Neuron - Glia Interactions

Module: Anatomy of the CNS
WS 2017-18

Tuesday 24.10.2017, 16:00 – 18:00

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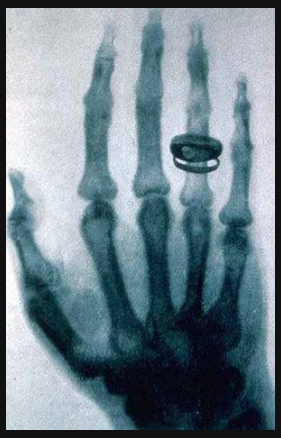


curriculum vitae *and aknowledgements*

- **Medicine** in Greece, Medical School University of Patras (1998-2004)
  - Lab assistant, Tight Junctions
- Rural Medical Service (2005-2007)
- **Master of Science** in Medical Neurosciences (2007-2009) and
- **Ph.D.** in Medical Neurosciences, Charite Universitätsmedizin zu Berlin (2009-2013)
  - Glia alterations in electrophysiological diseases (a.k.a. epilepsy)
  - Glia - Neuron interactions and synaptic plasticity
  - Electrophysiology, Morhology / Neuroananomy, Live cell imaging, Molecular biology, Neural Data Analysis (MatLab) ...
- **Post-Doc** in Neurophysiology, University of Heidelberg (2011-2014)
  - Microglial modulation of synaptic function, toxicity and neurodegeneration
- Since 2014: **Residency in Radiology**
  - Universitätsmedizin Göttingen
  - Südharz Klinikum Nordhausen

Prof.Dr.med. Uwe Heinemann

Prof.Dr.med. Uwe-Karsten Hanisch

Prof.Dr.med. Helmut Kettenmann

Timetable

- **16:00 – 17:00**

  Part I: Historical annotation

  Part II: Glia, an evolutionary outlook

  Part III: The tripartite synapse

  Part IV: Metabolic interactions: the lactate shuttle

  Summary, questions and take home message

- **17:15 – 18:00**

  Part V: Microglia. Mesodermal niches and lifelong turnover

  Part VI: Synaptoimmunology

  Part VI: Synaptic tagging, stripping, pruning

  Summary, questions and take home message

Part I
Historical annotation
The glial scientific heritage

Glia turns 171 this year

- Rudolf Virchow (1821 - 1902)
  - Über das granulierte Aussehen der Wandung der Hirnventrikel, *Virchow 1846*
  - "... the connective substance forms a sort of cement ... in which the nervous elements are embedded ..."
- Otto Deiters (1834 – 1863[1])
- Santiago Ramon y Cajal (1852 – 1934)
  - The Deiter´s cell

ASTROCYTE was born

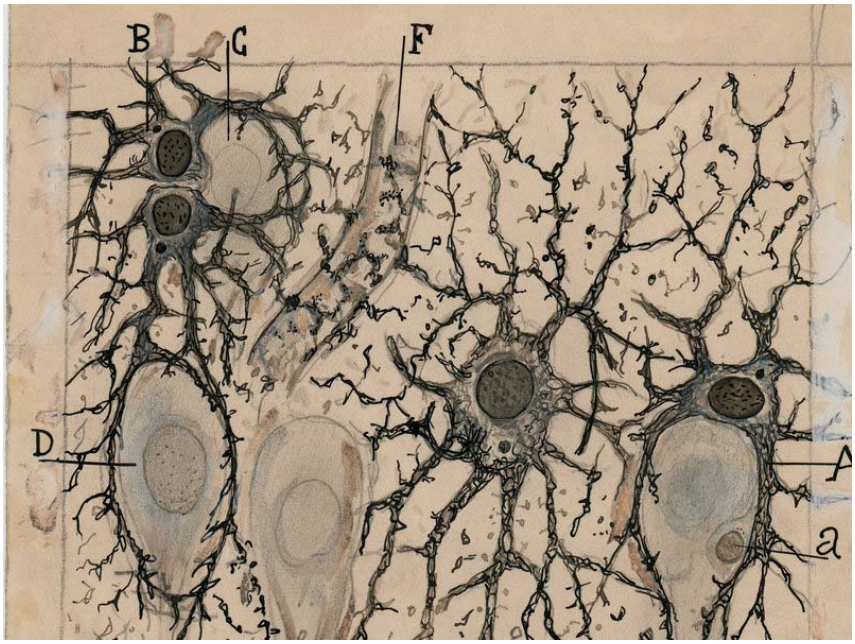
The brain

The one who died young

And the artist

Footnotes

1. Deiters died in 1863 from typhoid fever at the age of 29

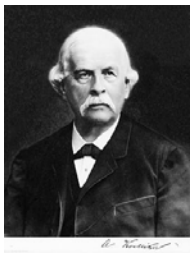


The Deiter´s cell of Ramon y Cajal

- Shiny nucleus
- No nucleolus
- Fibers ...
- That project all directions
- In white and gray matter

Glia turns 171 this year

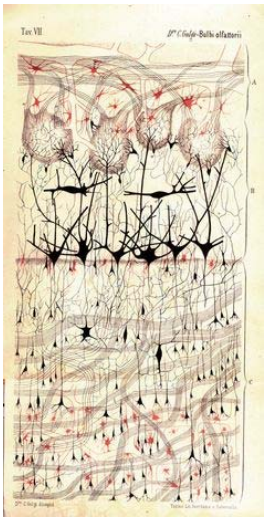
- Camillo Golgi (1843 - 1926)
  - "la reaziona nera"
  - Golgi staining
- Mihály Lenhossék (1863 – 1937)
  - ... coined the term "astrocyte" *Lenhossek, 1893*
- Albert von Kölliker (1817 – 1905)
  - Langstrahler == fibrous astros
  - Kurzstrahler == protoplasmic astros



Camillo Golgi

The Golgi staining

CAVE: Unspecific !!!



Albert von Kölliker (1817 – 1905)

„Physikalisch-Medizinische Gesellschaft“

1849 gründete er in Würzburg die „Physikalisch-Medizinische Gesellschaft“. Diese Institution erlebte ihre Sternstunde am 23.

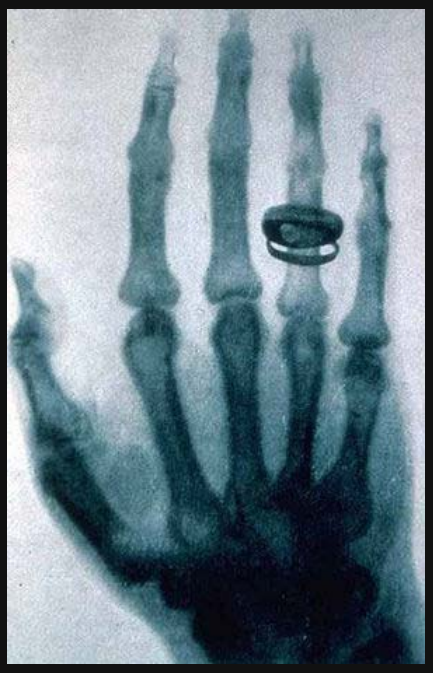
Januar 1896,
als der Würzburger Physikprofessor

Wilhelm Conrad Röntgen

über die von ihm entdeckten „X-Strahlen“ berichtete und

eine Aufnahme von Koellikers Hand anfertigte.

Auf Albert von Koellikers Vorschlag hin heißen sie heute Röntgenstrahlen.



Function of astrocytes: more than "glue"

- Virchow (1821-1902)

  " ... substance that lies between the nervous parts, holds them together and gives the whole its form ..." *Virchow, 1858*

  - The "filling" theory
  - The "isolation" theory

- Aloysius (Alois) Alzheimer (1864-1915)

  discribed "... glia reaction in brain plaques..." in one of the fist attempts infering to **glial function** *Alzheimer, 1910*

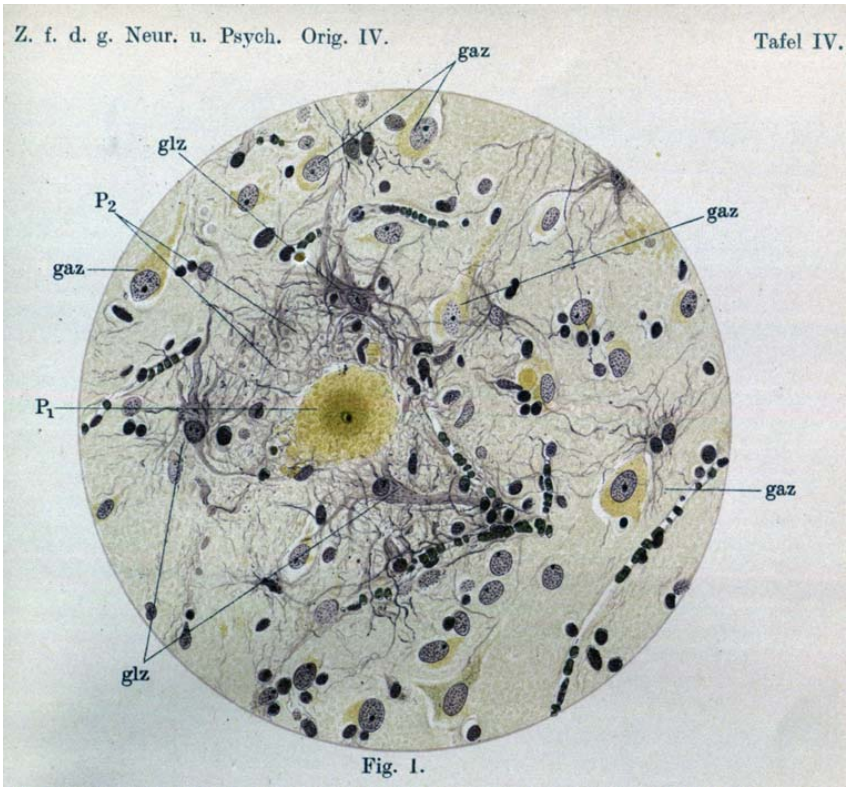


Fig. 1.

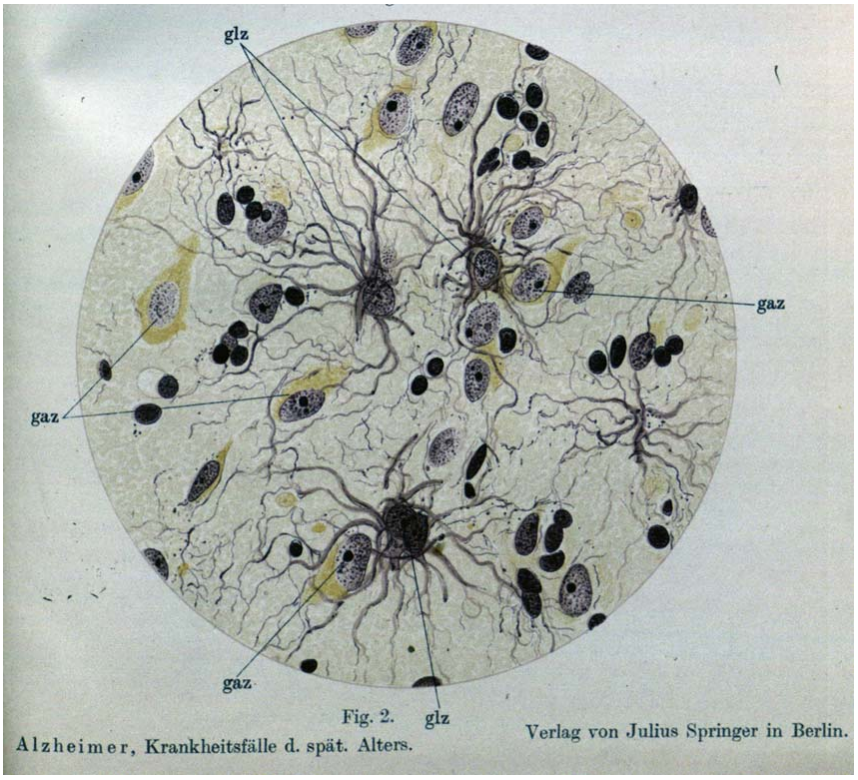
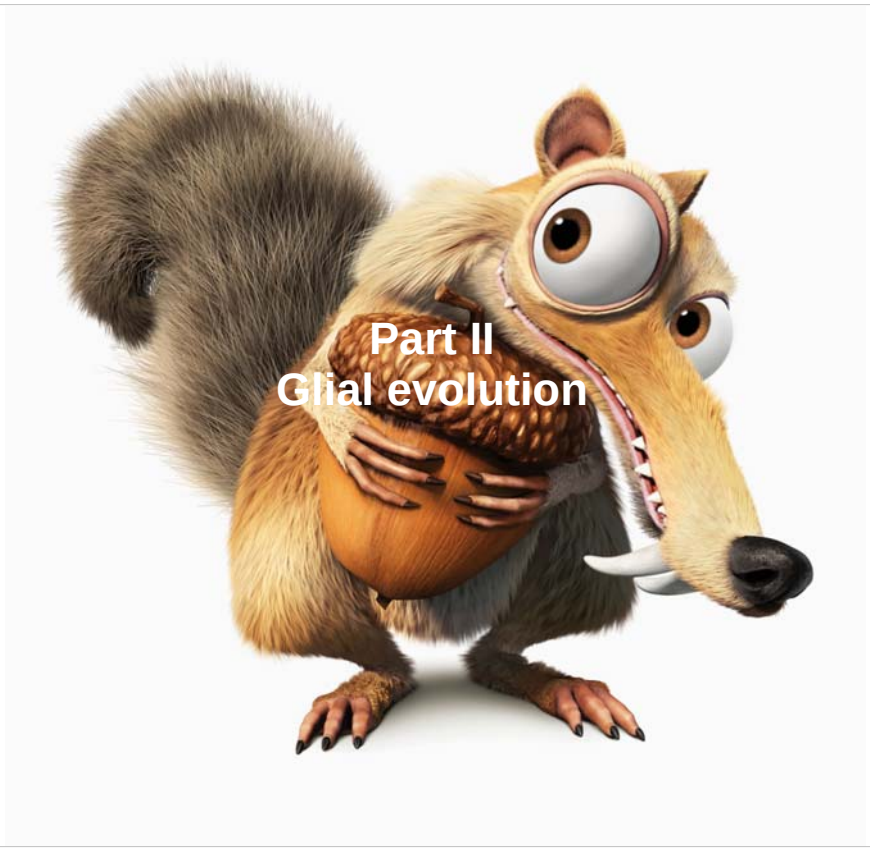


