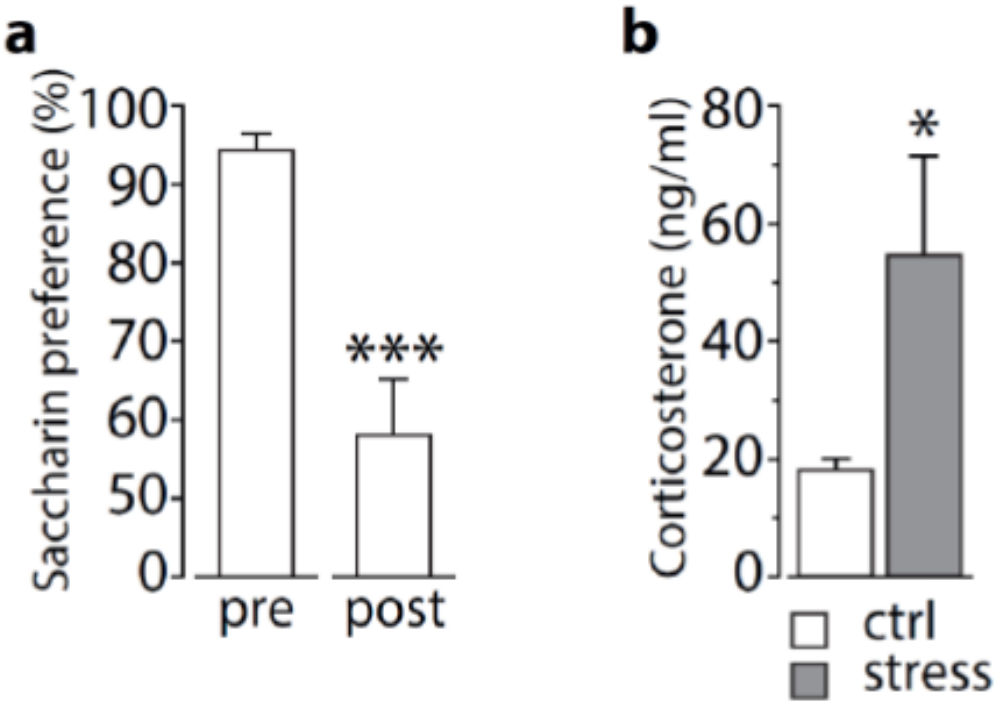


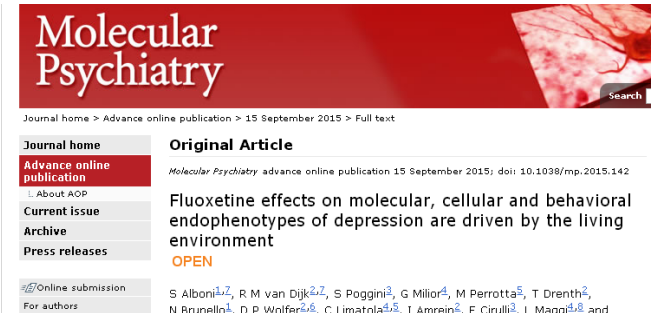
Liking-type anhedonia

preference =
saccharin/
(water + saccharin)

Dr. I. Branchi. ISS

Effects of the exposure to two weeks of stressful condition, before treatment, on anhedonic response and corticosterone levels





Molecular Psychiatry

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Original Article

Molecular Psychiatry advance online publication 15 September 2015; doi: 10.1038/mp.2015.142

Fluoxetine effects on molecular, cellular and behavioral endophenotypes of depression are driven by the living environment

OPEN

S Alboni[1,7], R M van Dijk[2,7], S Poggini[3], G Milior[4], M Perrotta[5], T Drenth[2], N Brunello[1], D P Wolfer[2,6], C Limatola[4,5], L Amrein[2], F Cirulli[3], L Maggi[1,8] and

Factors, systems, molecules ..participating in DM

ENVIRONMENT

NERVOUS SYSTEM

Neurotrofine (BDNF)

GC, CR

NT (5-HT, DA, NE, Glu, Gly, His)

