Nicotinic receptors: from structures to behaviours

Nicolas Le Novère
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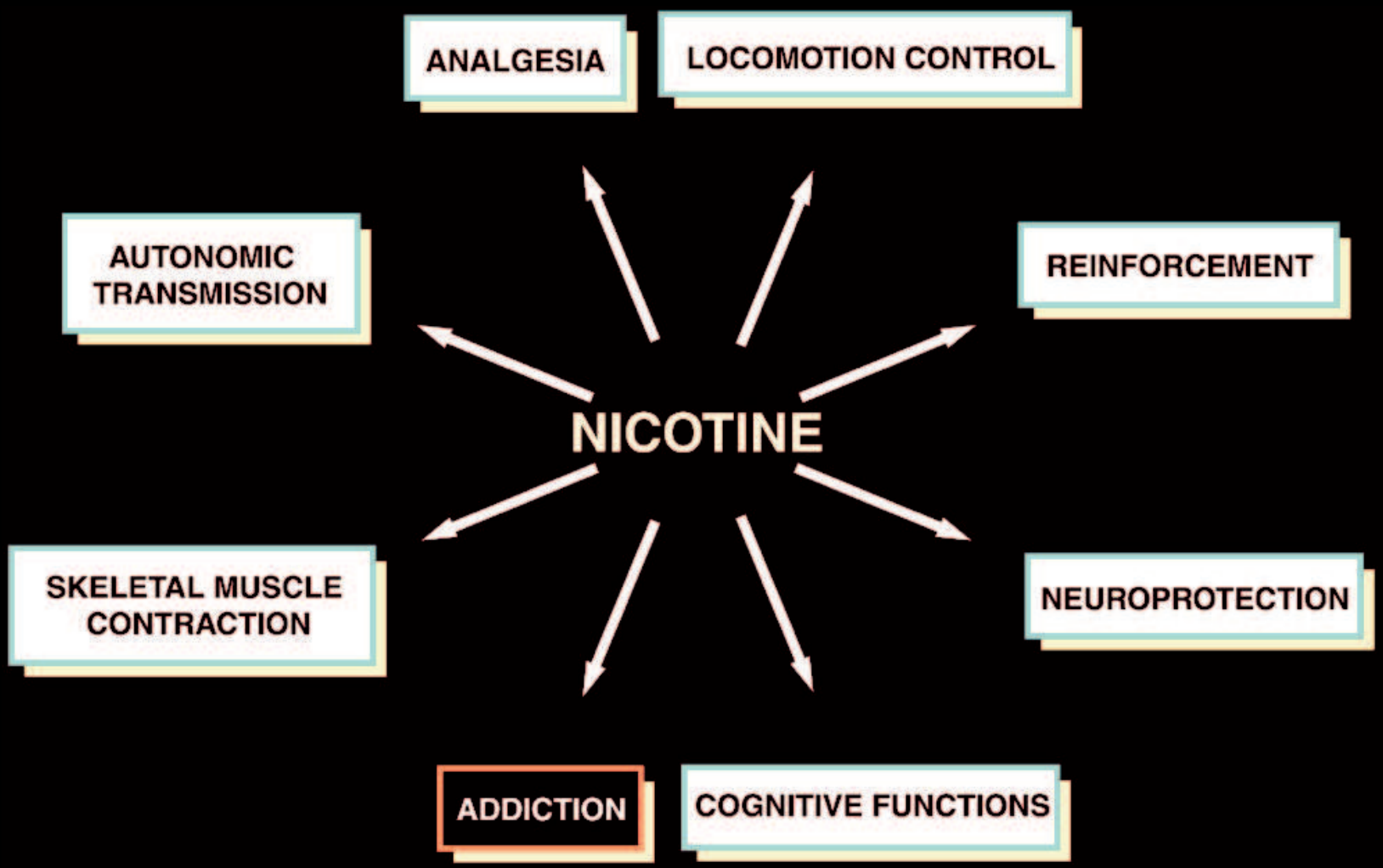
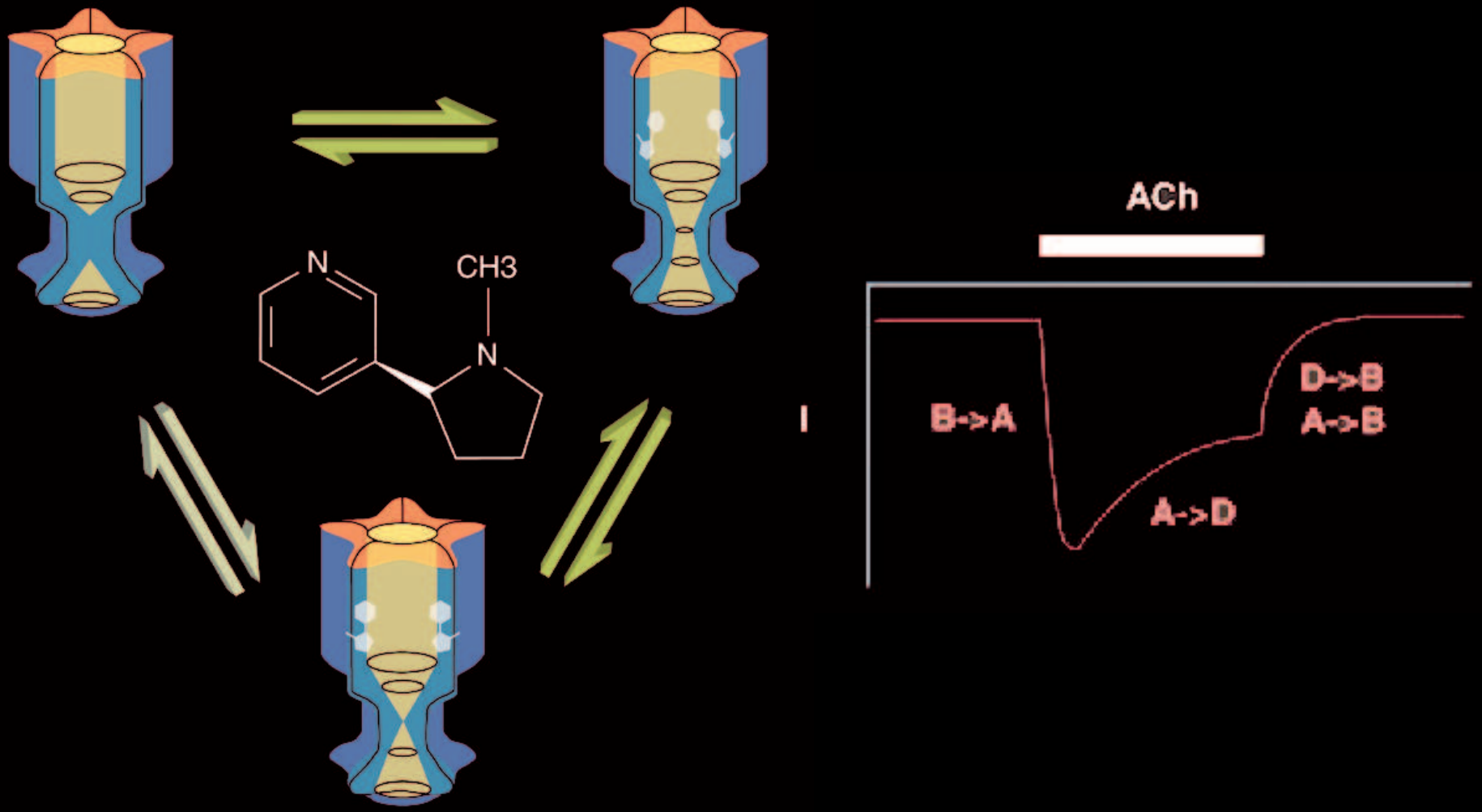
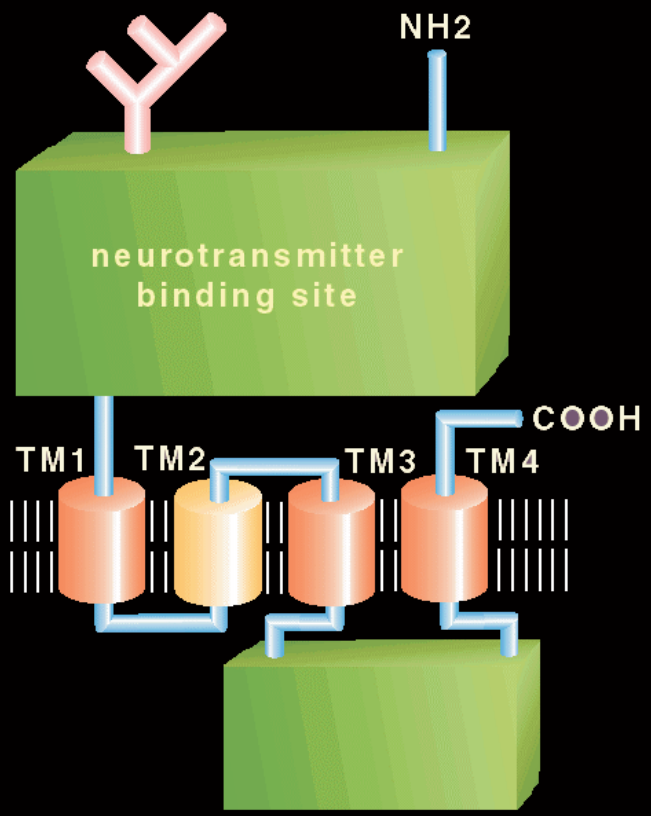
Nicotine neuropharmacology



An allosteric protein

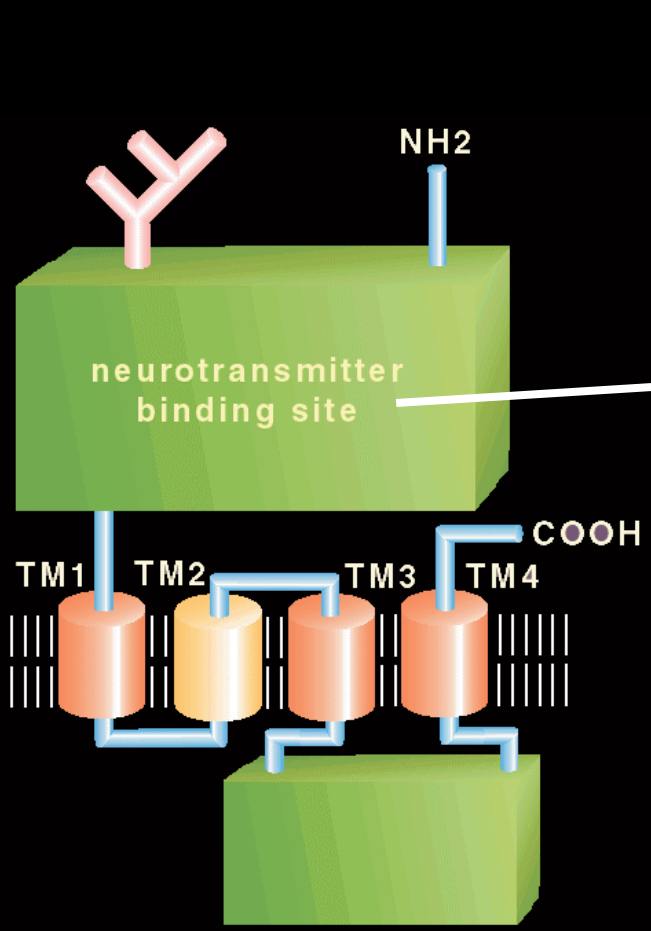


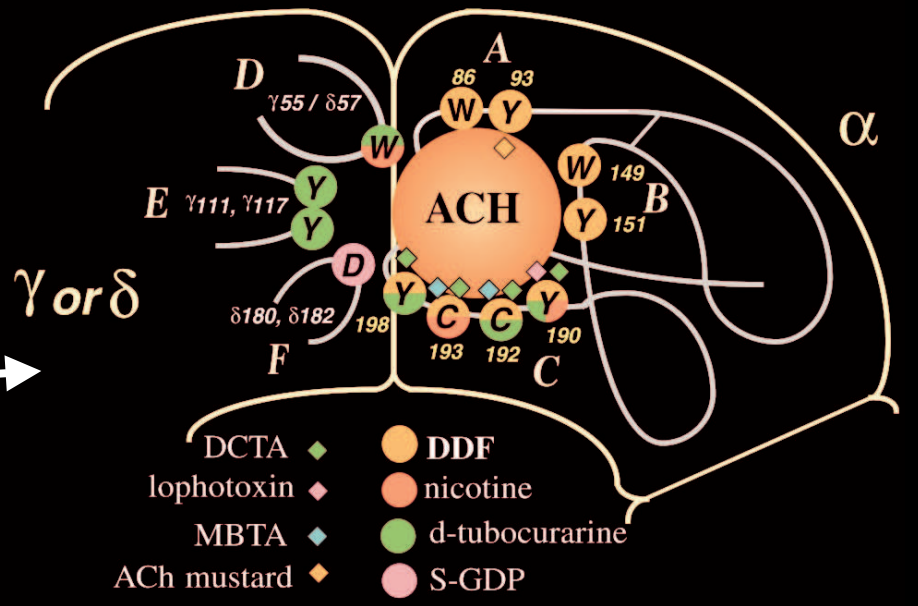
Insights about the structure of nAChRs



Review in CORRINGER *et al.* (2000)
Annu. Rev. Pharm. Tox.

Insights about the structure of nAChRs





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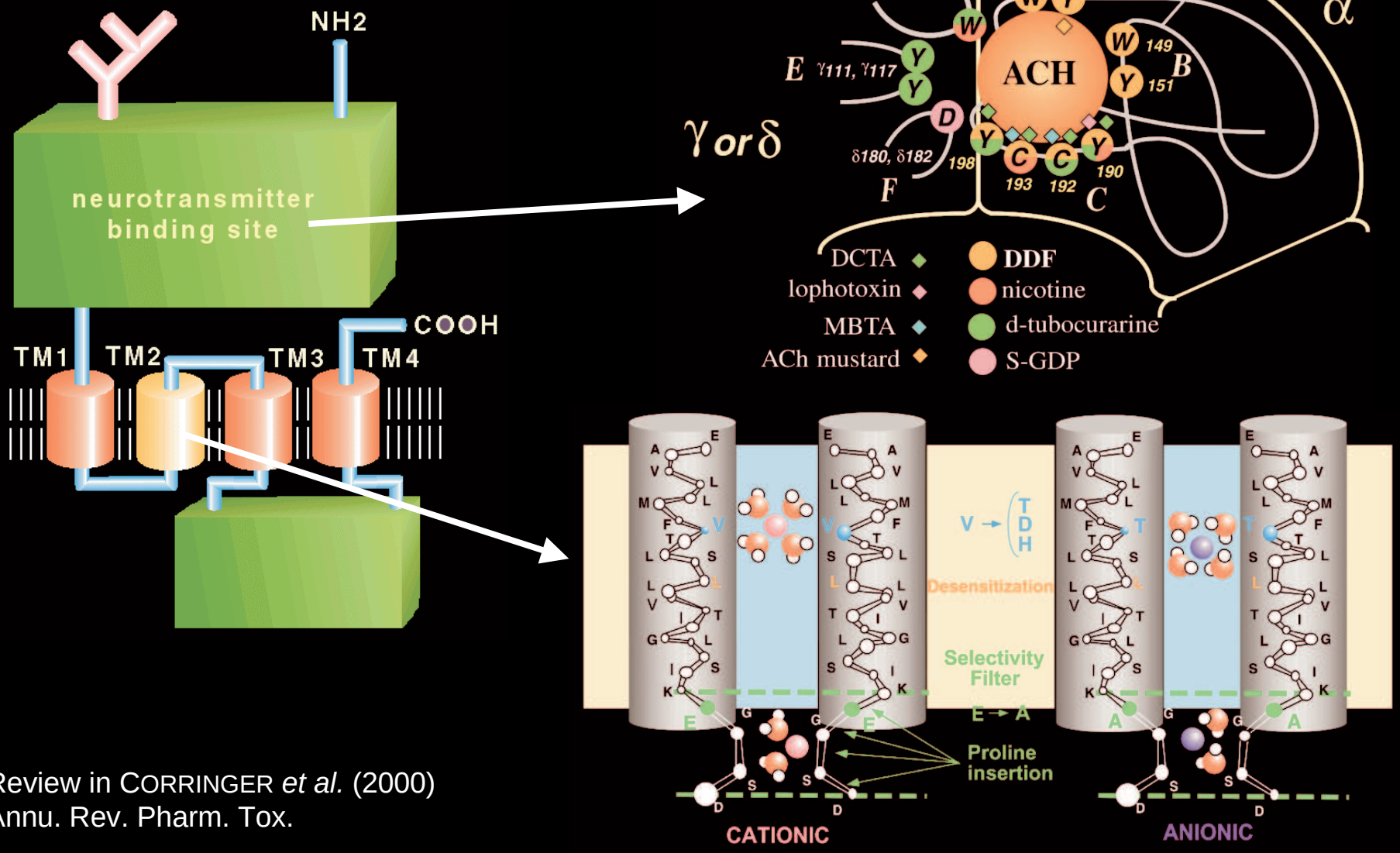
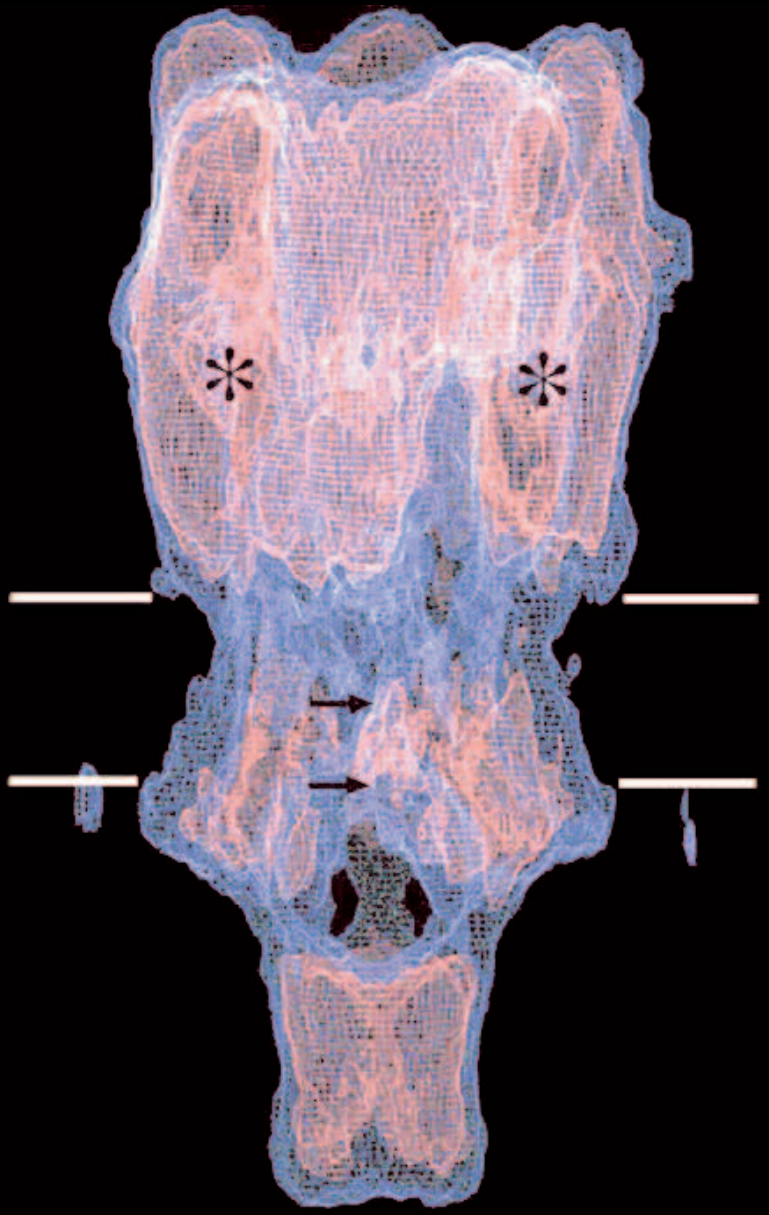


Review in CORRINGER *et al.* (2000)
Annu. Rev. Pharm. Tox.

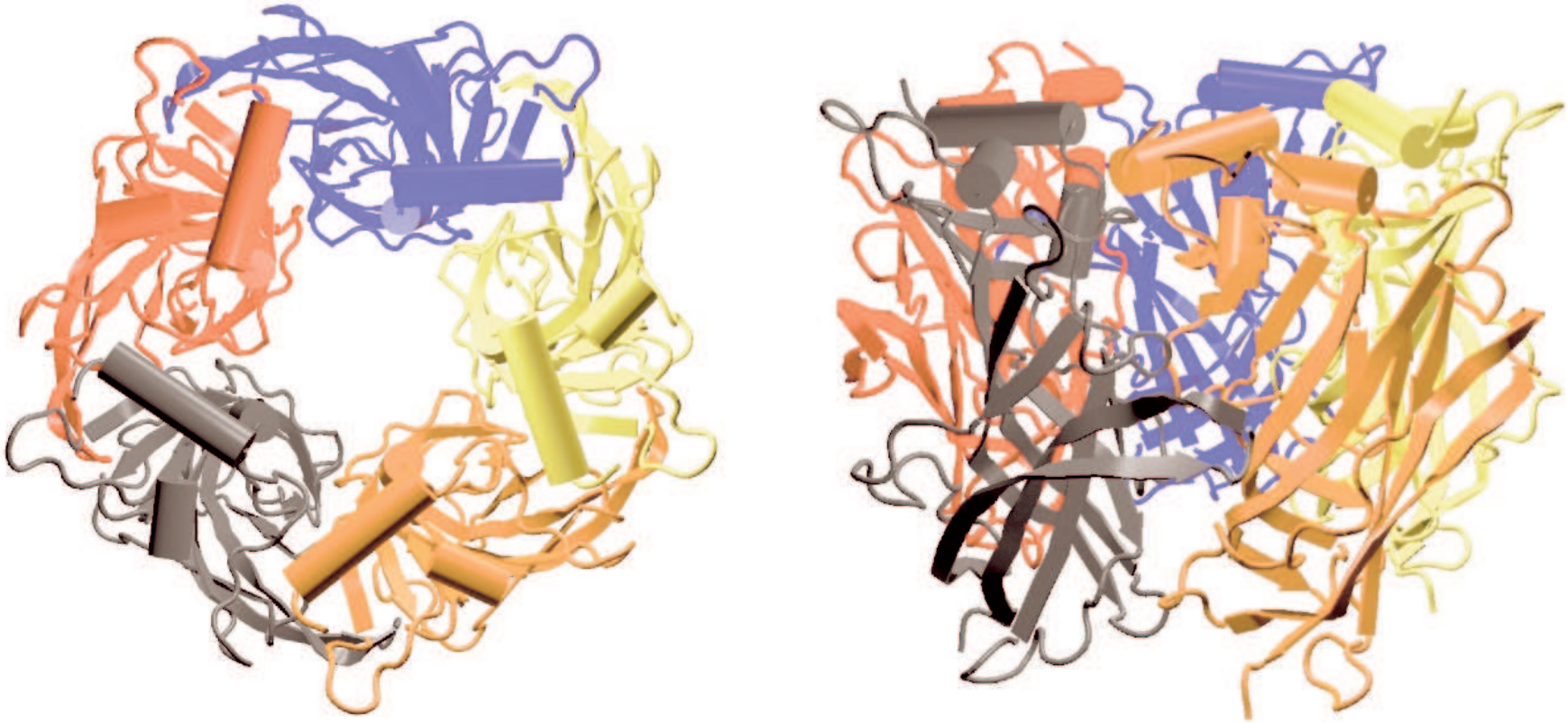
Five subunits around an ionic pore

UNWIN (2000)
Phil. T. Roy. Soc. B
355 : 1813-1829



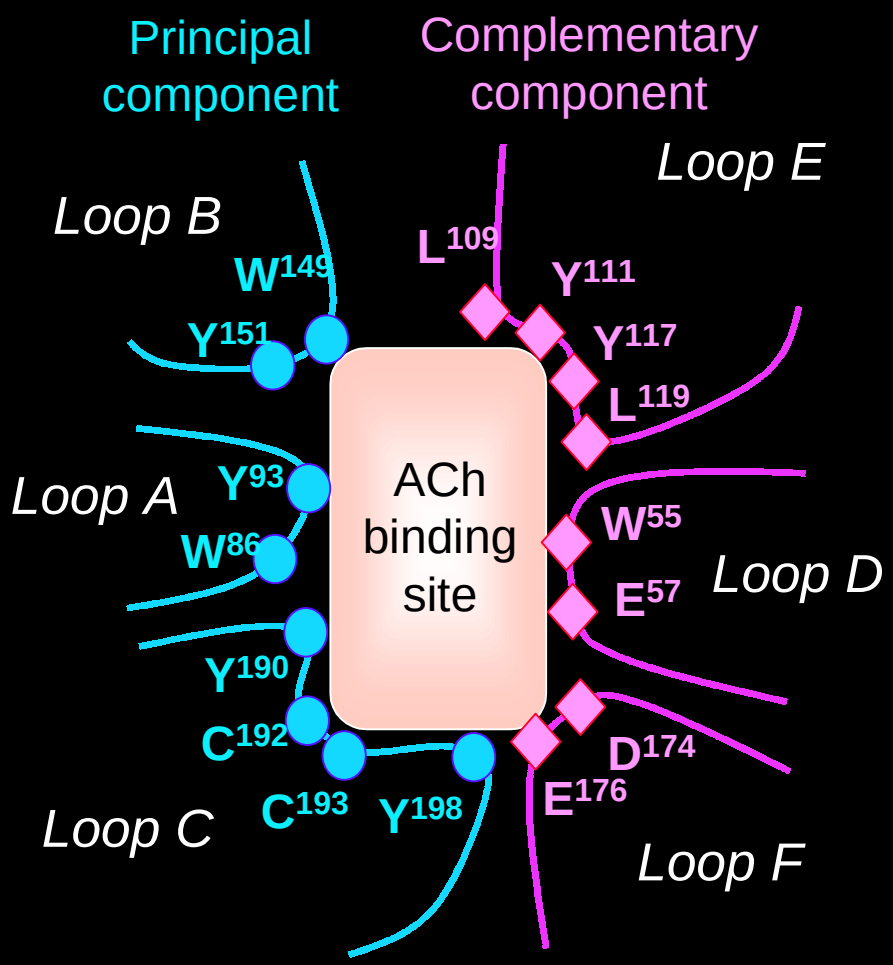
AChBP, a partial molluscan homolog

BREJC *et al.* (2001) *Nature* 411 : 269-276



- 20-25 % sequence identity with extra-cellular portion of nAChR subunits;
- AChBP secondary structure 61 % identical to prediction of nAChR subunits;
- Immunoglobulin-like fold as predicted for extra-cellular portion of nAChR.