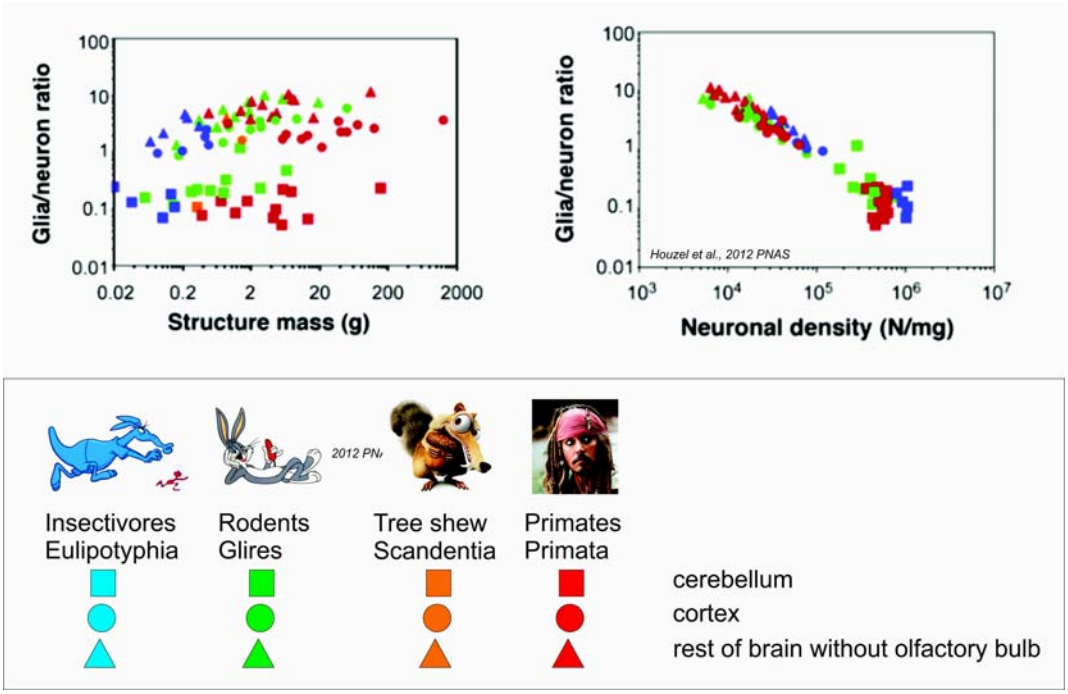
Fig. 2.

Alzheimer, Krankheitsfälle d. spät. Alters.

Verlag von Julius Springer in Berlin.

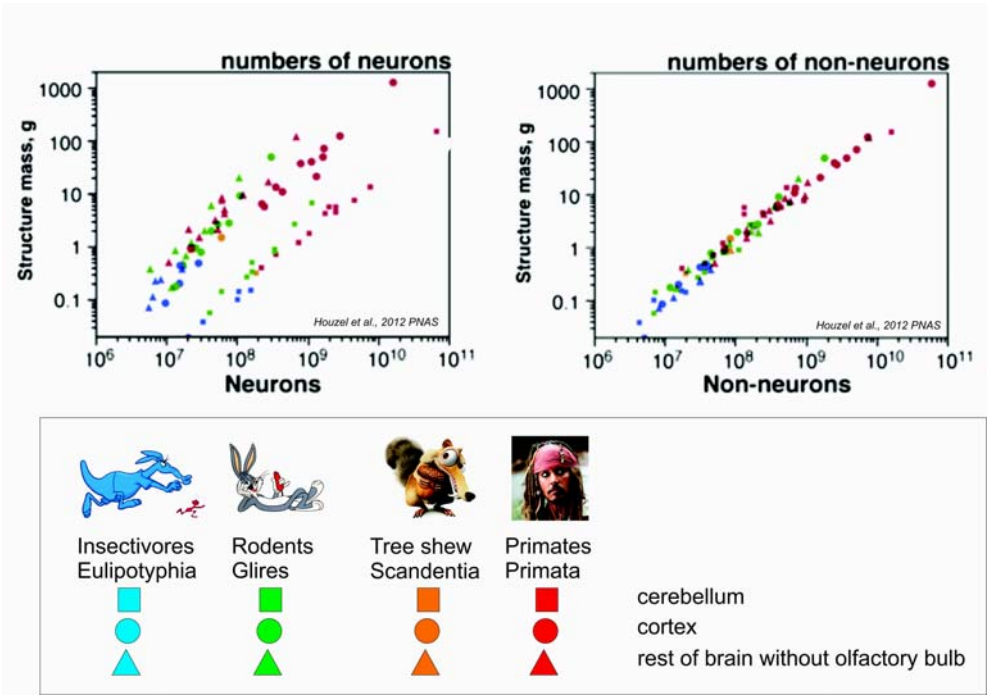


Part II
Glial evolution



Houzel et al., 2012 PNAS

Shared nonneuronal scaling rules and structure- and order-specific neuronal scaling rules for mammalian brains. Each point represents the average values for one species (insectivores, blue; rodents, green; primates, red; Scandentia, orange). Arrows point to human data points, circles represent the cerebral cortex, squares represent the cerebellum, and triangles represent the rest of the brain (excluding the olfactory bulb).

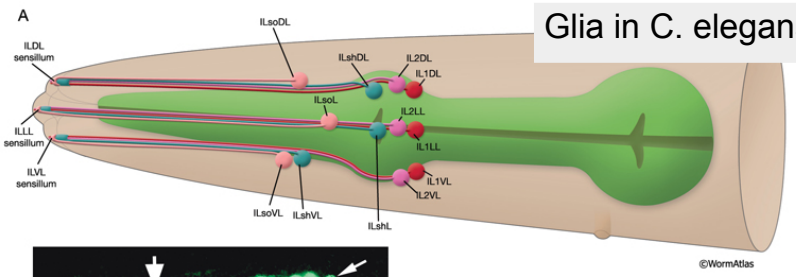


Houzel et al., 2012 PNAS

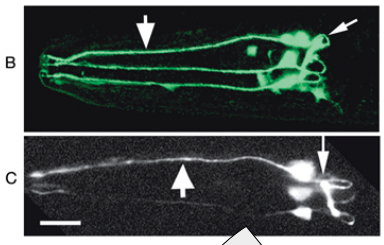
Fig. 5. G/N ratio scales differently across structures and orders with structure mass, but scales homogeneously with neuronal density. Each point represents the average other cell/neuron ratio (which approximates the G/N ratio) and structure mass (A) or neuronal density (B) in the cerebral cortex (circles), cerebellum (squares), or rest of brain (triangles) of a species. Notice that in contrast to the scattered distribution across species and structures in A, data points are aligned across species and structures in the lower plot, suggesting that it is smaller neuronal densities (i.e., larger average neuronal cell size), rather than larger structure mass, that is accompanied by a larger G/N ratio. Data are from studies by Herculano-Houzel and her colleagues (22–27).

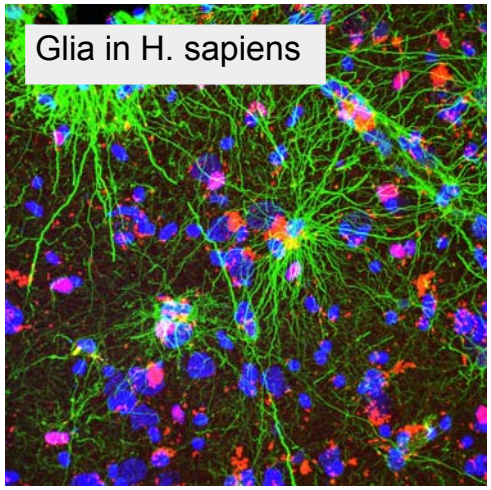
QUIZ

- What is your observation based on the study of Houzel et al., 2012 ?
- .....
- .....
- .....
- .....
- .....



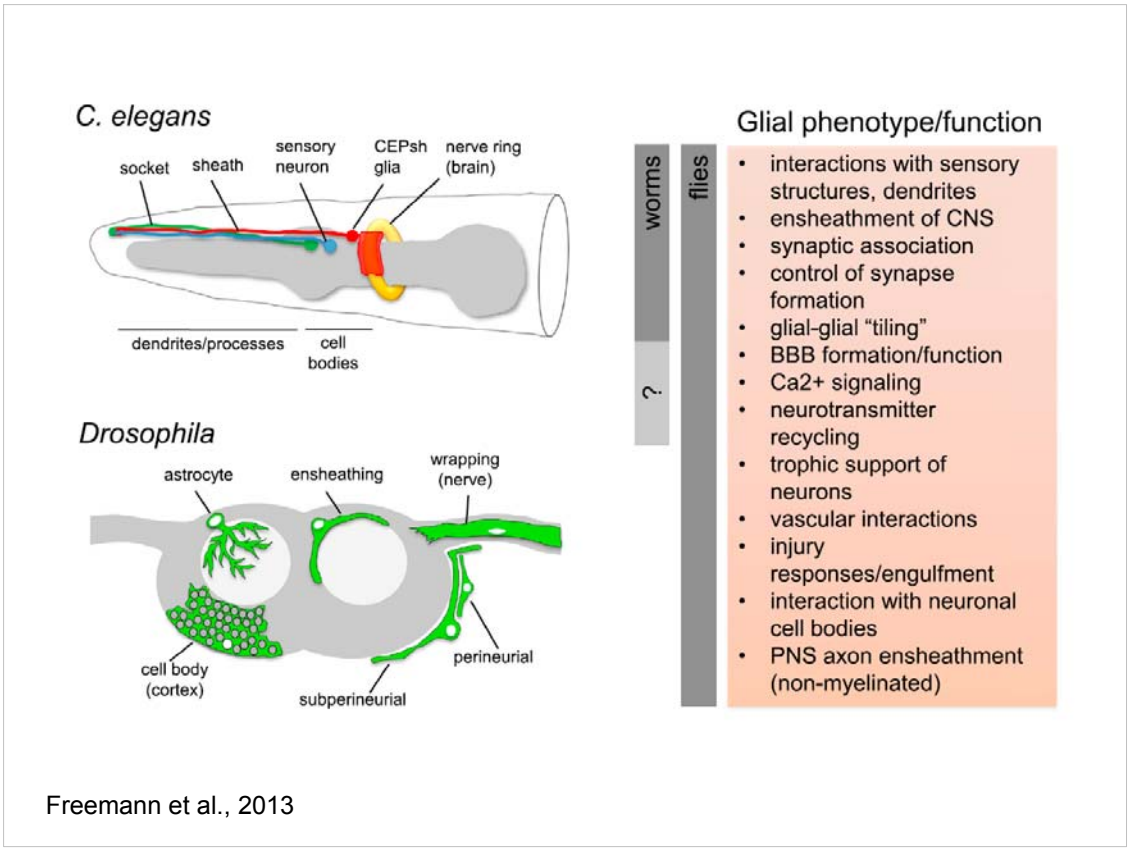
Glia in C. elegans (tapeworm)





Glia in H. sapiens

Scholey et al., 2007

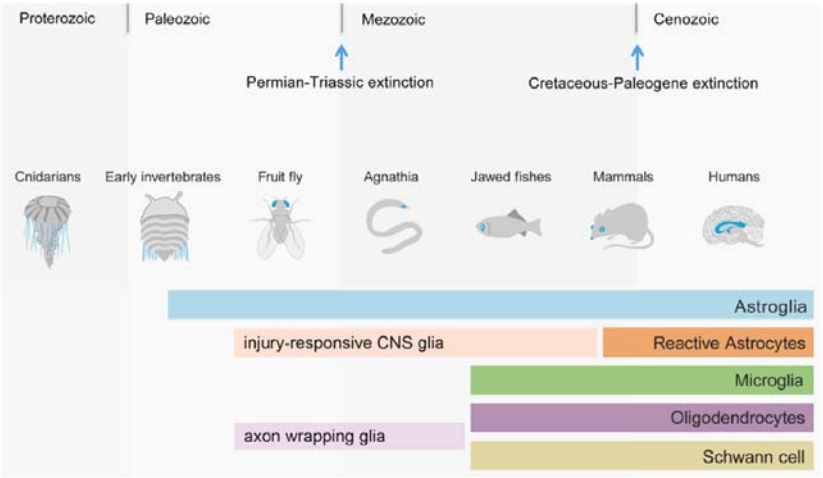


Freemann et al., 2013

Figure 1. Complex Glia in Even Simple Organisms

Glial cells in *C. elegans* and *Drosophila*. All *C. elegans* glia are associated with sensory structures, though the CEPsh glia also infiltrate the worm CNS. *Drosophila* have similar SOP-derived glial subtypes in the periphery (data not shown) and more elaborate and functionally distinct subclasses of glia in the CNS. A list of welldefined glial molecular or morphological phenotypes and functions that are conserved in worms and flies (indicated for each animal by gray bars to left) are listed.