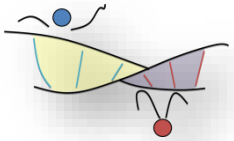
ENDOCRINE SYSTEM

IMMUNE SYSTEM

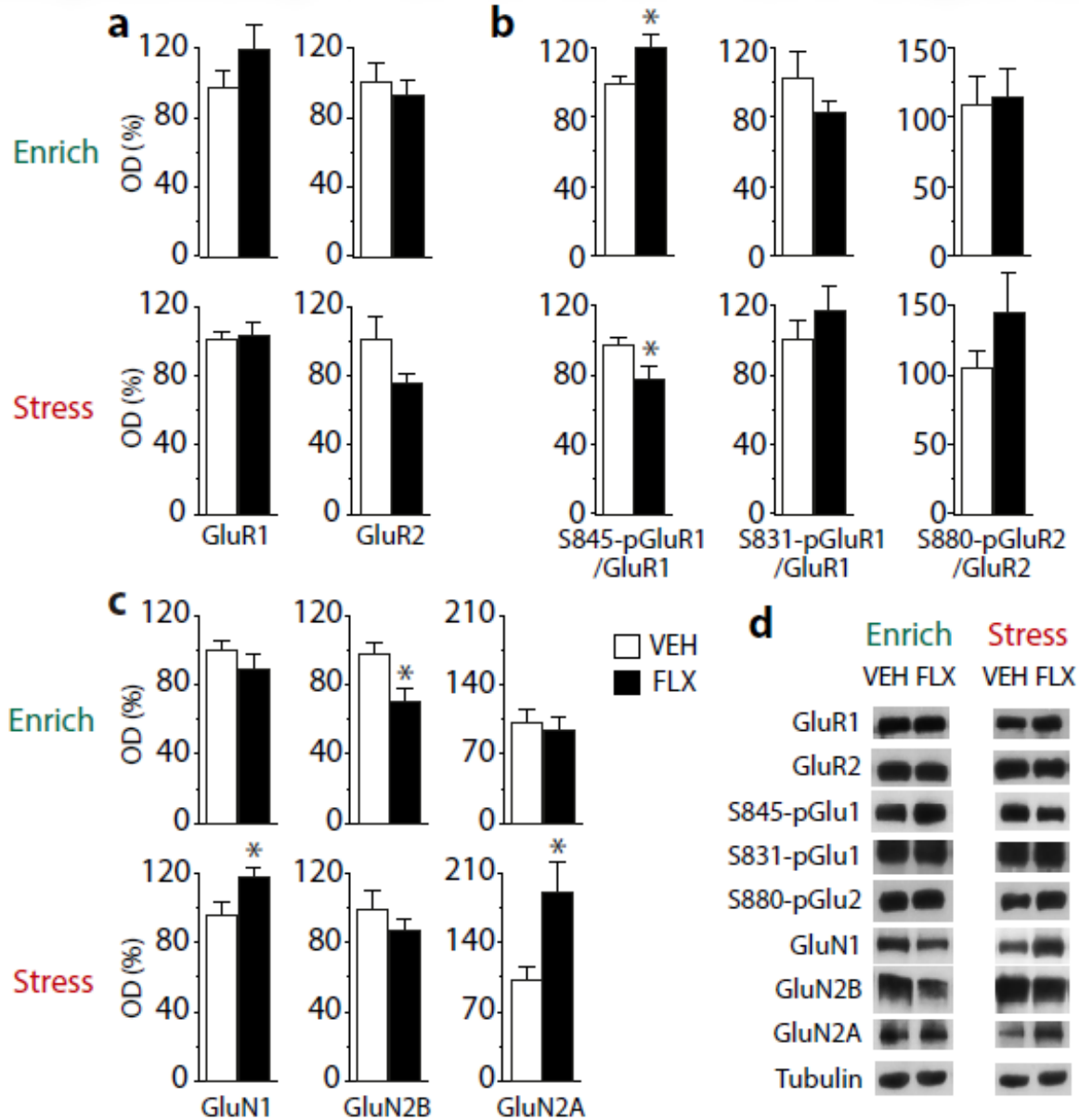
Citokines

EPIGENETICS

GENE



Fluoxetine modifies molecular and cellular correlates of synaptic plasticity in an environment-dependent manner



Symptoms of Depression

- Vary from person to person

Major depression - DSM 5

- Depressed mood
- Loss of interest or pleasure
- Change in weight or appetite
- Insomnia or hypersomnia
- Psychomotor retardation or agitation (observed)
- Loss of energy or fatigue
- Worthlessness or guilt
- Impaired concentration or indecisiveness
- Thoughts of death or suicidal ideation or attempt

Hippocamapal volume and neurogenesis

Fluoxetine treatment administered in stressful condition leads to a reduction of proliferation and hippocampal volume