nAChR Vs AChBP ACh sites



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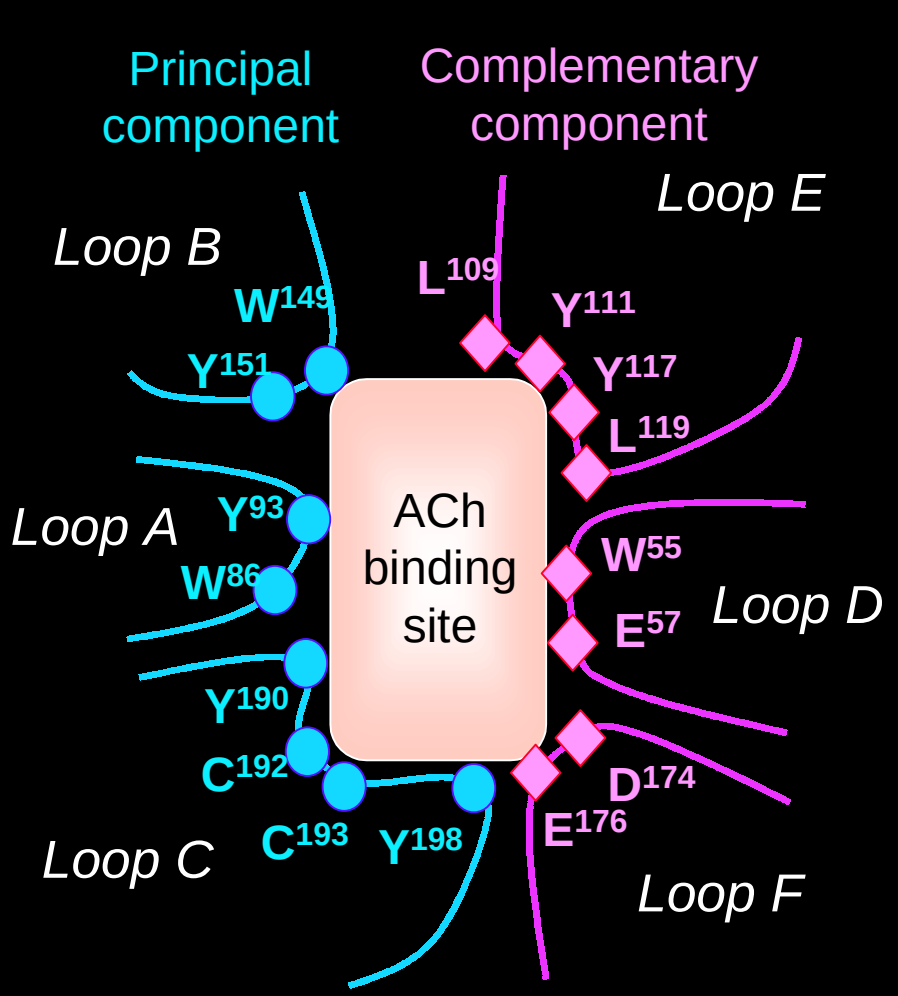
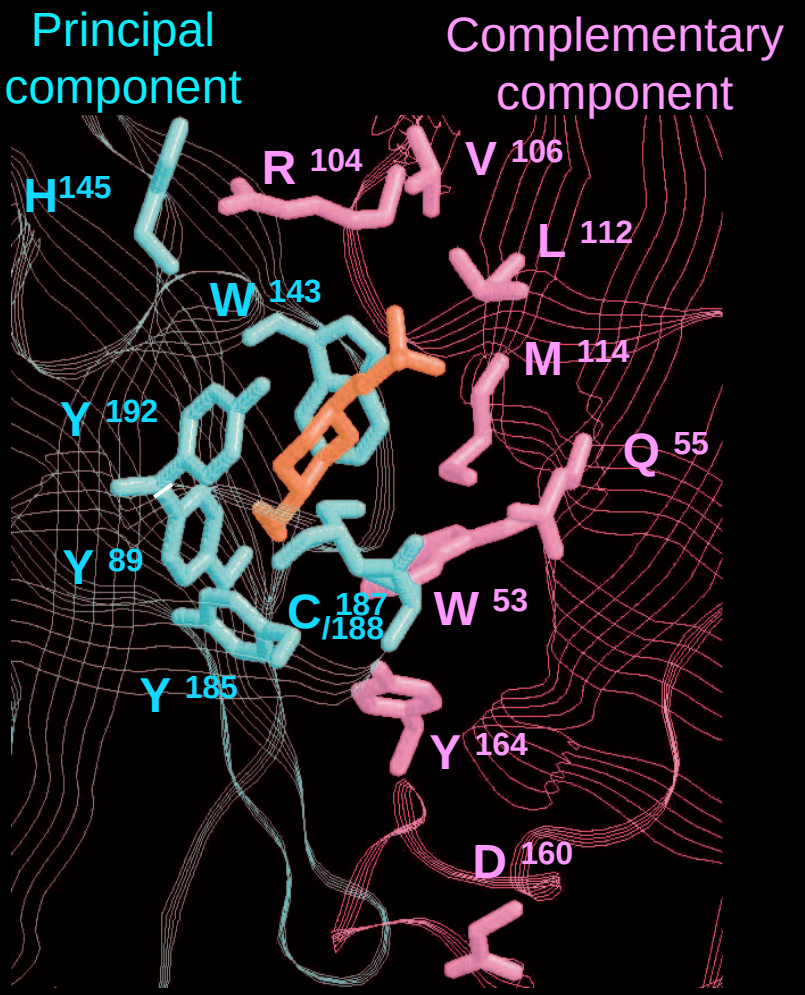
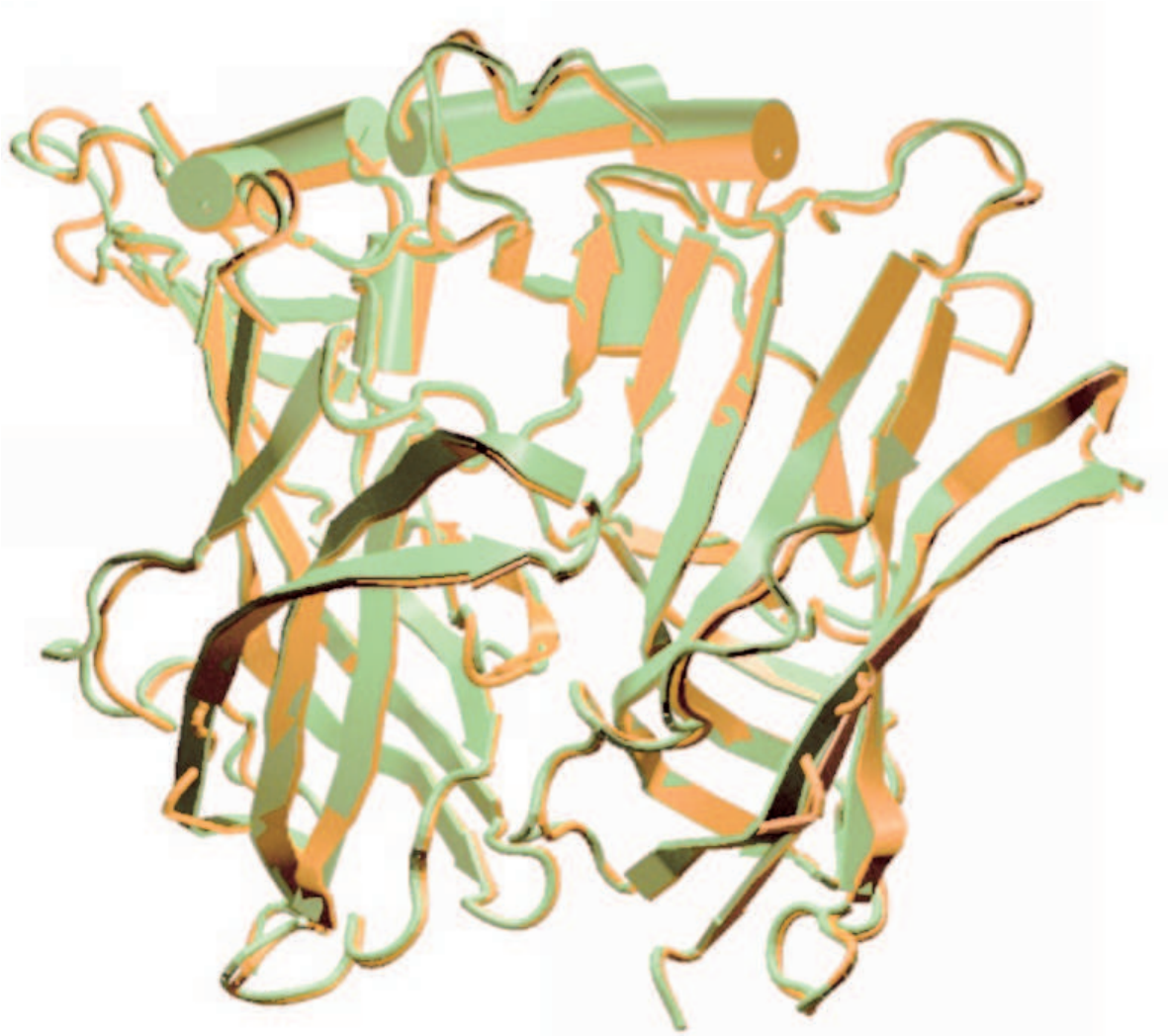


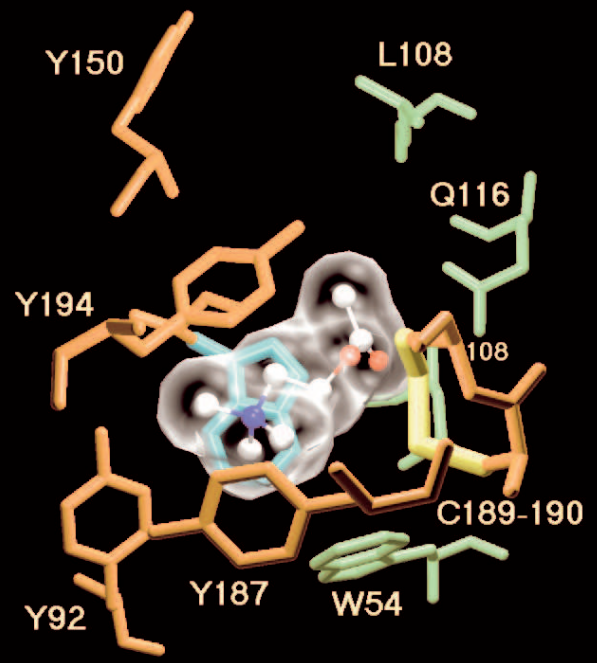


AChBP structure / model of nAChR α7



LE NOVÈRE *et al.* (2002) *Proc. Natl. Acad Sci. USA,* 99: 3210-3215

Docking of ACh, Nicotine, and Epibatidine



Exp :	$2.5\ 10^{-5}$ M	$0.55\ 10^{-6}$ M	$1.9\ 10^{-7}$ M
Comp :	$4.2\ 10^{-5}$ M	$4.2\ 10^{-6}$ M	$5.6\ 10^{-7}$ M

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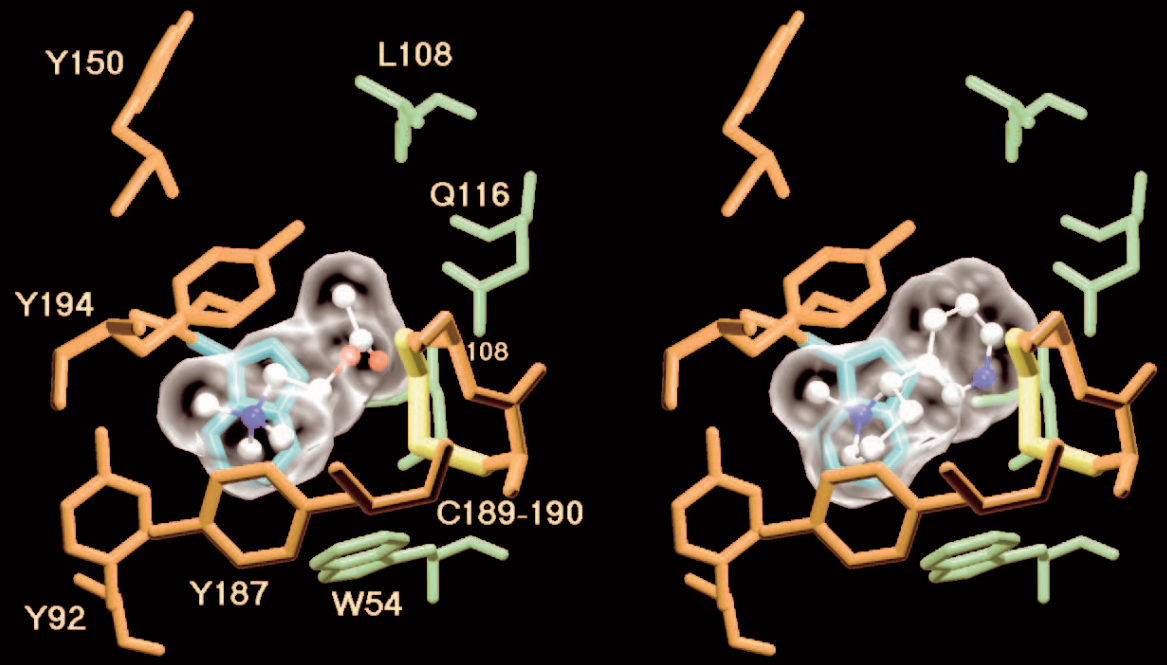

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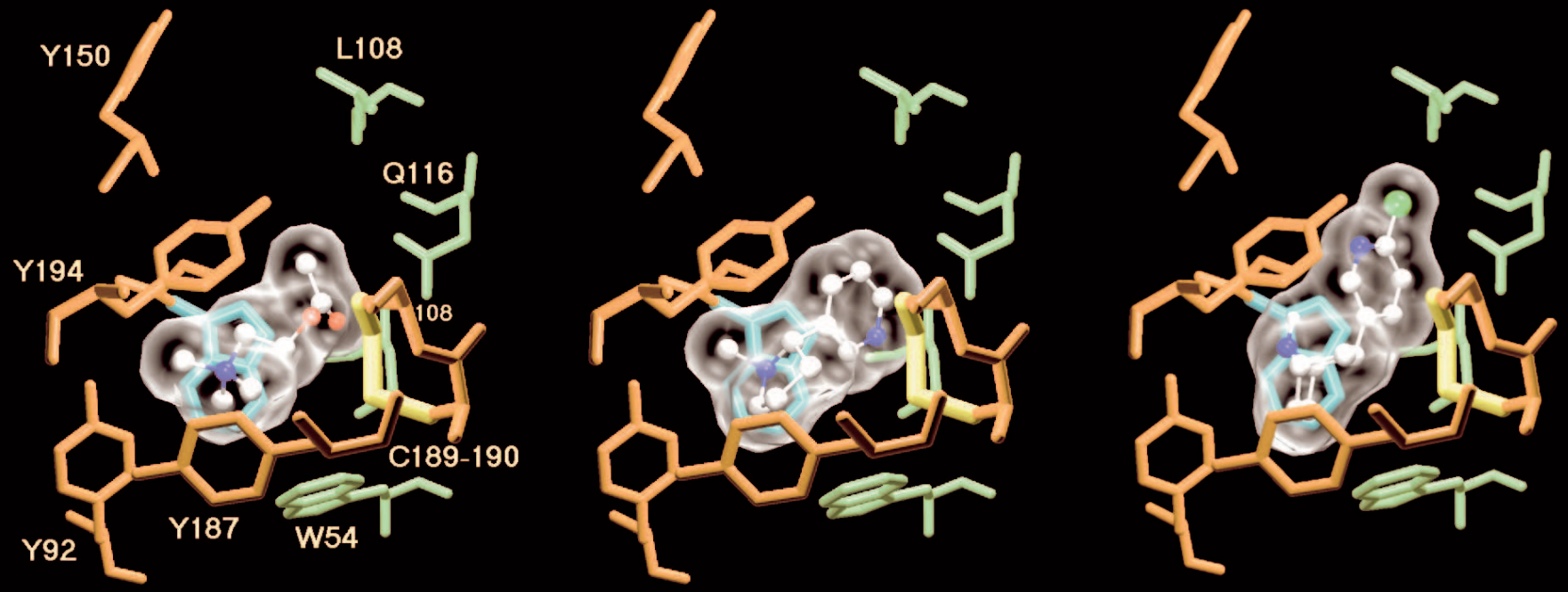

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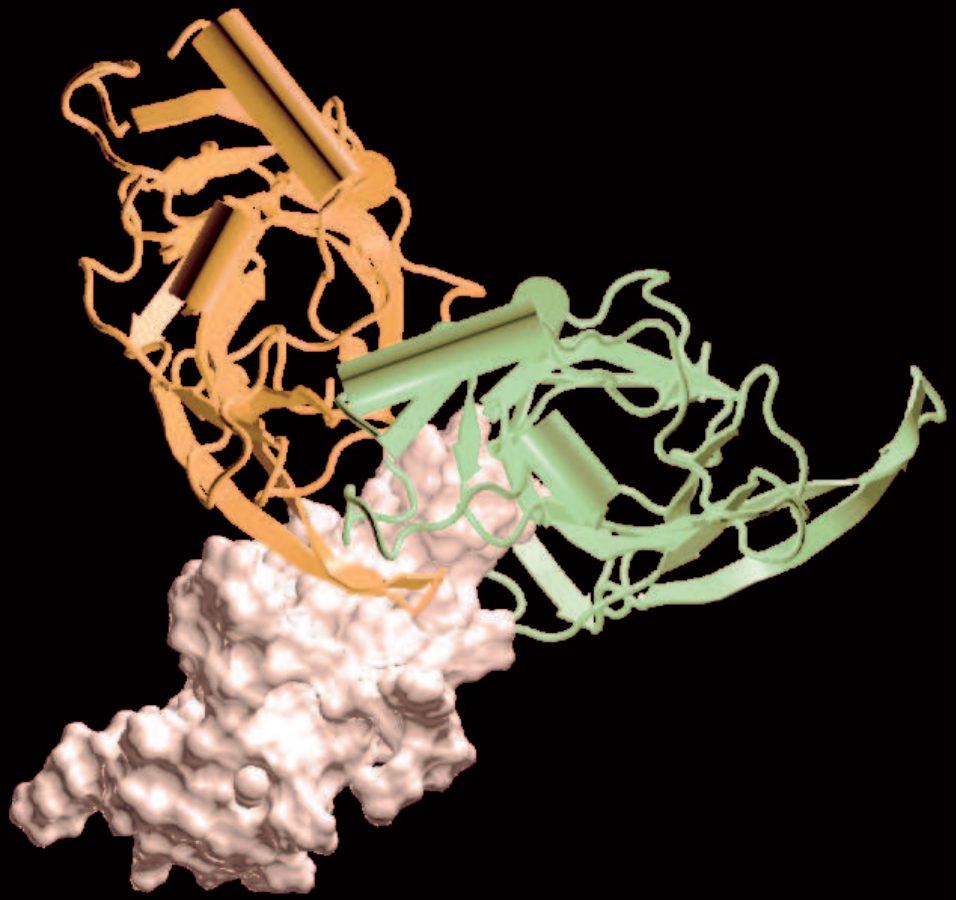
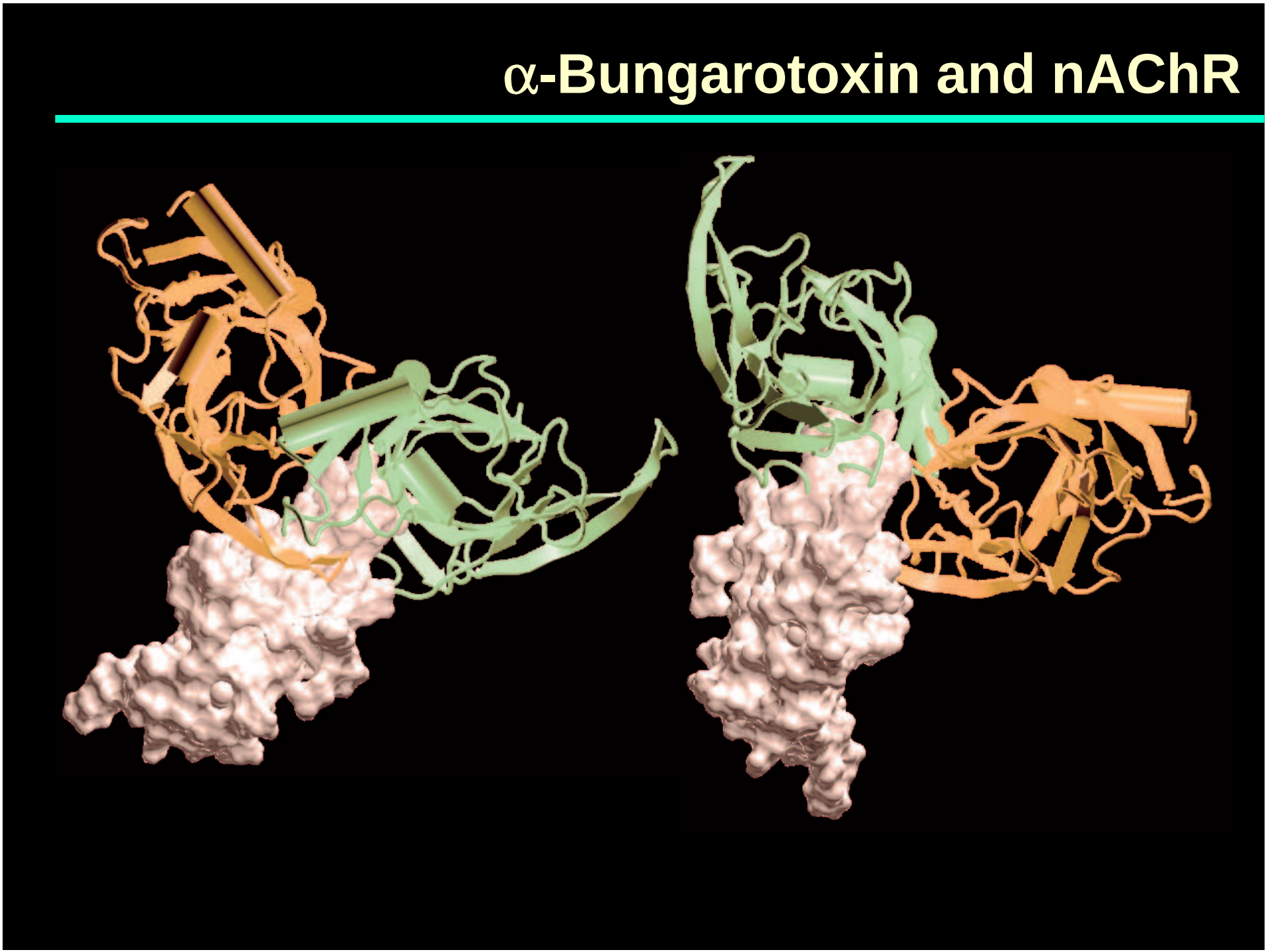
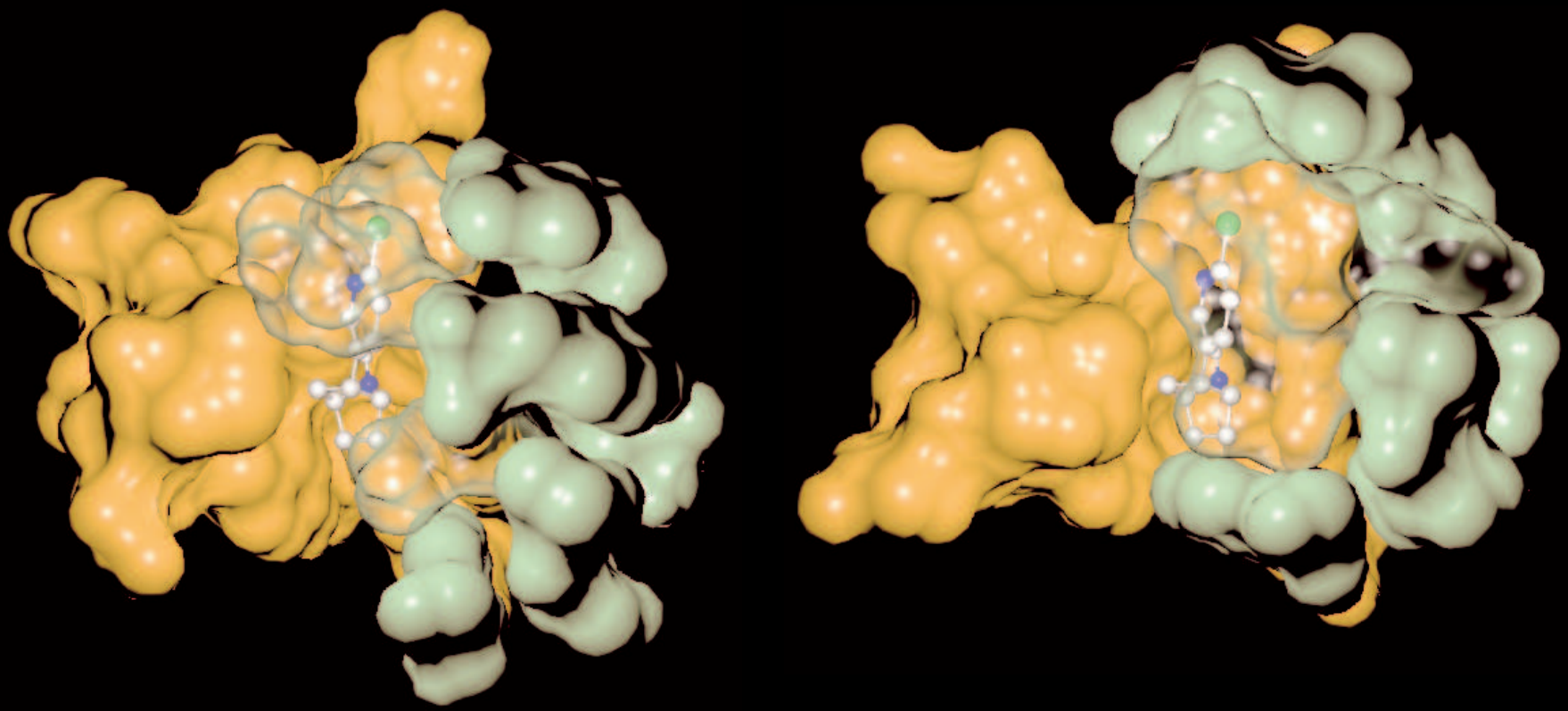
α-Bungarotoxin and nAChR



α-Bungarotoxin and nAChR



Epibatidine in models of different α7 states



Basal state: Ki = 1.1 10^{-5} M

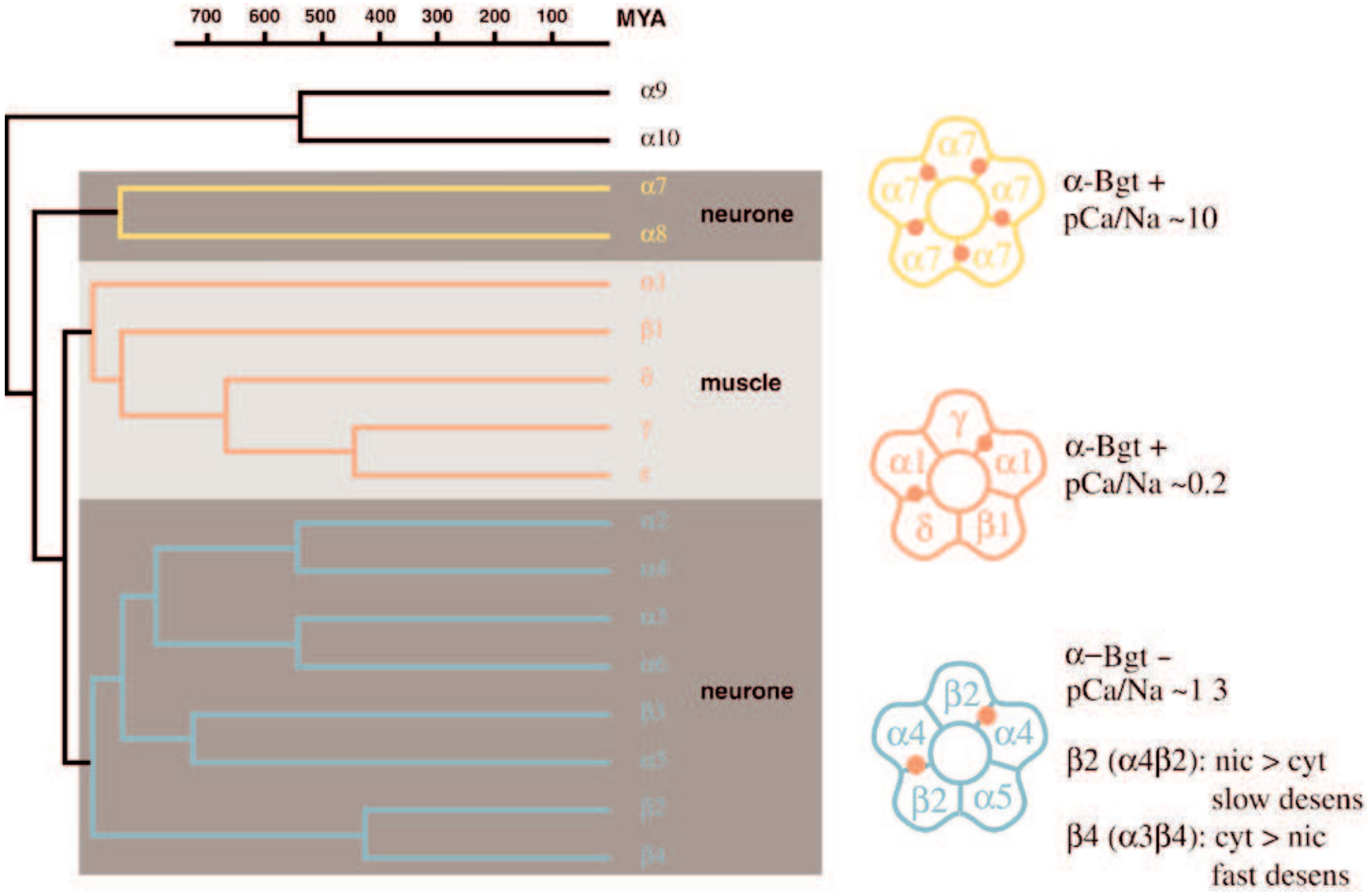
Desensitized state: Ki = 5.6 10^{-7} M

FRUCHART-GAILLARD *et al.* (2002) *Proc. Natl. Acad Sci. USA*, 99: 3216-3222

Perspectives

nAChRs can now be modelled at the atomic level under various conformations; We can envision to understand the structural basis of pharmacological specificity, and even the mechanisms of allosteric transitions.