Evolutionary glial epochs



Freemann et al., 2013

Summary I-II.

- Glia was first observed by Rudolf Virchow, 1846
- Glia first appeared in the NS of early invertebrates
- One of the primitive glia functions was control of synaptic formation !!
- Glia:neuron ratio STABLE across evolution for cerebrum and cerebellum
- Differences between berebrum and cerebellum are LARGER that differences between the cerebrum of different species.

Part III
Glial function
Astrocytes and the tripartite synapse
Gliotransmission

The tripartite synapse

Glia envelop synapses, abutting the synaptic cleft

Two-way affair communication (Araque et al., 1999)

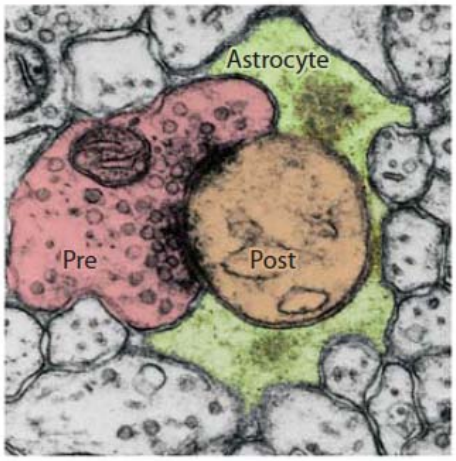
- Part 1: presynaptic terminus
- Part 2: Astrogytic process(es)
- Part 3: postsynaptic terminus

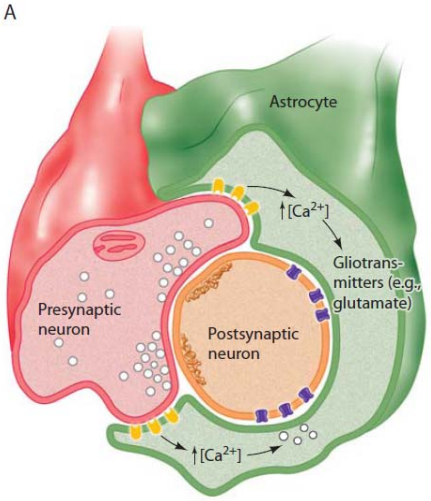
Multi-partite

- Quad-partite synapse + microglia (Kettenmann et al., 2013)
- Cinq-partite synapse + extracellular matrix (Dityatev et al., 2012)

... but then it´s getting too far

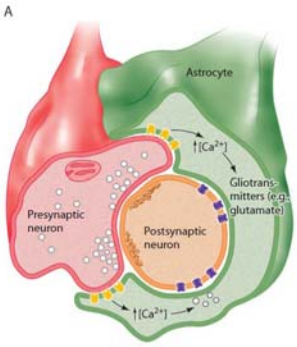
The tripartite synapse





Fellin et al., 2006

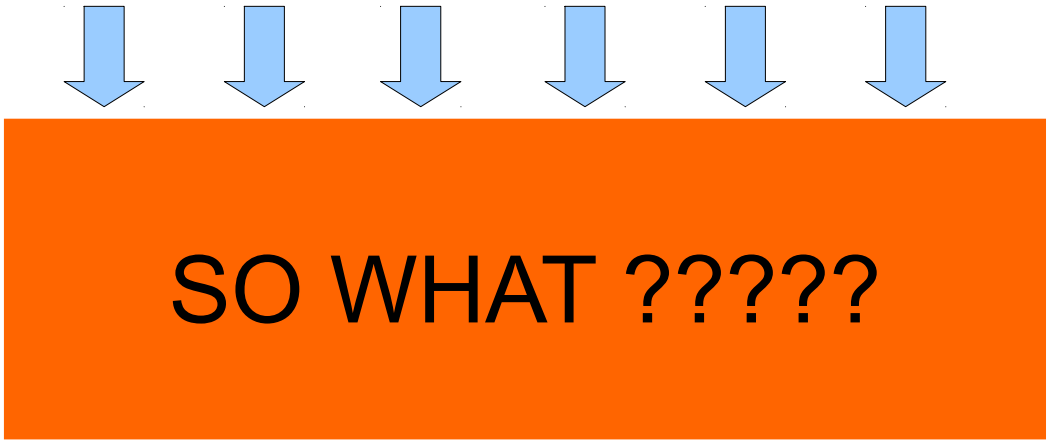
Neuronal – astrocytic signaling



- Astrocytes sense neurotransmission with **receptors**
  - AMPA (Glutamate)
  - NMDA (Glutamate)
  - mGluR (Glutamate)
  - GABA A/B (GABA)
  - A1, P2X, P2Y (purines)
  - HT (Serotonin)
  - Muscarinic (Acetylcholine)
  - Adrenergic (Norepinephrine)
  - Peptide (e.g. NPY) receptor

Gliotransmission

- Astrocytes **respond to** neurotransmitters with intracellular **calcium** elevation **[Ca^{2+}]**



Halassa et al., 2007; Halassa et al 2009

Other ways of neuron – astro communication:

- electrical synapses onto NG2 cells; Bergles et al., 2000
- neuroglial gap junction elecrical coupling; Alvarez-Maubecin et al., 2000

Astroglial excitability and gliotransmission: an appraisal of Ca^{2+} as a signalling route

Robert Zorec[*,†1], Alfonso Araque[‡], Giorgio Carmignoto[§], Philip G Haydon[‖], Alexei Verkhratsky[*,¶] and Vladimir Parpura[**,††,‡‡1]

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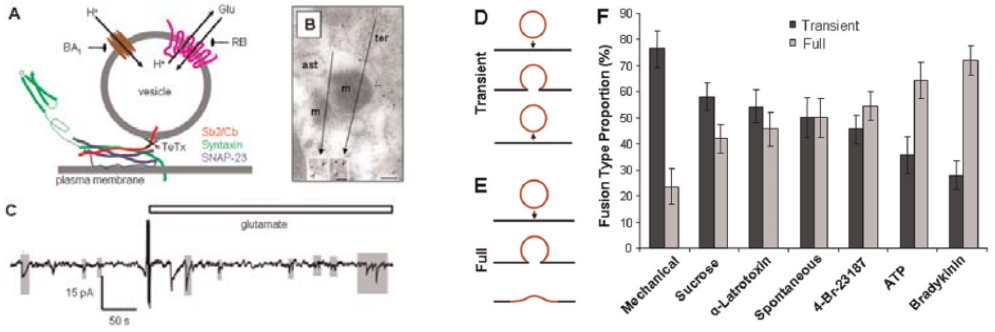
Slovenia
[†]Celica, Biomedical Center, Tehnološki park 24, 1000 Ljubljana, Slovenia
[‡]Instituto Cajal, CSIC, Madrid 28002, Spain
[§]Institute of Neuroscience, National Research Council and University of Padua, 3512
[‖]Department of Neuroscience, Tufts University School of Medicine, Boston, MA 021
[¶]Faculty of Life Sciences, The University of Manchester, Manchester M13 9PT, U.K.
[**]IKERBASQUE, Basque Foundation for Science, 48011, Bilbao, Spain
[††]Department of Neurobiology, Center for Glial Biology in Medicine, Civitan Internat
Nanotechnology Laboratories, and Evelyn F. McKnight Brain Institute, University of Alabama, Birmingham, AL 35242, U.S.A.
[‡‡]School of Medicine, University of Split, 21000 Split, Croatia

excitability displayed by astrocytes. An increase in cytosolic Ca^{2+} levels in astrocytes can lead to the release of signalling molecules, a process termed gliotransmission, via the process of regulated exocytosis. Dynamic components of astrocytic

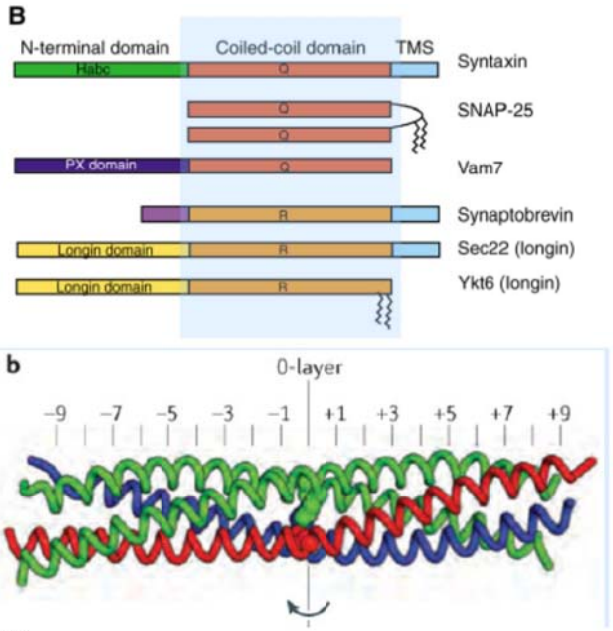


C: spontaneous inward currents corresponding to quantal ATP release

Zorec et al., 2012

SNARE

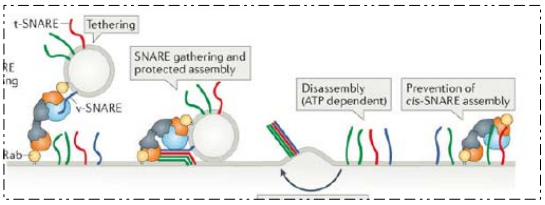
- **S**oluble
- **N**-ethylmaleimide-sensitive factor
- **A**ttachment
- **RE**ceptors

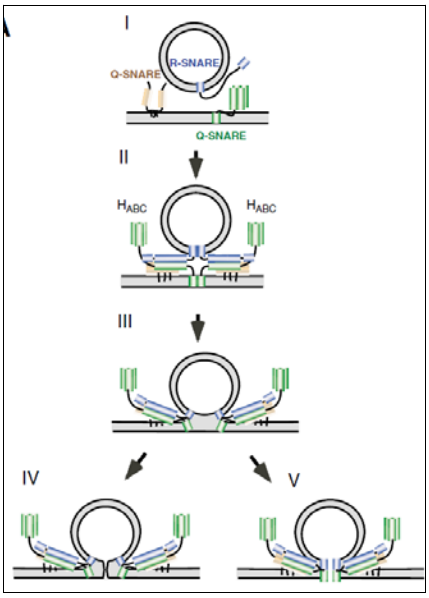


Ungermann et al., 2005; Baker et al., 2016

SNARE Vesicle trafficking

- Docking/Tethering
- Hemifusion ("kiss and run") and/or
- Complete Fusion





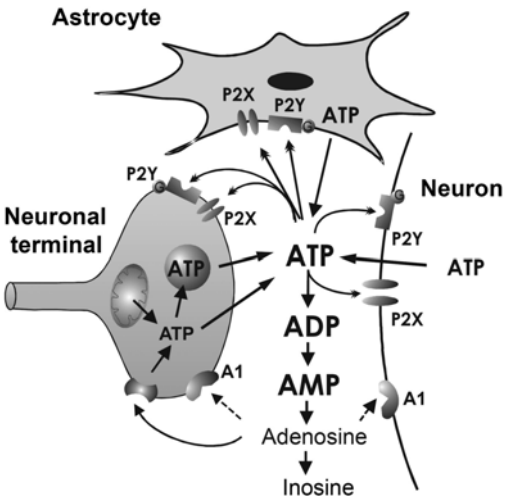
Ungermann et al., 2005; Baker et al. 2016

Gliotransmission

- Astrocytes **express**
  - **SNARE** complex
  - Glutamate (and Ach?) vesicles
  - ATP stored in lysosomes
- Astrocytes can **release**
  - Glutamate,
  - D-serine (NMDA agonist)
  - ATP
  - (and acetylcholine??)
- Presynaptic (and postsynaptic) **inhibition** via ...
  - Purinergic A1, P2Y, P2X receptors
  - mGLUT receptors
  - Muscarinic receptors ...