Putative progenitor cells

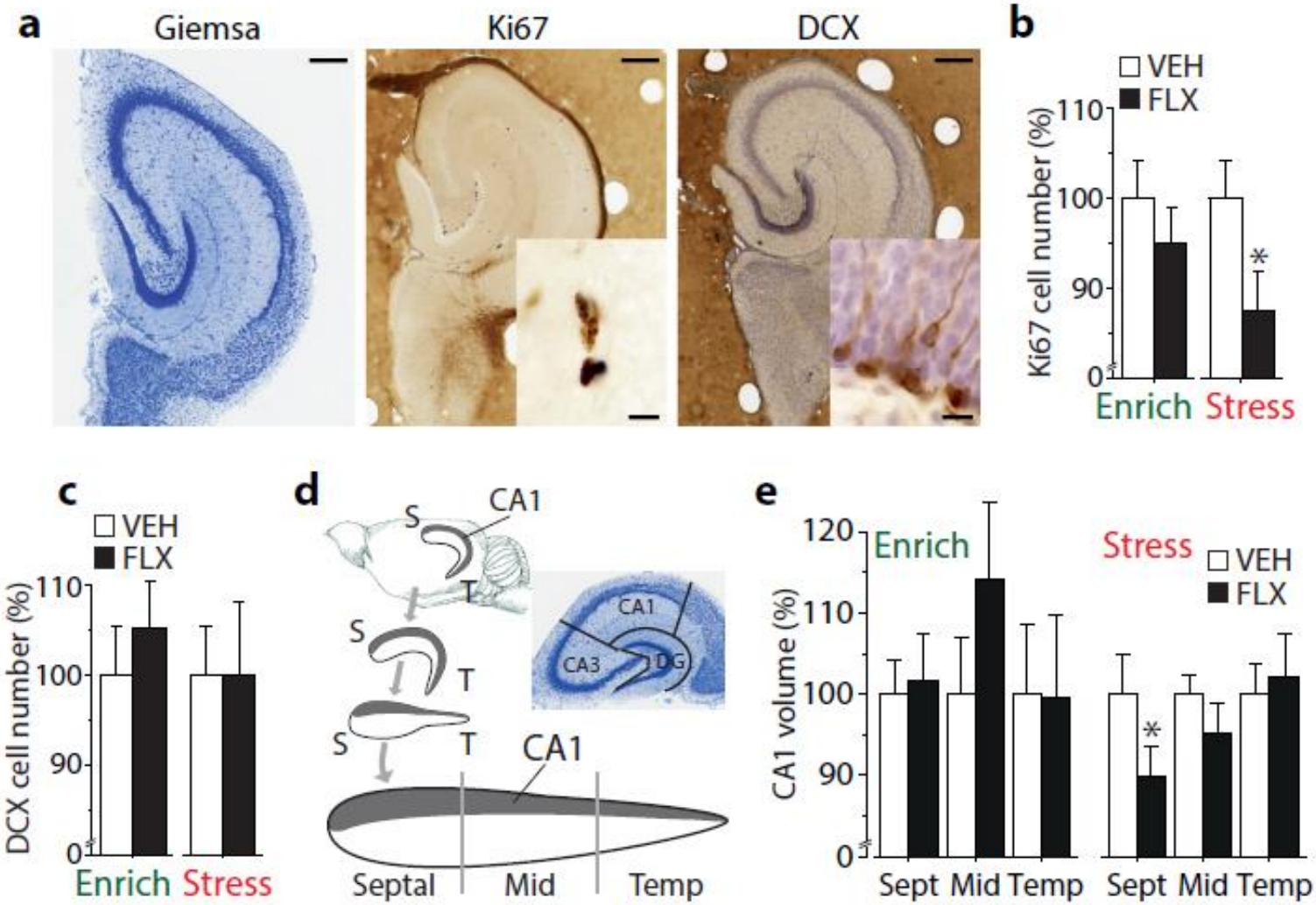
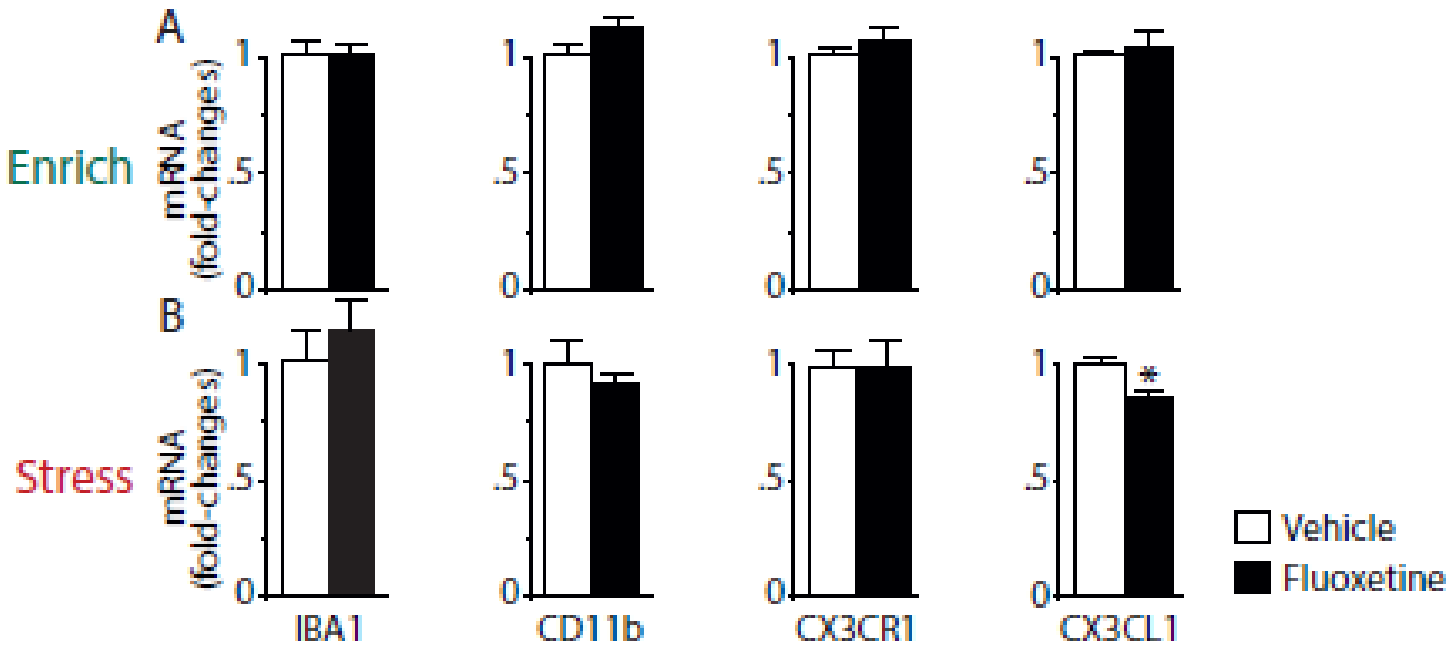


