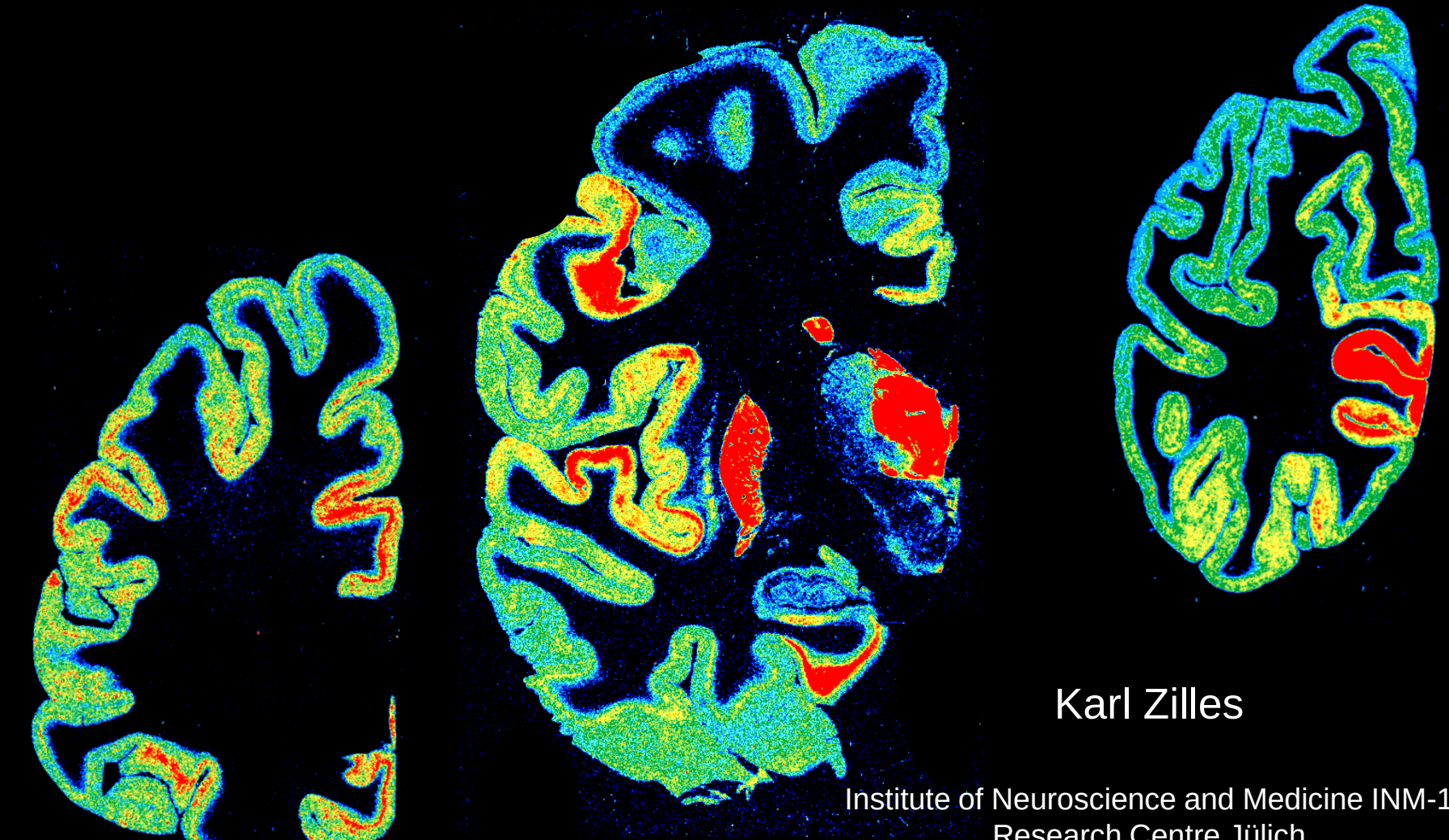
Receptorarchitecture and Neural Systems



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RWTH Universität Aachen

Receptors are protein complexes in the cell membrane, to which transmitters selectively bind.

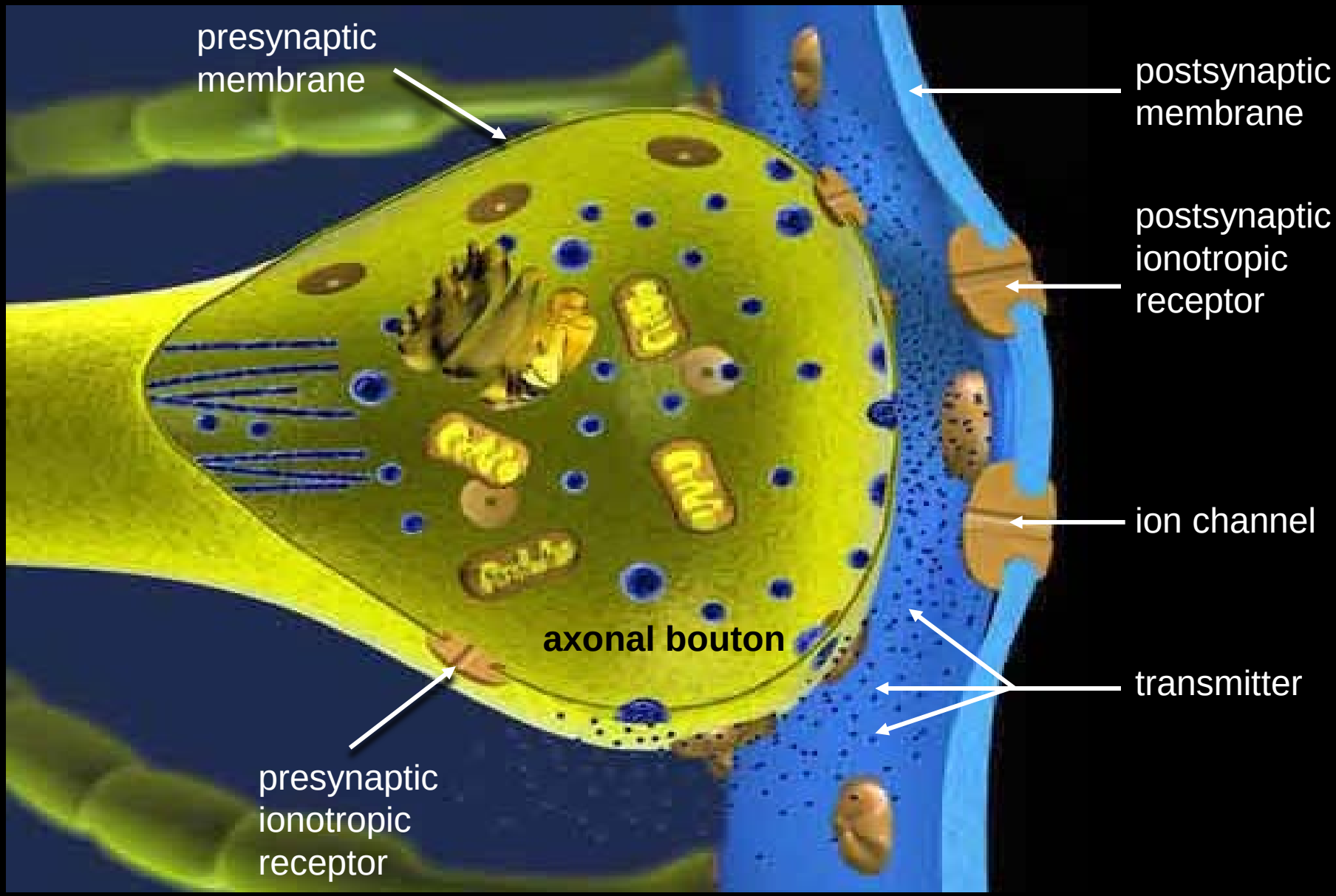
- ***ionotropic receptors*** have an integrated ion channel and regulate ion fluxes between extra- and intracellular space

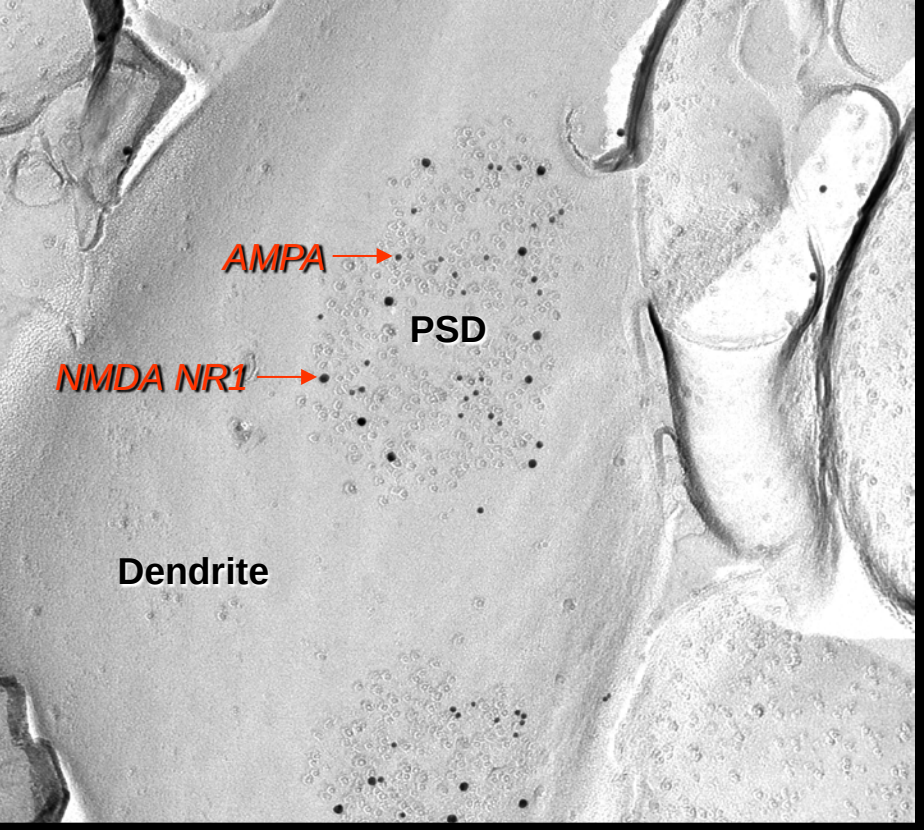
- ***metabotropic receptors*** are linked to intracellular second messenger systems, and control metabolic pathways, ion channels, gene activity, etc.

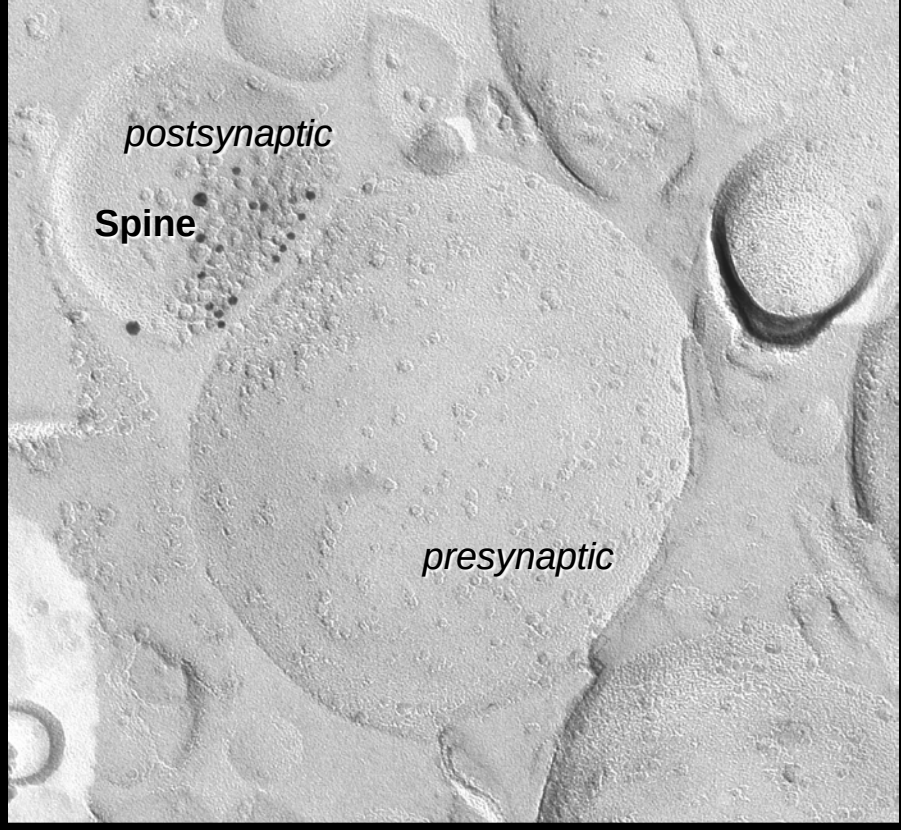
What does receptor mapping provide?