Phylogeny constrains physiology



LE NOVÈRE and CHANGEUX (1995) *J. Mol. Evol.*, 40: 155-172

nAChRs neuropharmacology

- Skeletic muscle
- Motor autonomic transmission
- Cognitive functions

  Nicotine improves cognitive functions and reverse impairments due to cholinergic deficit. Nicotine improves attention and learning performance.
- Locomotion and reward

  Nicotine causes an increase of dopamine release, and elicits locomotion in an habituated environment. Nicotine is a reinforcing substance and induces a strong dependence.
- Neuroprotection
- Analgesia
- Anxiety

- Myasthenic syndroms

  implication of $\alpha 1$, $\beta 1$, γ, ε
- Autonomic dysfunctions

  implication of $\alpha 3$, $\beta 4$
- Epilepsy

  implication of $\alpha 4$, $\beta 2$
- Schizophrenia

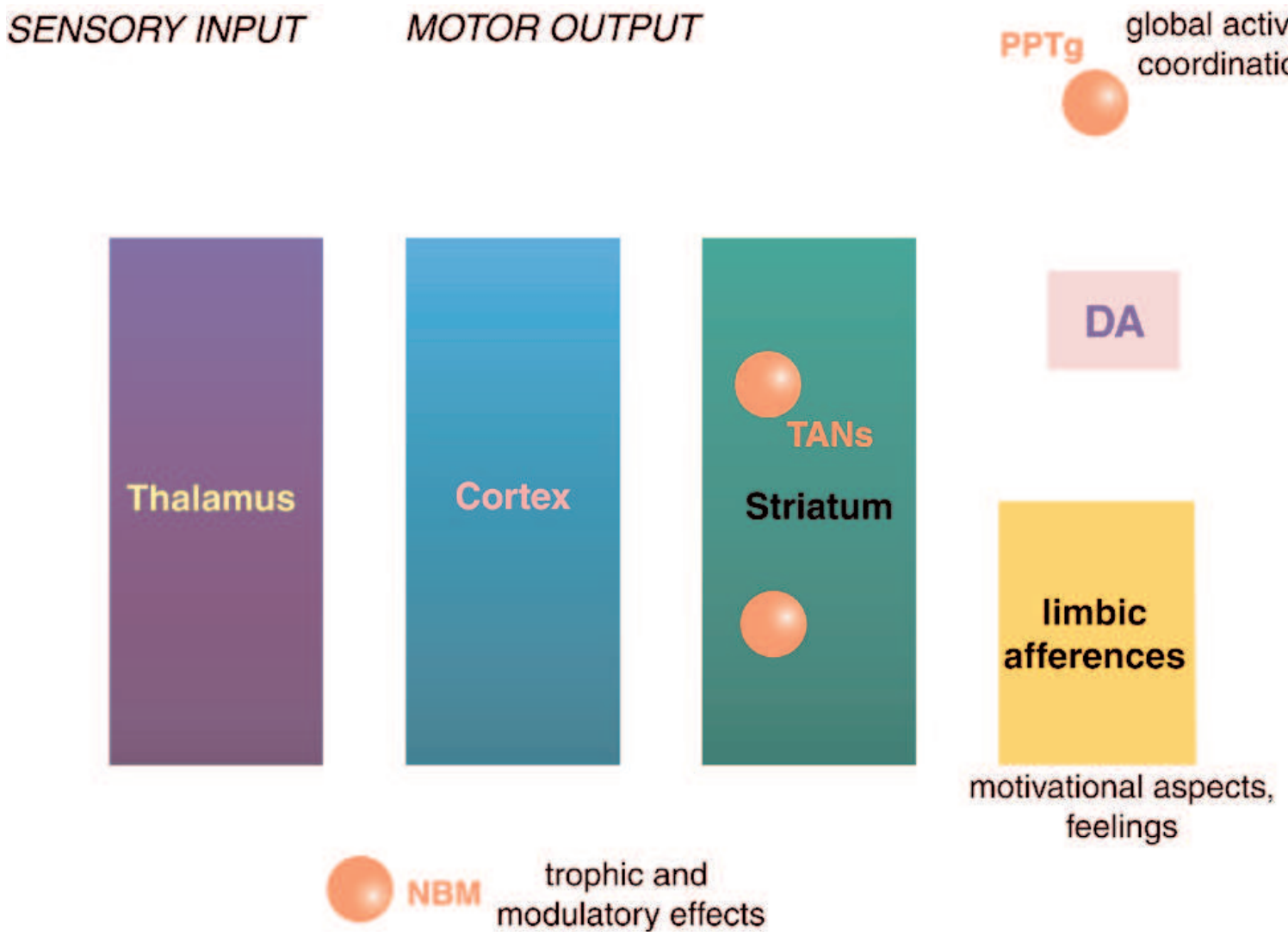
  implication of $\alpha 7$
- Reinforcement, nicotine addiction

  implication of $\alpha 6$, $\beta 2$

<u>indirect evidence for:</u>

- Parkinson's disease
- Alzheimer's disease
- Lewy bodies dementia

The thalamo-cortico-striatal loop



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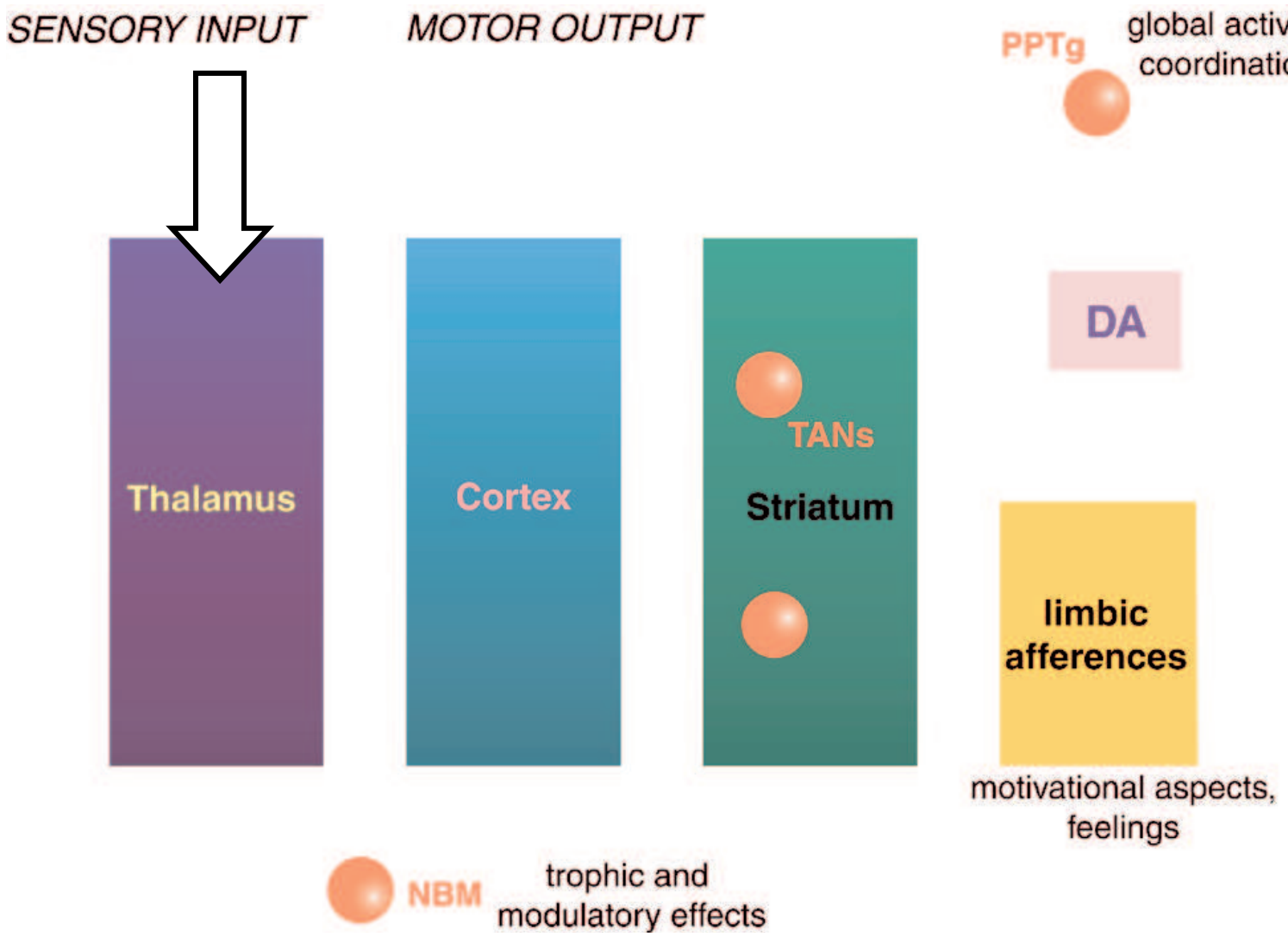

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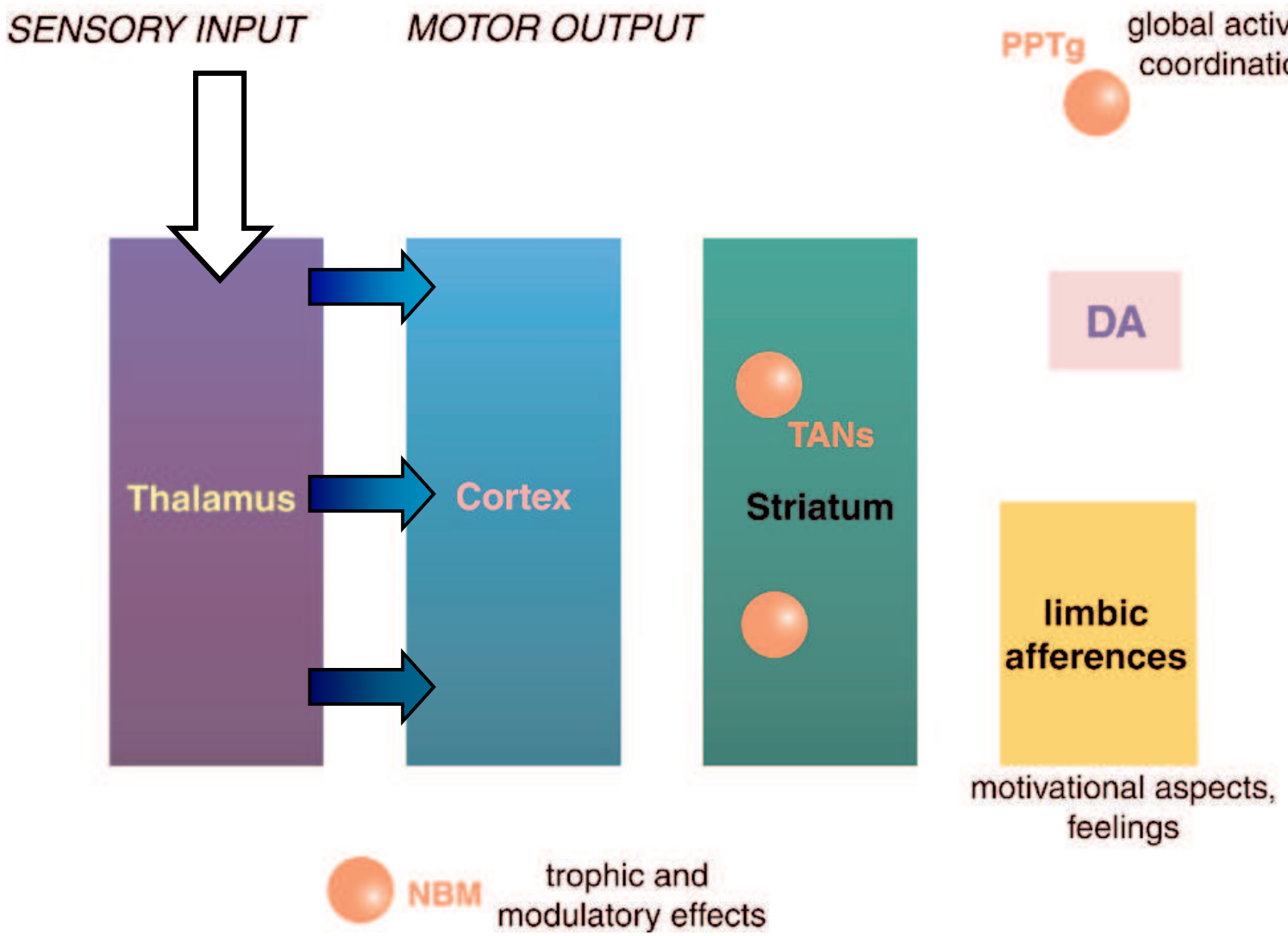

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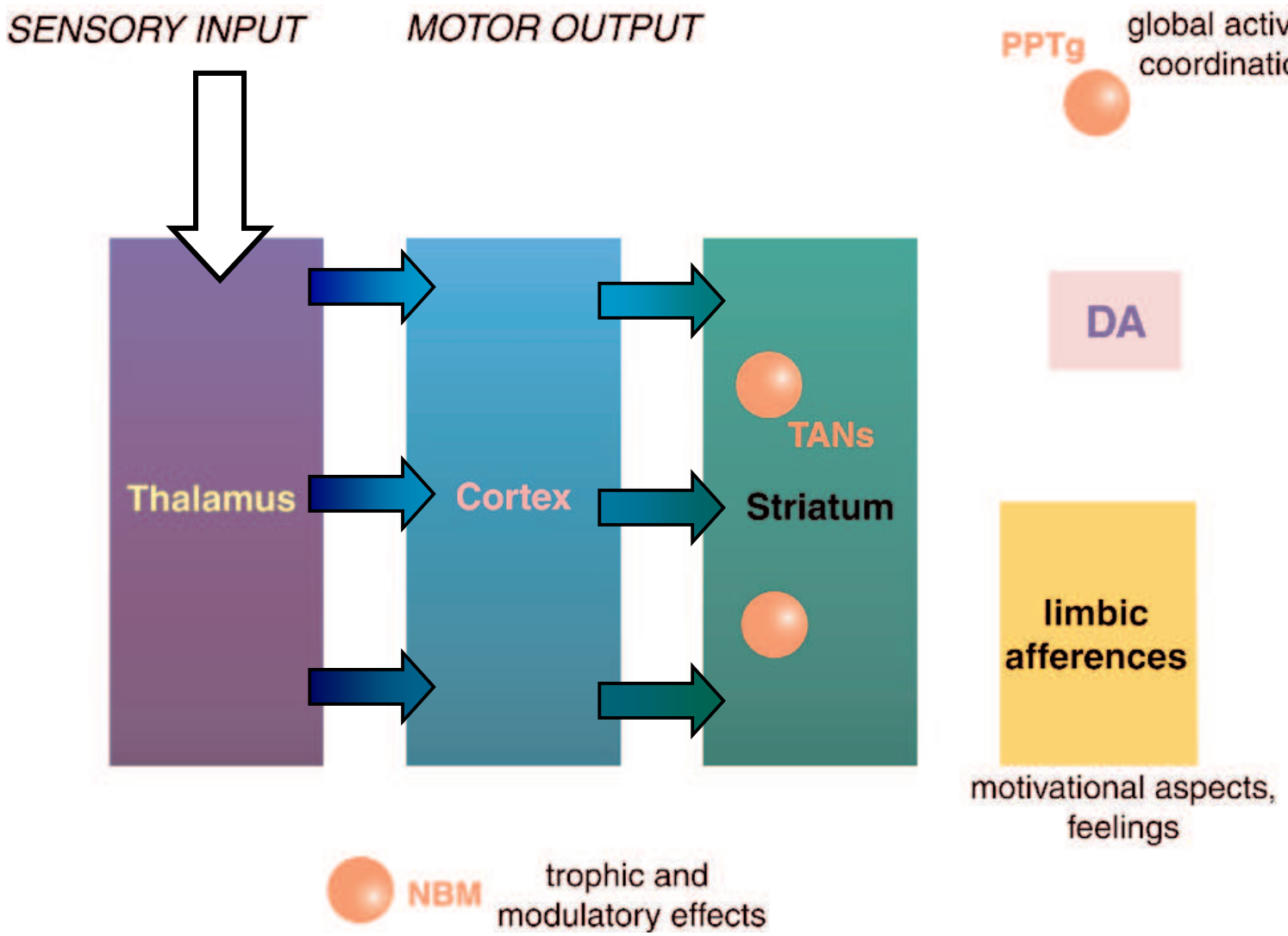

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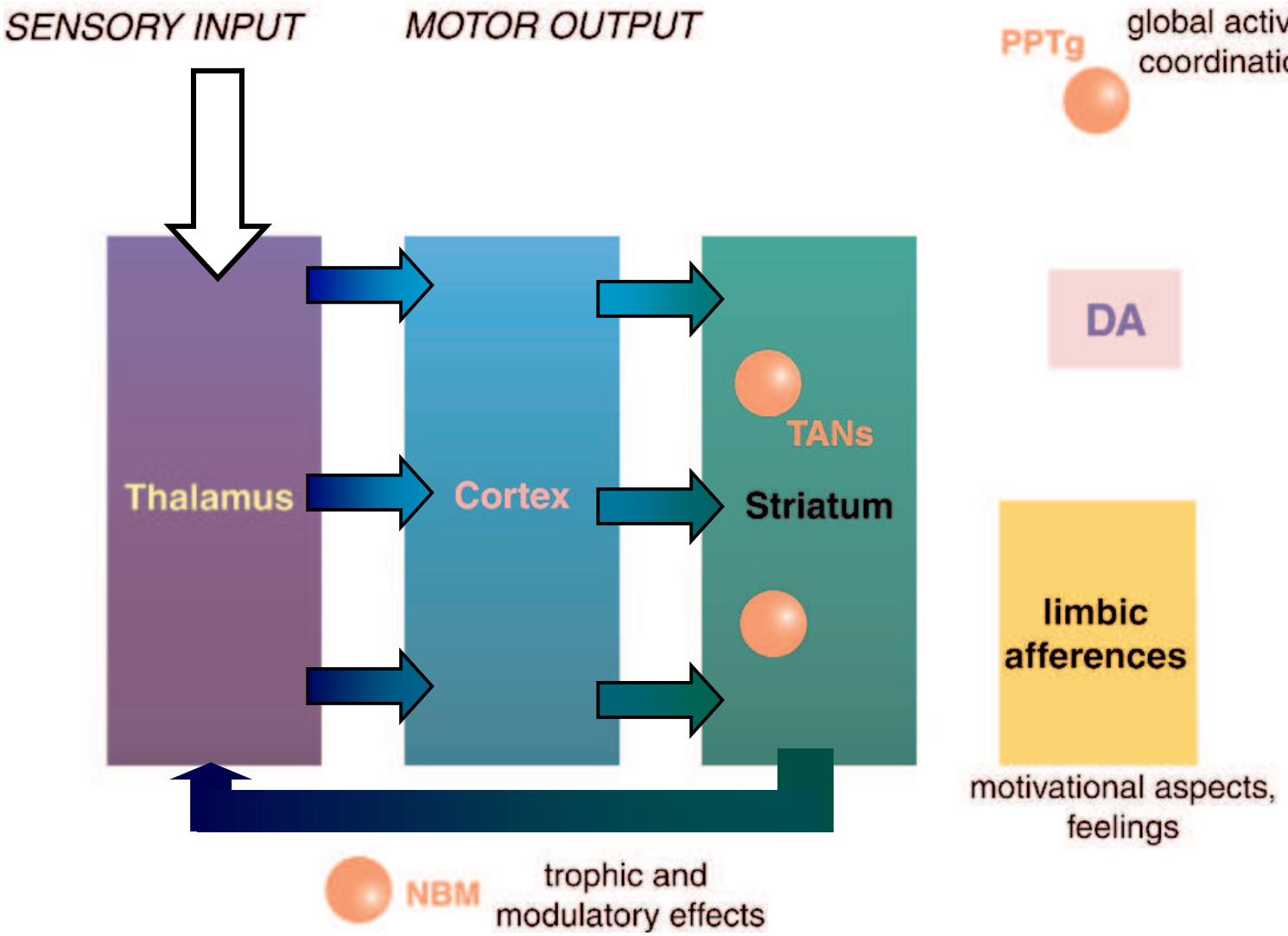

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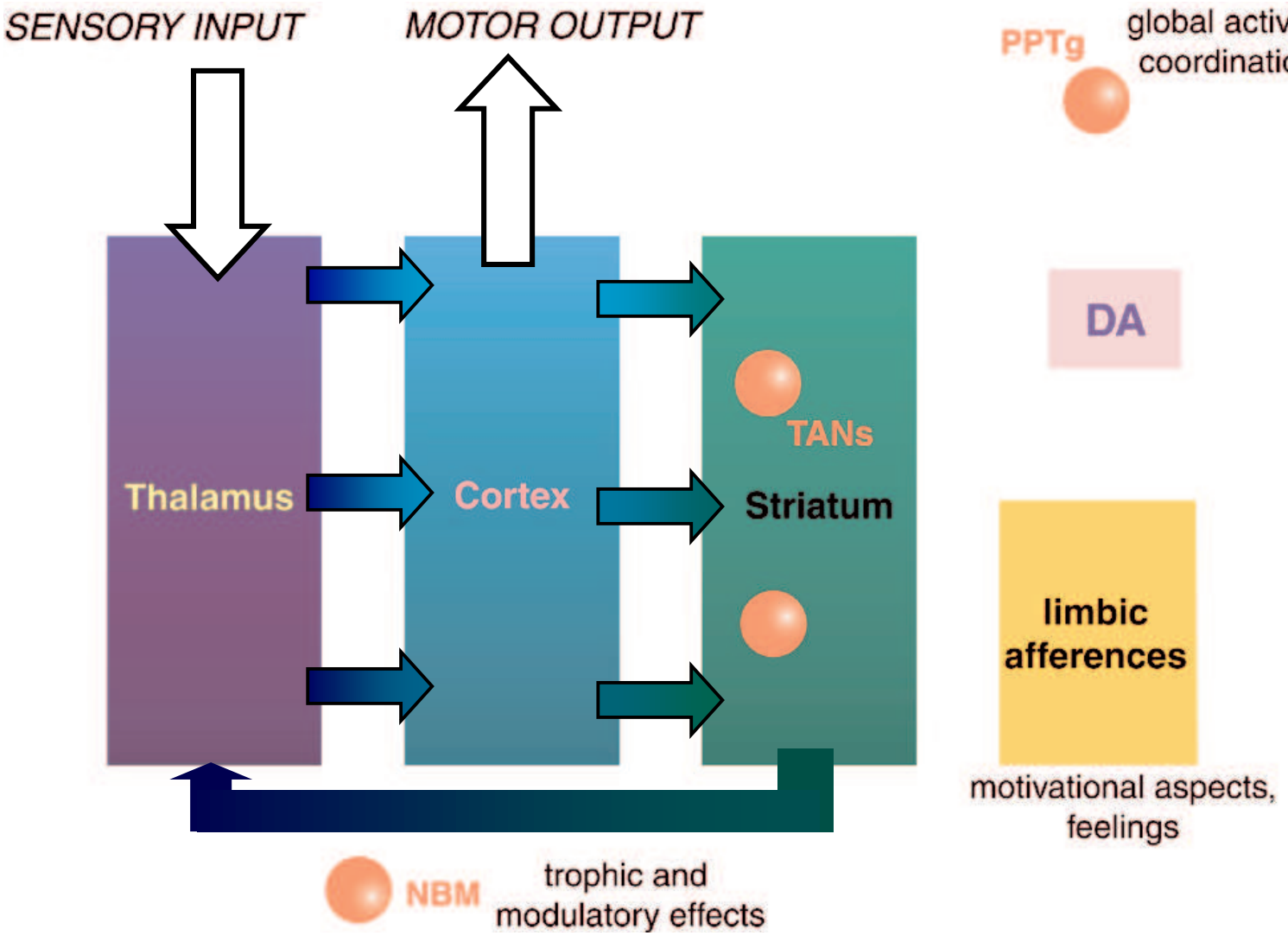