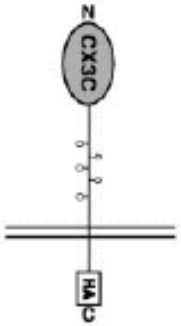
Table 1. Effects of fluoxetine, compared to vehicle, in the enriched and the stressful conditions

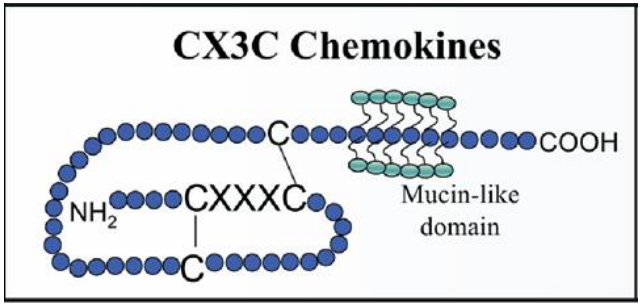
	Reduction in liking-type anhedonia	Reduction in wanting-type anhedonia	Cognitive bias	Neurogenesis (Ki67)	ERK signaling	CREB signaling	BDNF levels	Reduction in CORT levels	LTP
Enriched Condition	-	↑	↑	-	-	-	↑	↑	-
Stressful Condition	↓	↓	-	↓	↓	↓	-	-	↑

Microglial modulation by fluoxetine upon environmental stimulation



Why fractalkine?





Costitutively expressed in the brain (neurons) with particularly high levels in hippocampal neurons

Exists in membrane anchored and soluble form (cleaved by metalloproteases)

Binds to a unique G-protein coupled receptor on microglia: CX_3CR1

Is neuromodulatory on glutamatergic transmission

CX_3CR1 ko a defective microglial model

•Abnormal physiological microglial properties (hyperactive microglial cell)

•Abnormal morphology

•Reduced microglial monitoring

Dark microglia: A new phenotype predominantly associated with pathological states

Bisht K, Sharma KP, Lecours C, Sánchez MG, El Hajj H, Milior G, Olmos-Alonso A, Gómez-Nicola D, Luheshi G, Vallières L, Branchi I,Maggi L, Limatola C, Butovsky O, Tremblay MÈ