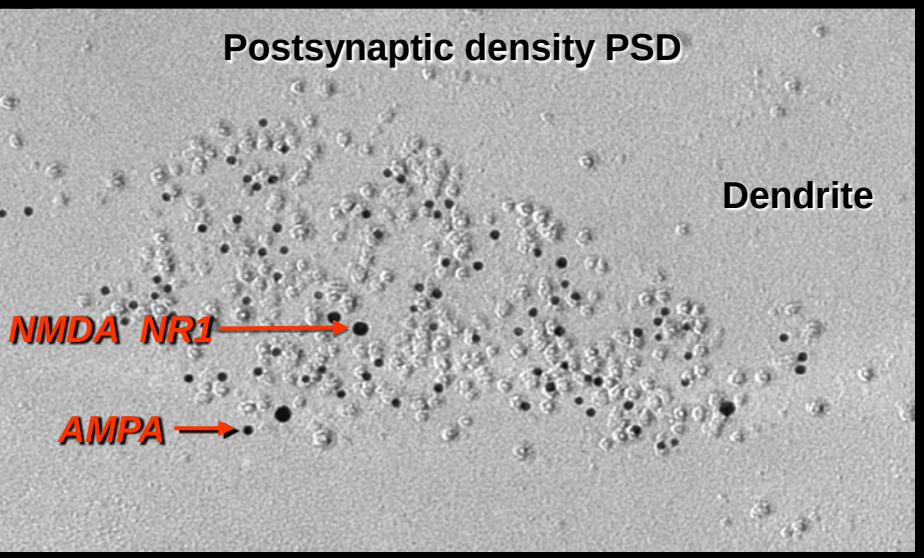
- It provides insight into the molecular basis of the resting state condition.
- Most of the brain‘s energy consumption is used for maintaining ion channel functions during resting state. Only a minority of the energy is required during stimulation conditions.
- Receptor mapping overcomes limitations of unimodal brain mapping approaches
- It provides brain maps based on molecules which are key elements of signal transmission within and between neural systems
- Areas within a given functional system have similar multireceptor expression patterns. Different functional systems differ by those expression patterns

Example: Ionotropic Transmitter Receptors





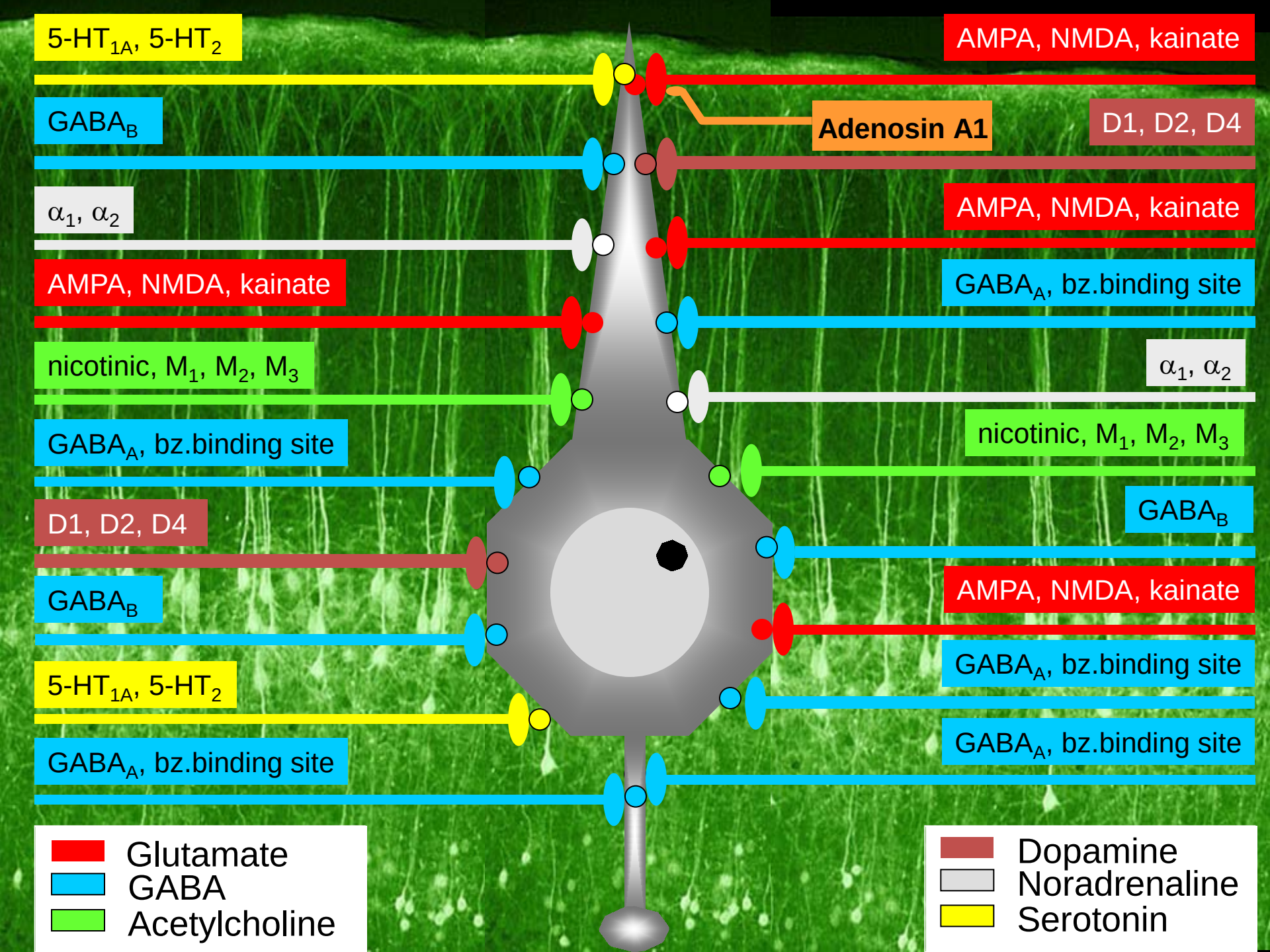




NMDA and AMPA are the most abundant glutamate receptor types in the human cerebral cortex.

Method: Cryo-Electron-Microscopy and Immunocytochemistry with specific antibodies labeled with gold nanoparticles of different size (for AMPA 9 nm, for NMDA 12 nm)

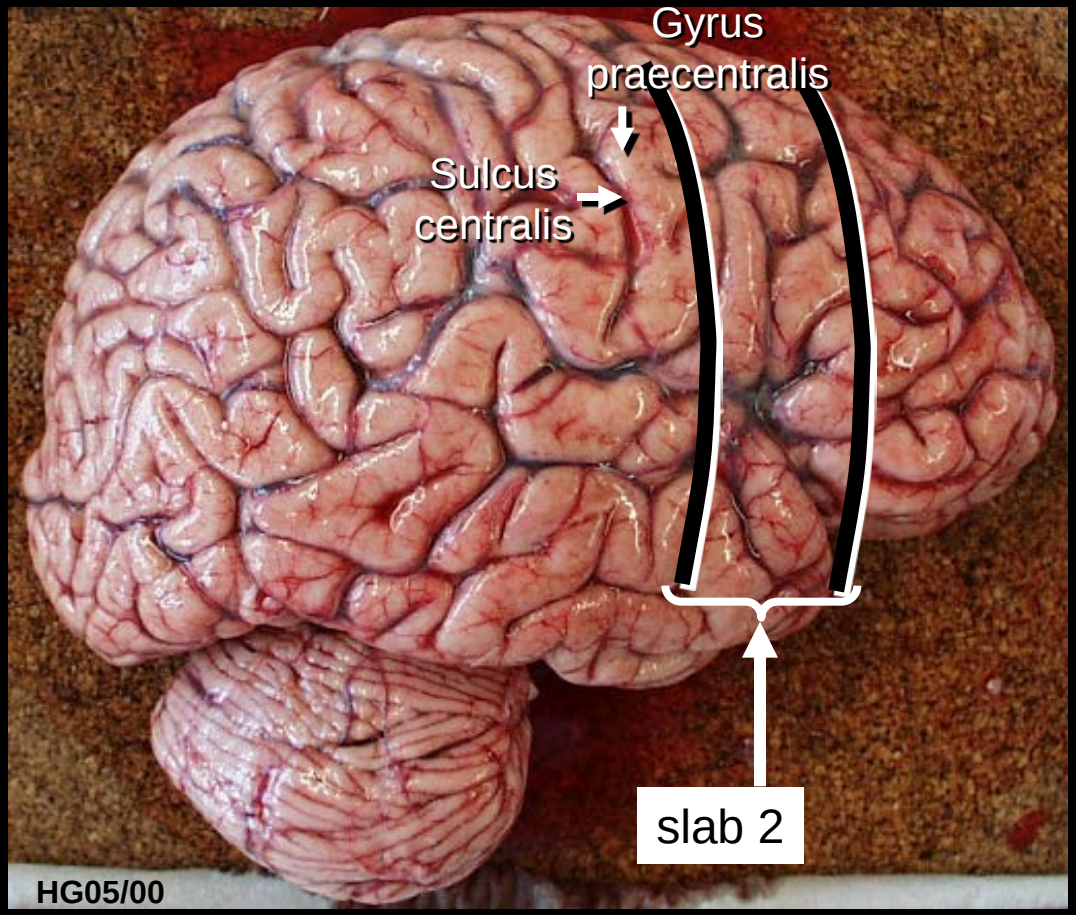
Joachim Lübke, Research Center Jülich, Germany (unpublished)


5-HT1A, 5-HT2
GABAB
α1, α2
AMPA, NMDA, kainate
nicotinic, M1, M2, M3
GABAA, bz.binding site
D1, D2, D4
GABAB
5-HT1A, 5-HT2
GABAA, bz.binding site
AMPA, NMDA, kainate
Adenosin A1
D1, D2, D4
AMPA, NMDA, kainate
GABAA, bz.binding site
α1, α2
nicotinic, M1, M2, M3
GABAB
AMPA, NMDA, kainate
GABAA, bz.binding site
GABAA, bz.binding site
Glutamate
GABA
Acetylcholine
Dopamine
Noradrenaline
Serotonin

How to map receptor distributions:

- ***in vivo*** **receptor PET**
- ***in vitro*** **quantitative receptor autoradiography**
- **immunohistochemistry of receptor proteins and subunits**
- **transcriptomics**

Quantitative *in vitro* Receptor Autoradiography: Method (1)

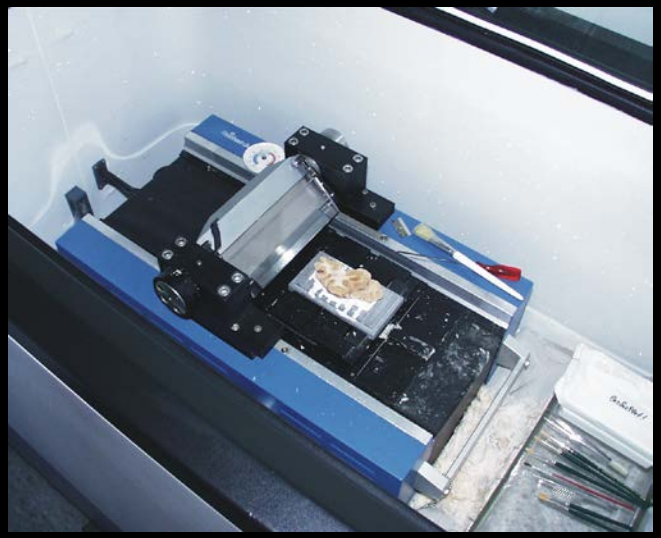


slab 2 native

slab 2 frozen at -70° C

Quantitative *in vitro* Receptor Autoradiography: Method (2)