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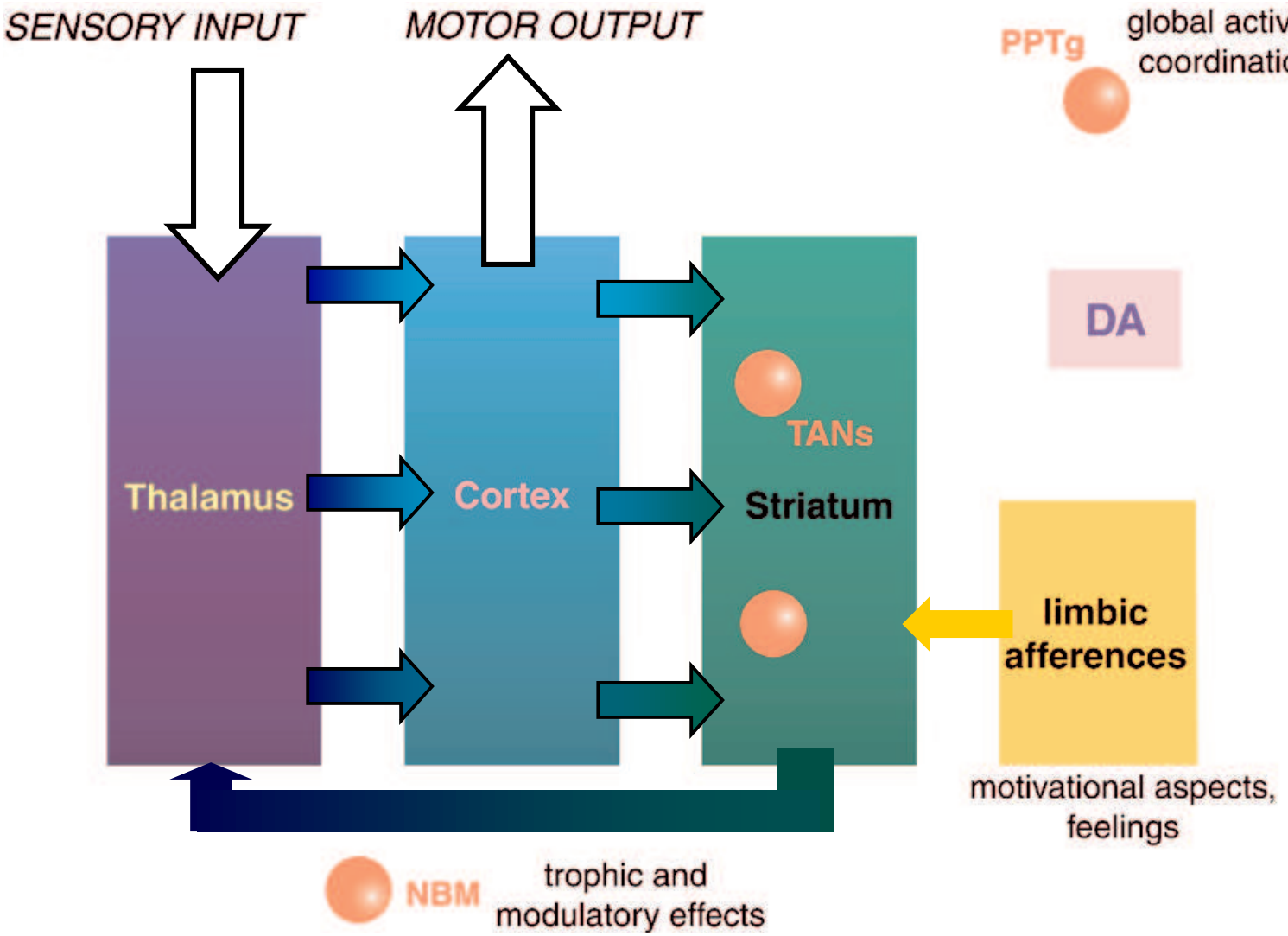

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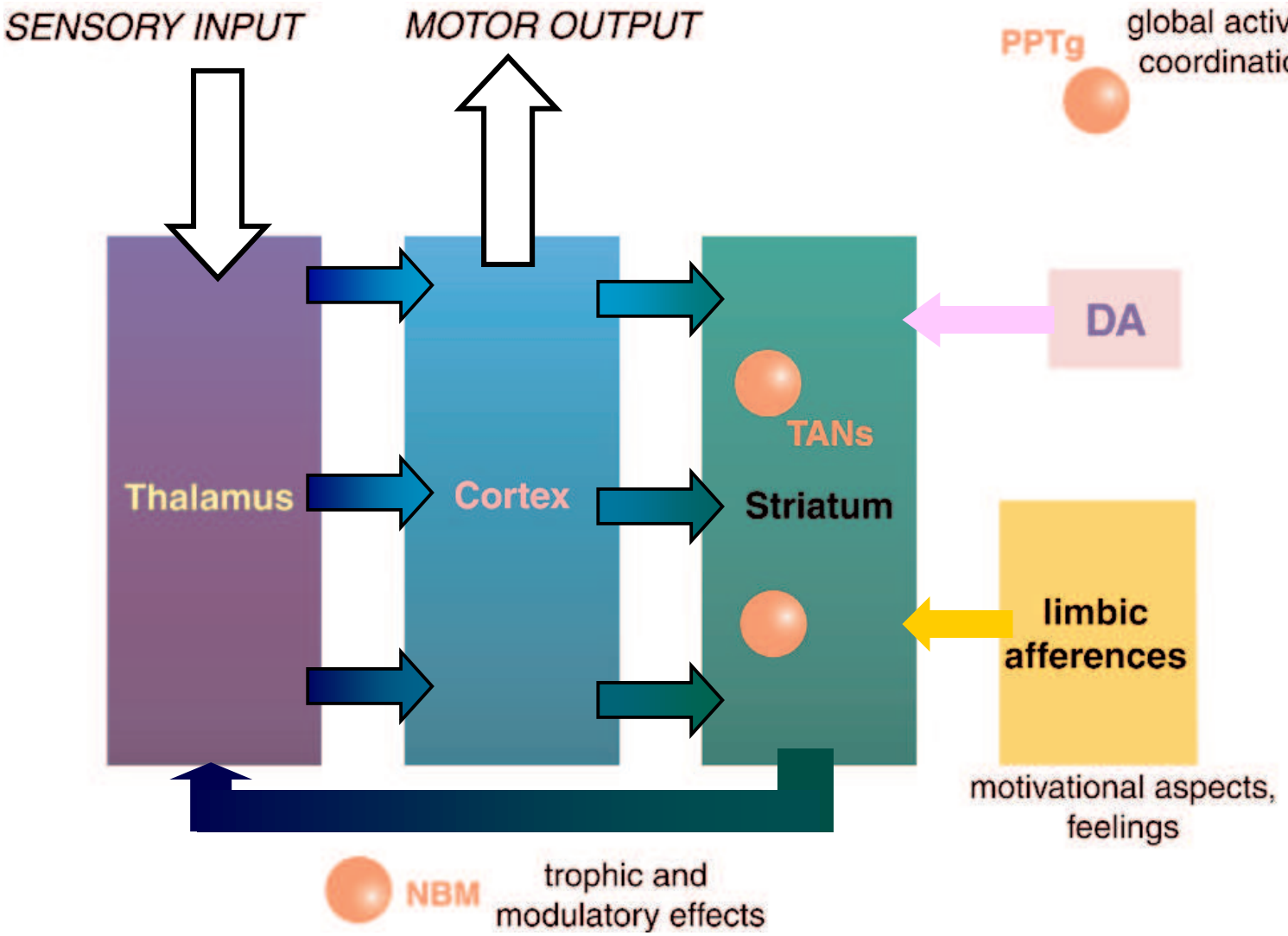

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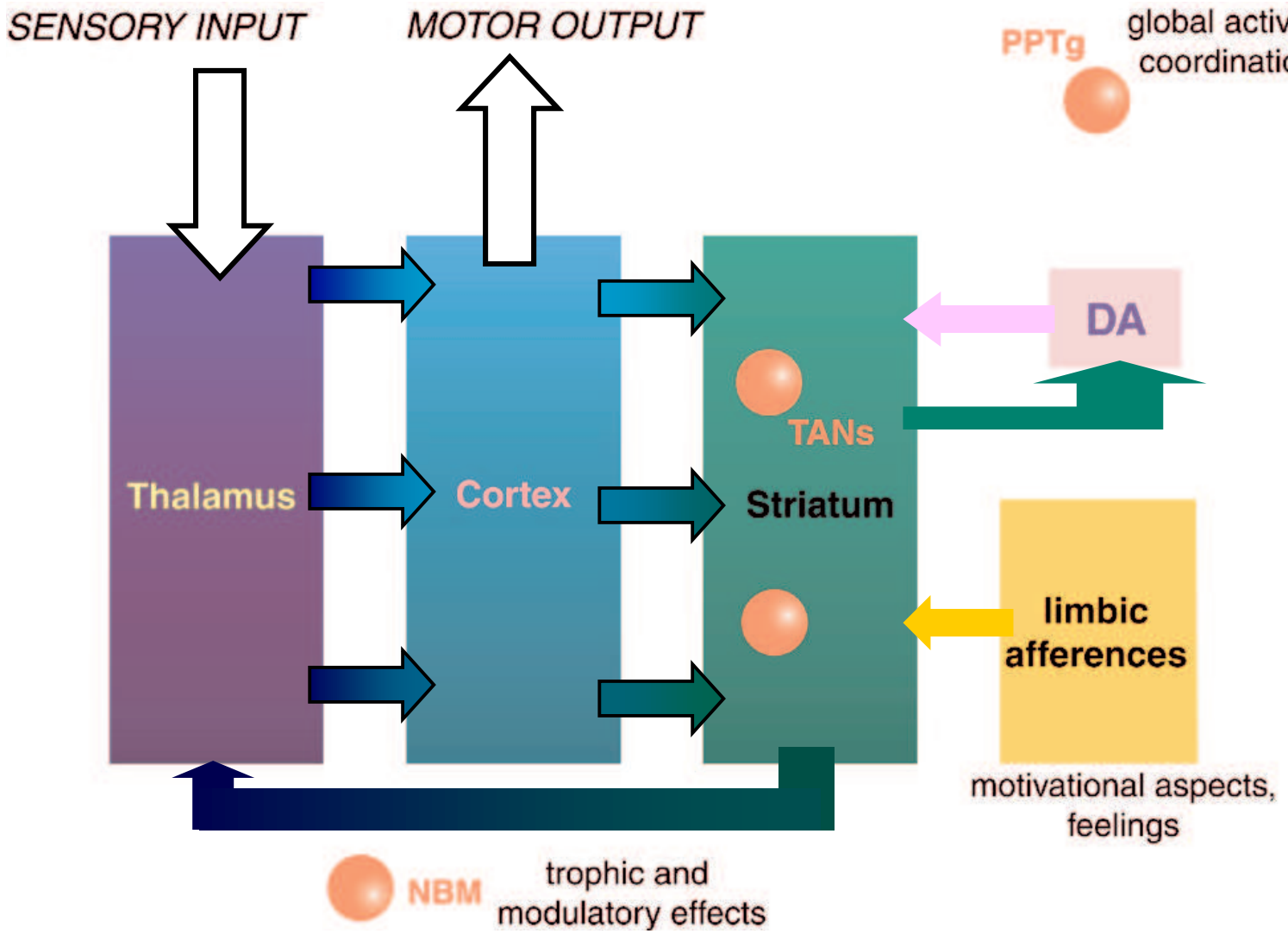

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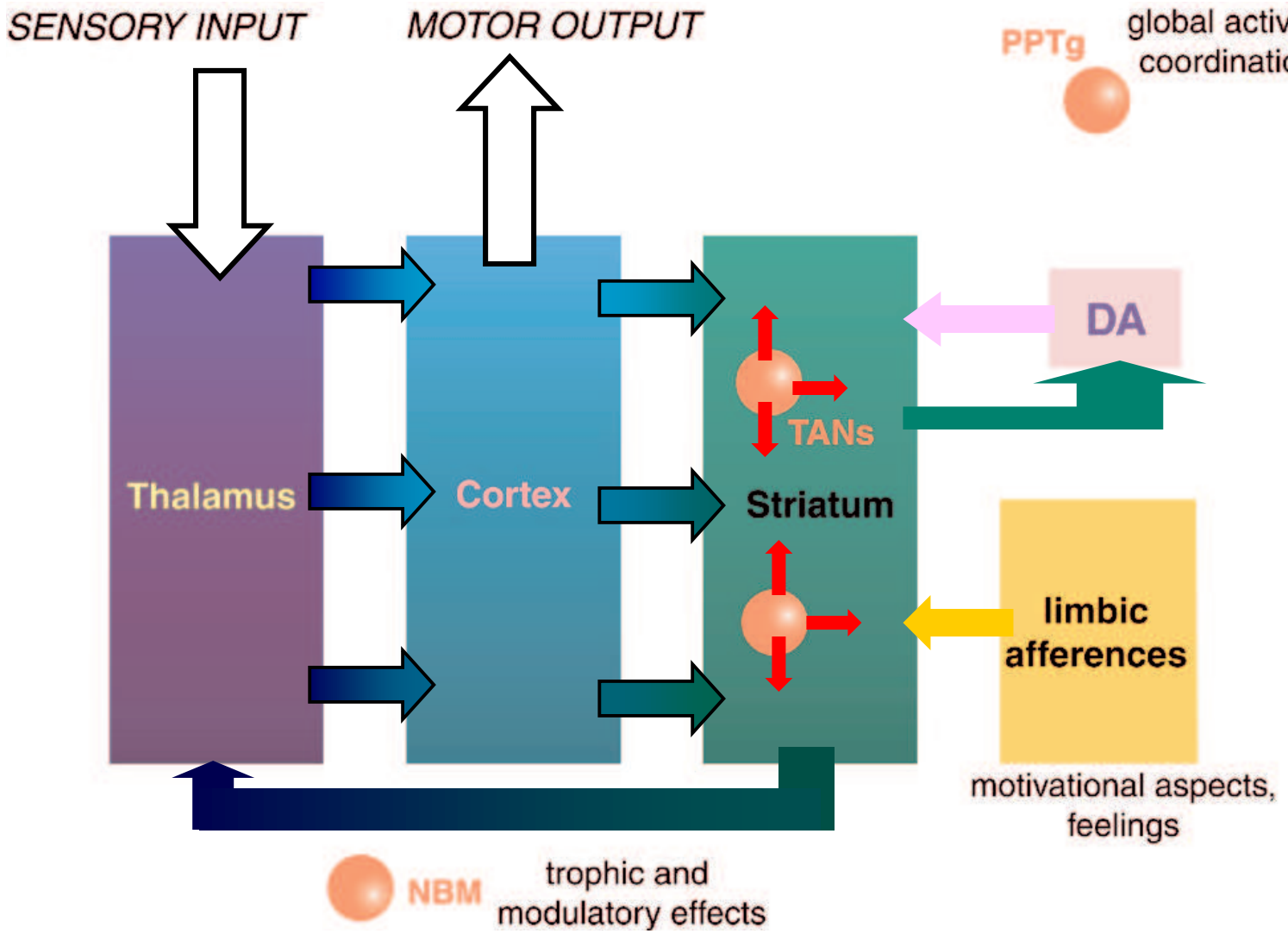

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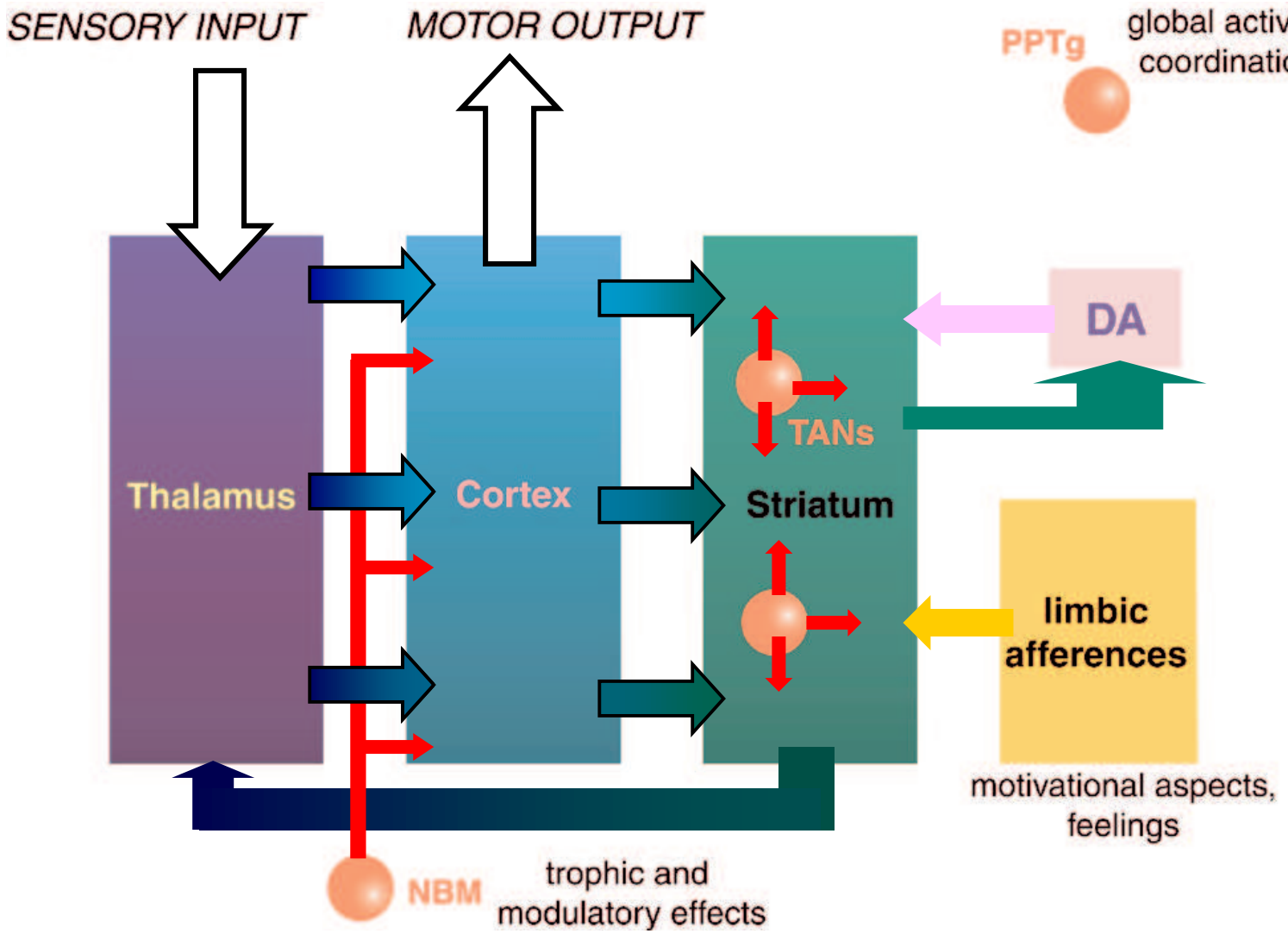

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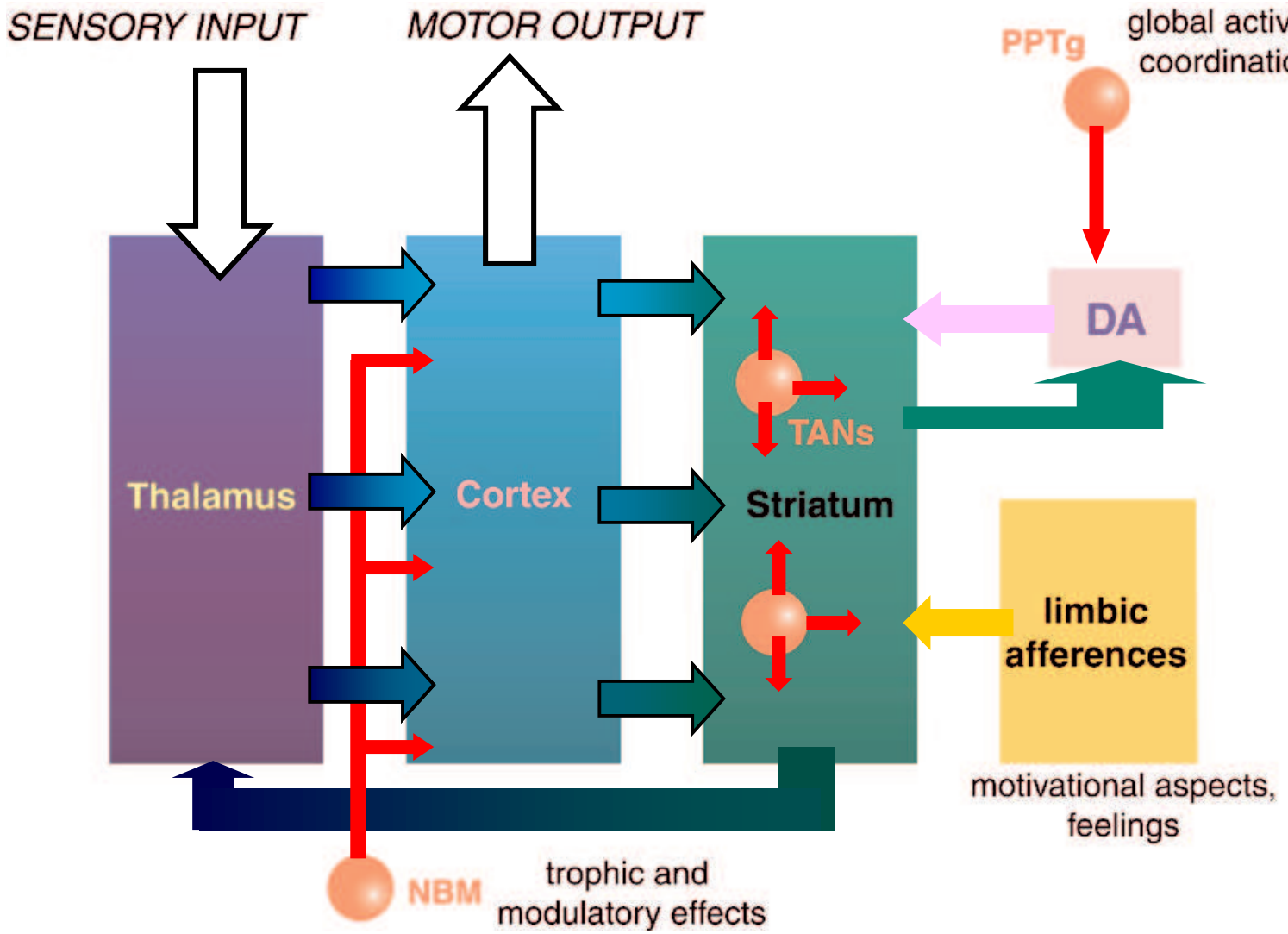

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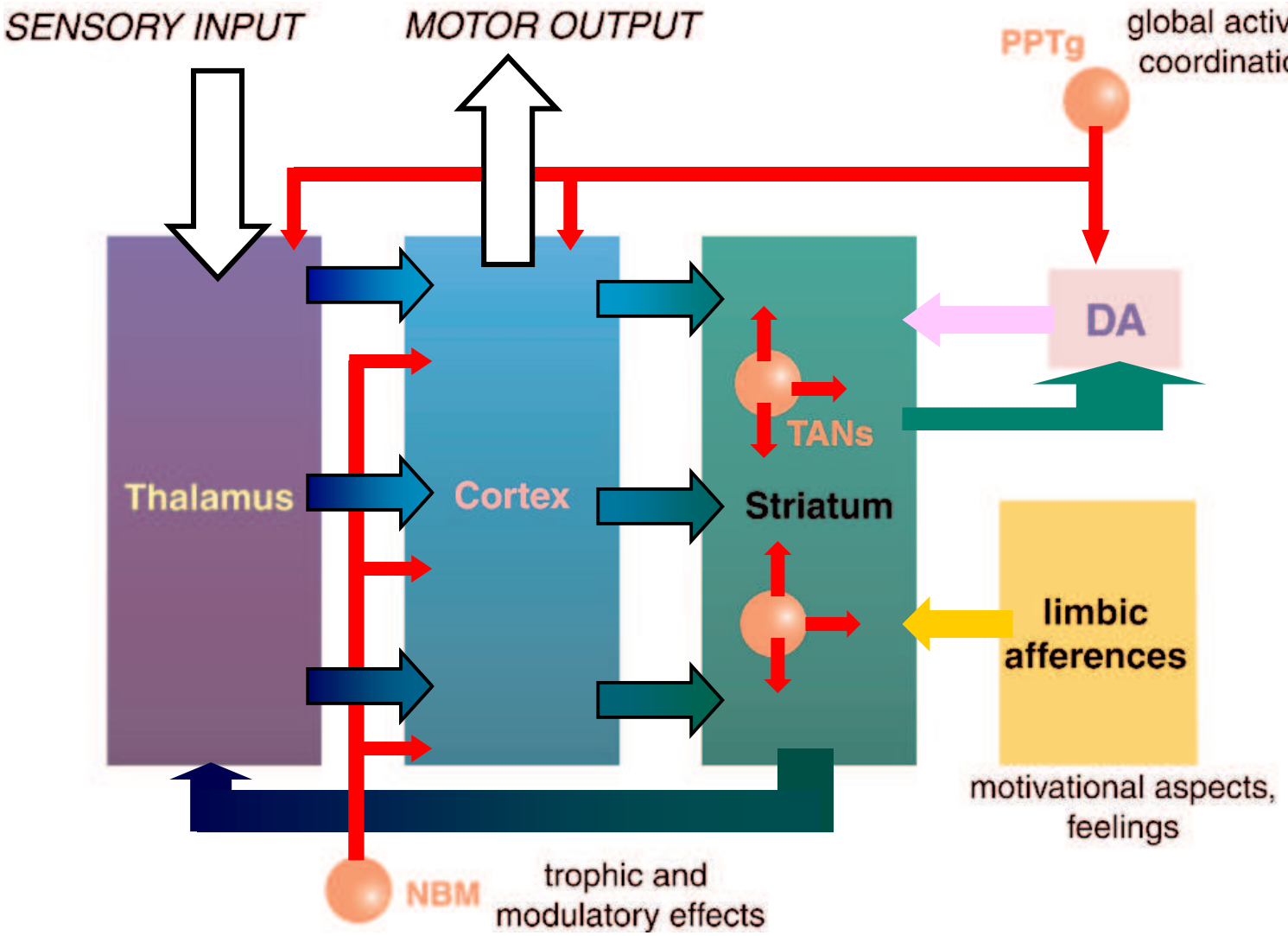
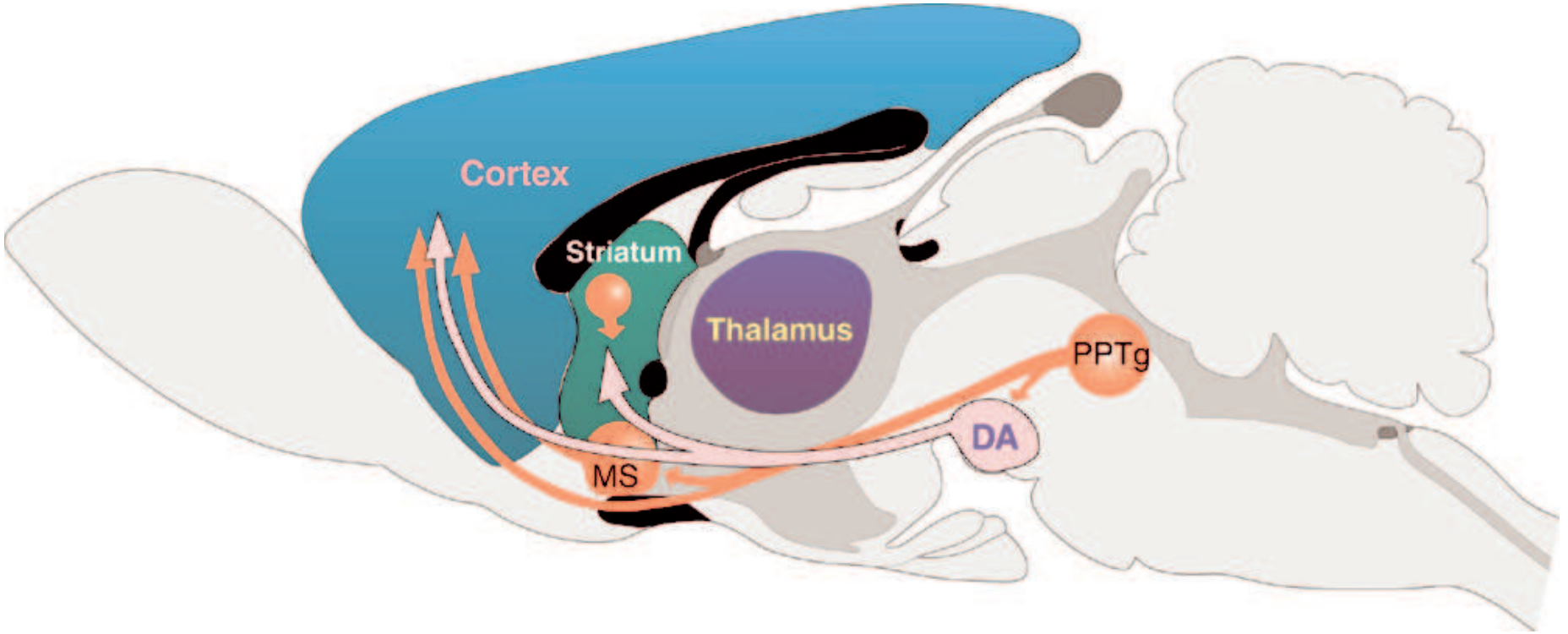