Zhang et al., 2004, 2007; Montana et al., 2004

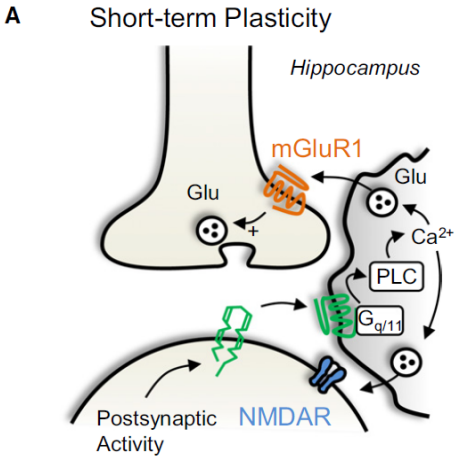
Gliotransmission
purines, ATP, adenosine



Illes et al., 2017

Endocannabinoid Signaling and Synaptic Function

Pablo E. Castillo,[1,*] Thomas J. Younts,[1] Andrés E. Chávez,[1] and Yuki Hashimotodani[1]
[1]Dominick P. Purpura Department of Neuroscience, Albert Einstein College of Medicine, Bronx, NY 10461, USA
*Correspondence: pablo.castillo@einstein.yu.edu
http://dx.doi.org/10.1016/j.neuron.2012.09.020



Cannabinoid mediated Gliotransmission Modifies the STP in the Hippocampus Via presynaptic mGluR

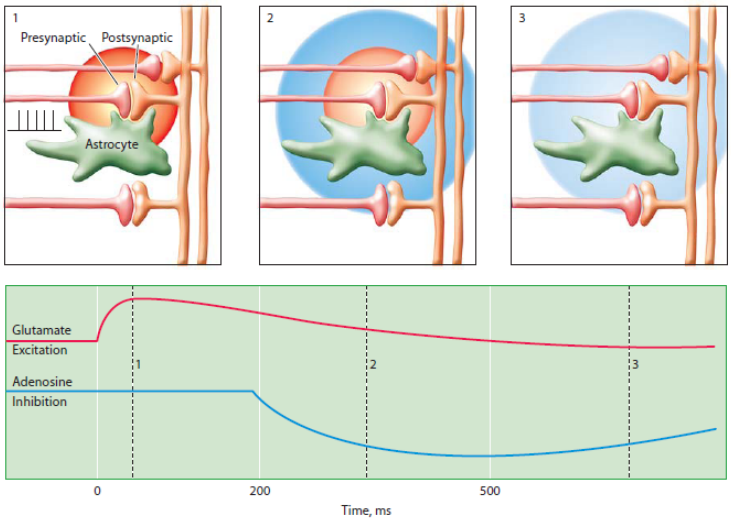
Castillo et al., 2012

Gliotransmission
local regulation

Spill-over effect

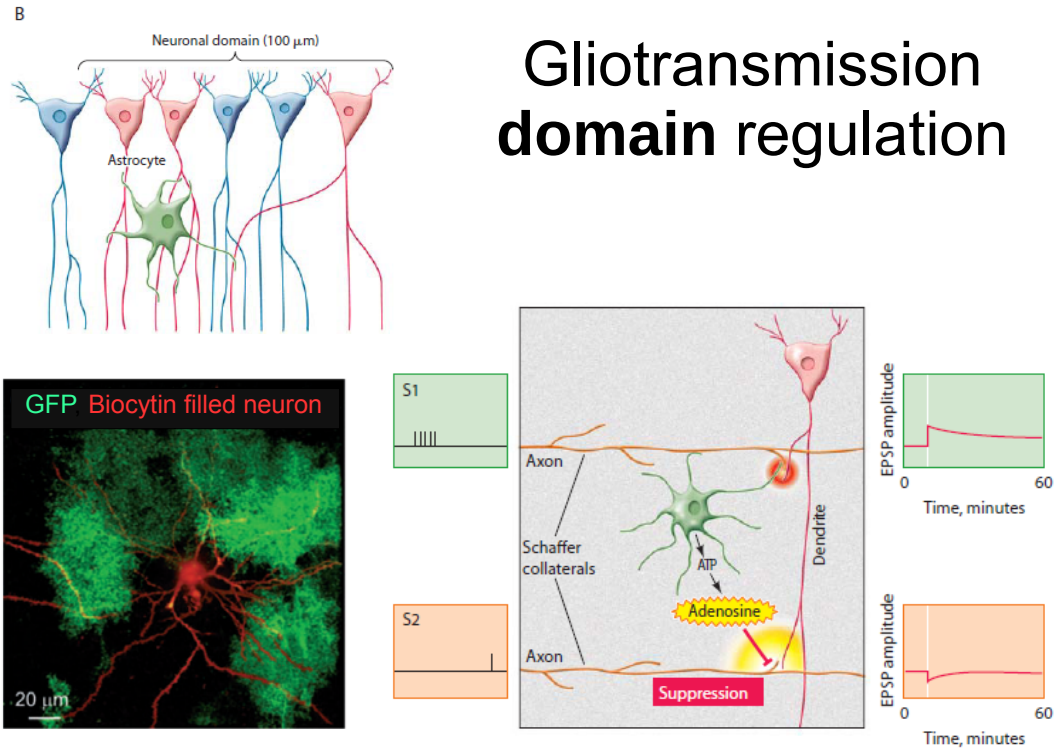
gradient transmitter spreading

Affecting neighboring synapses



Fellin et al., 2006

Gliotransmission **domain** regulation



Fellin et al., 2006; Fellin, 2009

Proximal astrocytic activation might provoke distal synaptic downregulation thus enhancing the proximal input in a form of **Feedback inhibition**

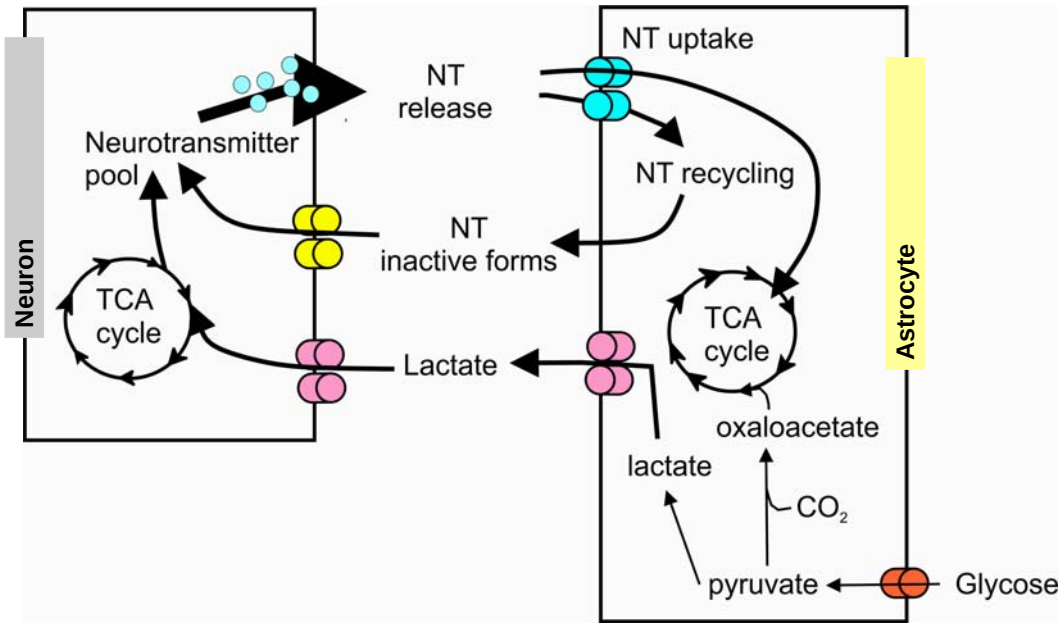
Summary III.

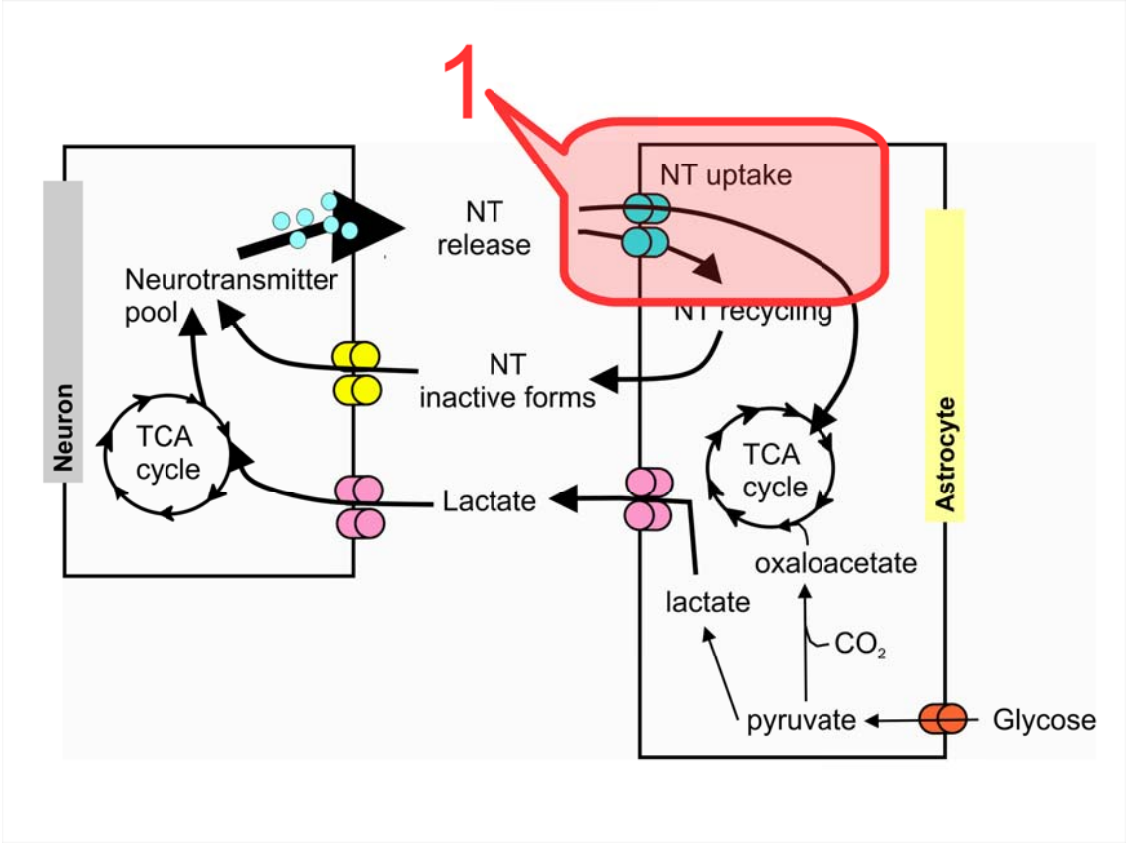
- The tripartite synapse concept
- Astrocytes sense synaptic activity
- Gliotransmission
- Local and domain regulations

Part IV
Metabolic crosstalk between neurons and astrocytes

Neurotransmitter recycling
Energy supply

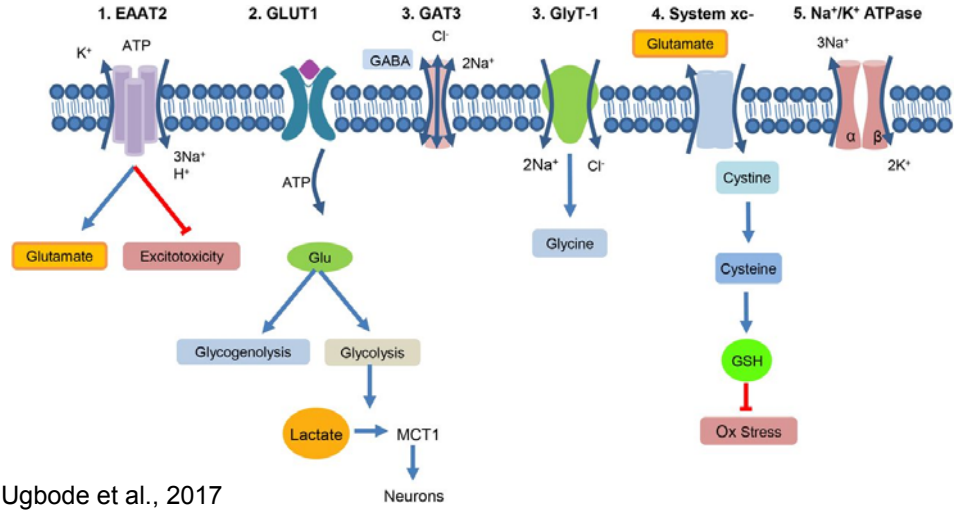
“ … serve alla distribuzione del materiale nutrizio …
Golgi, 1886




1
NT uptake
NT
release
Neurotransmitter
pool
NT recycling
NT
inactive forms
Neuron
TCA
cycle
Lactate
TCA
cycle
Astrocyte
oxaloacetate
lactate
CO_2
pyruvate
Glycose

Neurotransmitter uptake

Astrocytes expresss (many!!!) neurotransmitter **transporters**



Ugbode et al., 2017

TABLE 27.1 *Cloned Neurotransmitter Transporters Expressed By Astrocytes and Neurons*

Neurotransmitter	*Transporter Subtypes expressed By Astrocytes*	*Transporter Subtypes Expressed by Neurons*
Glutamate	EAAT1 (GLAST) EAAT2 (GLT-1), (GLT-1b)	EAAT3 (EAAC1), EAAT4* EAAT5,† (GLT-1b)
GABA	GAT-3 > GAT-1, GAT-2, BGT-1‡	GAT-1 > GAT-2, GAT-3
Glycine	GlyT1	GlyT2 > GlyT1
Histamine	Not determined	Not determined
Noerepinephrine	NET, OCT3	NET
Dopamine	DAT, OCT3	DAT
Serotonin	SERT	SERT
Adenosine	ENT1, ENT2	ENT1, ENT2, CNT2

Note. Transporter expression for neurotransmitters other than glutamate, GABA, and glycine have been assessed only in cell cultures. For the glutamate