- Cryostate serial sections (10 – 20 μm) – mounting on glass slides

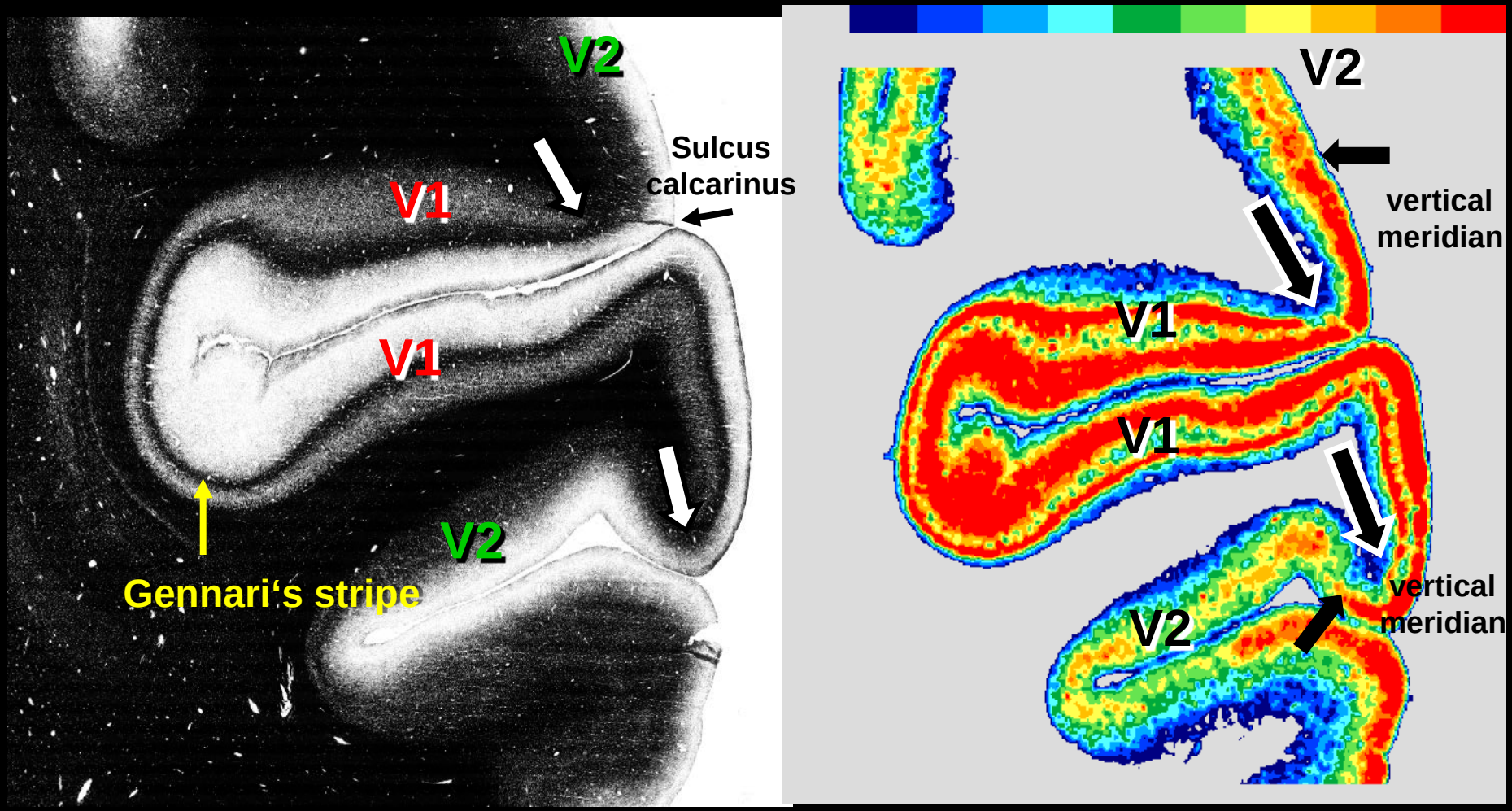


- Incubation of alternating serial sections with tritium-labeled ligands
- Labeling of different receptors of all classical transmitter systems (Glutamate, GABA, Acetylcholine, Dopamine, Serotonin, Noradrenaline)
- Exposition against β-sensitive film together with radioactive scales
- Digitization, quantification and colour coding of the film
- Identification of cytoarchitectonic areas by comparison with neighbouring cell-body stained sections

Histological staining:
Cell bodies
Myelin

Examined receptor binding sites

Neurotransmitter	Receptor	[^{3}H] Ligand
Glutamate	AMPA	AMPA
	Kainate	kainate
	NMDA	MK-801
GABA	$GABA_A$	muscimol, SR 95531
	$GABA_B$	CGP 54626
	BZ	Flumazenil
Acetylcholine	M_1	pirenzepine
	M_2	oxotremorine-M, AF-DX 384
	M_3	4-DAMP
	N	epibatidine
Noradrenaline	α_1	prazosin
	α_2	UK 14,304 RX-821002
Serotonin	$5\text{-}HT_{1A}$	8-OH-DPAT
	$5\text{-}HT_2$	ketanserin
Dopamine	D_1	SCH 23390
	D_2	Fallypride or Raclopride



Myelin **$GABA_A$ Receptor**

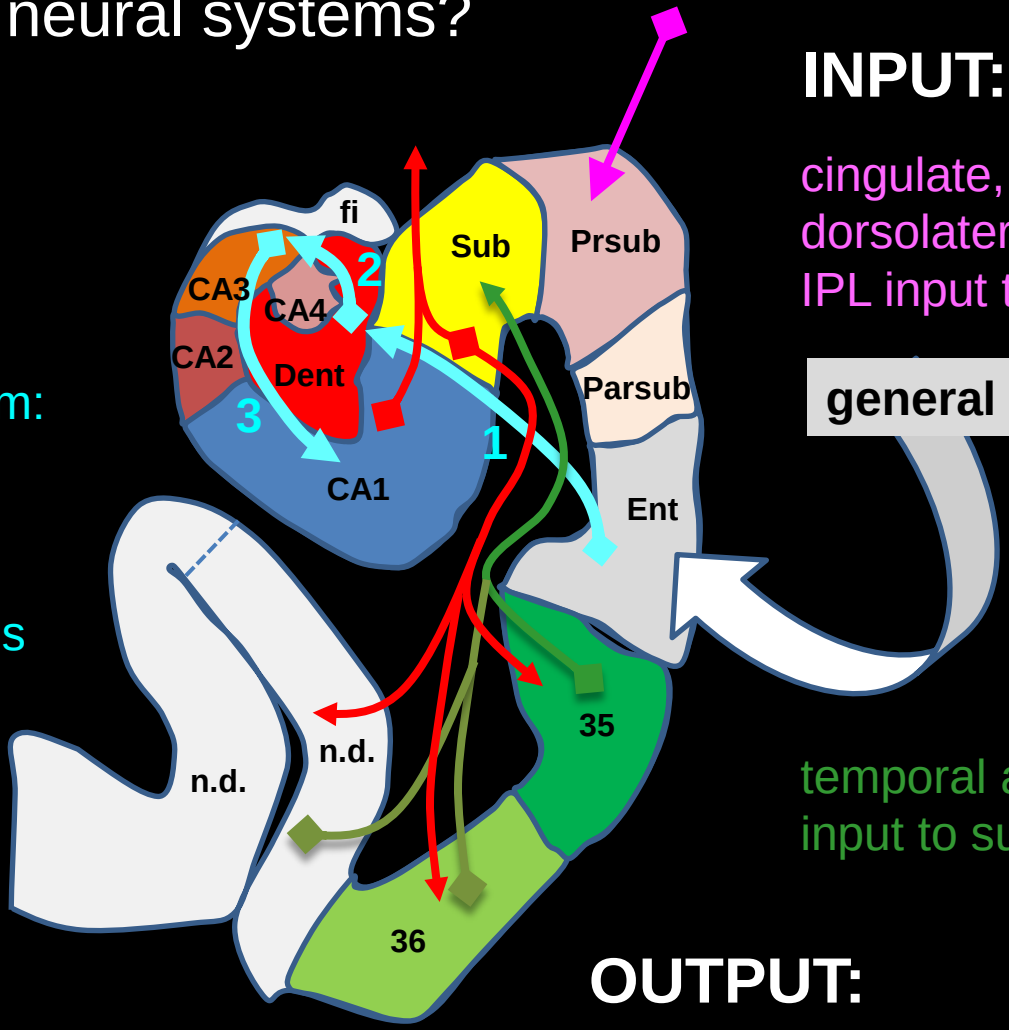
Zilles, K., Palomero-Gallagher, N. , Schleicher, A.: Transmitter receptors and functional anatomy of the cerebral cortex. *J. Anat.* **205**: 417-432 (2004)

Entorhinal-Hippocampal System

Why are architectonic studies essential for understanding the organization of neural systems?

trisynaptic glutamatergic system:

1 perforant path
2 mossy fibers
3 Schaffer collaterals



dorsal
lateral
medial
ventral

INPUT:

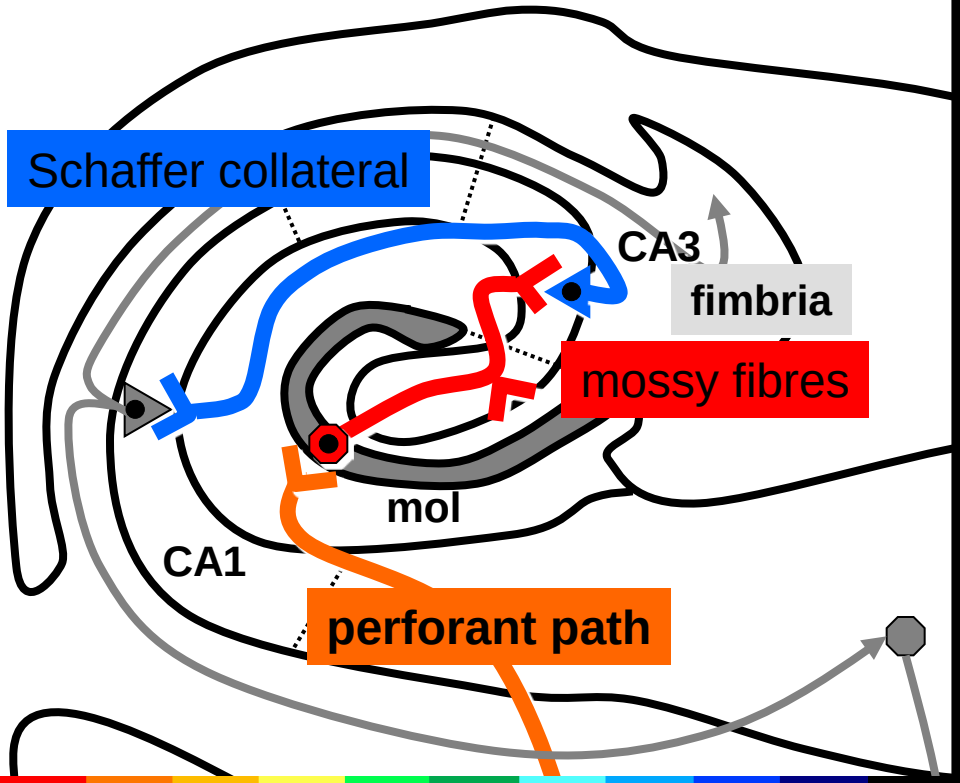
cingulate, superior temporal, dorsolateral prefrontal, and IPL input to presubiculum