DA-ACh relationships



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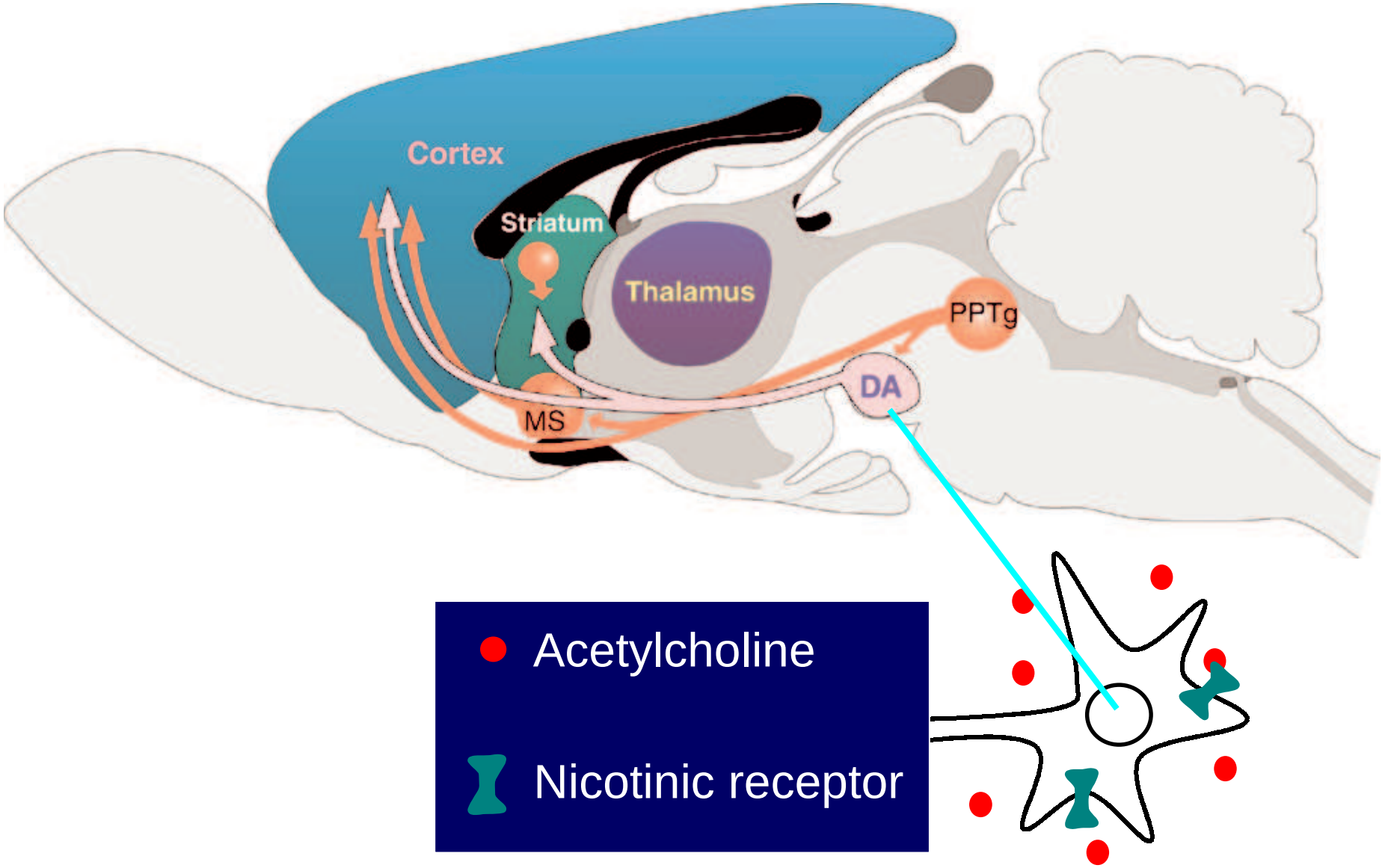

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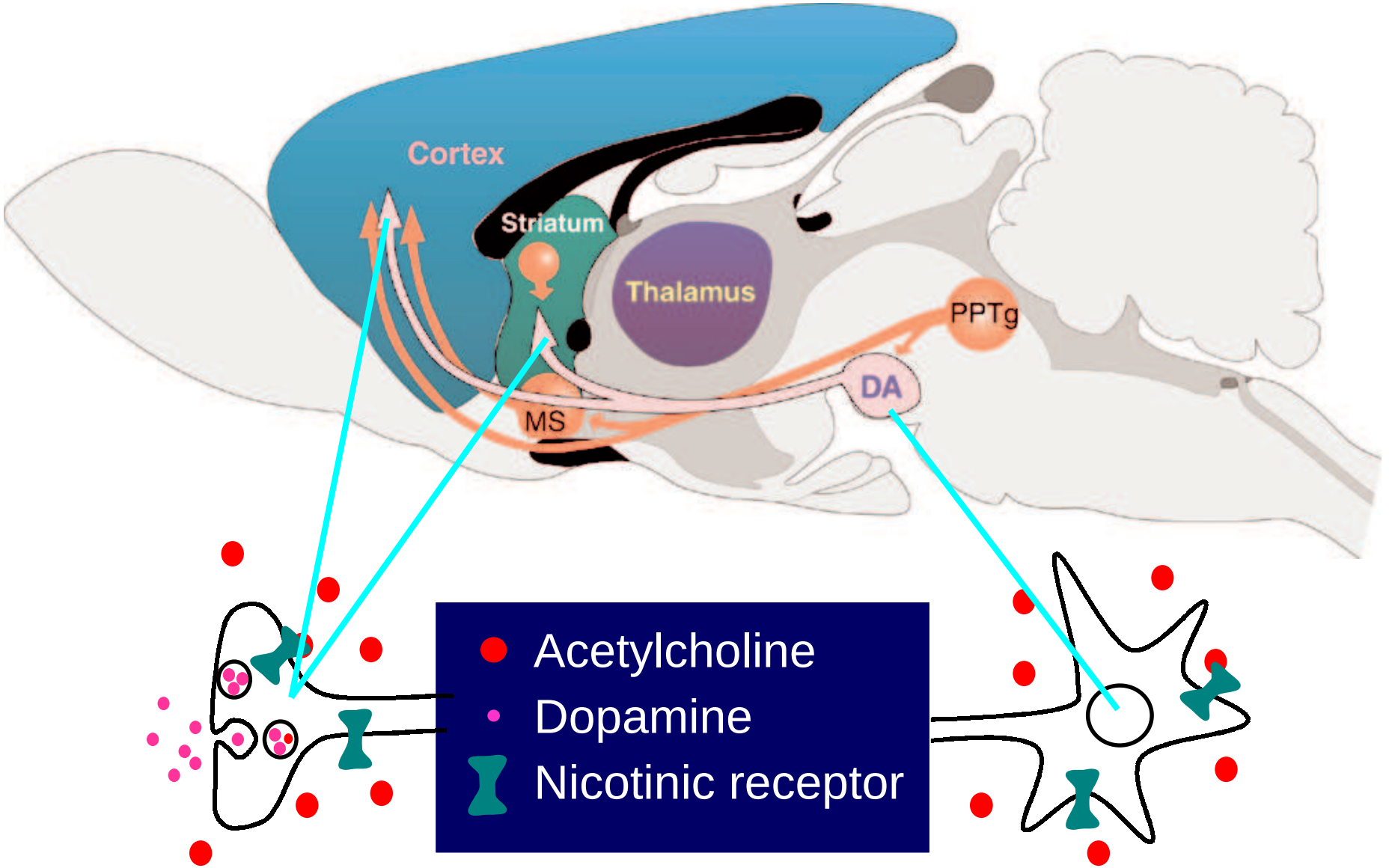
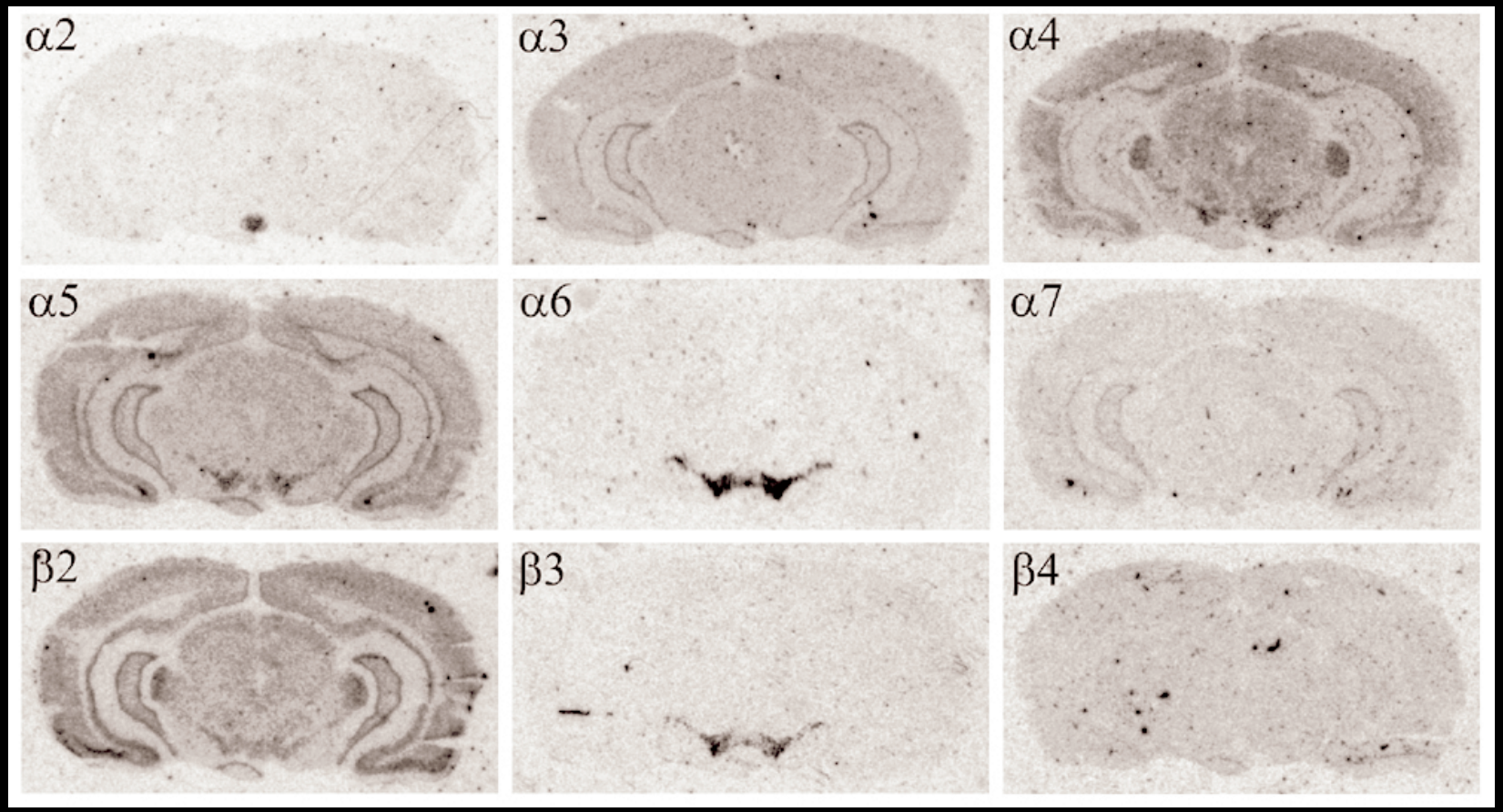


nAChRs subunits mRNA in DA nuclei



LE NOVÈRE *et al.* (1996) *Eur J Neurosci*, 8 2428-2439

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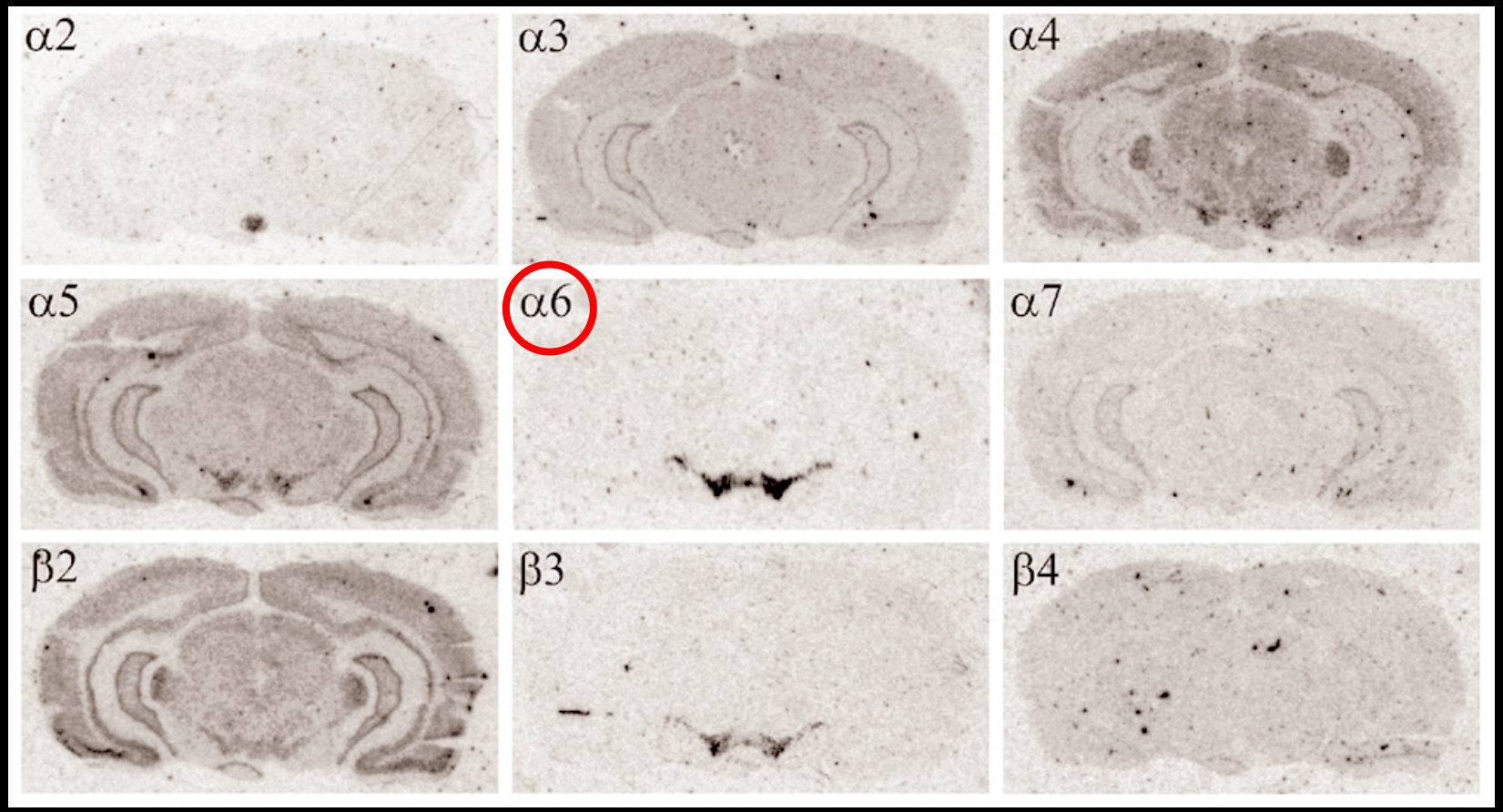

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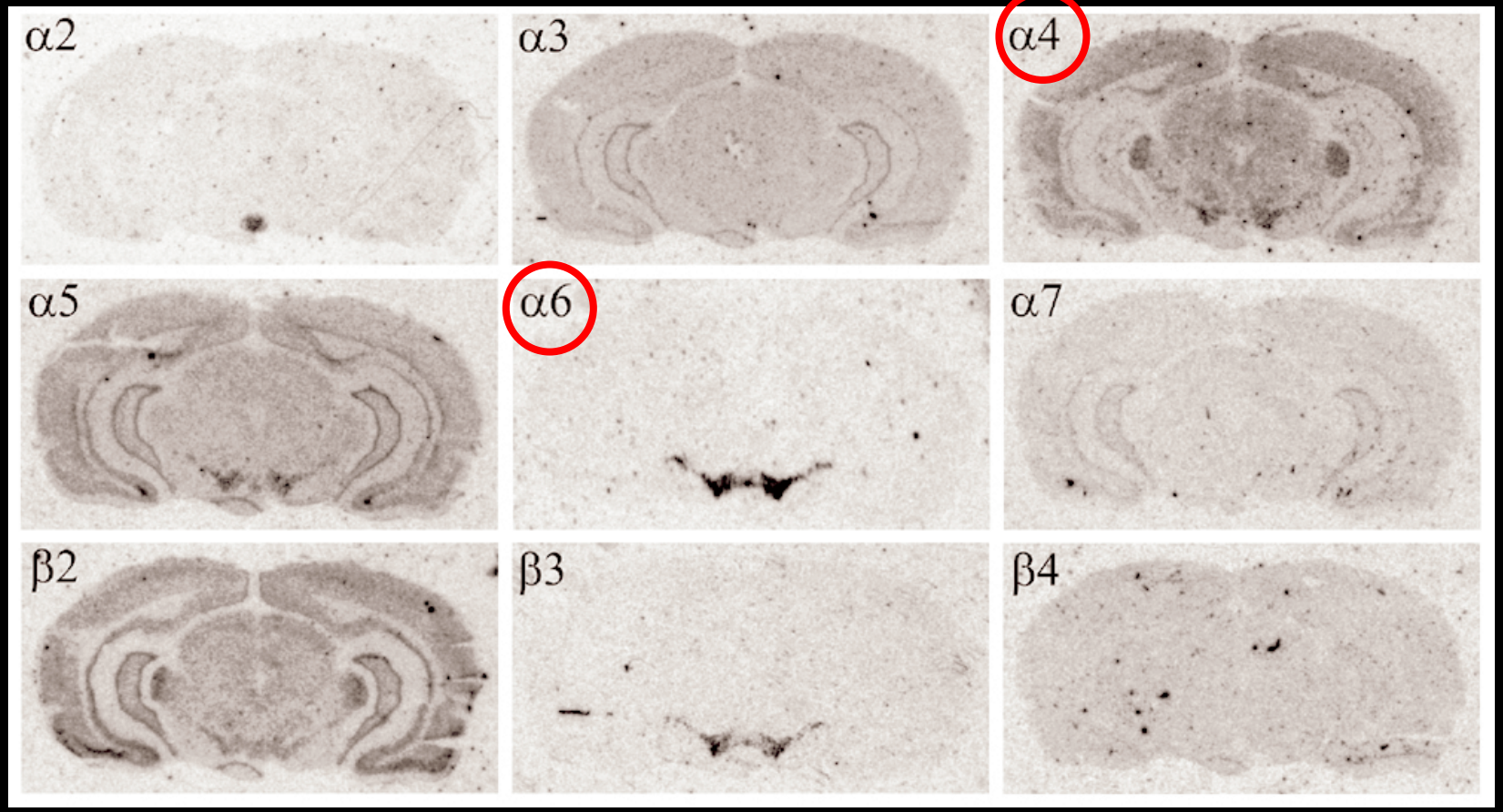

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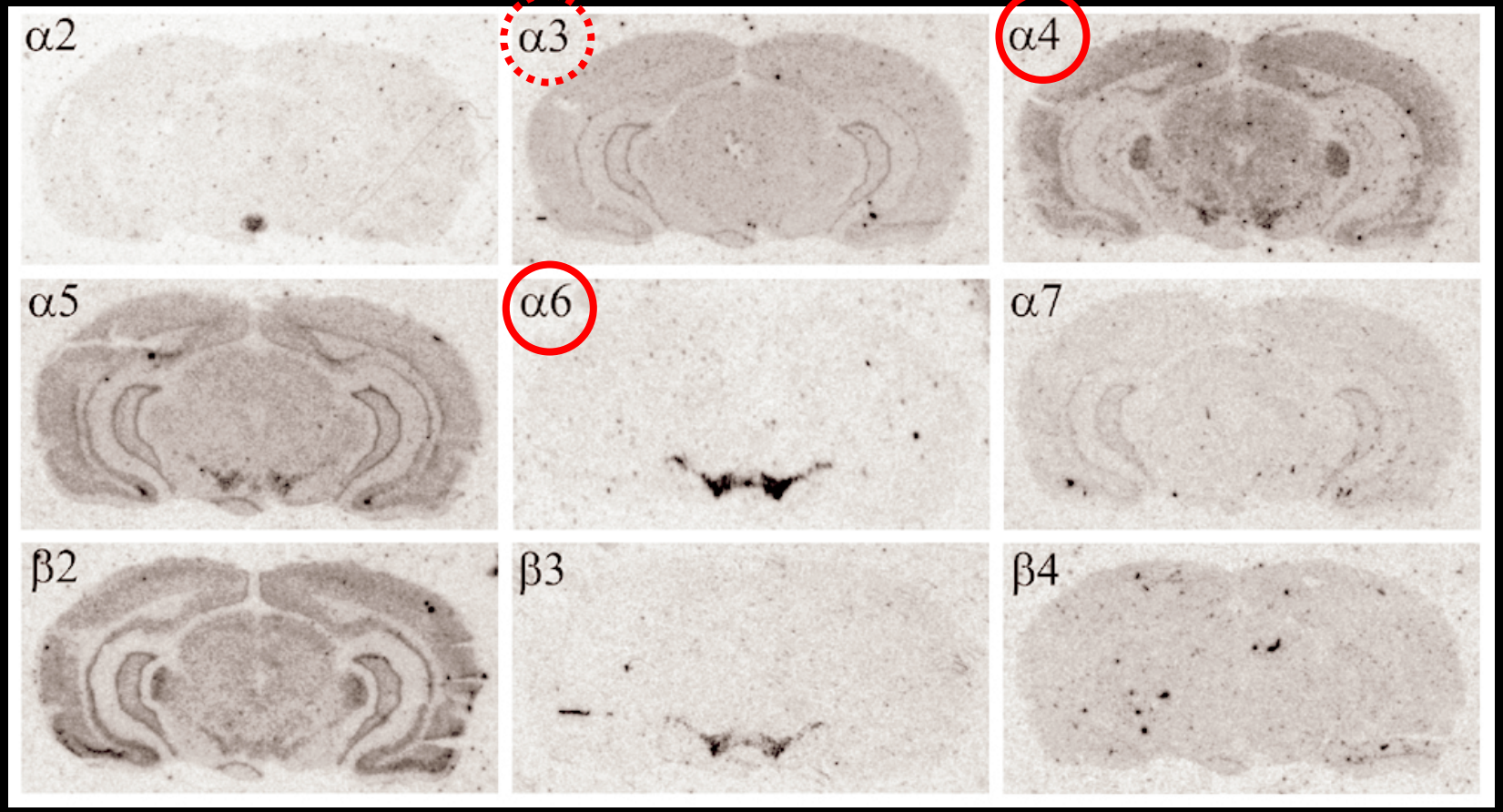

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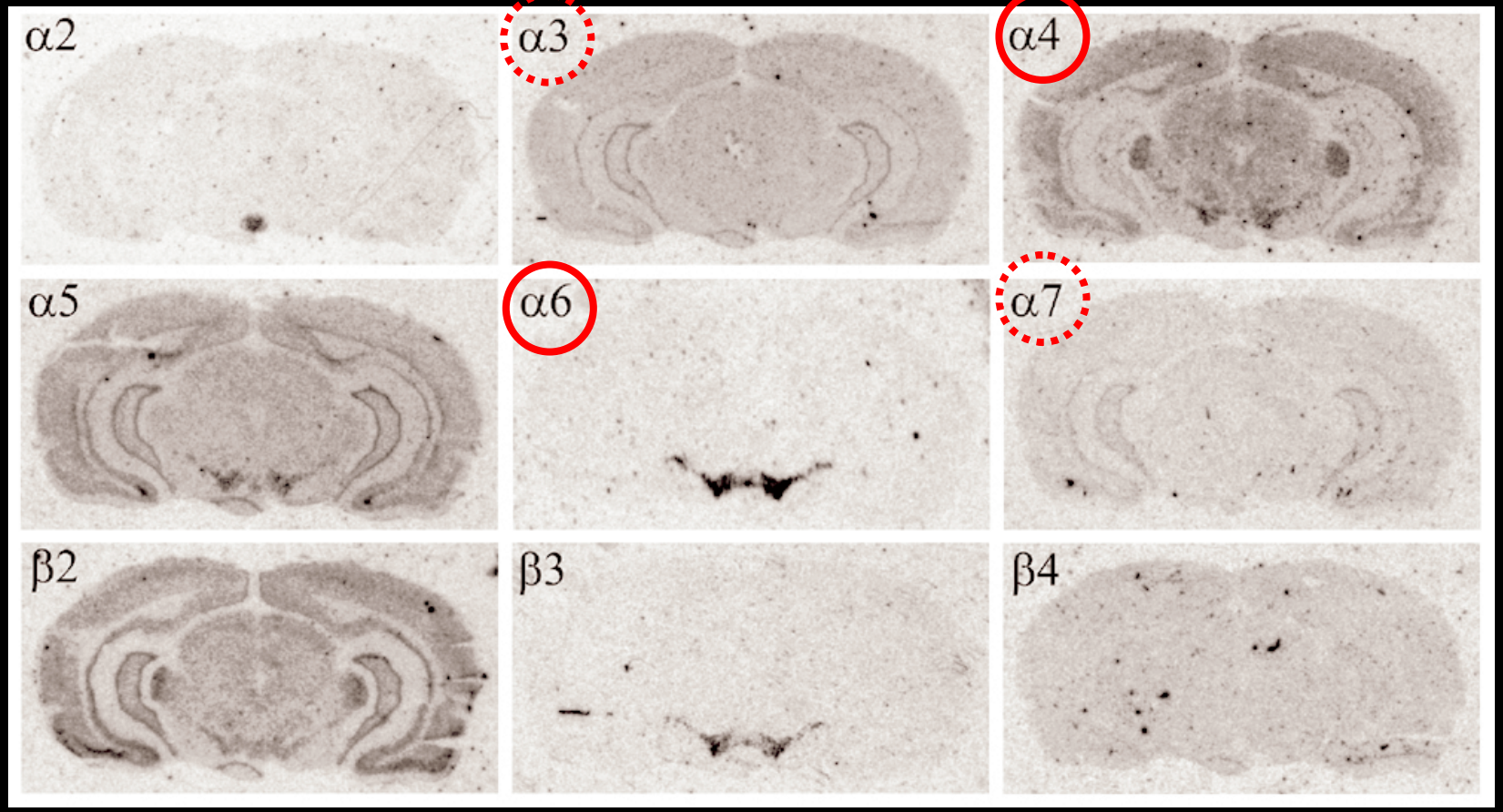