*Primarily expressed by cerebell

†Primarily expressed by retinal r

‡May function as an osmoregul

DAT: dopamine transporter; EA

2; ENT1, 2: equilibrative nucleosid

glutamate/aspartate transporter; G

cation transporter 3; SERT: seroto

GLT-1: glutamate transporter-1

BGT-1: betaine and GABA tran

CNT-1: concentrative nucleosid

ter-1, -
LAST:
organic

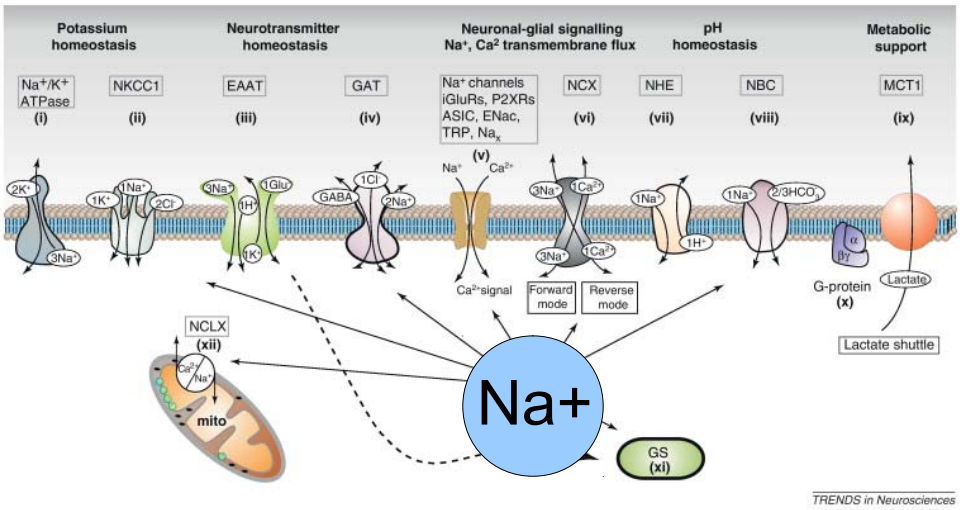
Transportation is an ACTIVE process

REQUIRES ENERGY

What fuels transportation ????

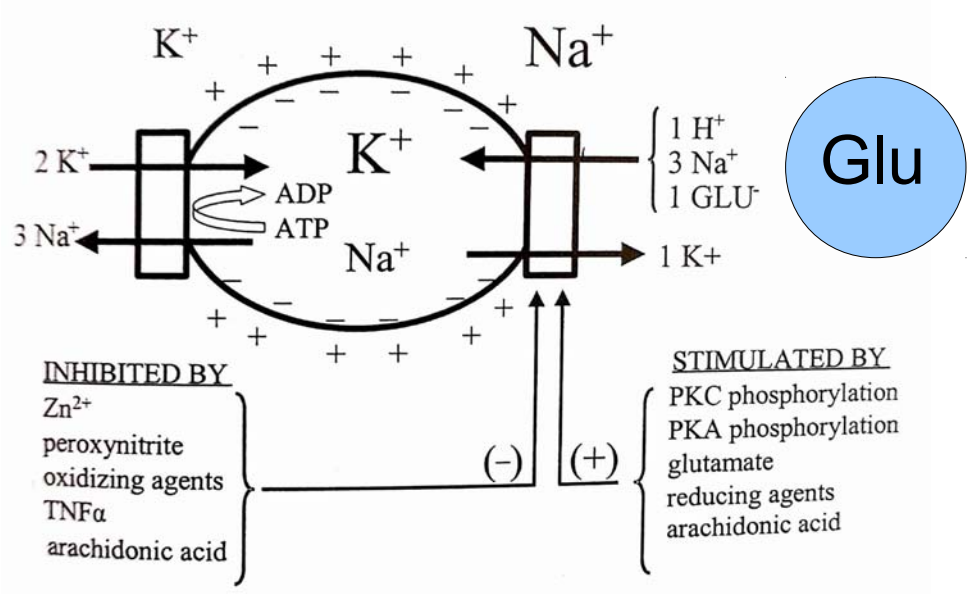
Neuroglia, 2nd edition, Ranson and Kettenmann

Sodium gradient fuels neutotransmitter transporters



Kirischuk et al., TINS 2012

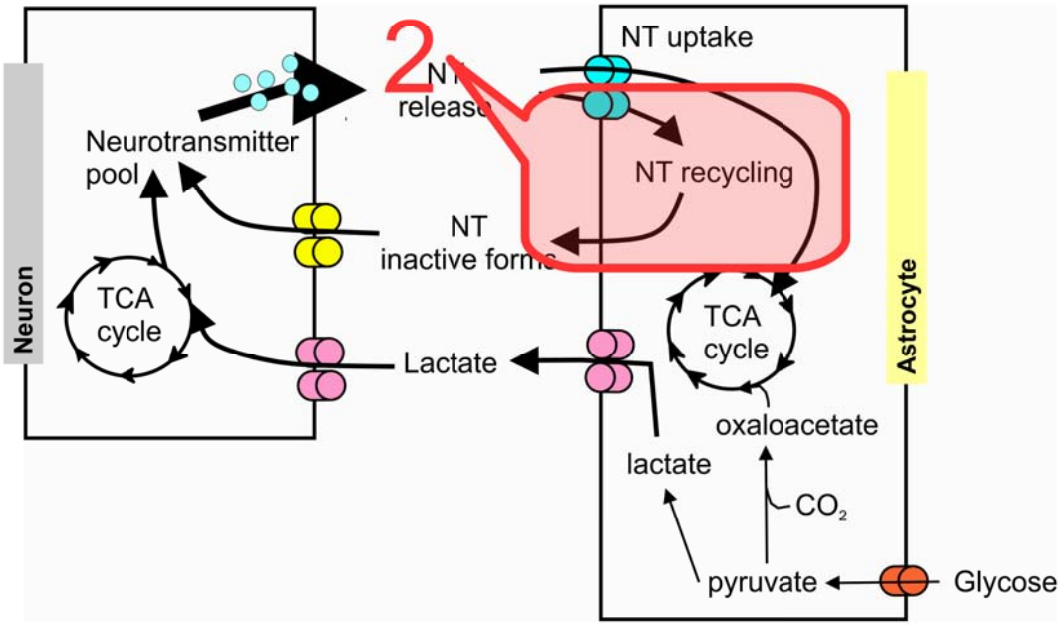
Sodium gradient fuels neutotransmitter transporters



Neuroglia, 2nd edition, Ranson and Kettenmann

Some neuroenergetics:

Manipulation	Effect on Glu Uptake
Mitochondrial blockade, O2 depletion	No effect immediately. Astrocytic ATP is dominantly anaerobe
ATP depletion	Crushes Glu uptake immediately, due to Na+K+ATPase crush
Hyponatremia	No effect. Hyponatremia is well compensated by astrocytes by lowering of intracellular Na+ to keep gradient stable
Hyperkaliemia	Nothing survives hyperkaliemia. Nor Glu uptake does.

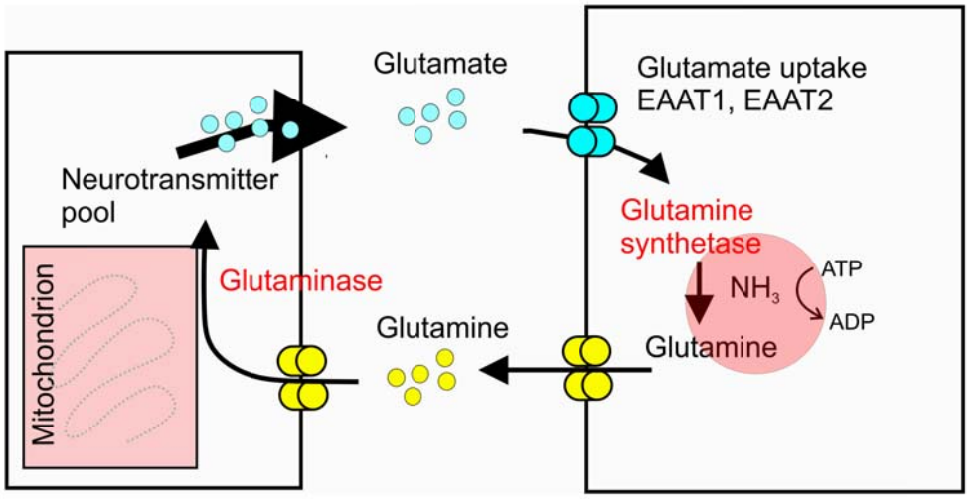

2
NT uptake
Neurotransmitter pool
NT recycling
NT
inactive form
Neuron
TCA cycle
Lactate
TCA cycle
Astrocyte
oxaloacetate
lactate
CO_2
pyruvate
Glycose

In the astrocyte: Fates of glutamate

- Theory 1 (Peng et al., 2001)
  - Glutamate enters TCA cycle at the stage of 2-ketoglutarate –> Used as energy substrate
- Theory 2 (Pellerin and Magistretti, 1994)
  - Glutamate is recycled to neurons as glutamine

- Theory 1 (Peng et al., 2001)
  - Glutamate enters TCA cycle at the stage of 2-ketoglutarate –> Used as energy substrate
    - Glutamate Dehydroxylase (GDH) or
    - Transaminase
    - Both enzymes catalyse Two-Way reactions
- Theory 2 (Pellerin and Magistretti, 1994)
  - Glutamate is recycled to neurons as glutamine
    - Glutamine synthetase
    - ATP, One-Way reaction
    - Neurons take up glutamine and transform it to glutamate (glutaminase)

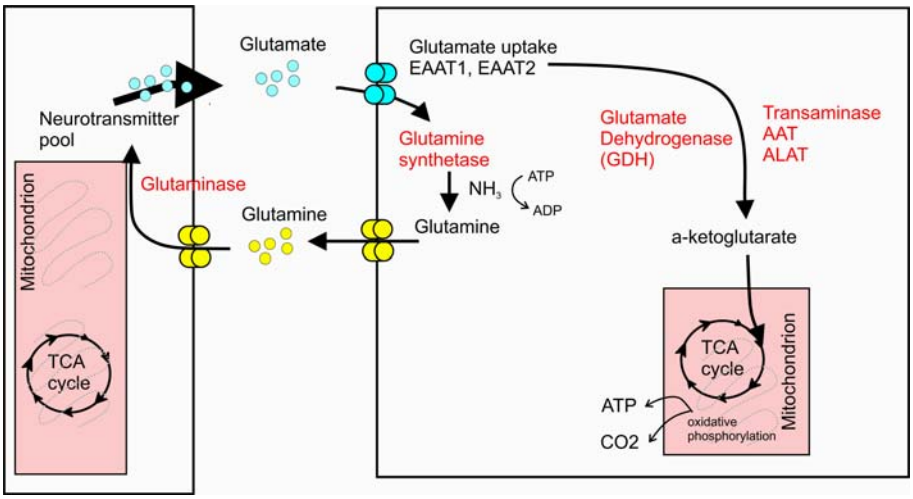
Theory 2:
The glutamate-glutamine cycle



Pellerin & Magestretti, 1994; Chaudhry et al., 2002; Daikhin and Yudkoff, 2000 ...

Glutamate synthetase has multiple functions.
One of them is ammiónia detoxification in the brain,
in the ASCENCE of the UREA CYCLE.

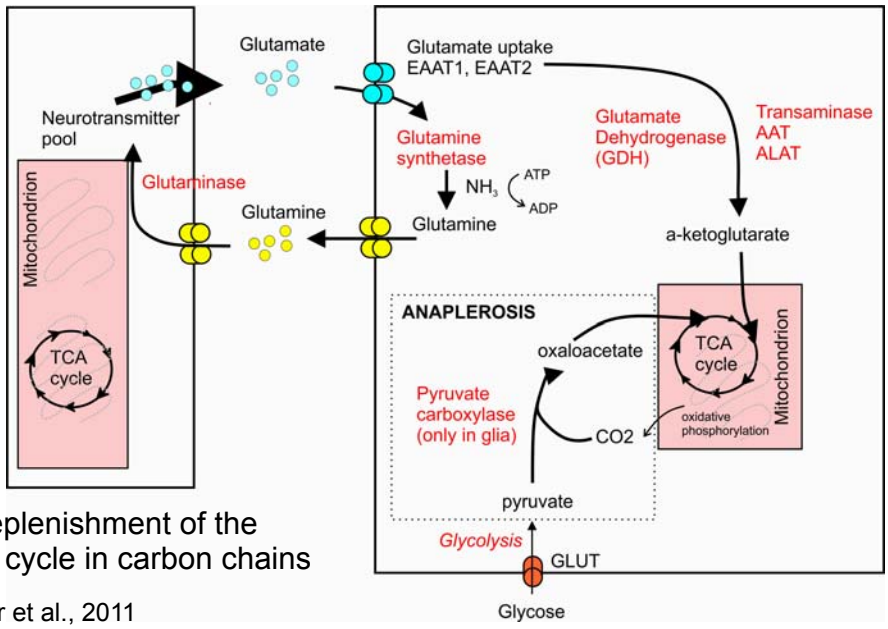
Theory 1:
Glu "sinks" into the TCA cycle