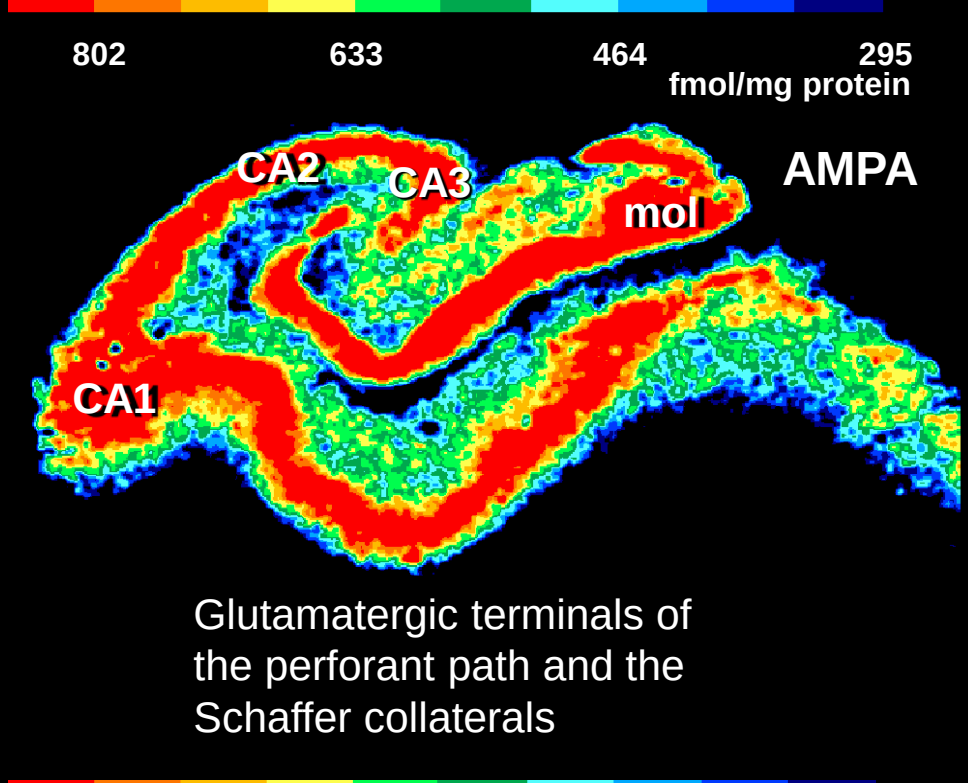
general neocortical input

temporal and perirhinal input to subiculum

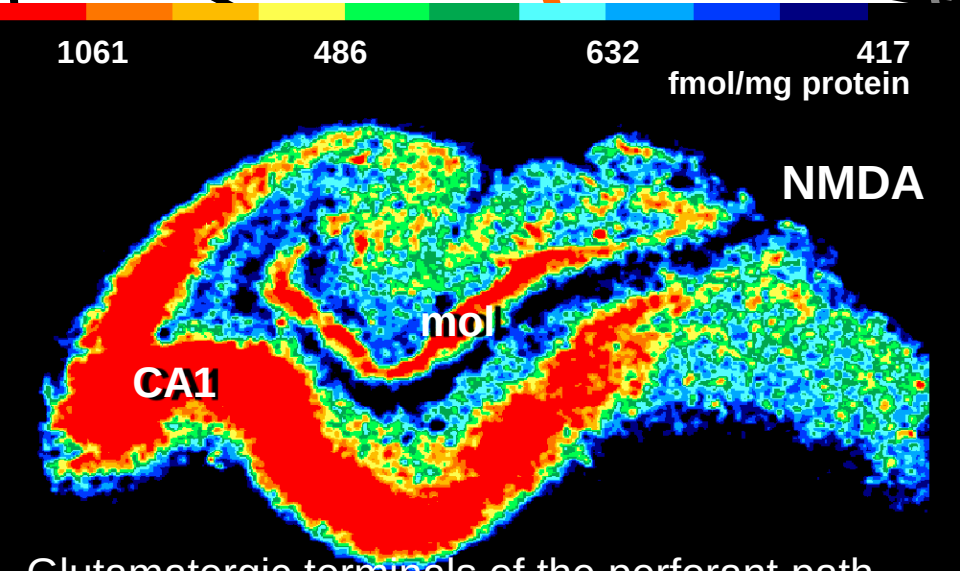
OUTPUT:

from the subiculum and CA1 to temporal, parahippocampal, perirhinal, cingulate, prefrontal, and orbitofrontal areas