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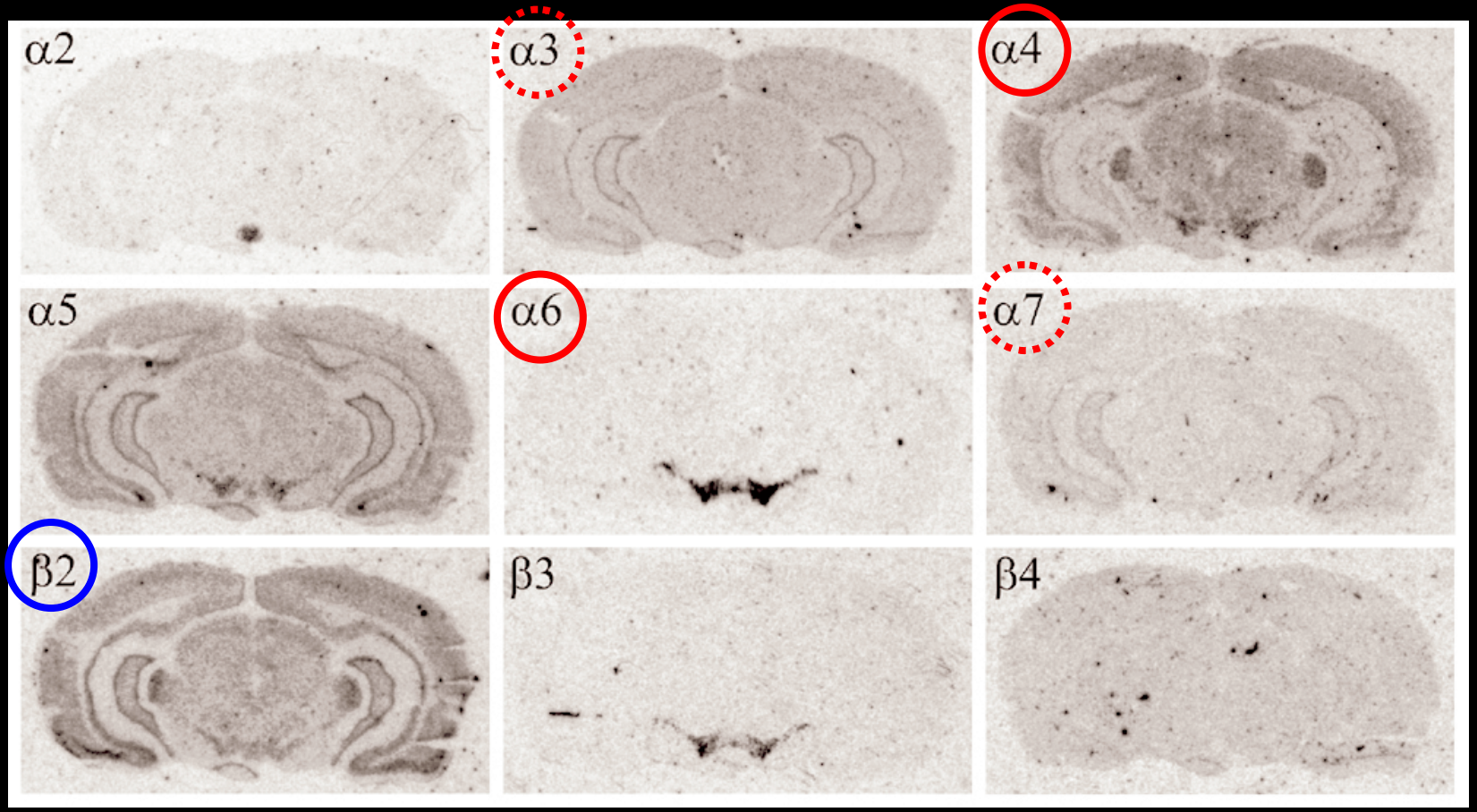

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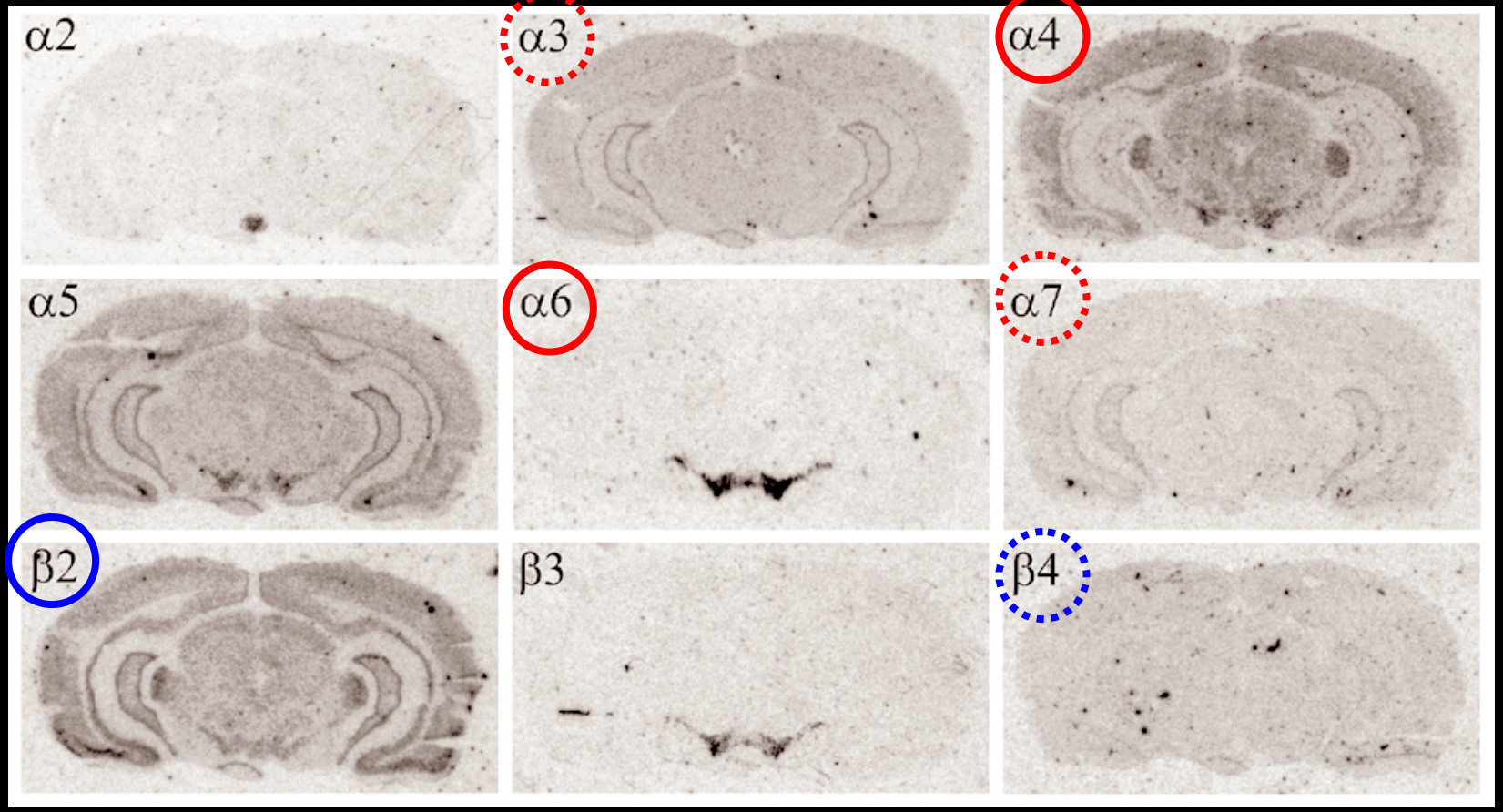
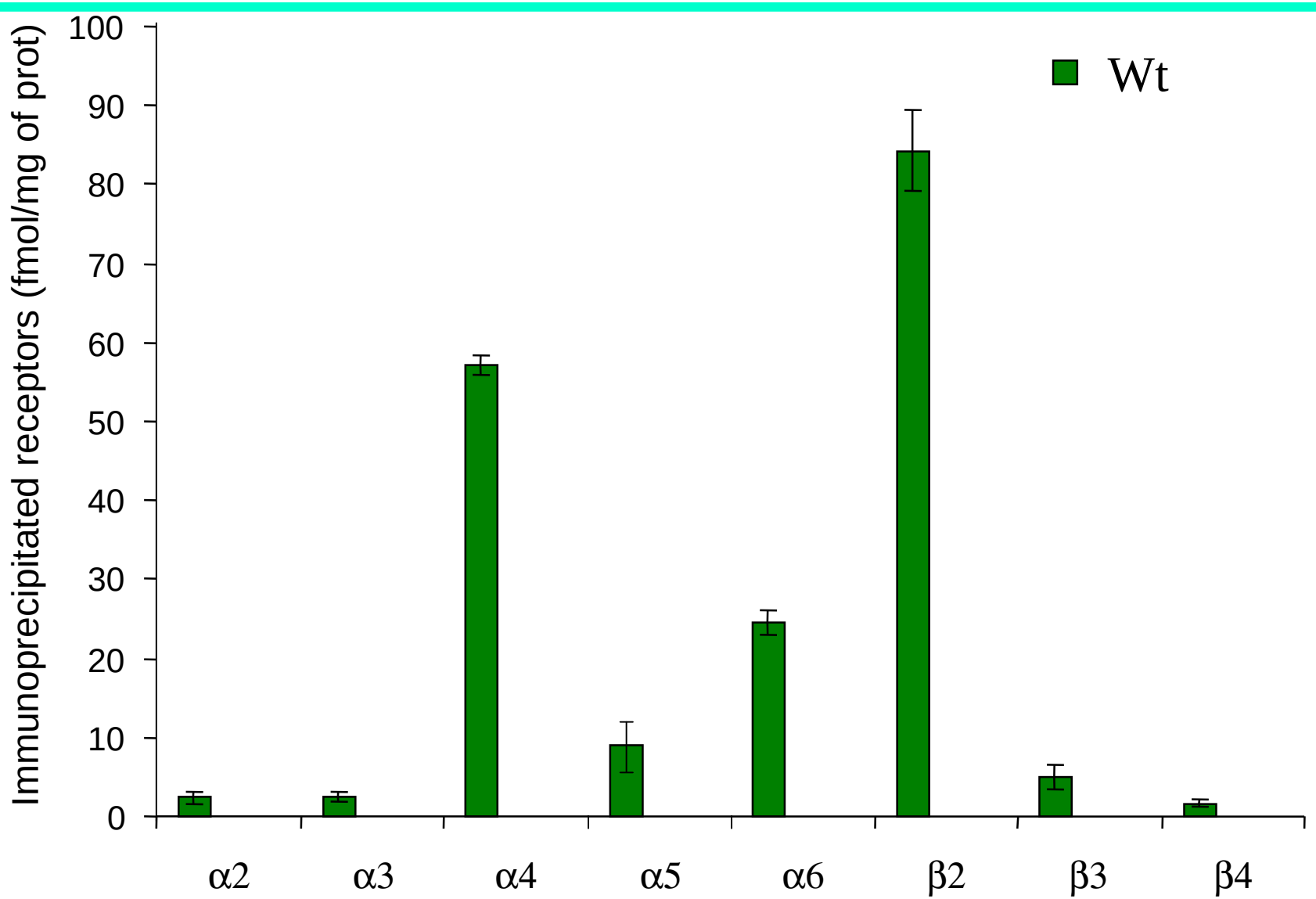


LE NOVÈRE *et al.* (1996) *Eur J Neurosci*, 8 2428-2439

nAChRs from striatal membranes



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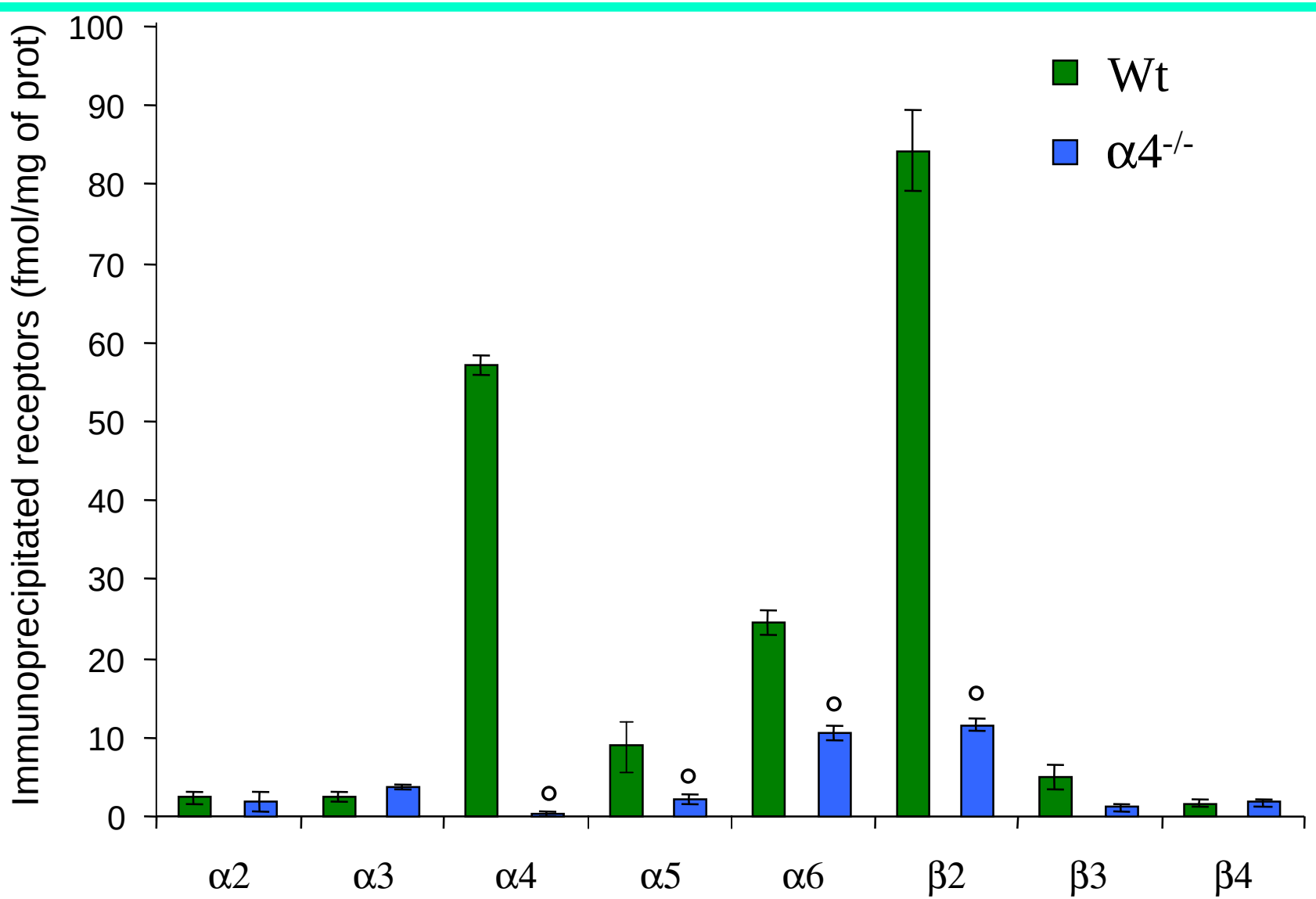
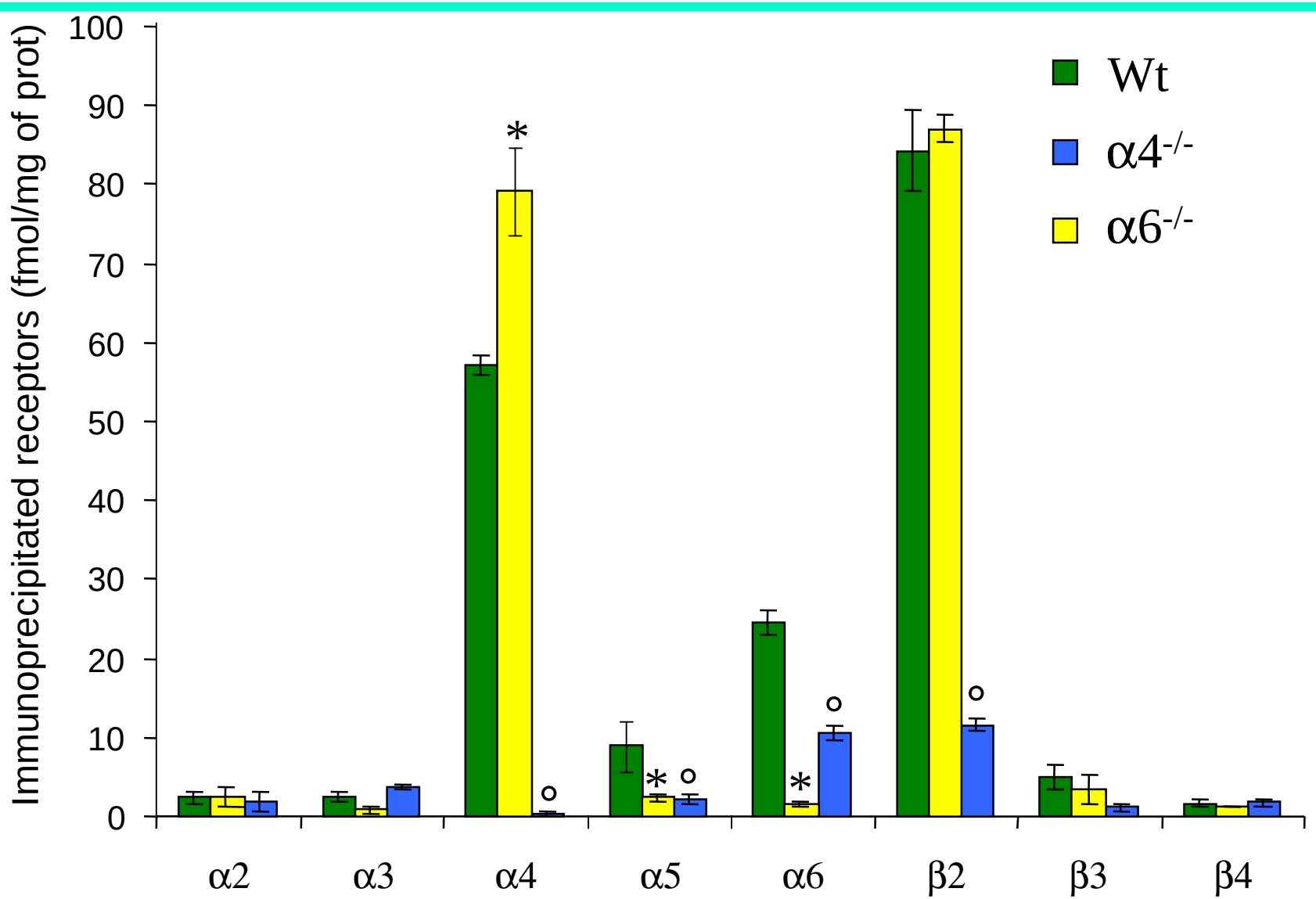


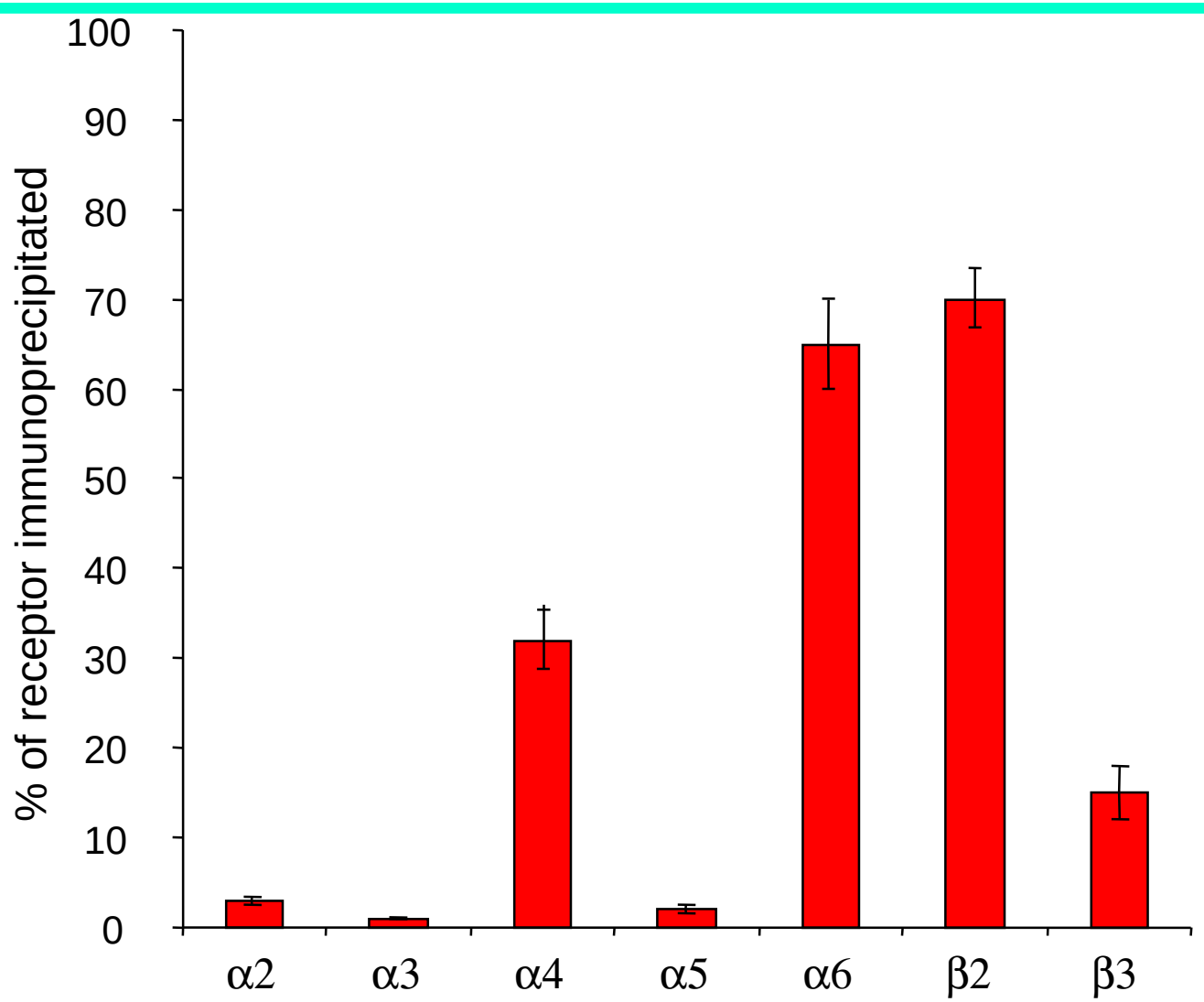
MARUBIO *et al*. (1999) *Nature*, 398: 805-810,

nAChRs from striatal membranes

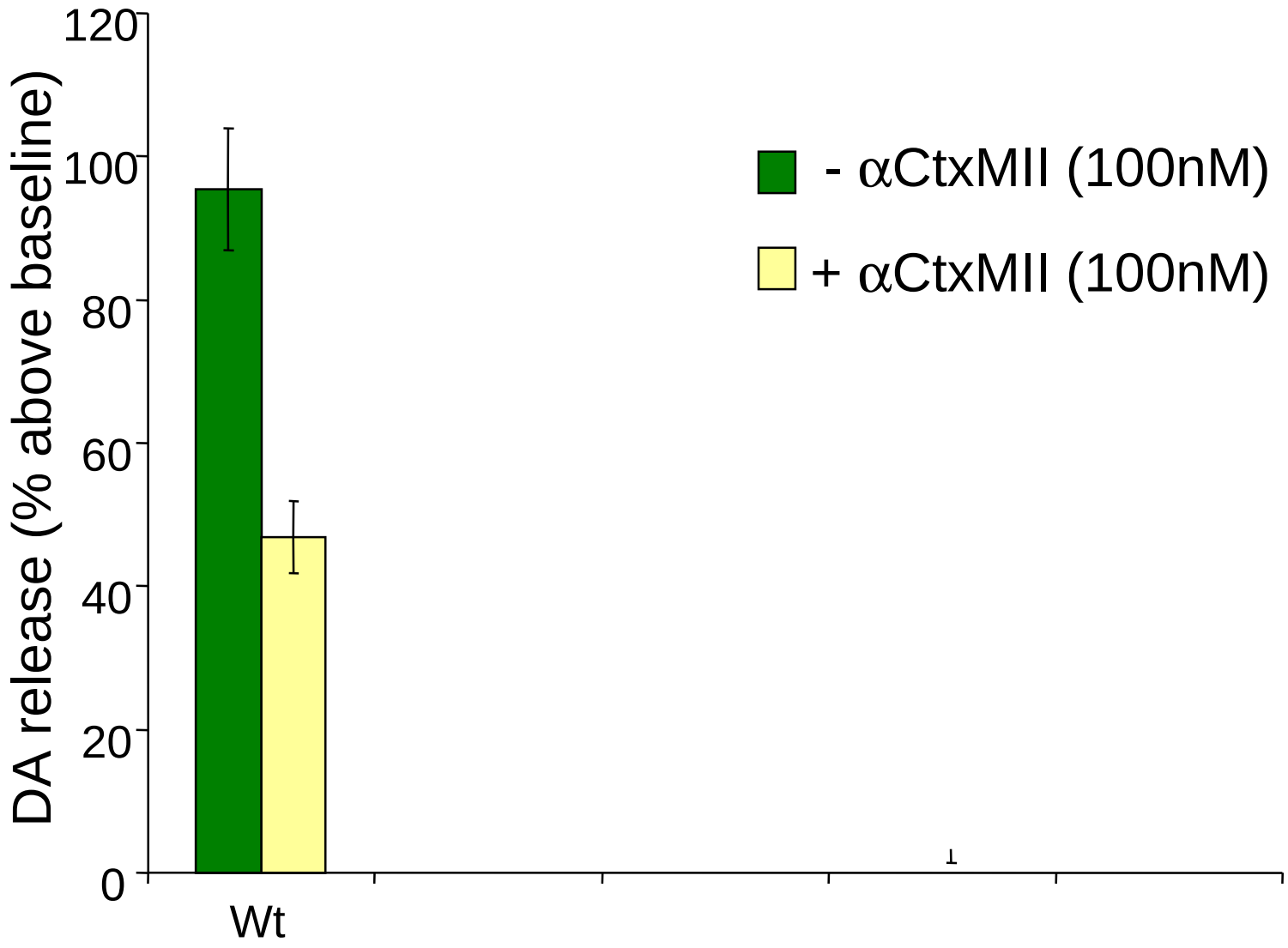


MARUBIO *et al*. (1999) *Nature*, 398: 805-810, CHAMPTIAUX, GOTTI *et al.* (2002), unpublished

Composition of α6 purified receptors



Nicotine-induced DA release (synaptosomes)