Loss of carbon chains into the TCA cycle !!!!
This system is not balanced

Belanger et al., 2011

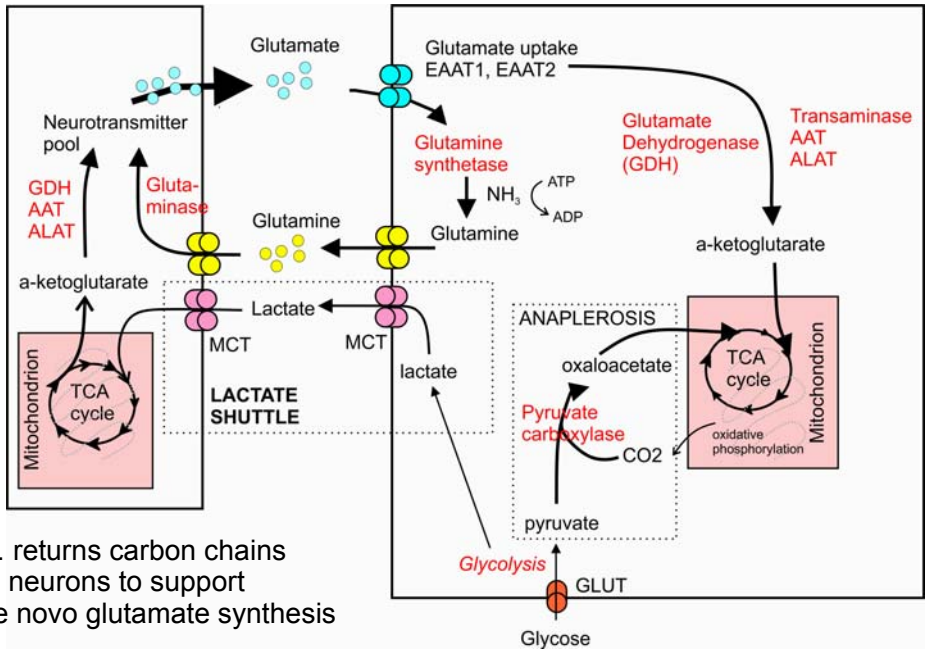
Anaplerosis and metabolic compartementalization



… replenishment of the TCA cycle in carbon chains

Belanger et al., 2011

Lactate shuttle

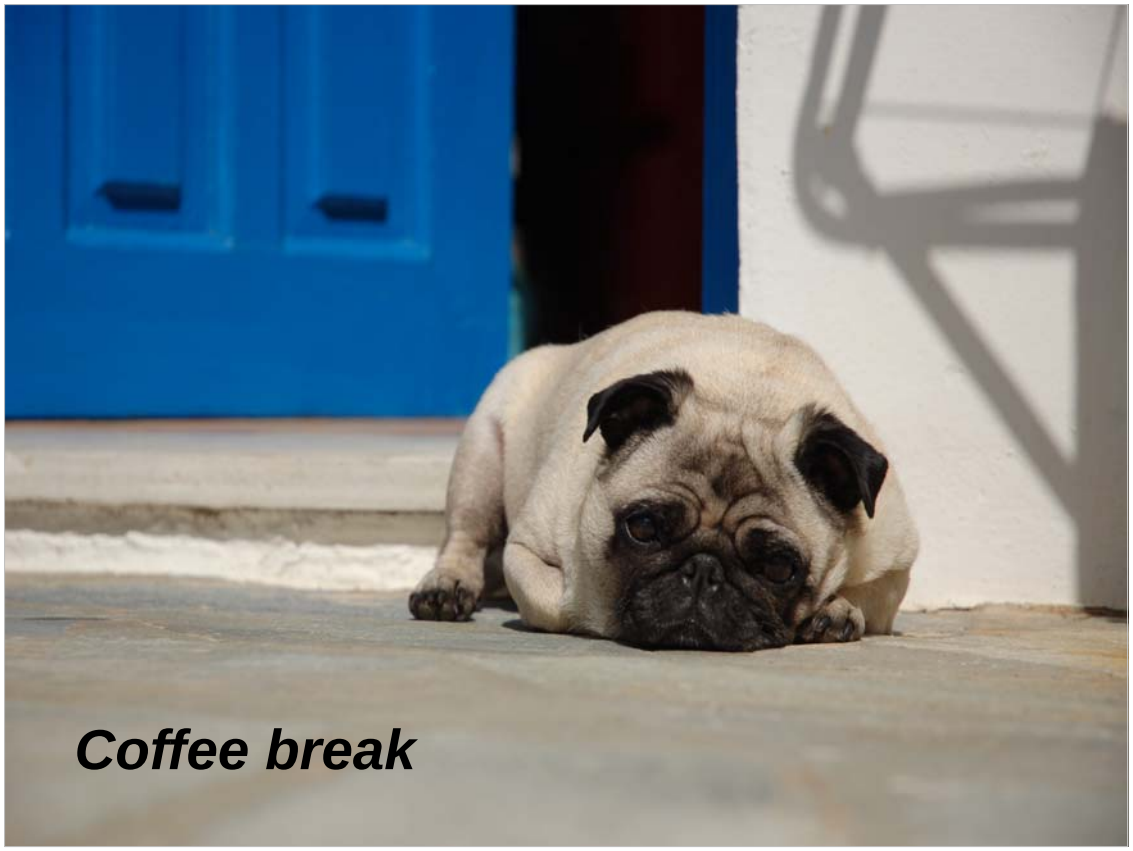


… returns carbon chains
to neurons to support
de novo glutamate synthesis

Pellerin et al, 1998; Belanger et al., 2011

Summary IV.

- Neurotranmitter uptake by astrocytes
- SODIUM GRADIENT
- Glutamate fates:
  - Glutamine cycle
  - TCA cycle
- Anaplerosis and
- Lactate shuttle

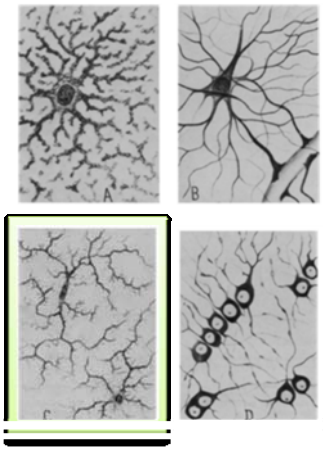

Coffee break

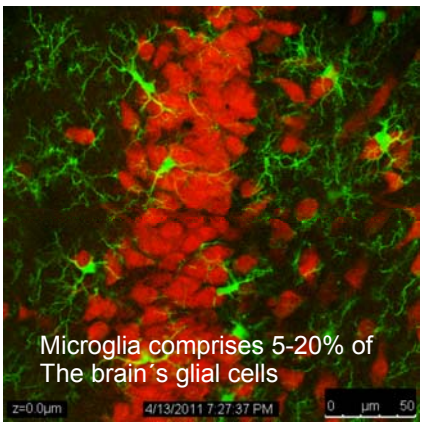
Part V
Microglia in the CNS´ network

Who is microglia?

- Microglia is CNS´ macrophages

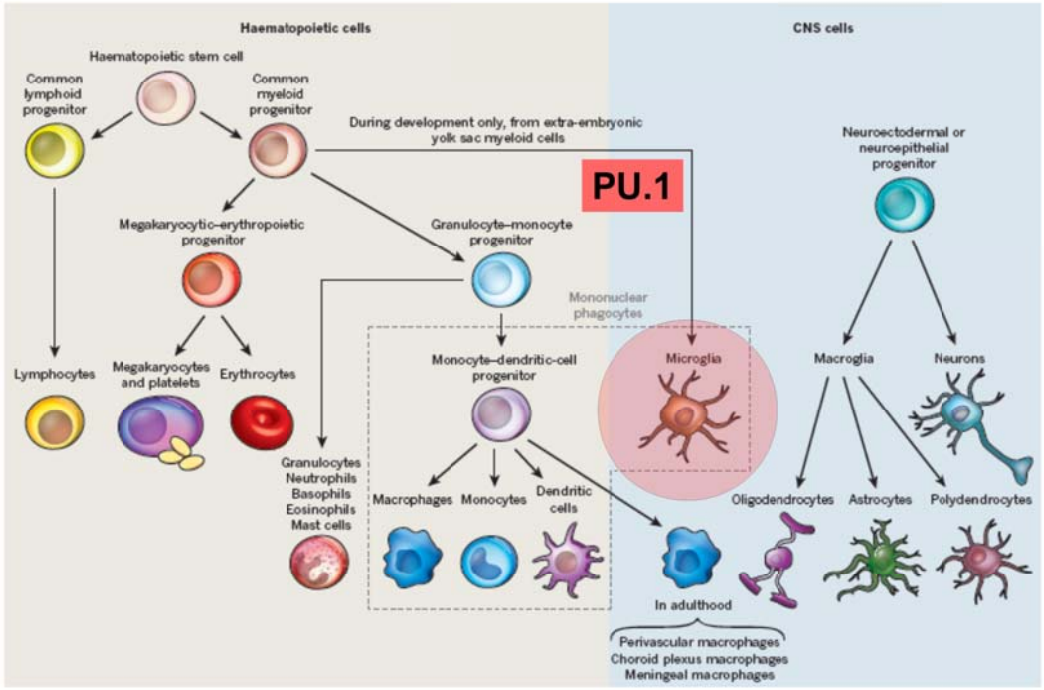
del Rio Hortega 1932





NeuN (neurons), Iba1 (microglia)

Santiago Ramón y Cajal (1913): The ´´third element´´
Pio del Rio–Hortega (1919, 1932): oligodendroglia, **microglia**



Ransohoff & Cardona, 2010; McKercher et al., 1996, 1999; Beers et al., 2006

Microglia Niches

Microglia do not share the neuron-glia lineage

Microglia derive from the Hematopoietic stem cell progenitor in the yolk sac

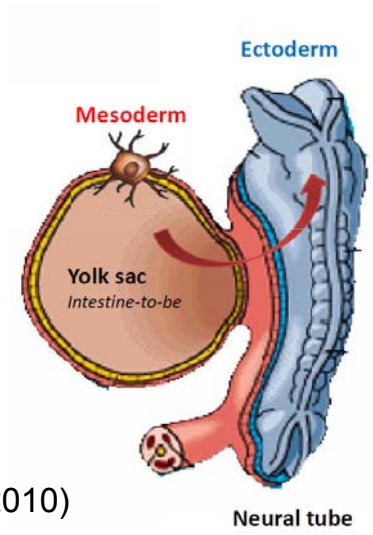
McKercher et al., 1996 and 1999
PU.1 KO mice
PU.1 transcription factor for macrophage and B-cell maturation (and not for myeloid commitment).

Beers et al., 2006
Rescued the phenotype of ALS-PU.1 KO mice with wild type microglia

The intruders of the CNS

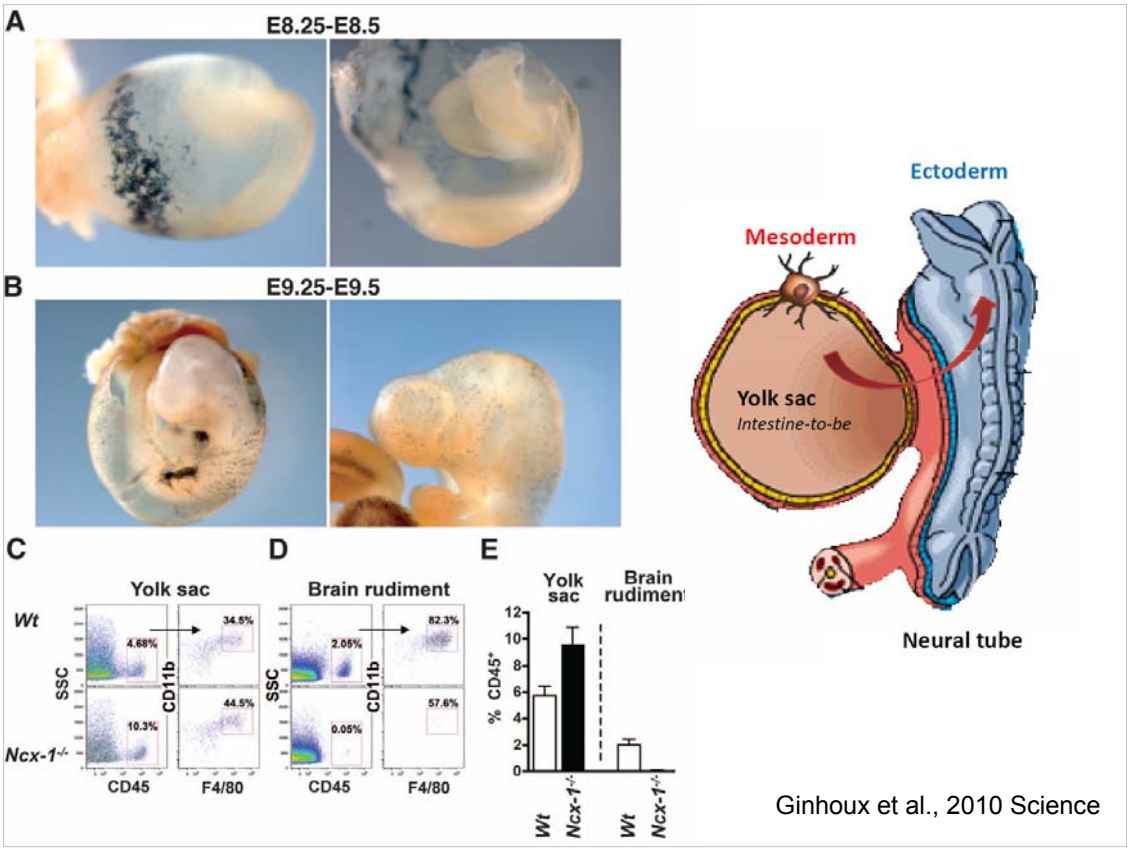
Migration from yolk sac in vertebrates

Carnegie stage 18-20



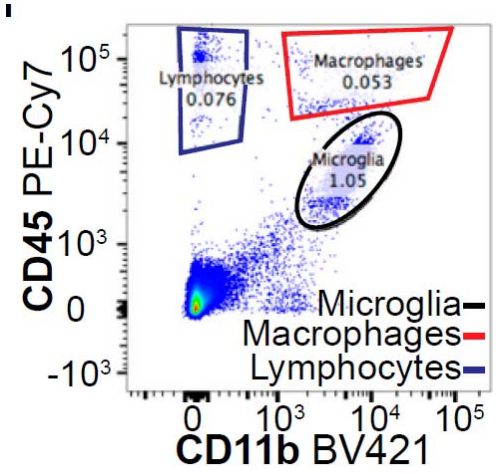
- E 7-9 in mouse, rat (Ginhoux et al., 2010)

- GW 4.5 or 6.5–8 in human (Monier et al, 2007)



Ginhoux et al., 2010 Science

Microglia or macrophages?