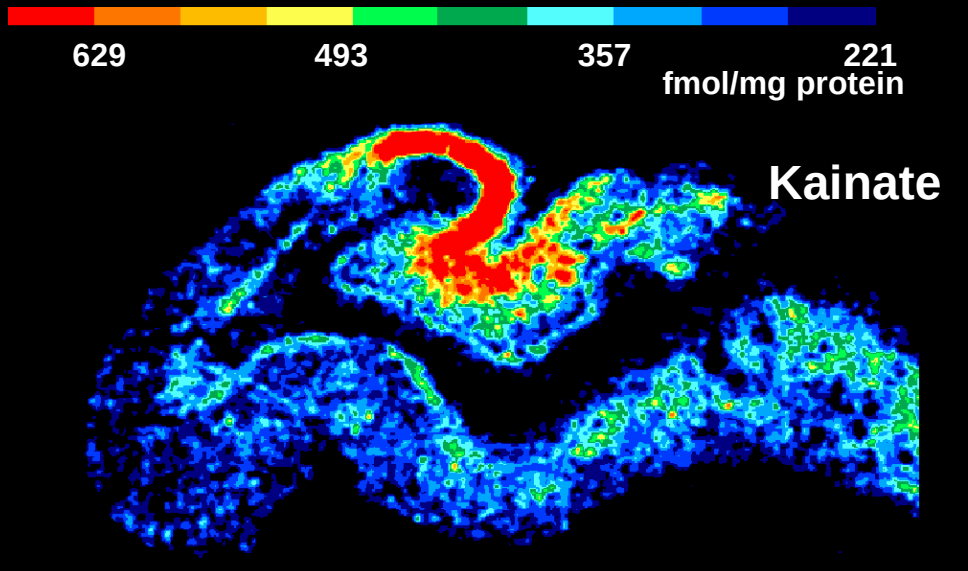




Glutamatergic terminals of the perforant path and the Schaffer collaterals

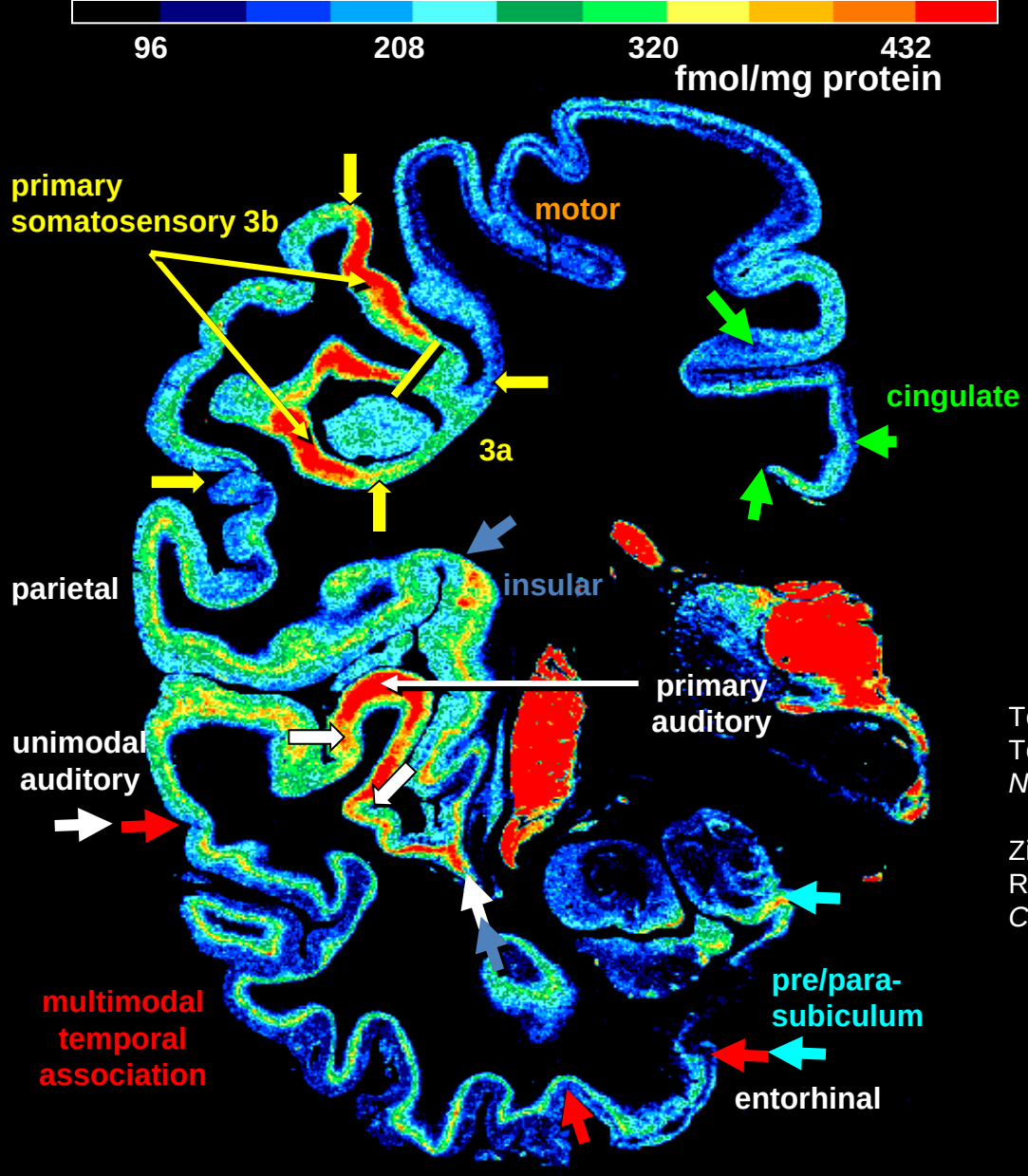


Glutamatergic terminals of the perforant path and the Schaffer collaterals



Glutamatergic terminals of the mossy fibers

Primary Sensory Cortices

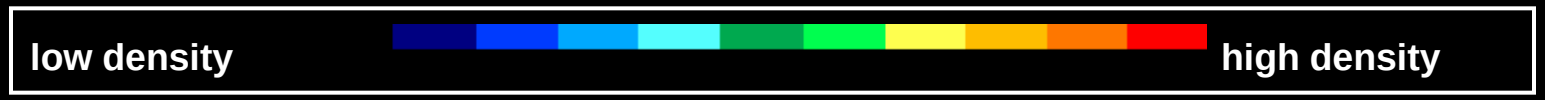


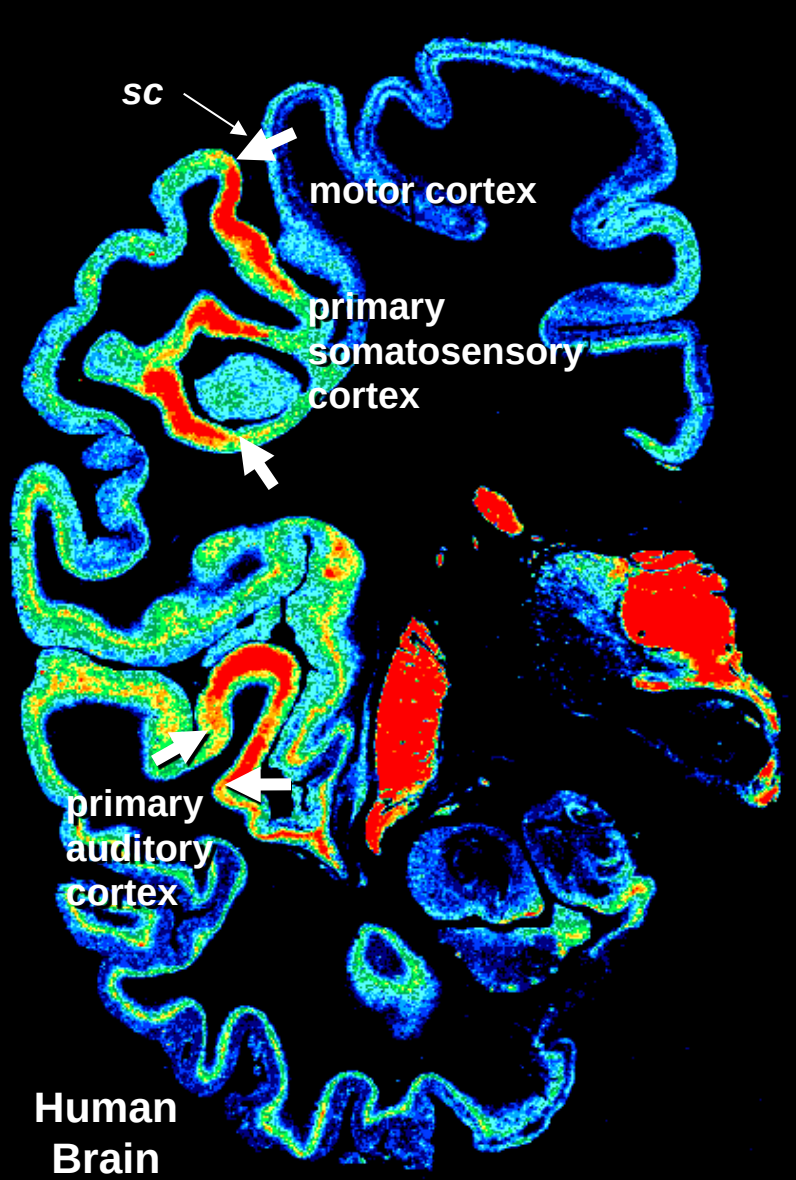
cholinergic muscarinic M2 receptor

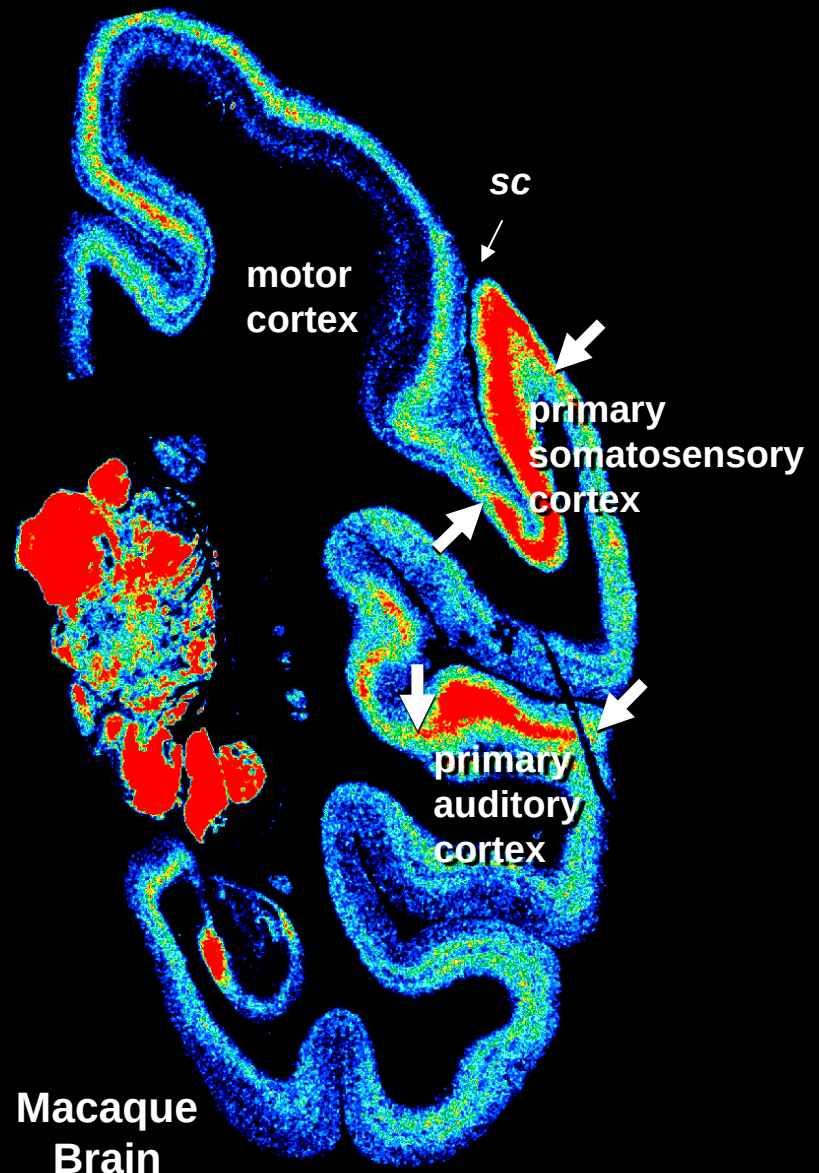
Toga AW, Thompson PM, Mori S, Amunts K, Zilles K (2006)
Towards multimodal atlases of the human brain.
Nature Rev. Neurosci. **7**: 952-966

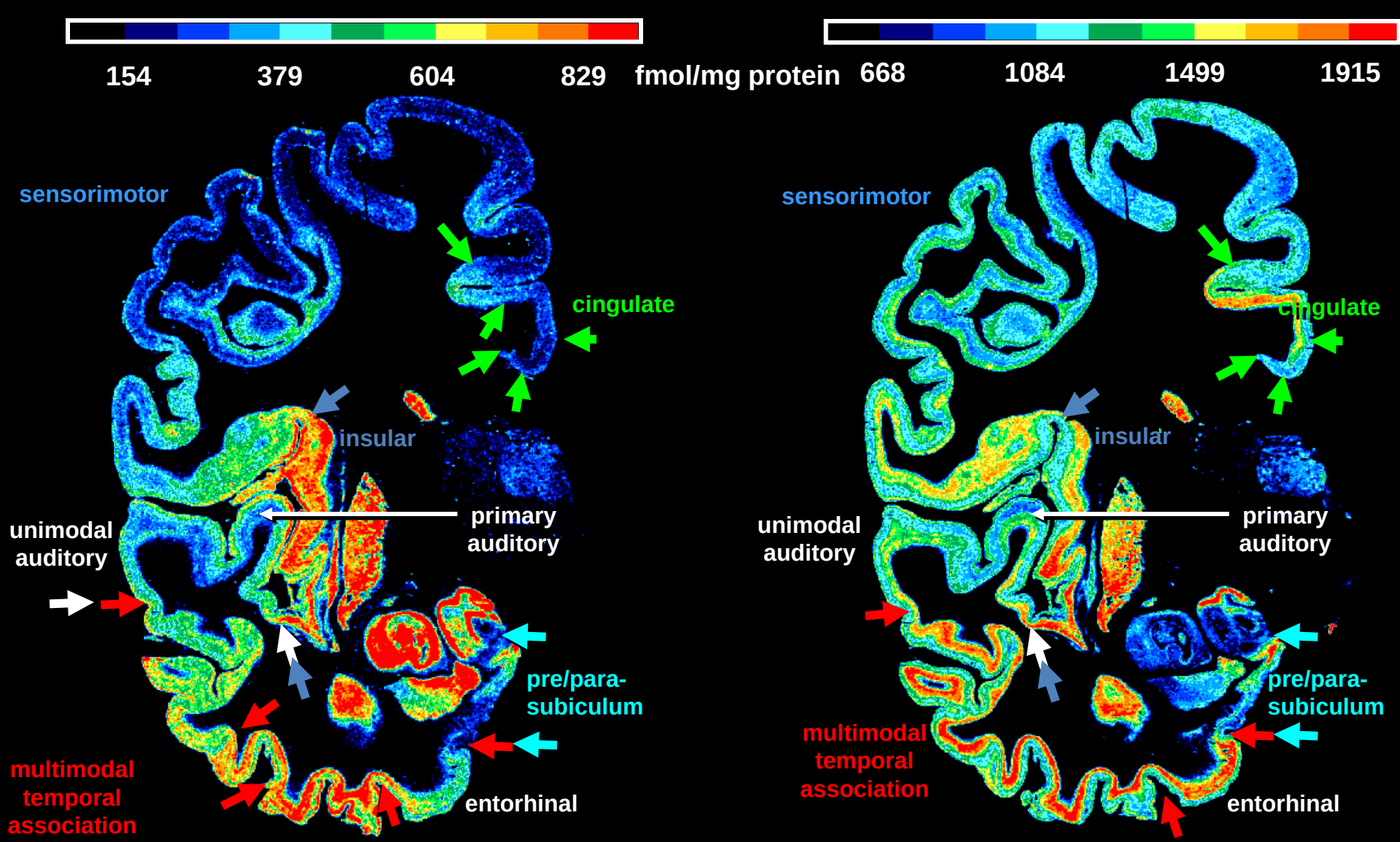
Zilles K, Amunts K (2009)
Receptor mapping: Architecture of the human cerebral cortex.
Current Opinion Neurol. **22**: 331–339