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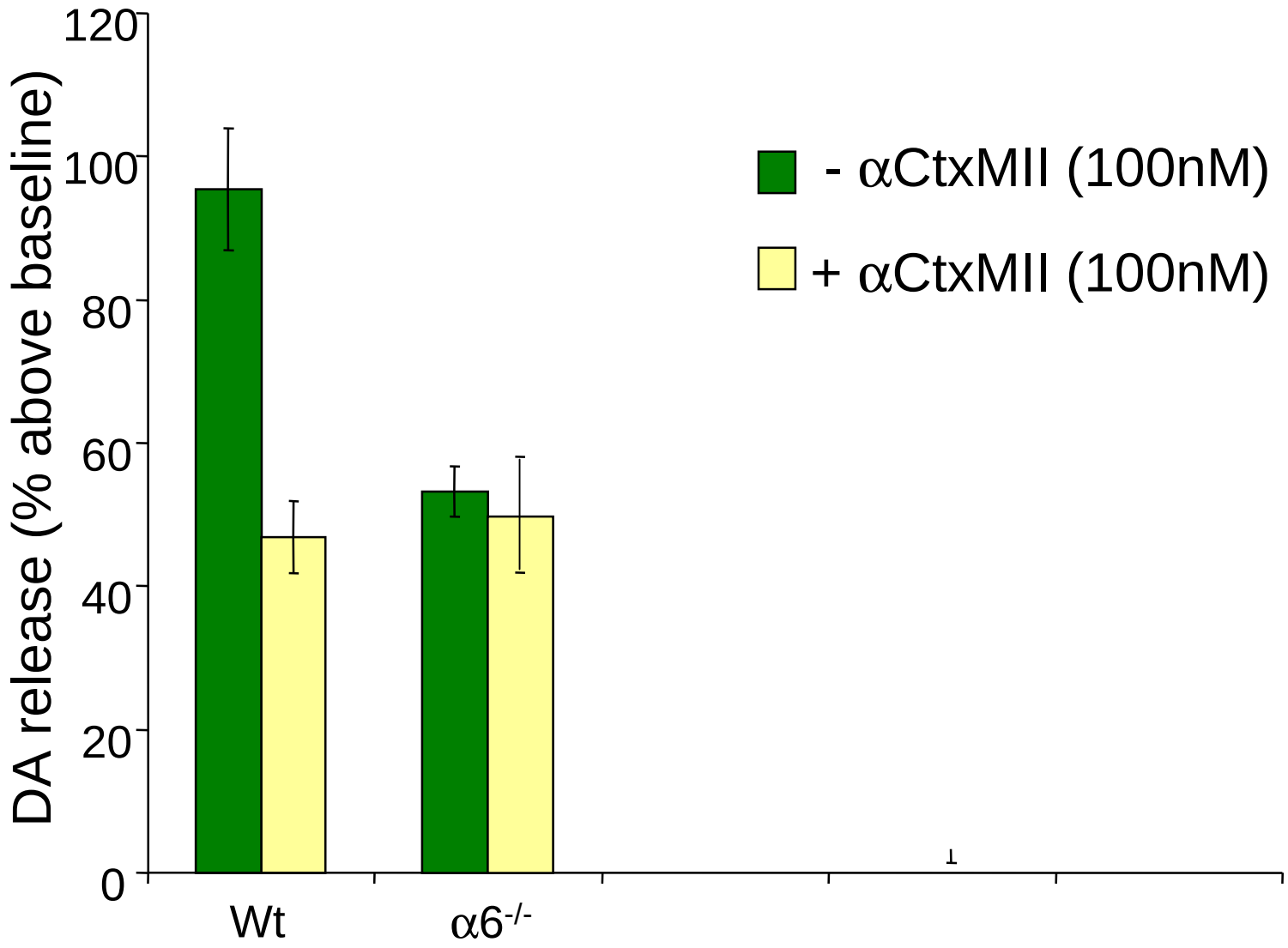

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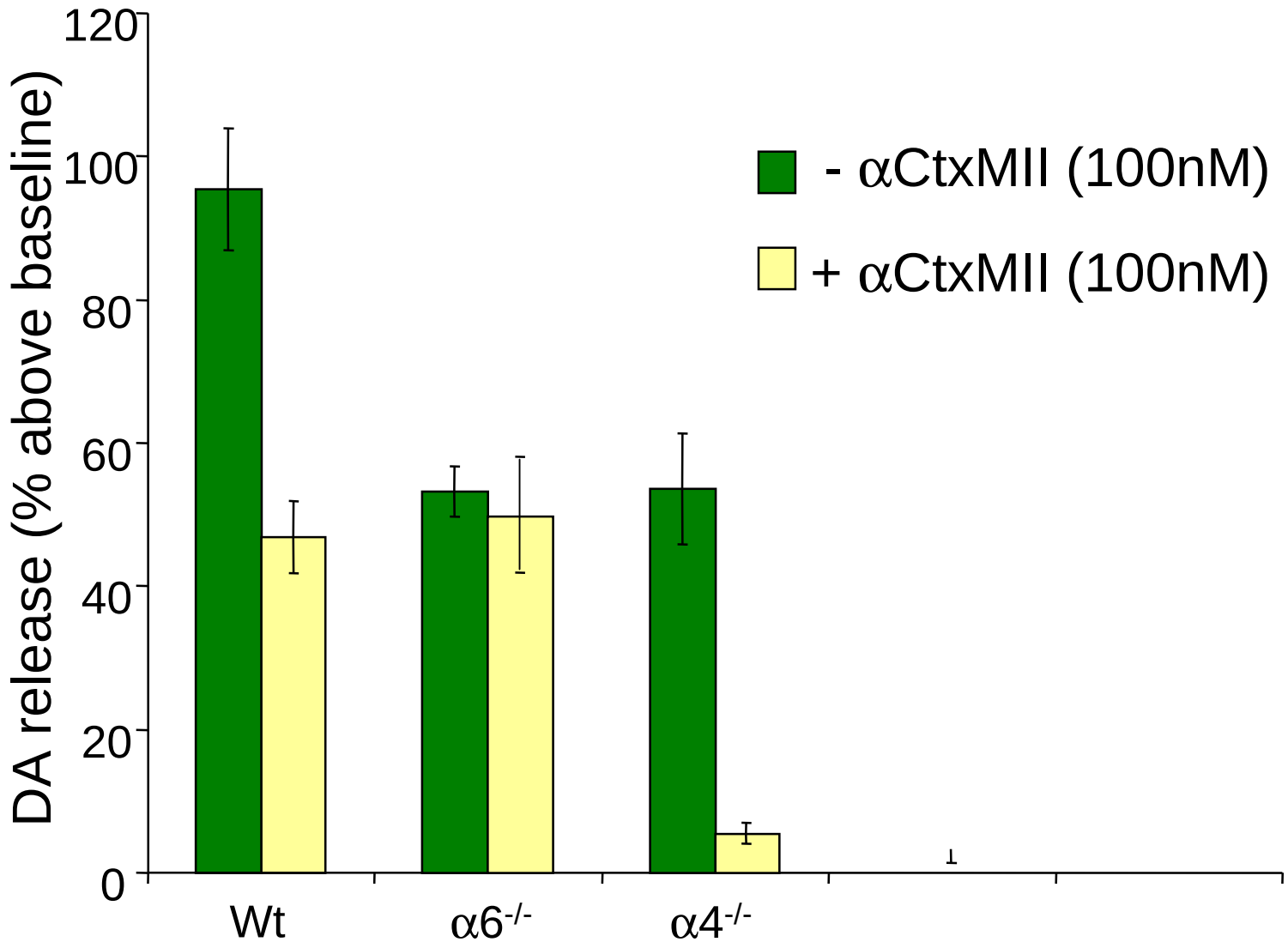
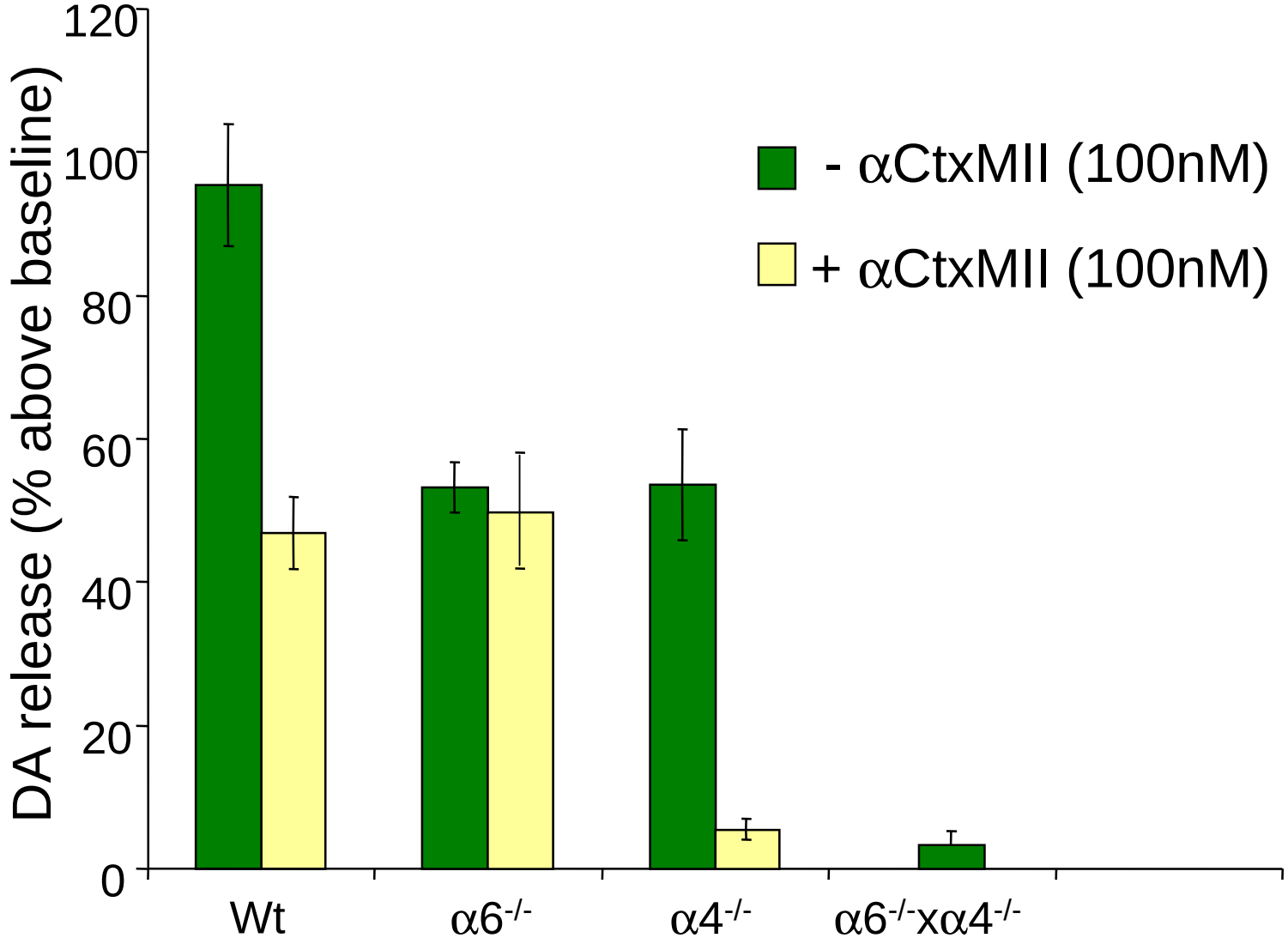


Nicotine-induced DA release (synaptosomes)



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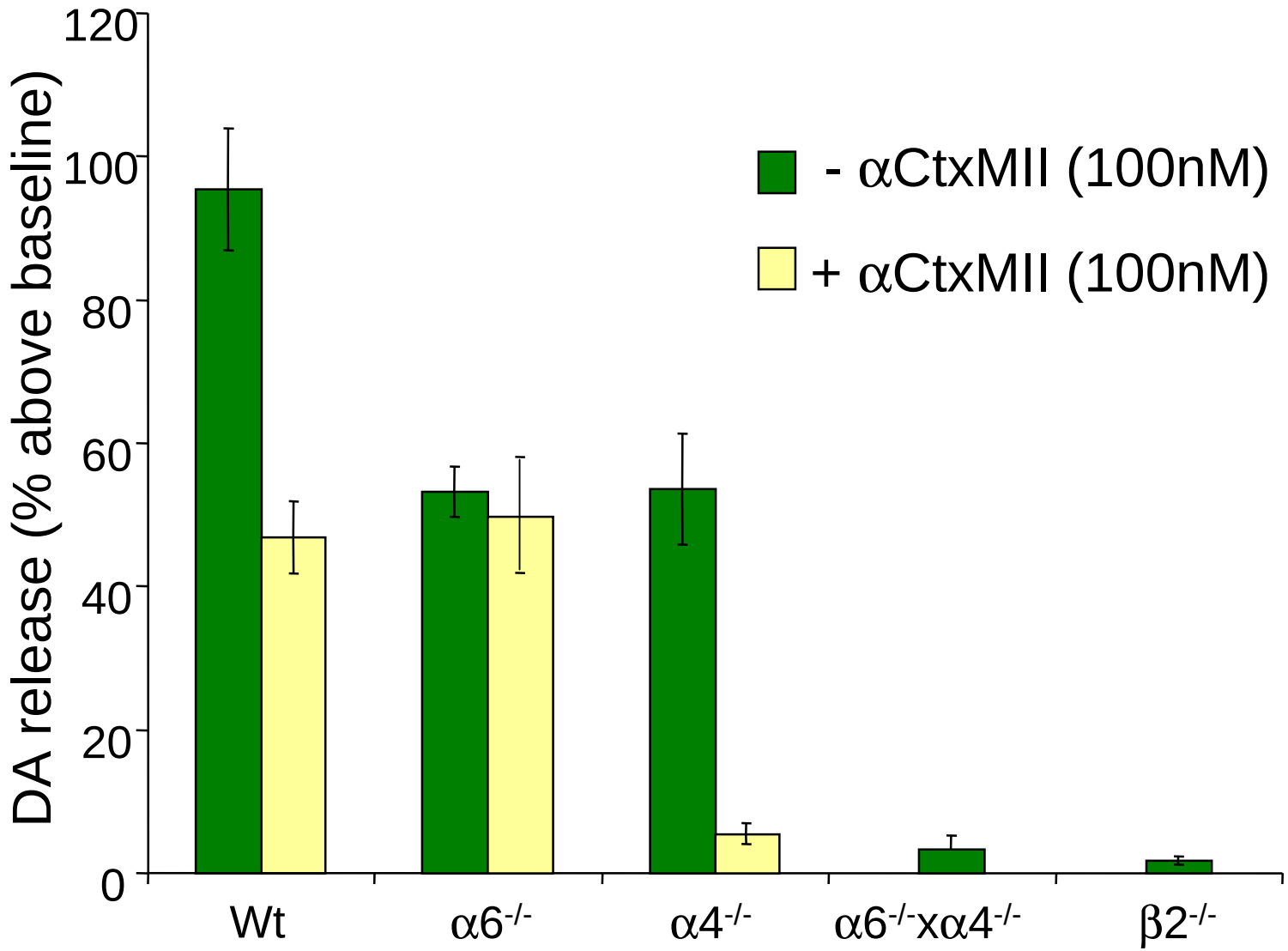
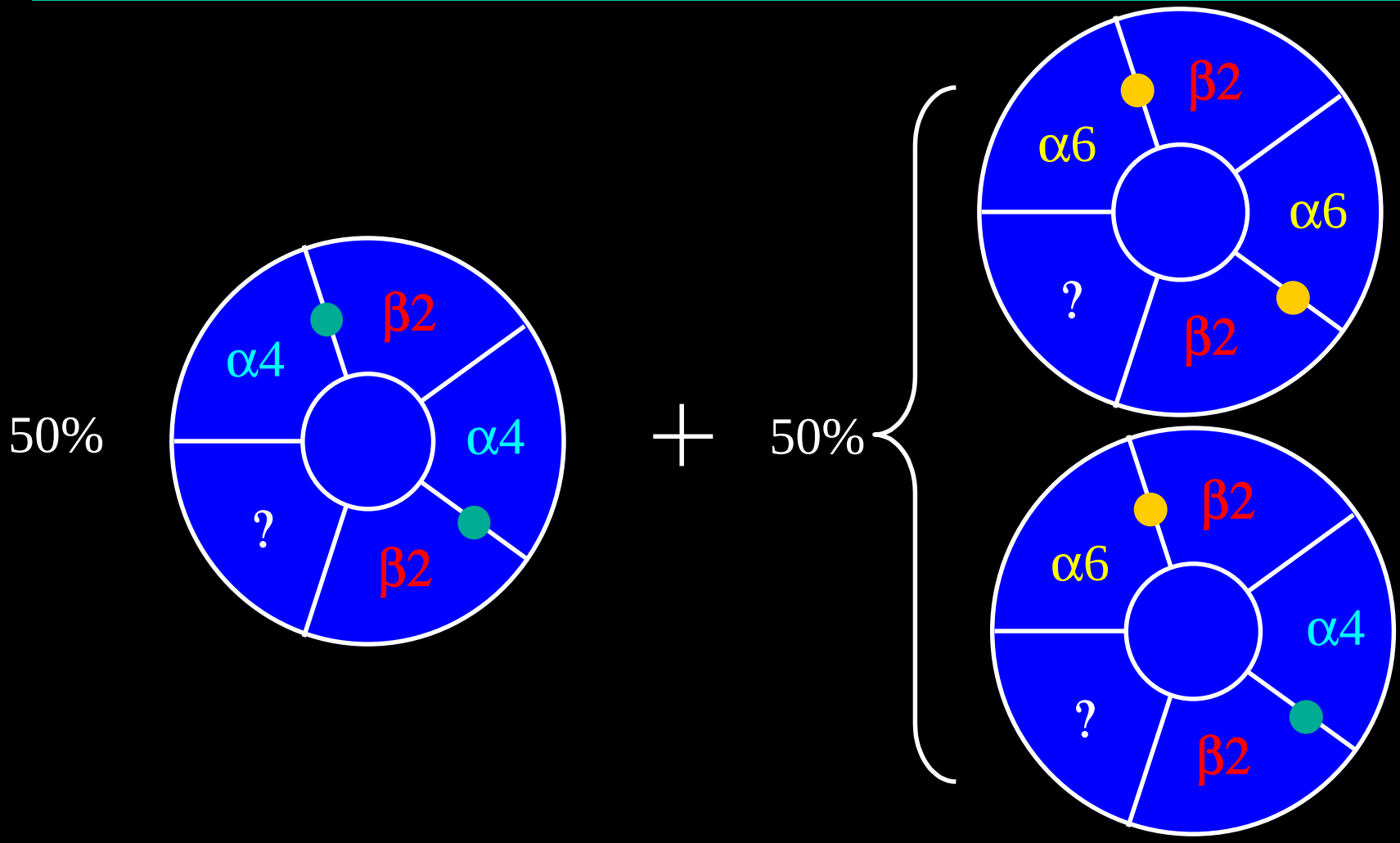


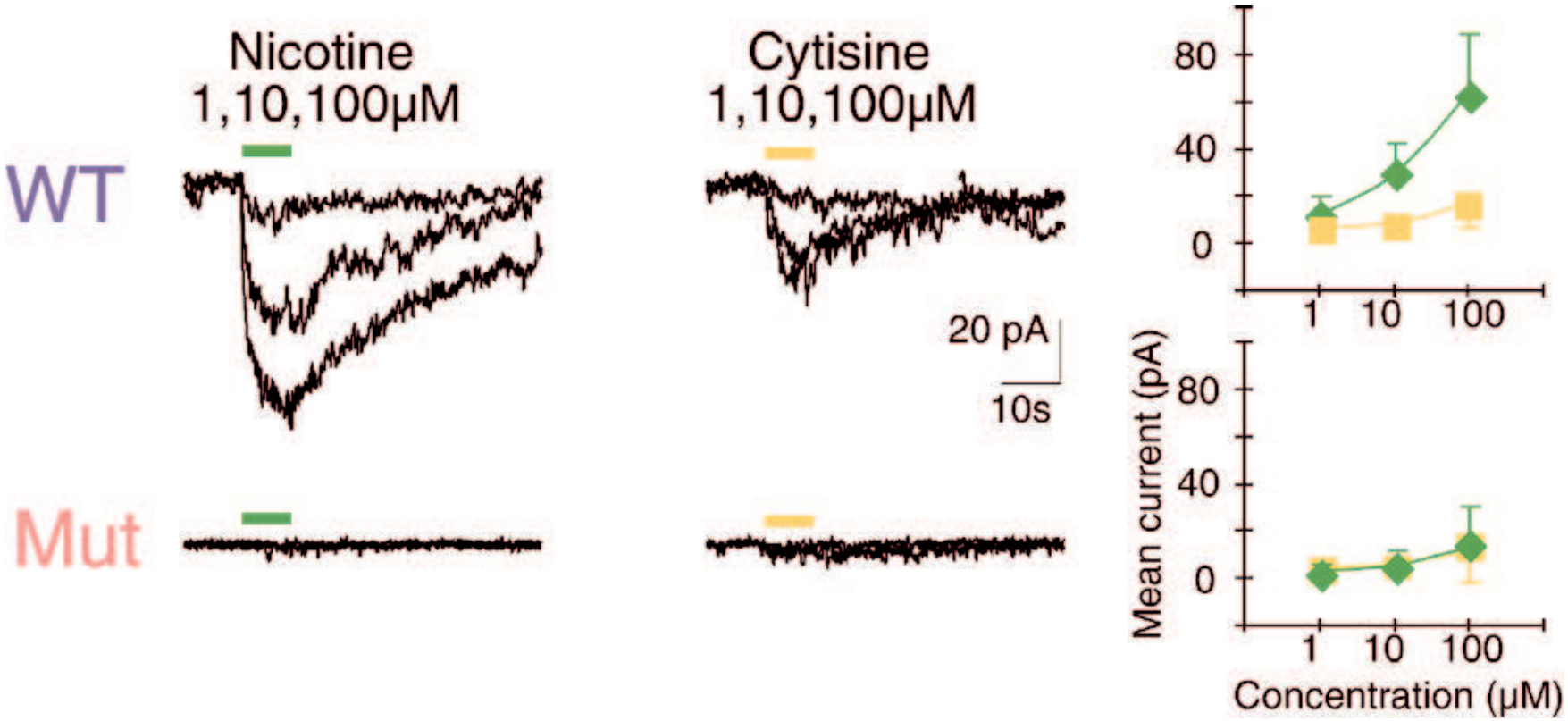
PICCIOTTO *et al.* (1995) *Nature*, 374: 65-67,

nAChRs isotypes on DA terminals



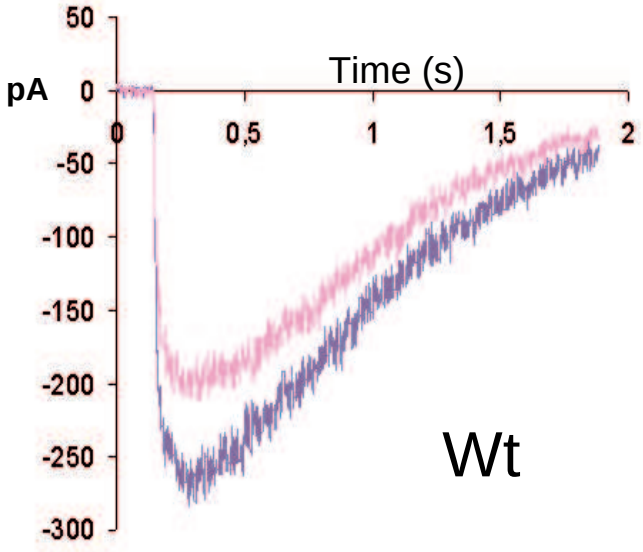
- α4β2 interface
  Low affinity for αCtxMII
- α6β2 interface
  High affinity for αCtxMII