FACS them!

- MG CD11b^{+}CD45^{low}
- Mφ CD11b^{+}CD45^{high}

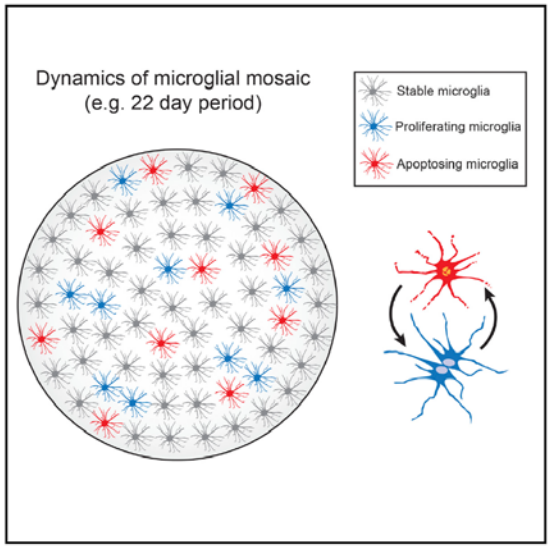
In situ its hard to differentiate

- Tmem119 as promising new marker

Bennett et al., 2016

LARGE overlap migroglia (MG)-macrophages (Mφ)!!!

Lifelong turnover
Coupled proliferation and apoptosis



Askew et al., 2017 CELL REPORTS

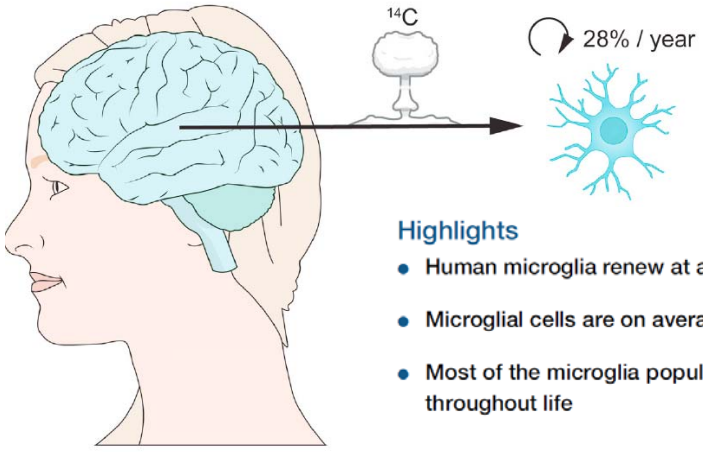
Self-renewable population

Ajami et al., 2007

Postnatal hematopoietic progenitors are NOT involved in microglial population maintanence

Ginhoux et al., 2010
Goldmann et al., 2016

Lifelong turnover



Highlights

- Human microglia renew at a median rate of 28% per year
- Microglial cells are on average 4.2 years old
- Most of the microglia population (>96%) is renewed throughout life

Reu et al., 2017 CELL REPORTS

Part VI
Microglia in the tripartite synapse

Synaptoimmunology
Tagging Stripping Pruning

Surveying microglia **sense synaptic activity**

Ionotropic

- AMPA, kainate, NMDA (Glutamate)
- P2x (purines)

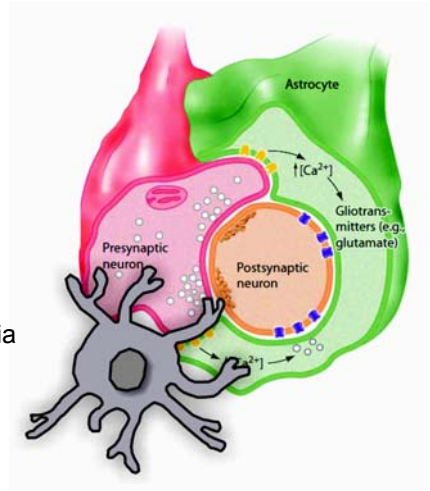
Metabotropic neurotransmitter receptors

- mGluR (Glutamate)
- GABA B (GABA)
- P2y (purines)
- Adrenergic a and b
- D1 & D2 (dopamine)
- CB1 and CB2 (Cannabinoids)

Mainly activate NfkB and JAK-STAT pathways

The tripartite synapse ***revisited***

Microglia



Nistico et al., 2017

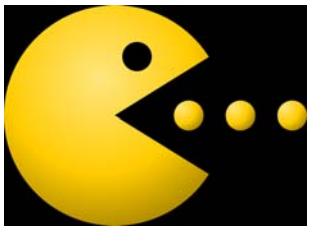
Synaptoimmunology

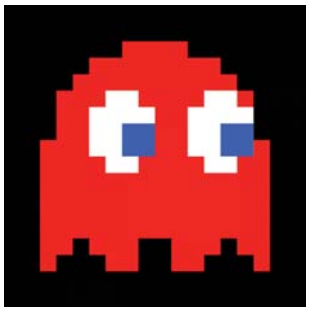
- Synaptic tagging, stripping and pruning
- Cytokines modulate synaptic activity

*CAVE: We will **not** go into mechanisms of classical neuroinflammation / neurodegeneration (EAE, MS, Alzheimer, Lewy bodies a.s.o.)*

"Eat-me" and "Eat-me-not"

- Microglia are professional eaters
- In the CNS they are kept in surveillance, patrolling neuronal activity
- Upon activation, microglia EAT (phagocytose) elements tagged with "eat-me" signals
- "Eat-me-not" tags prevent phagocytosis





"Eat-me" tags

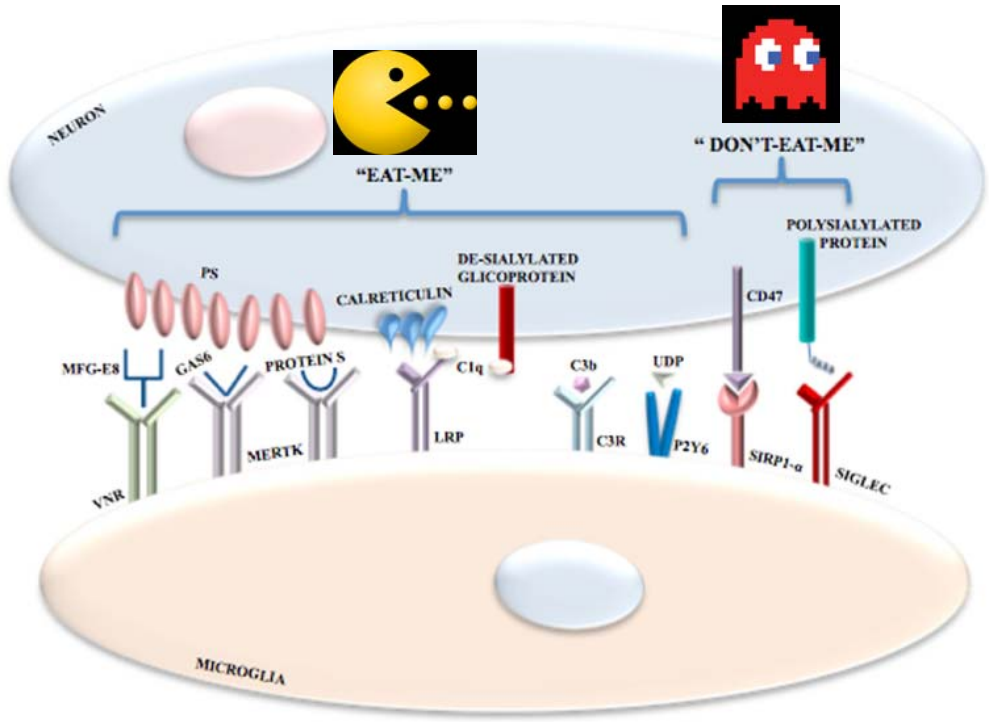
“Eat-me” tag	**Microglial receptor**
Uridine diphospate (UDP)	P2Y6
PAMPS DAMPS	TLR
DAMPS	TREM2
PS after oxidative stress	VNR MERTK
C1q, calreticulin C3	LRP CD37

Arcuri et al., 2017

Abbreviations:

"Eat-me-not" tags
Surveillance and how to maintain it

“Eat-me-not” tag	Microglial receptor
CD200	CD200R
CD22	CD45
CX3CL1 (fractalkine, also soluble !!!)	CX3CR1
CD47	SIRP-a

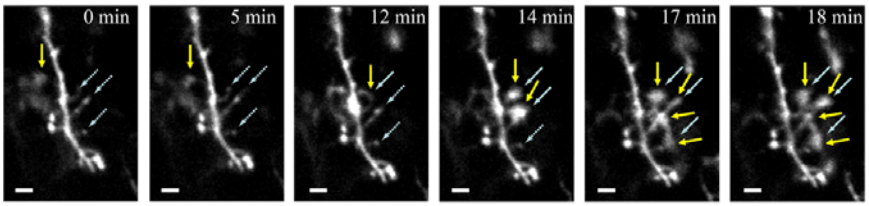


Arcuri et al., 2017

Brief Communications

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

A



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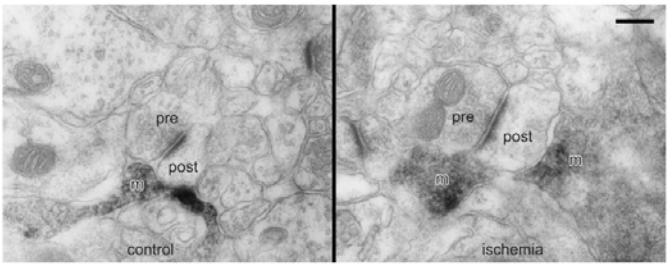


Microglia contact synapses
Yellow arrow =
contacted synapse

Contact increases
with ischemia

pre=presynaptic term
post=postsynaptic term
m=microglia

Wake et al., 2009

Wake et al., 2009

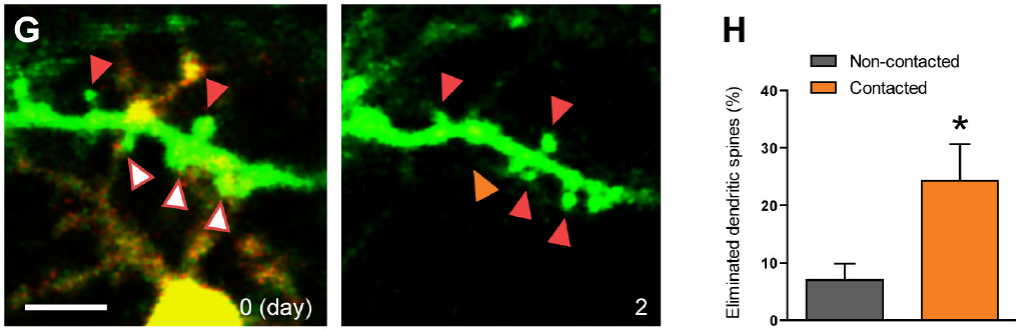
Contact of MF processes with synapses and contact prolongation upon ischemia.
2-photon microscopy time lapses

OPEN ACCESS Freely available online PLOS BIOLOGY

Microglial Interactions with Synapses Are Modulated by Visual Experience

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

Department of Neurobiology and Anatomy and Center for Visual Science, University of Rochester, Rochester, New York, United States of America



Sensory experience, contacted synapses = empty arrows, eliminated synapses after sensory experience = orange arrows