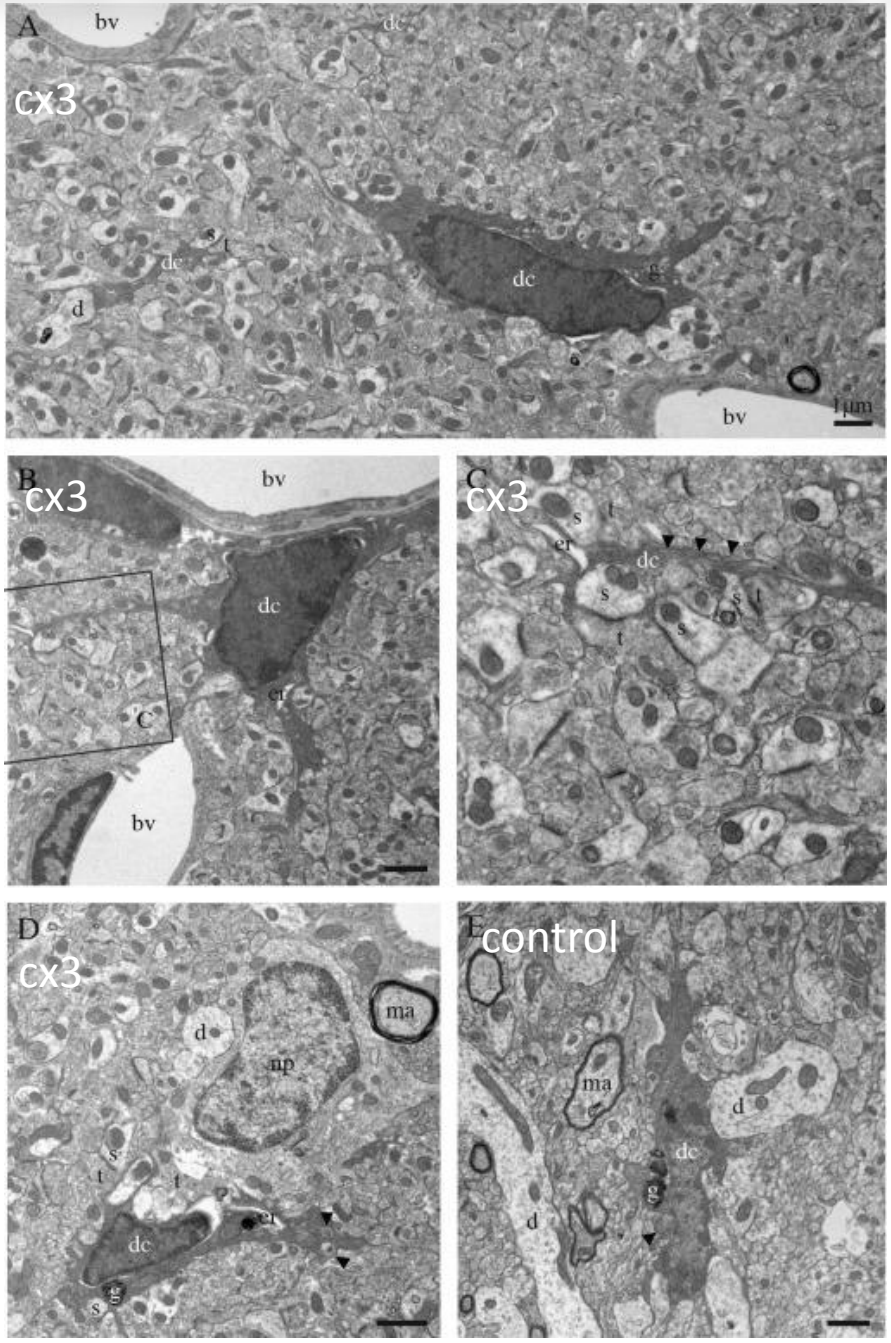
Glia. 2016 May; 64(5): 826–839

Exhibit several signs of oxidative stress, including a condensed, electron-dense cytoplasm and nucleoplasm making them as “dark” as mitochondria, accompanied by a pronounced remodeling of their nuclear chromatin

Appear to be much more active than the normal microglia, reaching for synaptic clefts, while extensively encircling axon terminals and dendritic spines with their highly ramified and thin processes

Stain for the myeloid cell markers IBA1 and GFP (in CX_3CR1-GFP mice), and strongly express CD11b and microglia-specific 4D4 in their processes encircling synaptic elements

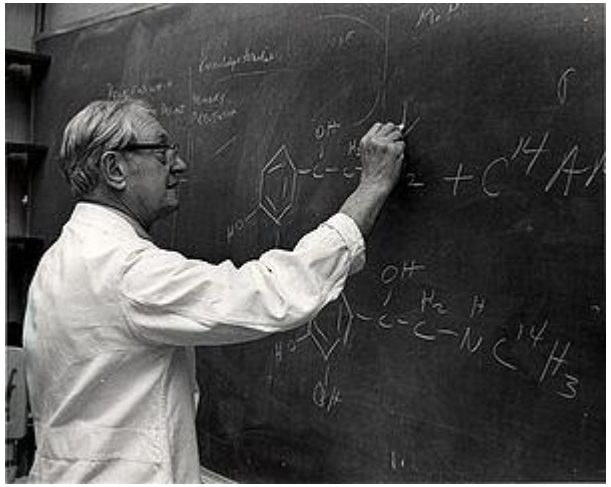
Ultrastructural features of the dark microglia