Cholinergic muscarinic M2 receptor









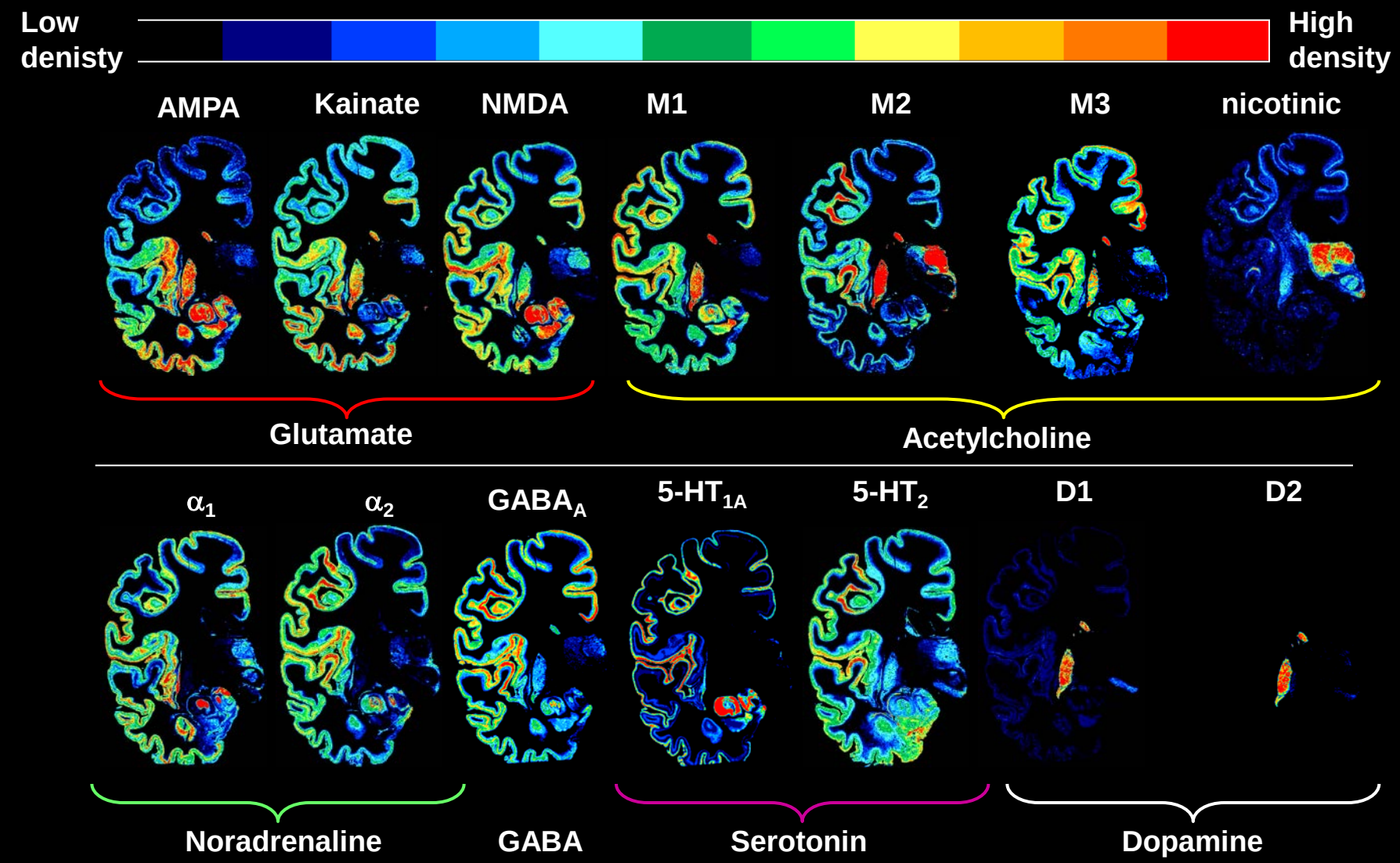
AMPA receptor
[^{3}H] AMPA

Kainate receptor
[^{3}H] kainate

GLUTAMATE SYSTEM

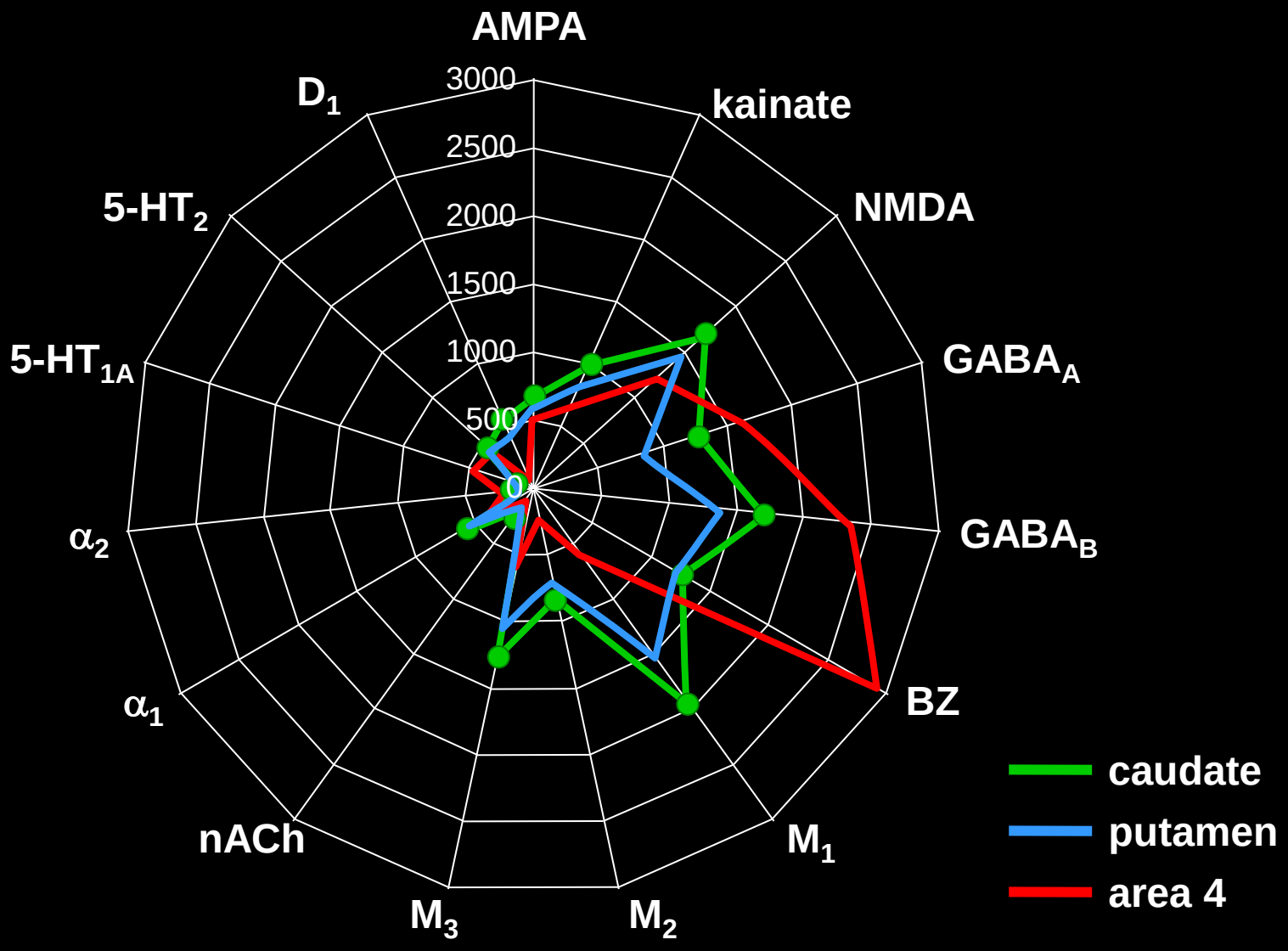
Receptor Fingerprints

Multimodal visualization of receptor organization in human cerebral cortex

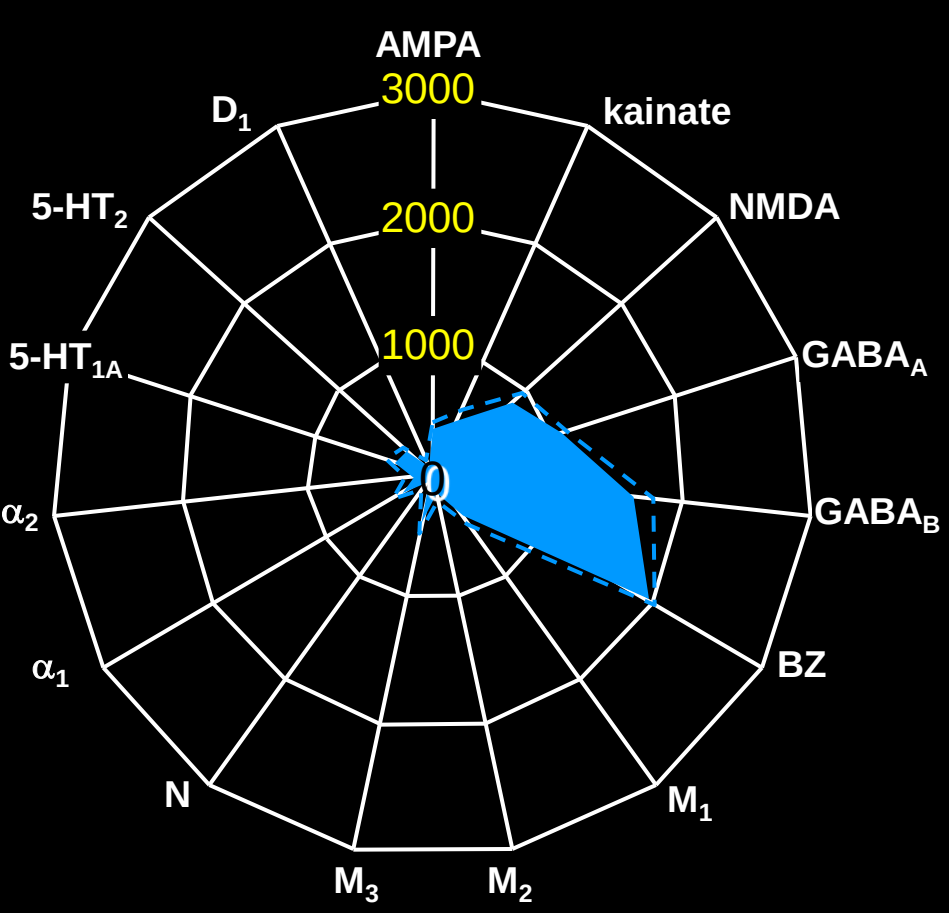


Zilles, K., Schleicher, A., Palomero-Gallagher, N., Amunts, K.:
Quantitative analysis of cyto- and receptorarchitecture of the human brain, pp. 573-602.
In: Brain Mapping: The Methods, 2nd edition (A.W. Toga and J.C. Mazziotta, eds.). Academic Press (2002)