Tremblay et Majewska, 2010

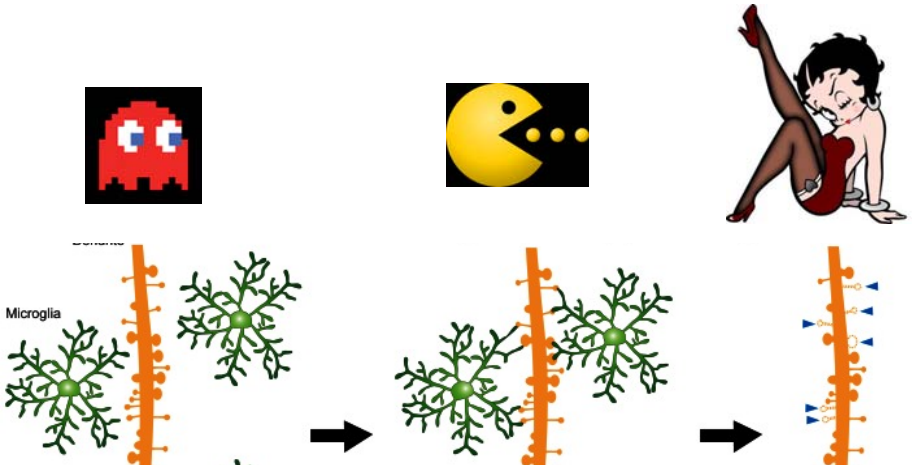
The classical complement cascade mediates CNS synapse elimination (Stevens et al., 2007)

- Synapse elimination during development and disease: immune molecules take centre stage. (Schafer and Stevens, 2010)
- Enhanced synaptic connectivity and epilepsy in C1q knockout mice. (Chu et al., 2010)
- Microglia sculpt postnatal neural circuits in an activity and complement-dependent manner. (Schafer et al., 2012)
- The complement system: an unexpected role in synaptic pruning during development and disease. (Stephan et al., 2012)
- TGF-β signaling regulates neuronal C1q expression and developmental synaptic refinement. (Bialas & Stevens, 2013)
- Complement C3-Deficient Mice Fail to Display Age-Related Hippocampal Decline. (Shi et al., 2015)
- Complement and microglia mediate early synapse loss in Alzheimer mouse models. (Hong et al., 2016)
- A complement-microglial axis drives synapse loss during virus-induced memory impairment. (Vasek et al., 2016)
- Complement C3 deficiency protects against neurodegeneration in aged plaque-rich APP/PS1 mice. (Shi et al., 2017)

Beth Stevens, Ph.D.
Assistant Professor of Neurology

Children's Hospital Boston
300 Longwood Avenue
Center for Life Sciences 12th Floor
Boston, MA 02115

C1q and C3 for synaptic elimintation



Surveillance

"Eat-me" tagging
Development, low activity

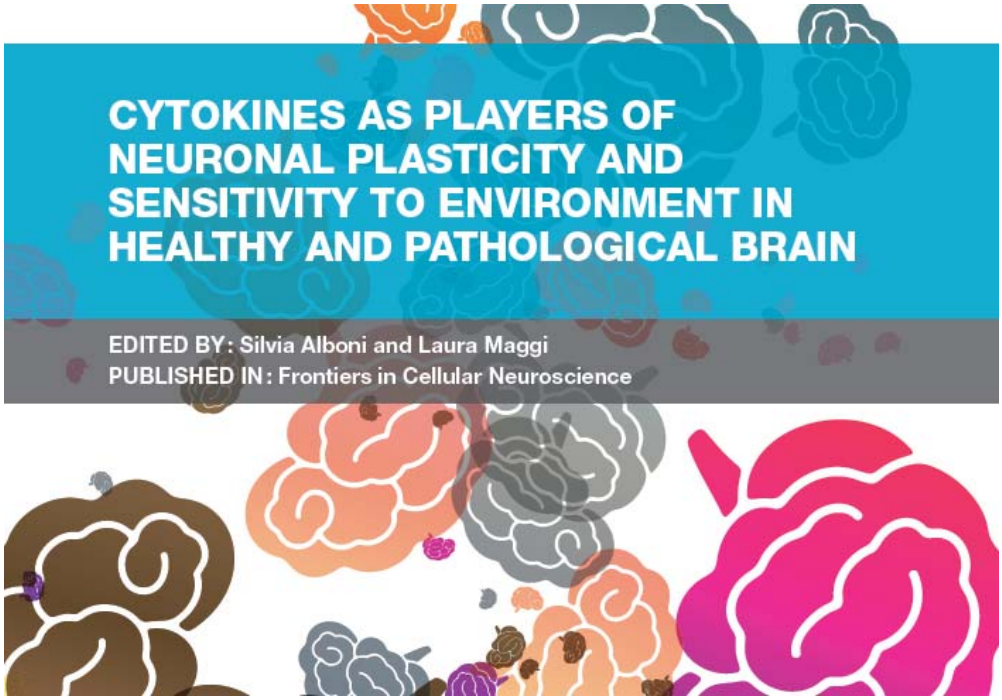
Stripping, Pruning
Synaptic phagocytosis

Miyamoto et al., 2013; Stevens et al., 2007

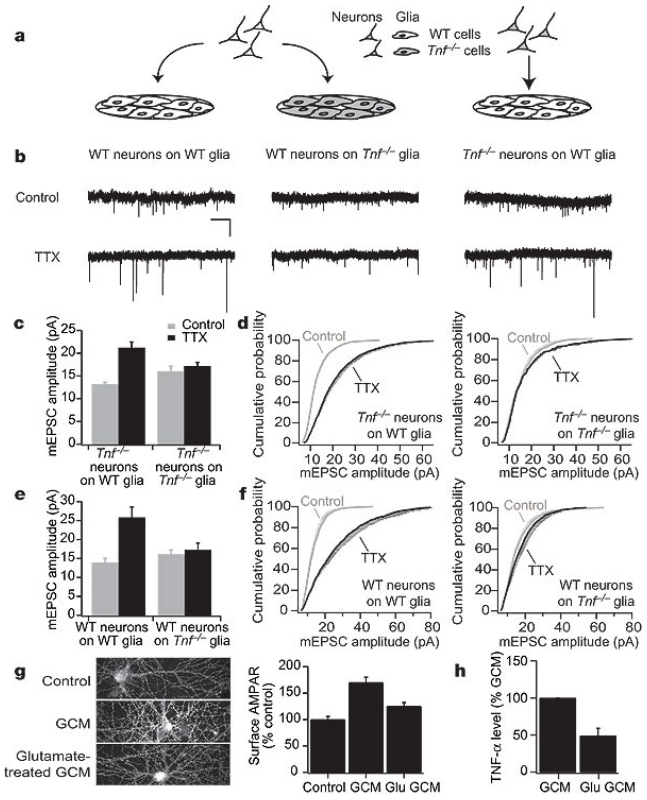
Part VI
Microglia in the tripartite synapse

Synaptoimmunology

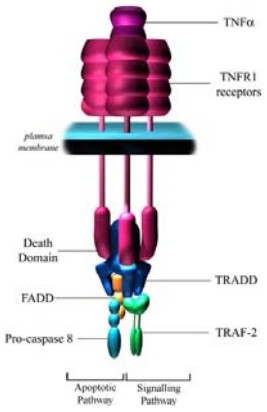
Cytokines regulate homeostatic plasticity
Synaptic scaling

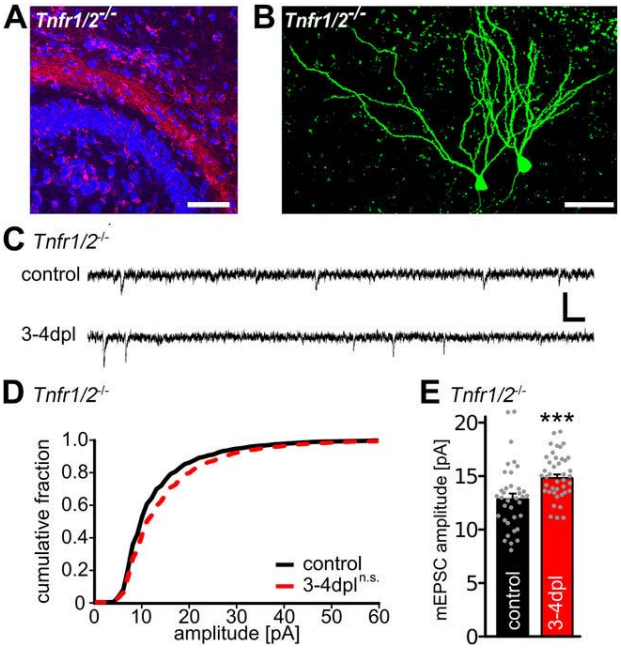

CYTOKINES AS PLAYERS OF NEURONAL PLASTICITY AND SENSITIVITY TO ENVIRONMENT IN HEALTHY AND PATHOLOGICAL BRAIN
EDITED BY: Silvia Alboni and Laura Maggi
PUBLISHED IN: Frontiers in Cellular Neuroscience

TNFa Synaptic scaling



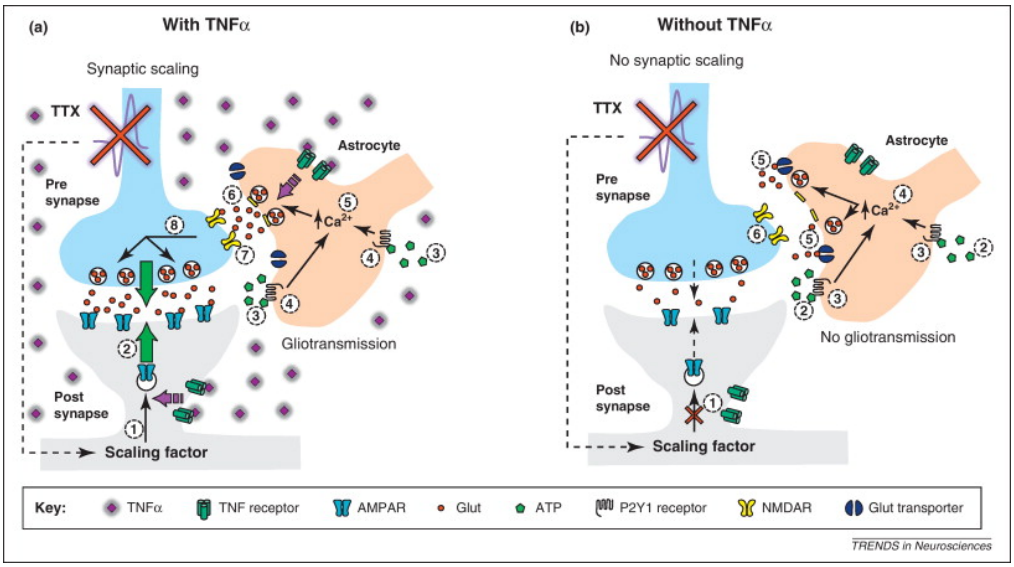
TNFa receptor (Tnfr1/2) Synaptic scaling





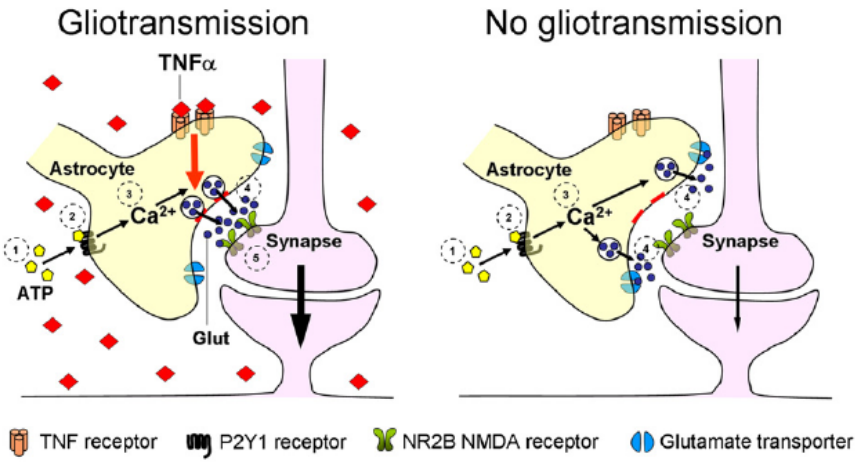
Becker et al., 2015

TNFa Synaptic scaling



Stellwagen et al., 2006; Santello et al., 2011, 2012

TNFa in synaptic function



Stellwagen et al., 2006; Santello et al., 2011, 2012

TNFa promotes DOCKING of glutamate vesicles
Fusion is not possible without Calcium signaling
Calcium signaling is induced by (between others) ATP signaling
ATP might derive from (tha same or other) astrocytes

Figure 7. Schematic Summary of the TNFa Control on Gliotransmission at PP-GC Synapses in the Hippocampal Dentate Gyrus

Left: in the presence of constitutive TNFa (red diamonds), astrocyte vesicles containing glutamate (Glut., blue dots) are functionally docked at putative active zones on the plasma membrane of a perisynaptic astrocytic process. When ATP (yellow pentangles) is released (1) from GC synapses or the astrocytes (Jourdain et al., 2007), it activates P2Y1 receptors (2) and causes Ca^{2+} release from the internal stores in the astrocyte microcompartment (3). This in turn triggers fusion of the astrocyte vesicles in proximity of presynaptic NR2B containing NMDARs (4), eventually causing an increase in excitatory synaptic activity (5).

Right: in the absence of TNFa, astrocytic glutamatergic vesicles are not correctly docked and ready to fuse. Therefore, when ATP triggers the usual signal-transduction in astrocytes, glutamate release occurs slowly and asynchronously and is scavenged by glutamate transporters before reaching pre-NMDA receptors to induce synaptic modulation.

Summary V-VII.

- Microglia are brain macrophages
- Sense synaptic activity with NT-receptors
- Eat-me and Eat-me-not
- Activity dependent synaptic shaping: tagging and stripping
- Cytokines (TNFa) and synaptic scaling


Thanks for your attention