Endoplasmic reticulum

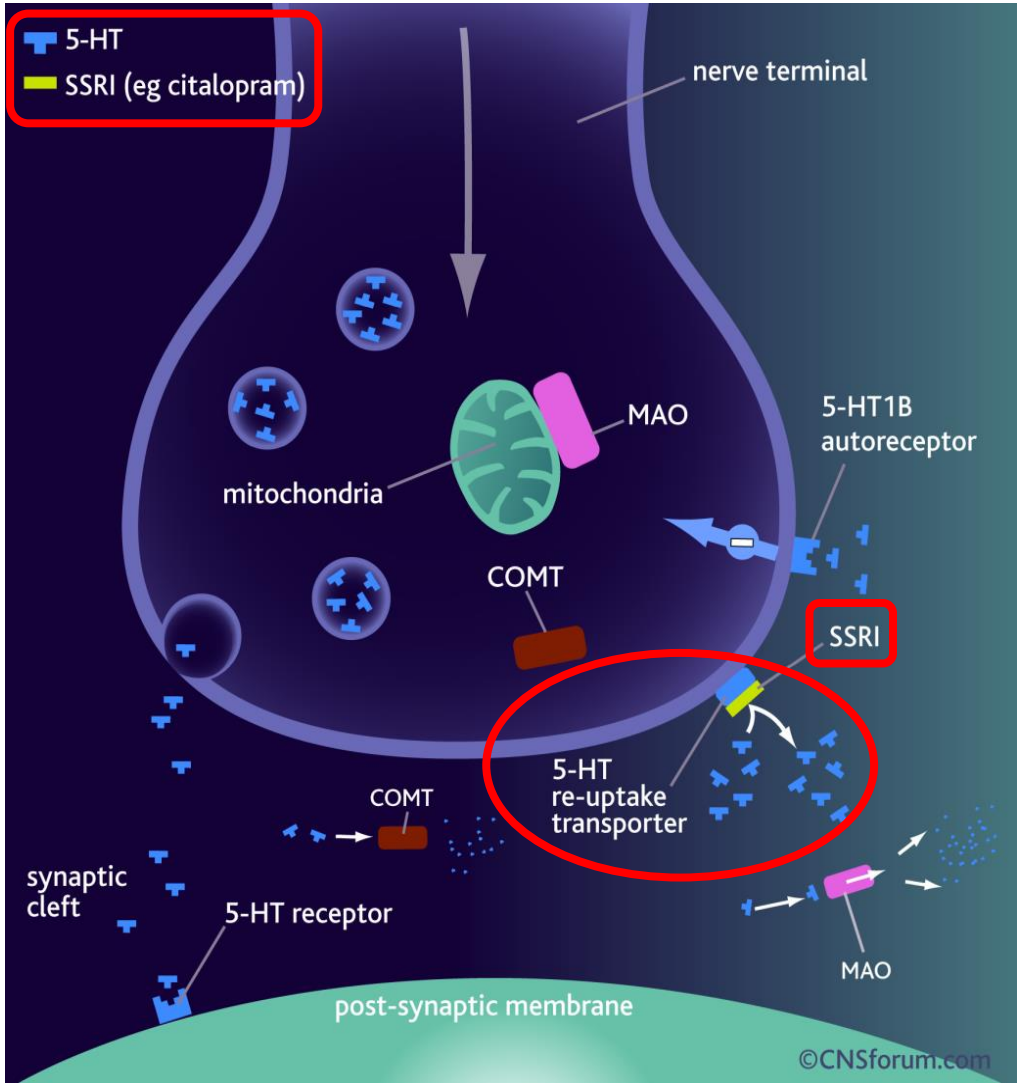
ANTIDEPRESSANTS

Selective Serotonin Reuptake Inhibitors (SSRI)



Julius Axelrod
awarded with the Nobel Prize in physiology or medicine for his work on neurotransmitters in 1970