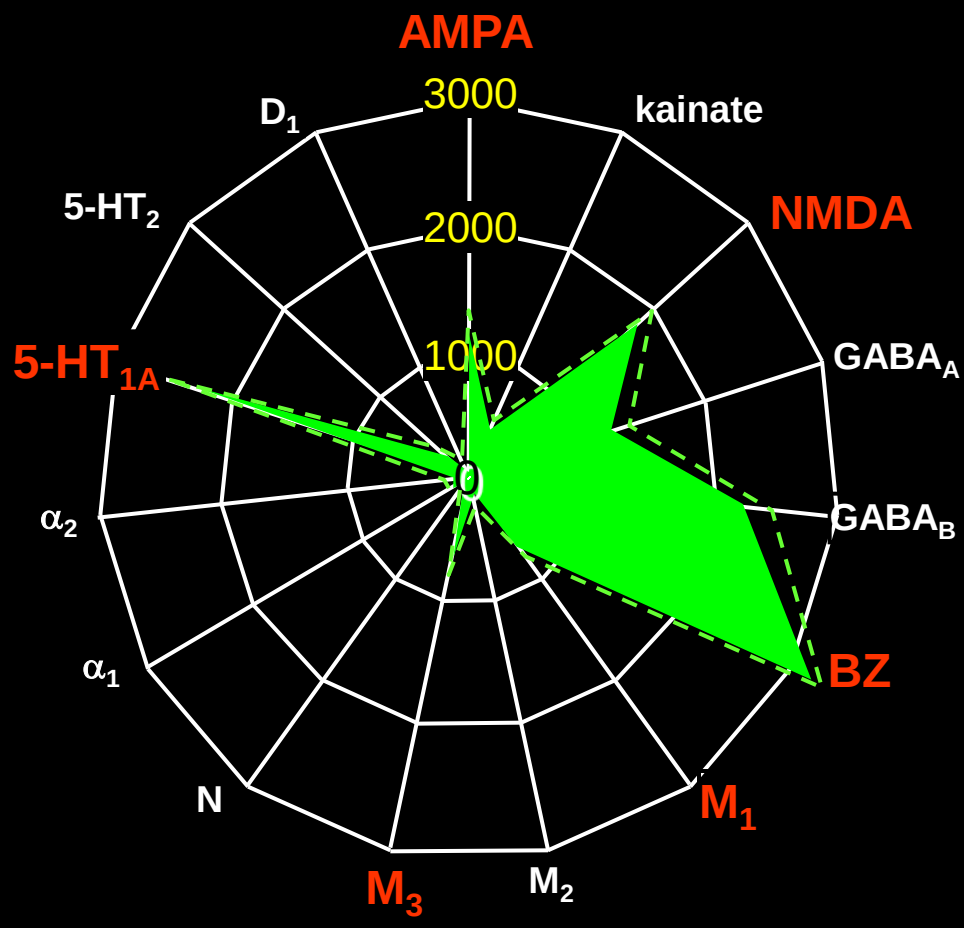
A receptor fingerprint is…



„Receptor Fingerprints“

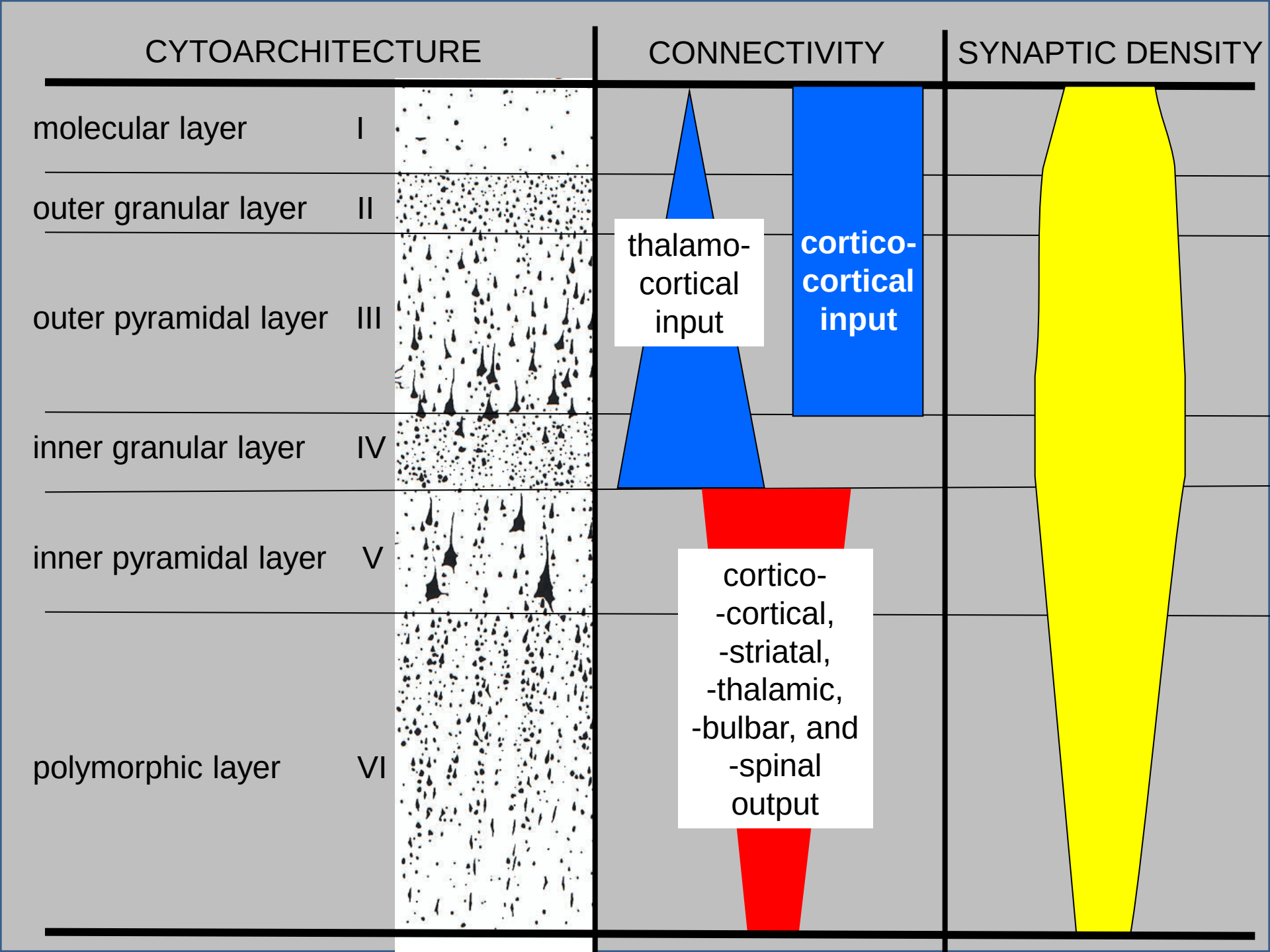


primary motor cortex



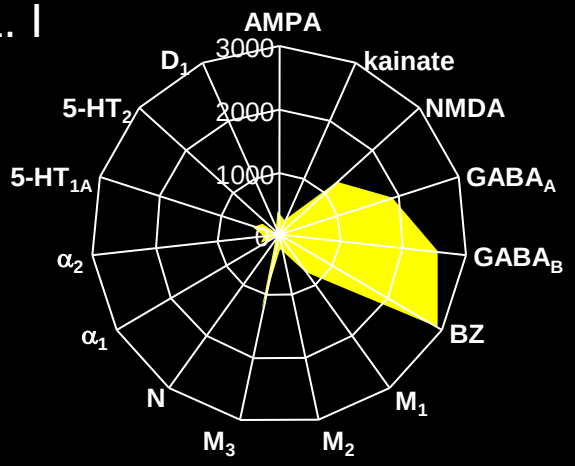
Hippocampus
CA1-3

What receptors tell us about laminar segregation and input-output relations in the cerebral cortex

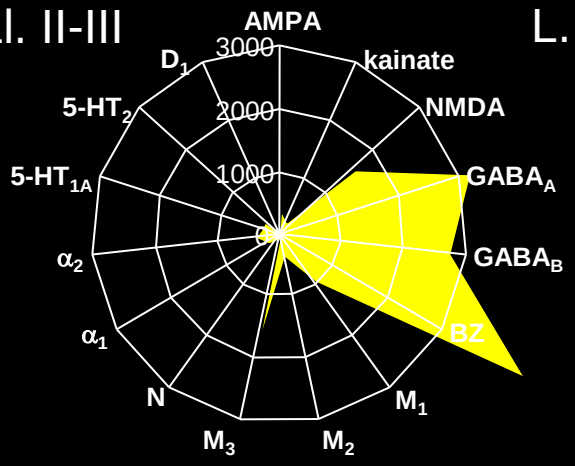

CYTOARCHITECTURE
CONNECTIVITY
SYNAPTIC DENSITY
molecular layer I
outer granular layer II
outer pyramidal layer III
inner granular layer IV
inner pyramidal layer V
polymorphic layer VI
thalamo-cortical input
cortico-cortical input
cortico--cortical, -striatal, -thalamic, -bulbar, and -spinal output

Receptor Fingerprints of the primary visual cortex: layer specificity

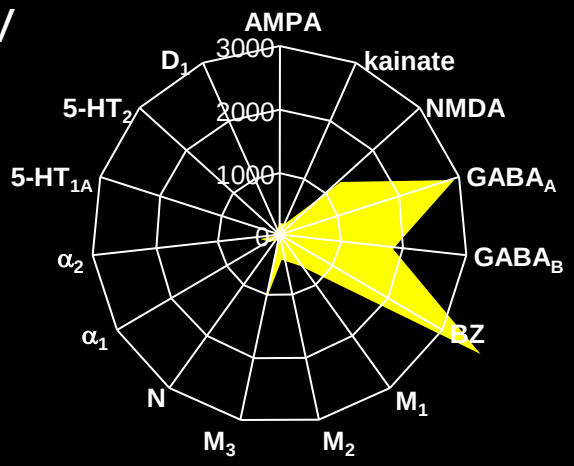
L. I



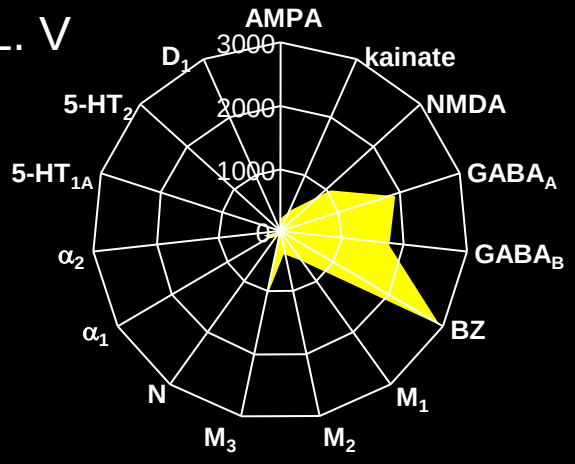
LI. II-III



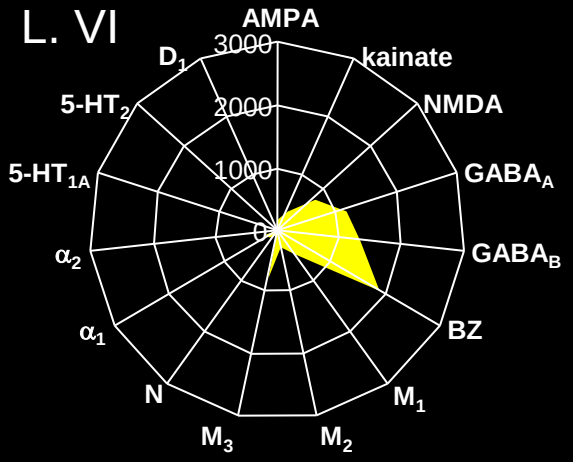
L. IV



L. V



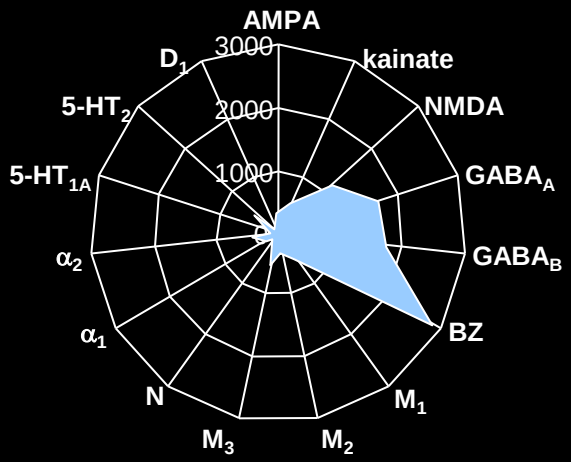
L. VI



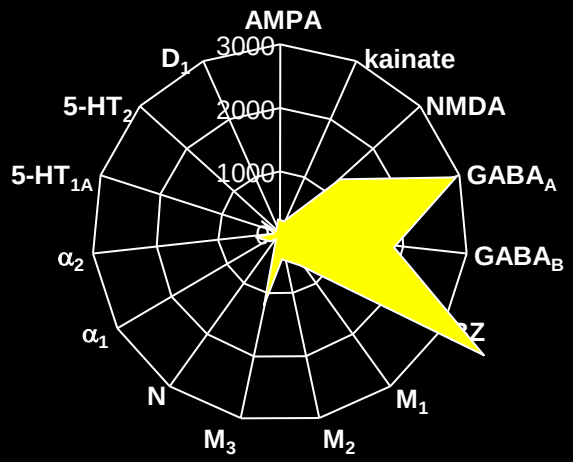
Layer IV: Thalamo-cortical Input

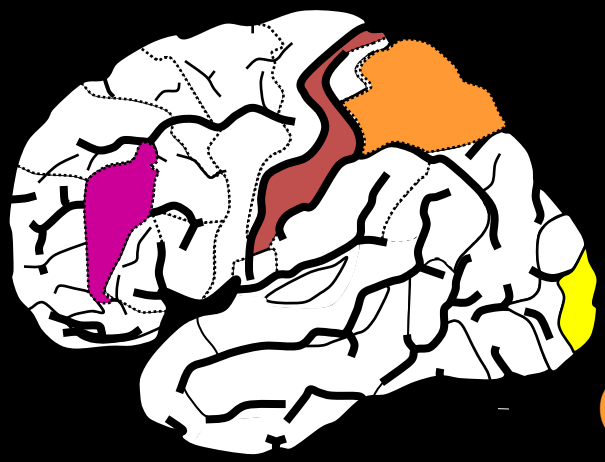
modality-specific balance between receptors

primary somatosensory (touch)