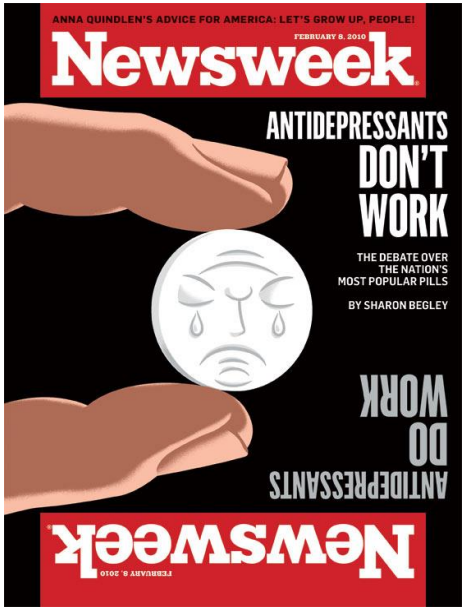
the 5-HT synapse

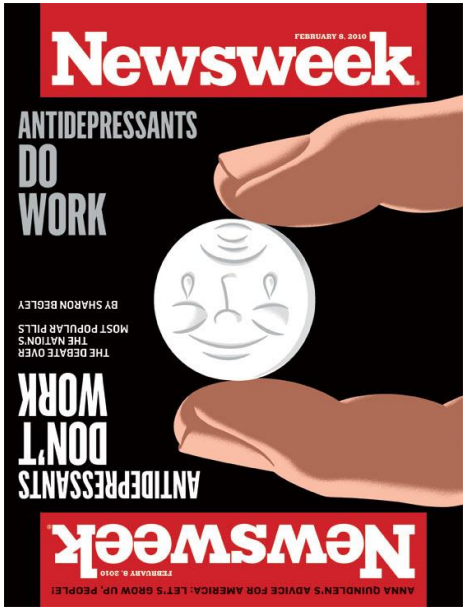


Antidepressant have incomplete efficacy

30-40% does not show a significant response to antidepressants

60-70% of depressed patients does not experience remission

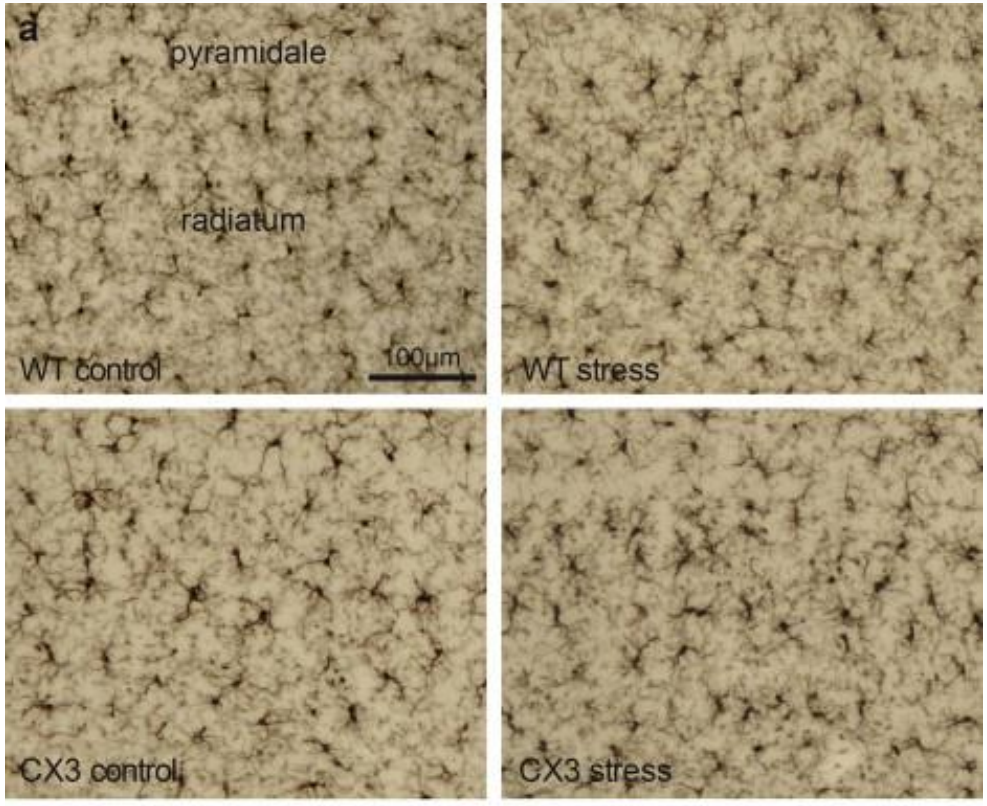


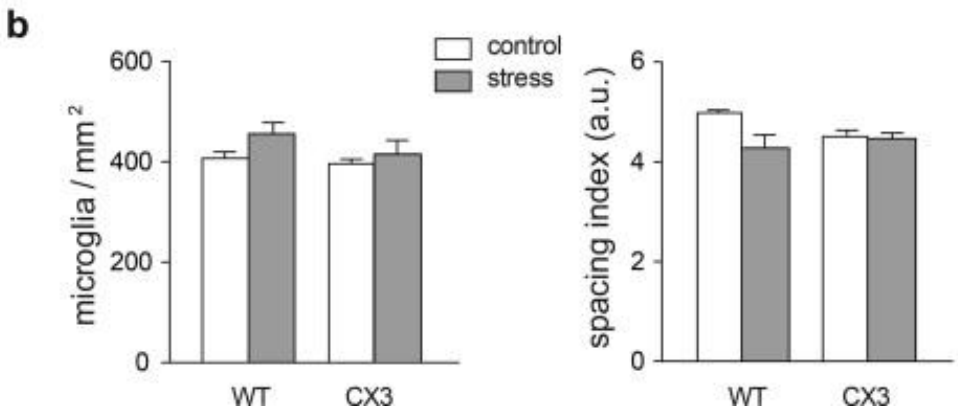


the debate is open and hot

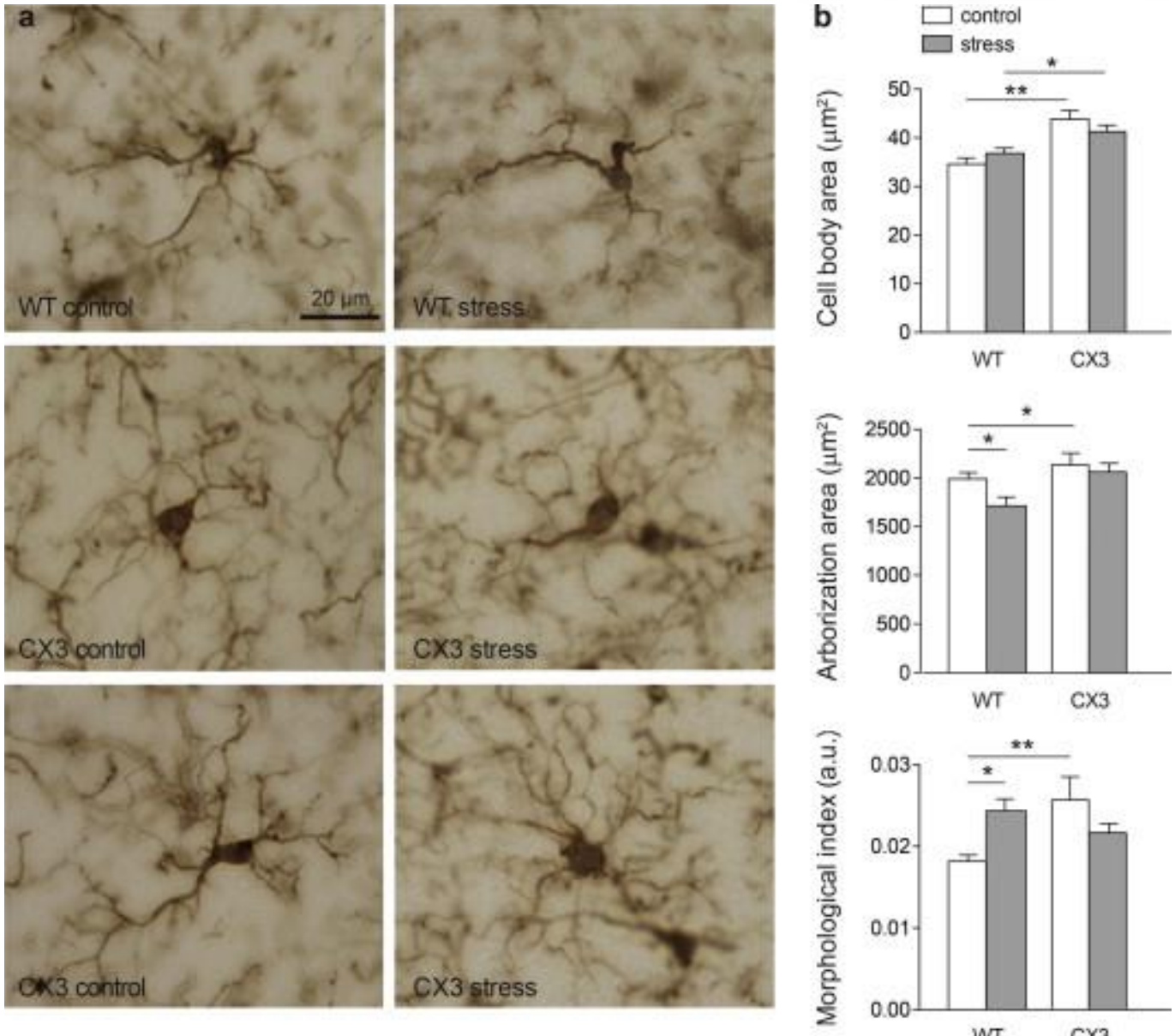
Effects of chronic unpredictable stress on microglial density and spacing in CA1 radiatum

Microglia morphology



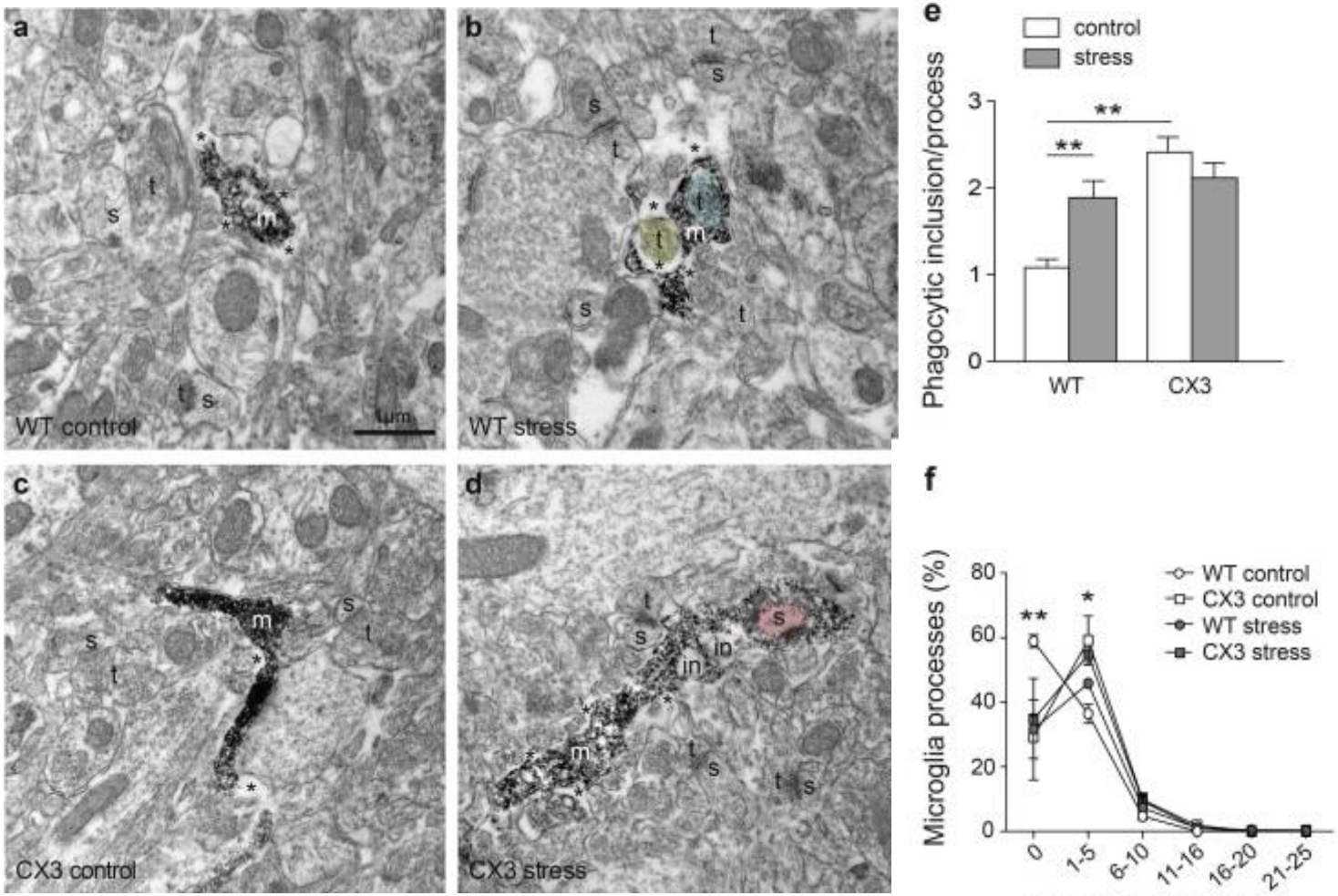


Effects of chronic unpredictable stress on microglial cell body and arborization area, and morphological index



Effects of chronic unpredictable stress on microglia phagocytosis of synaptic elements

Electron Microscopy



Electron microscopy Iba-1 immunostaining

Microglia participate in the remodeling of neuronal circuits by their phagocytic elimination of synapses *(Tremblay E et al. 2013)*