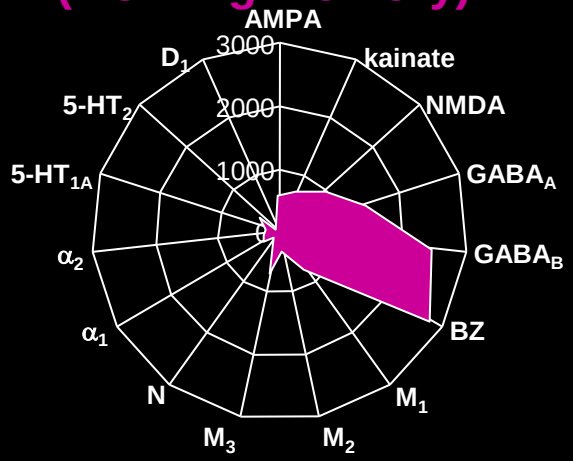


primary visual

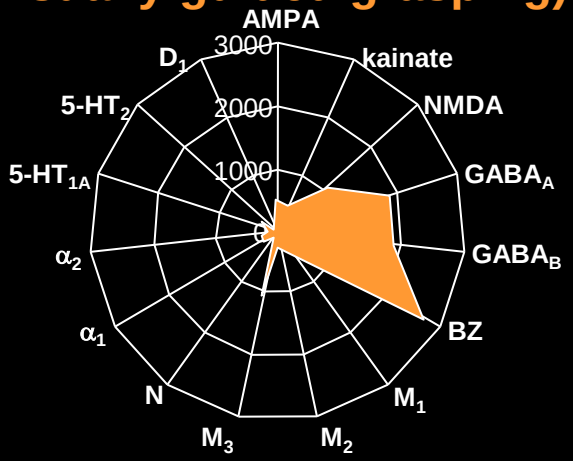




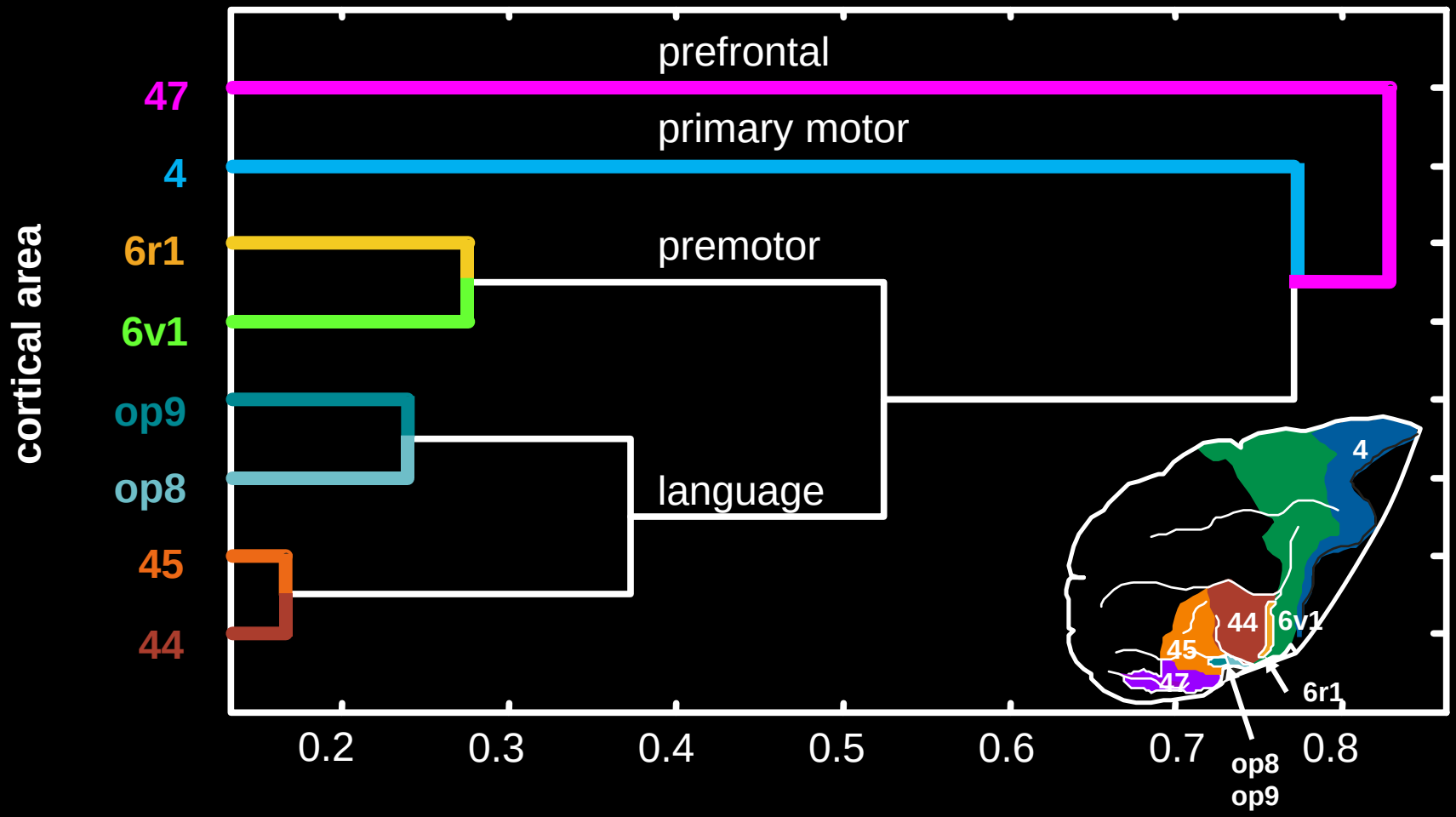
prefrontal association (working memory)



parietal association (visually guided grasping)



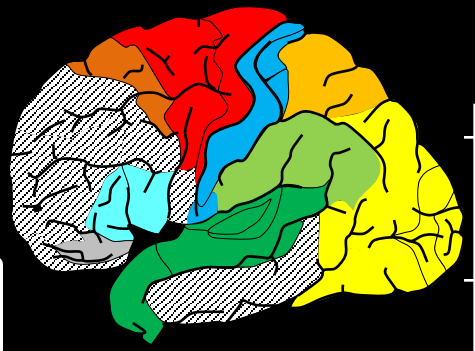
Cluster analysis of the multi-receptor fingerprints of BROCA‘s region, prefrontal and motor cortex

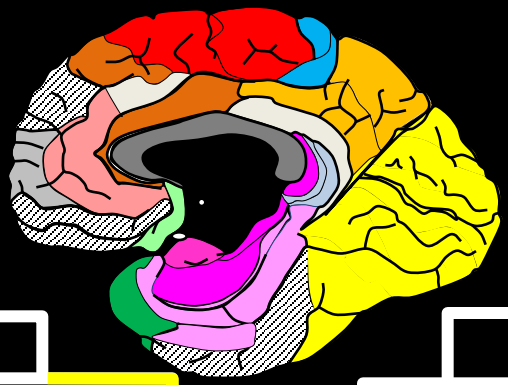


Amunts, K., Lenzen, M., Friederici, A.D., Schleicher, A., Morosan, P., Palomero-Gallagher, N., Zilles, K.: Broca's region: Novel organizational principles and multiple receptor mapping. PLoS Biology 8(9): e1000489. doi:10.1371/journal.pbio.1000489 (2010)

Whole brain hierarchical cluster analysis based on multi-receptor fingerprints

- Normalization: divide by mean
- Euclidean distances, Ward linkage
- Cophrenetic coefficient: 0.58





Euclidean distance

0 1 2 3 4 5 6

CA ent subic dg BA36 BA20' 25 p32 s32 10m BA47 PFt PFop PFcm PGa PGp PFm PF 32' v23 24 OP a24' 6d V1 FG2 FG1 v4v Oc3v 3b BA45 BA44 p24' BA8 BA4 BA38 5l 7pc 5m BA2 Te4 Te3 Te2 Te1 3a BA1 30 29 d23 Oc3d Oc4d v2v v2d 7ma 7la 31 7mp 7lp

entorhinal -hippocampal circuit

perilimbic proisocortex

anterior cingulate-prefrontal

inferior parietal multimodal cortex

sensorimotor limbic

visual ventral stream

Broca

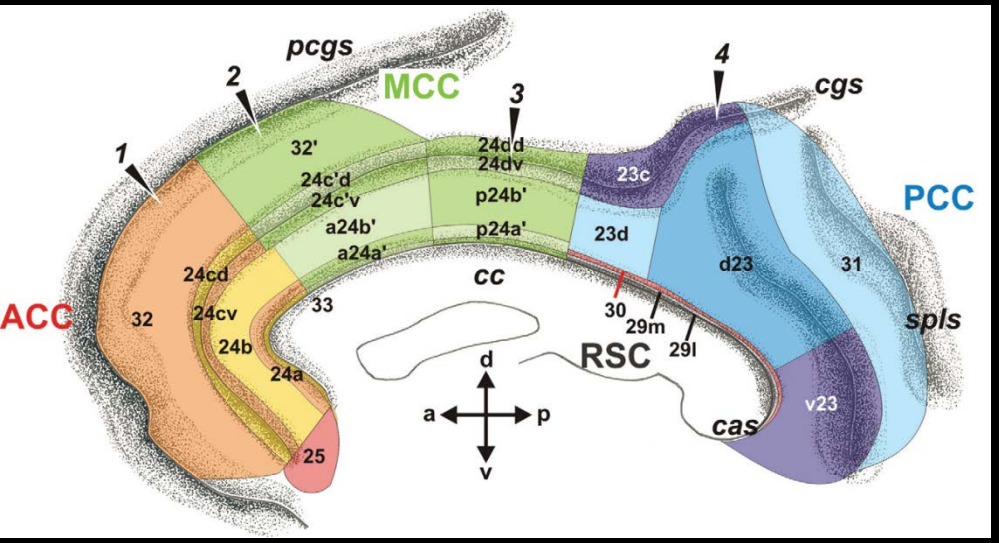
motor

somatoauditory -sensory domaine

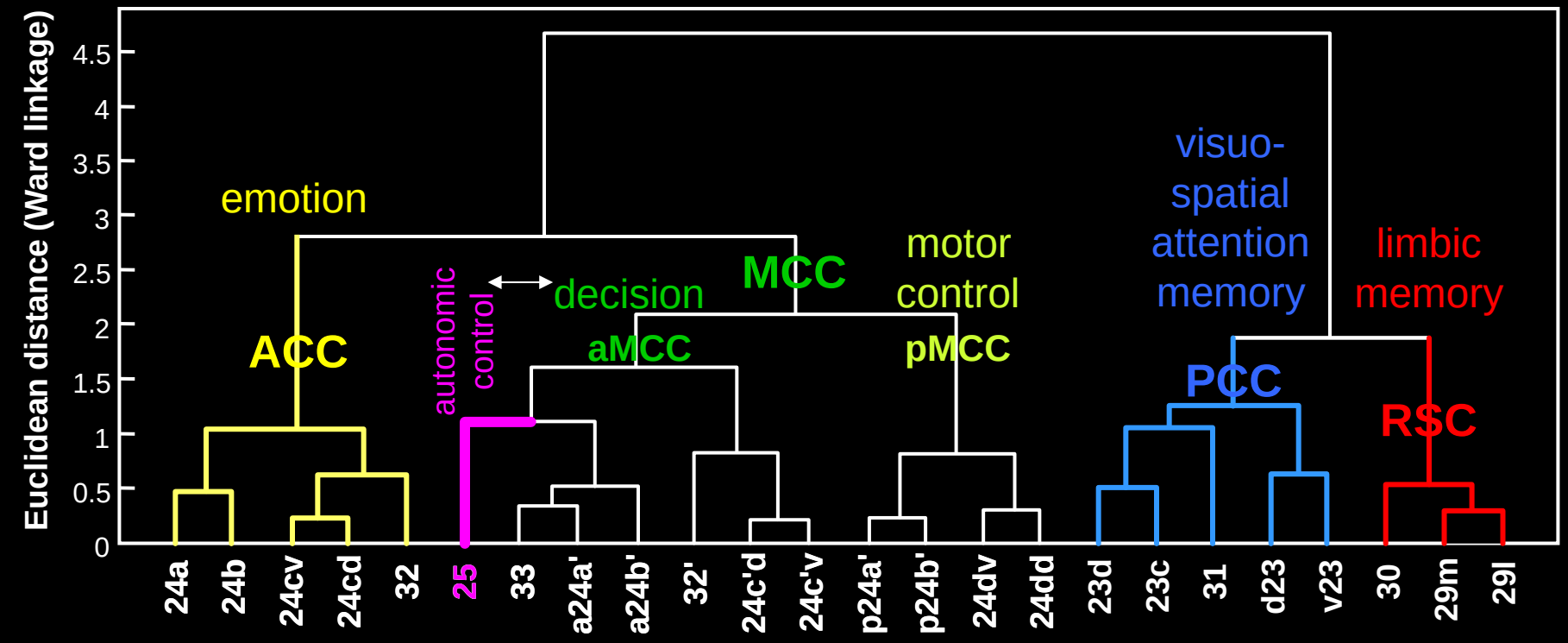
retro-splenial

visual superior parietal dorsal stream

Cluster analysis of the human cingulate cortex: A multi-region model based on receptor fingerprints



Palomero-Gallagher, N., Vogt, B.A., Schleicher, A., Mayberg, H.S., Zilles, K. (2009) Receptor architecture of human cingulate cortex: Evaluation of the four-region neurobiological model.
Human Brain Mapping **30**: 2336-2355



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Katrin Amunts
Svenja Caspers
Joachim Lübke
Hartmut Mohlberg
Nicola Palomero-Gallagher
Axel Schleicher