β2 KO on currents in DA neurones



PICCIOTTO *et al.* (1998) *Nature* 391 : 173-188

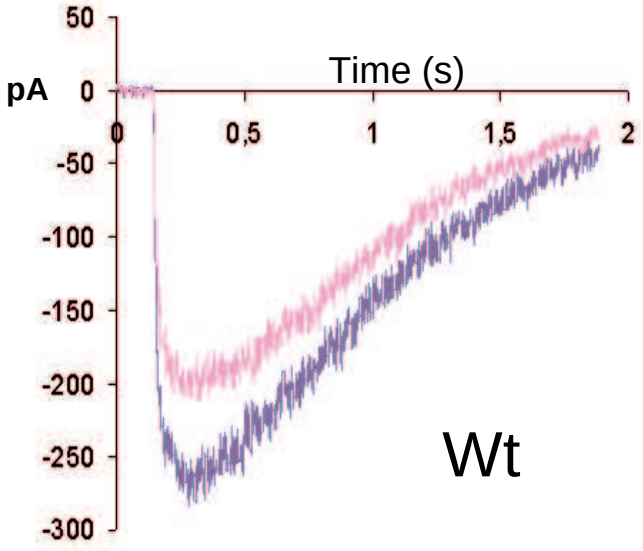
ACh induced currents in DA neurones



Wt

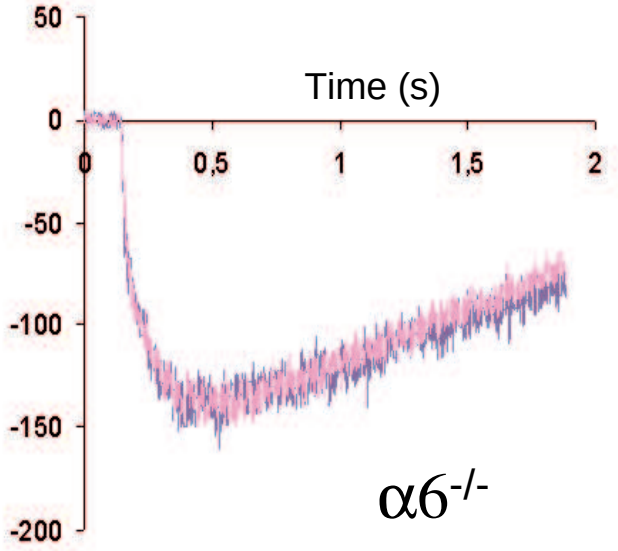
- No antagonist
- αCtxMII

ACh induced currents in DA neurones



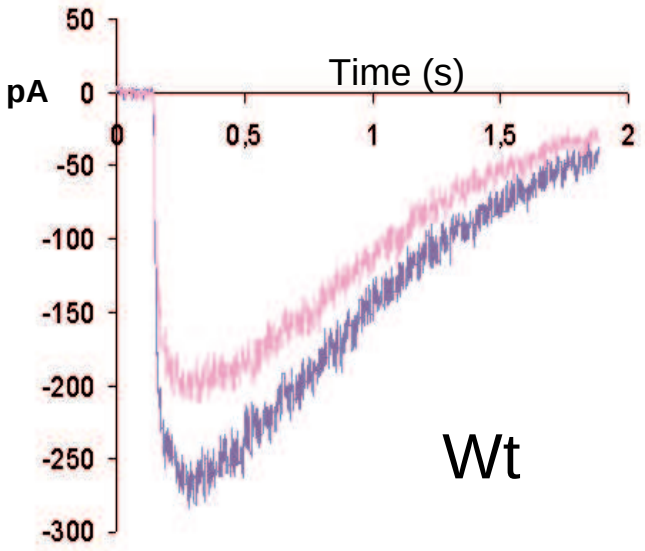
Wt

- No antagonist
- αCtxMII

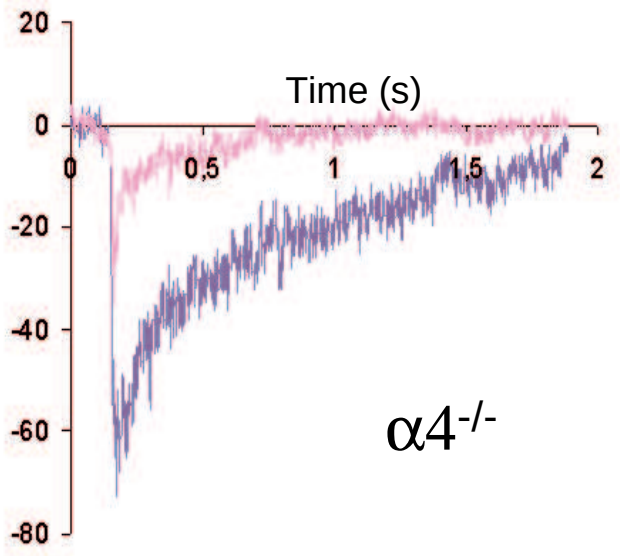


$\alpha 6^{-/-}$

ACh induced currents in DA neurones

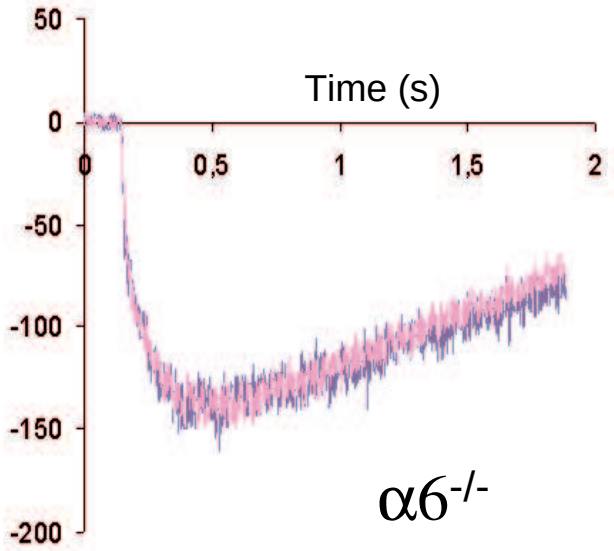


Wt



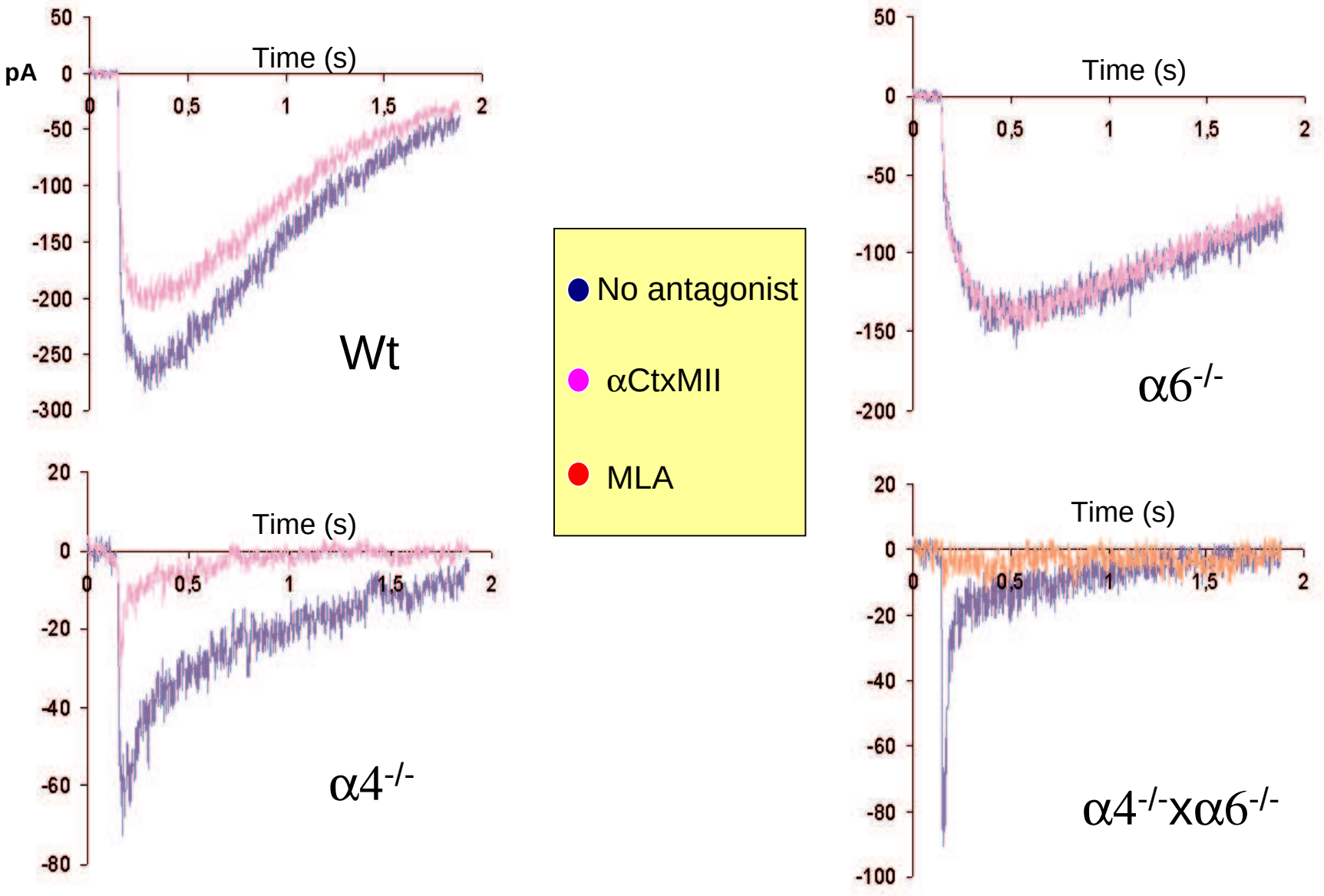
$\alpha 4^{-/-}$

- No antagonist
- αCtxMII

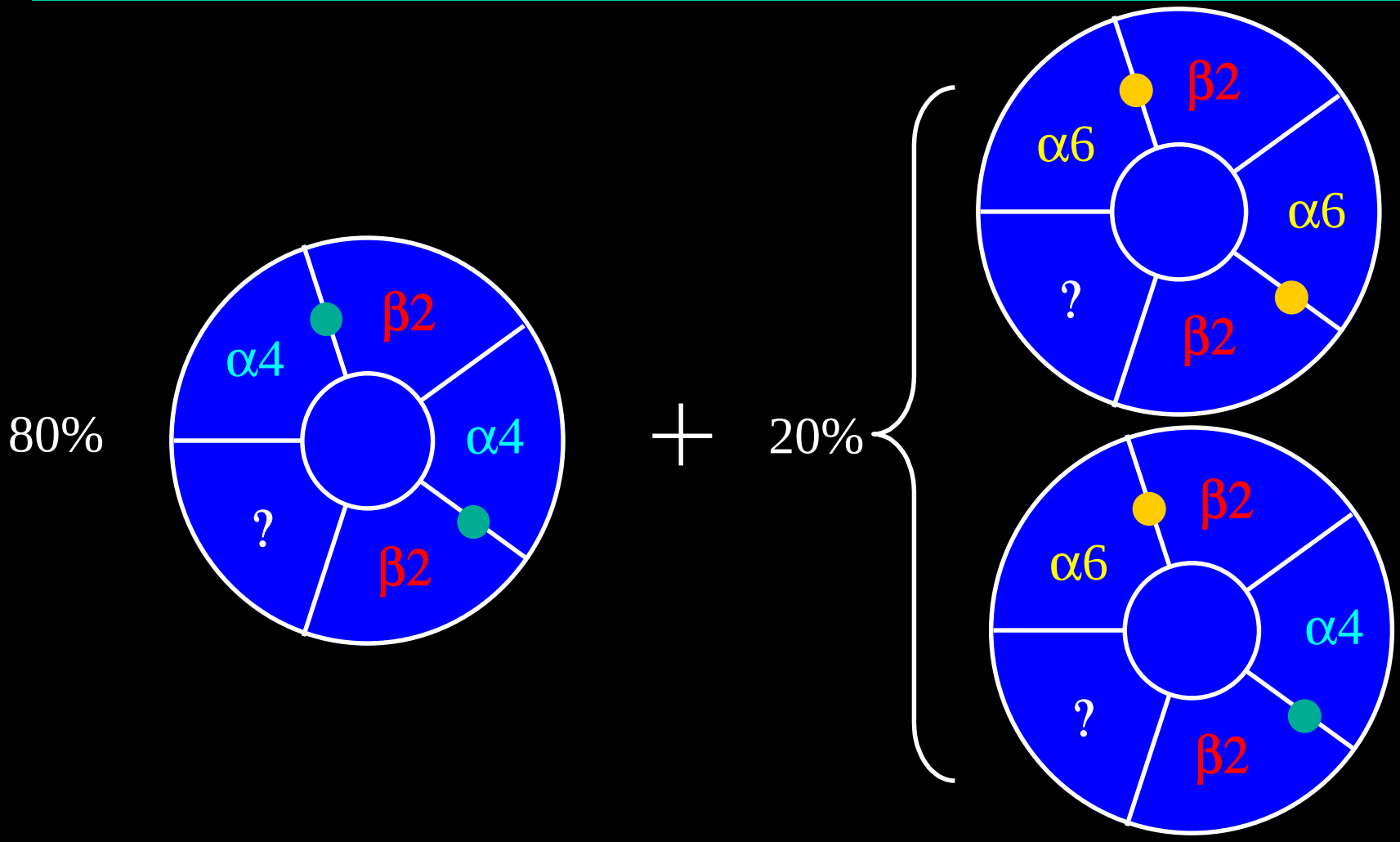


$\alpha 6^{-/-}$

ACh induced currents in DA neurones



nAChRs isotypes on DA soma



- α4β2 interface
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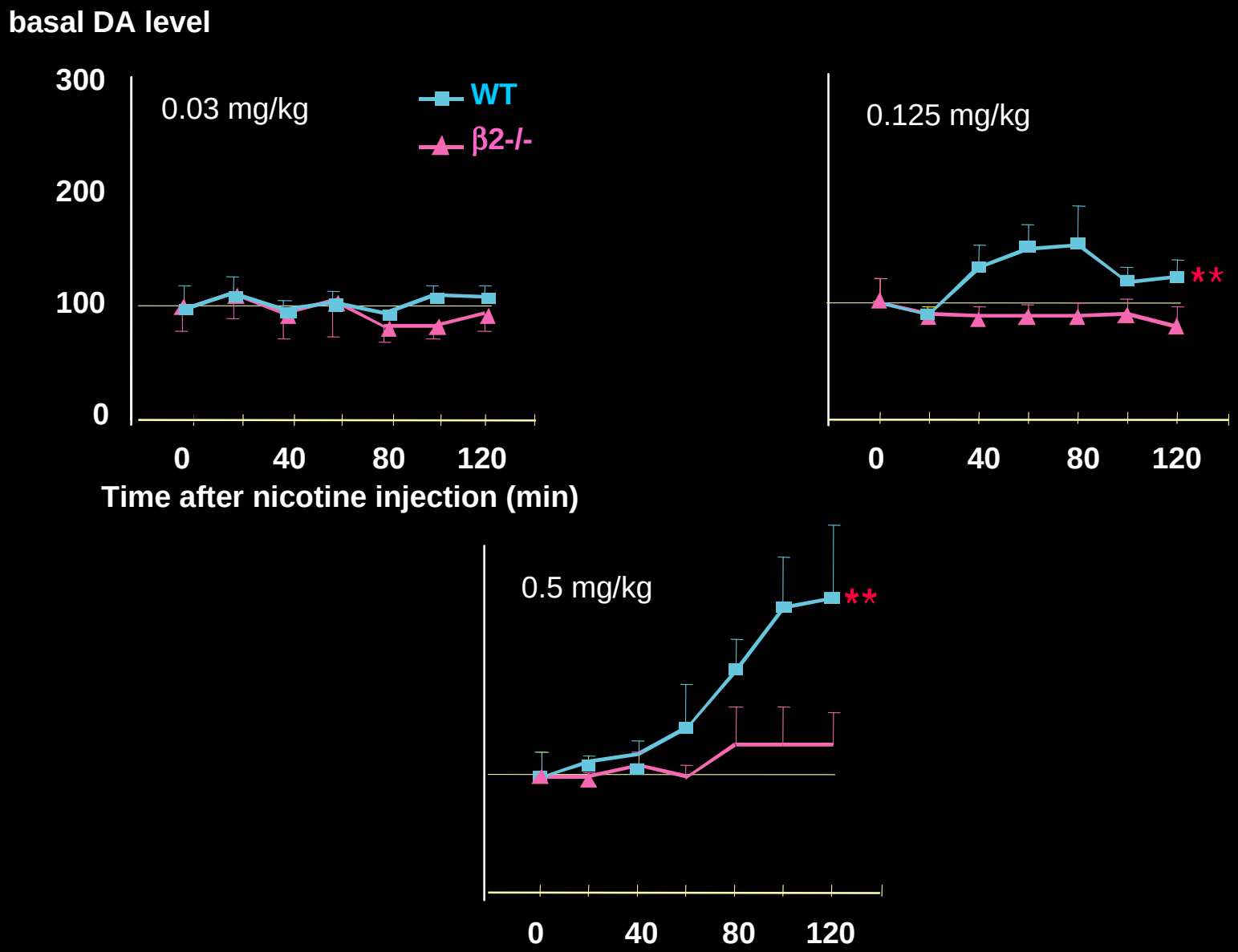
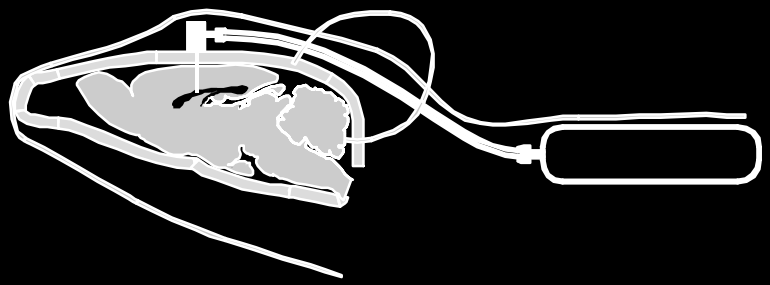
Nicotine-induced DA release in β2$^{-/-}$

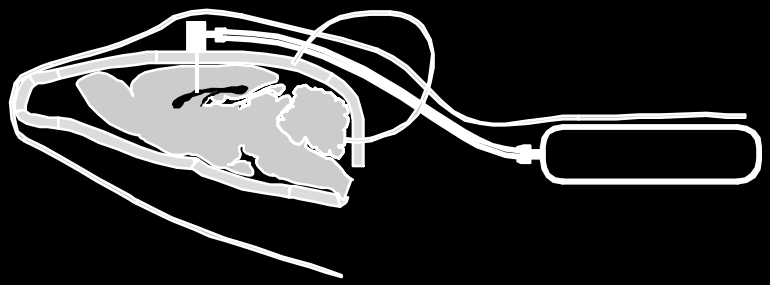


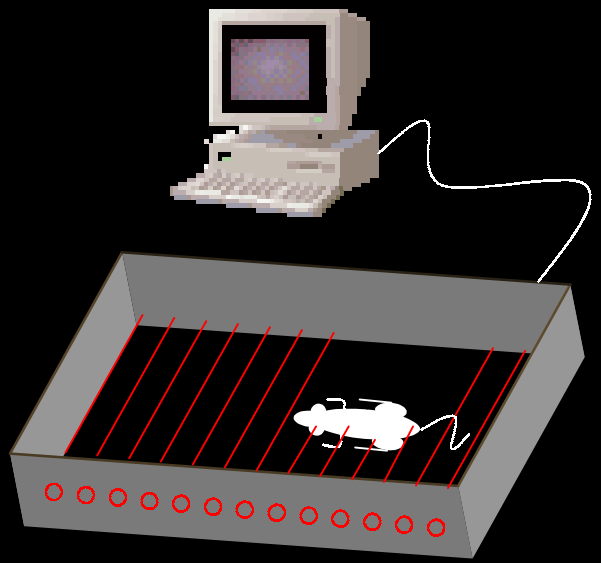
α6 and nicotine-induced locomotion



LE NOVÈRE *et al.* (1999) *NeuroReport* 10 : 173-188

α6 and nicotine-induced locomotion





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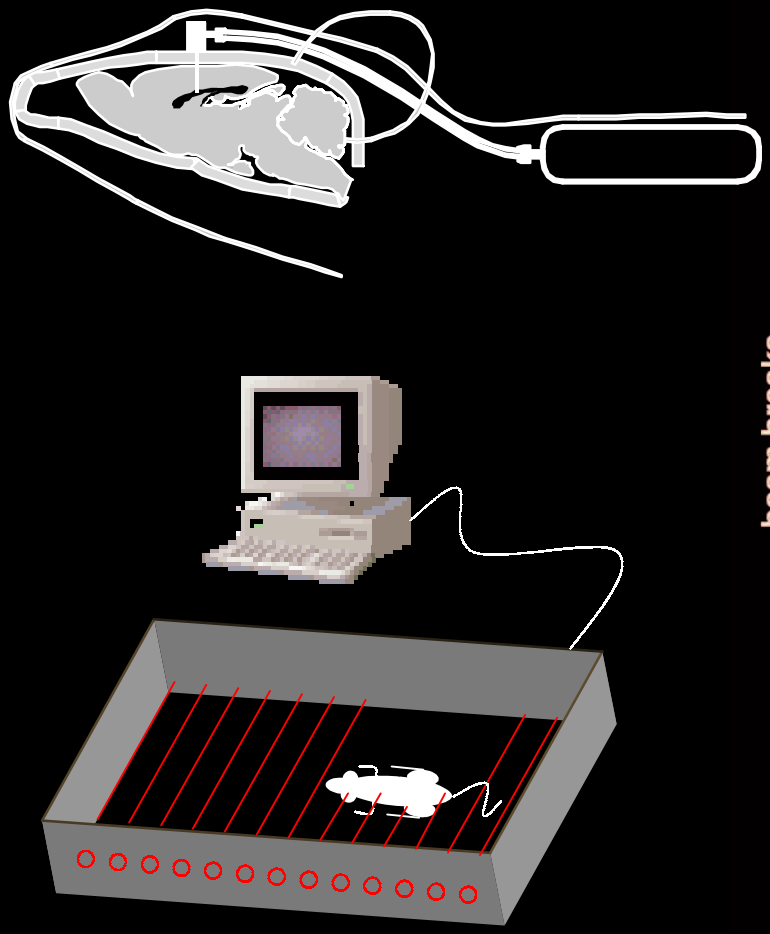

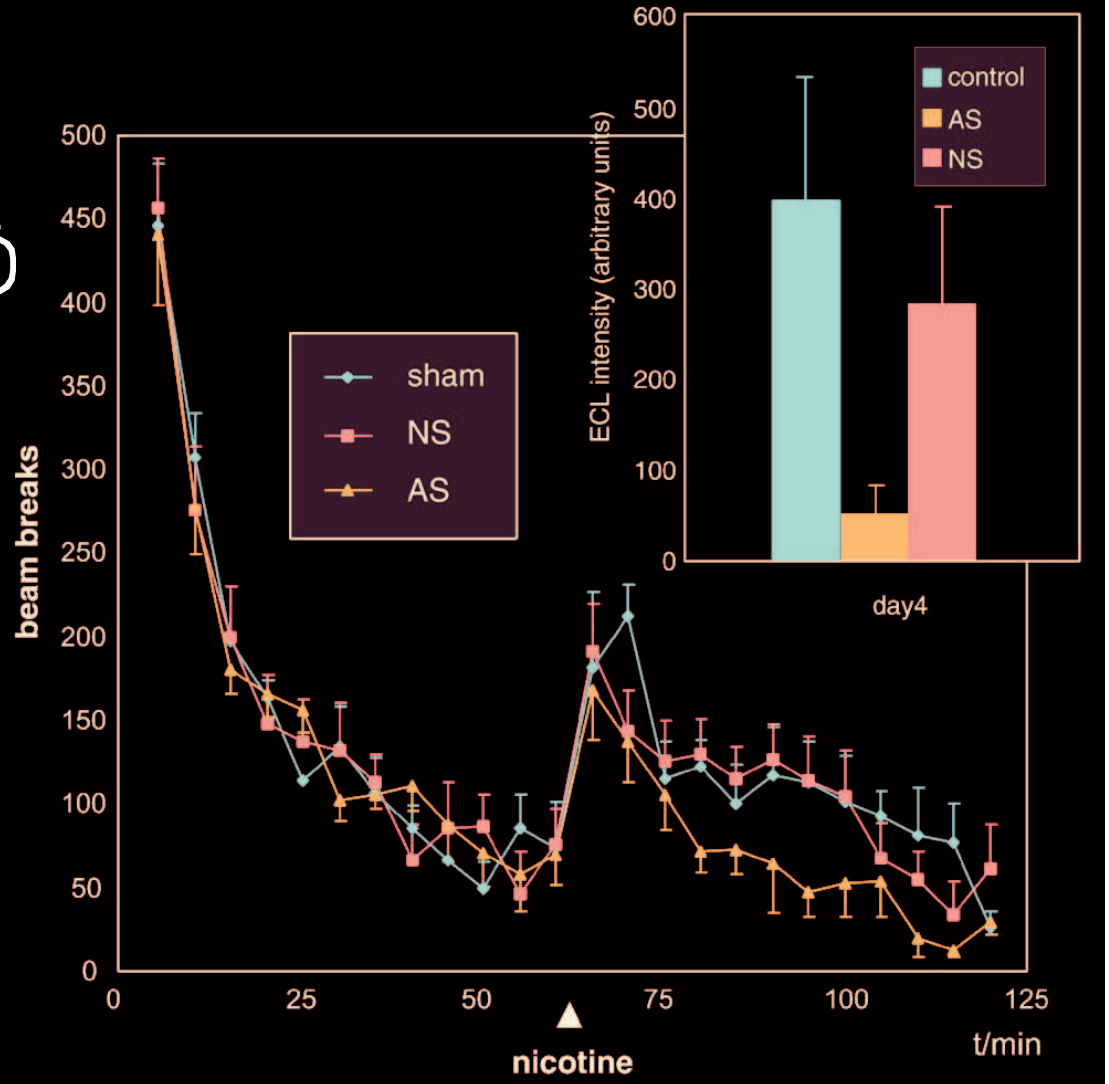

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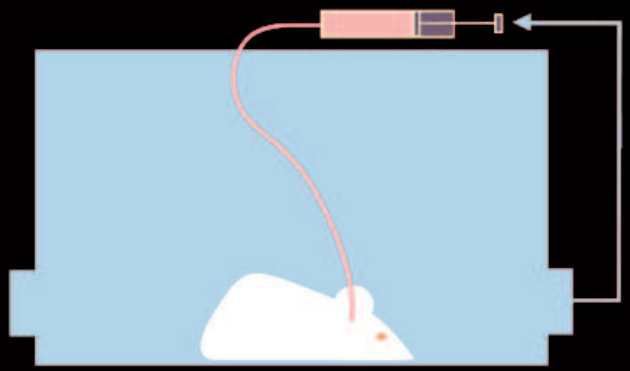
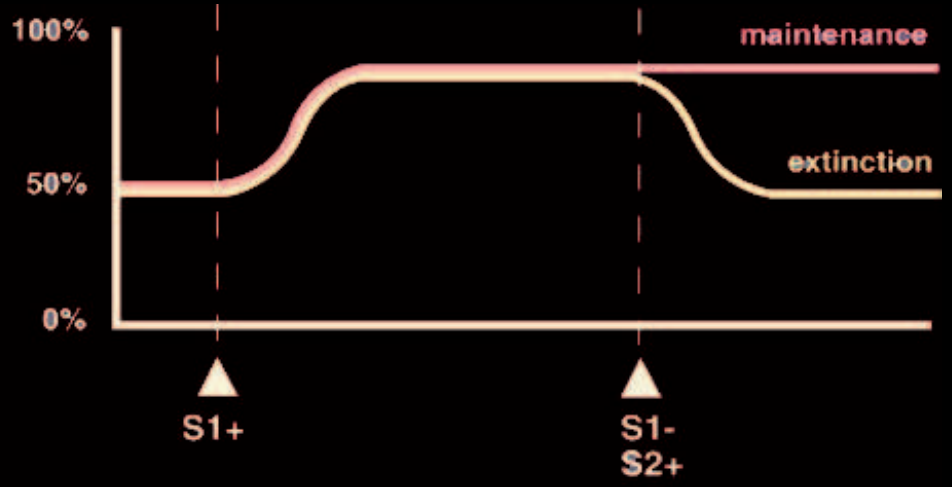
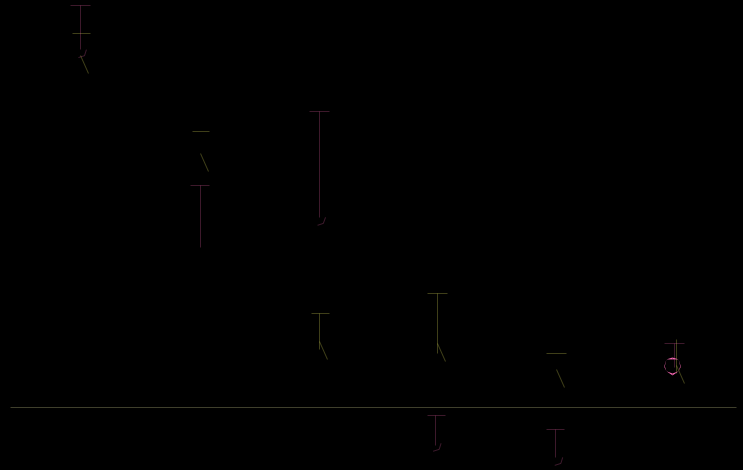
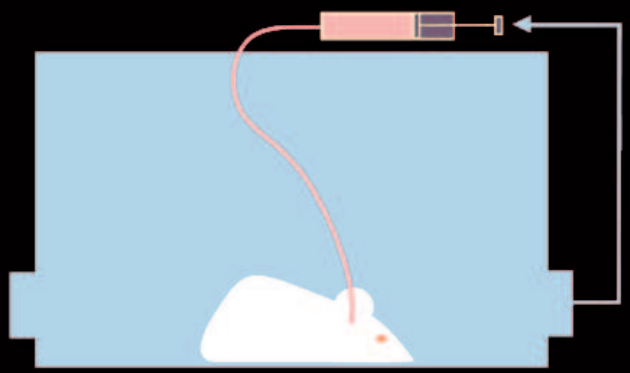
β2 and nicotine self-administration

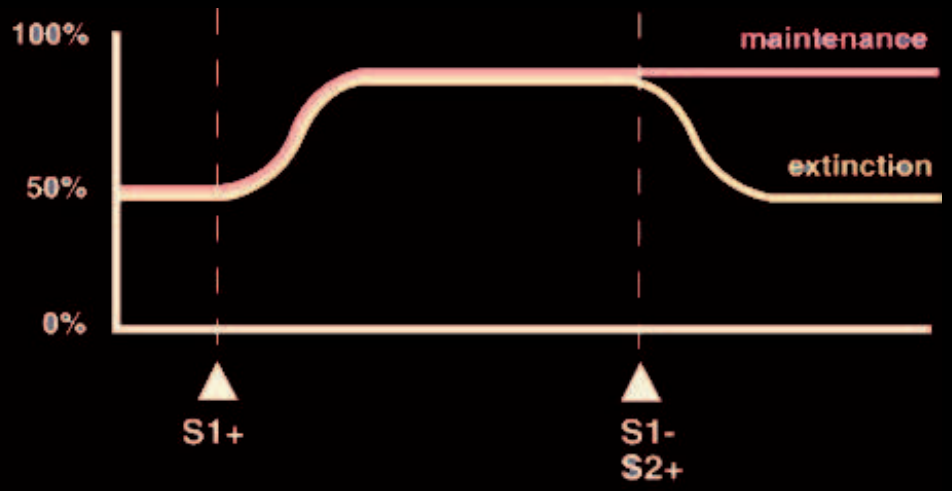


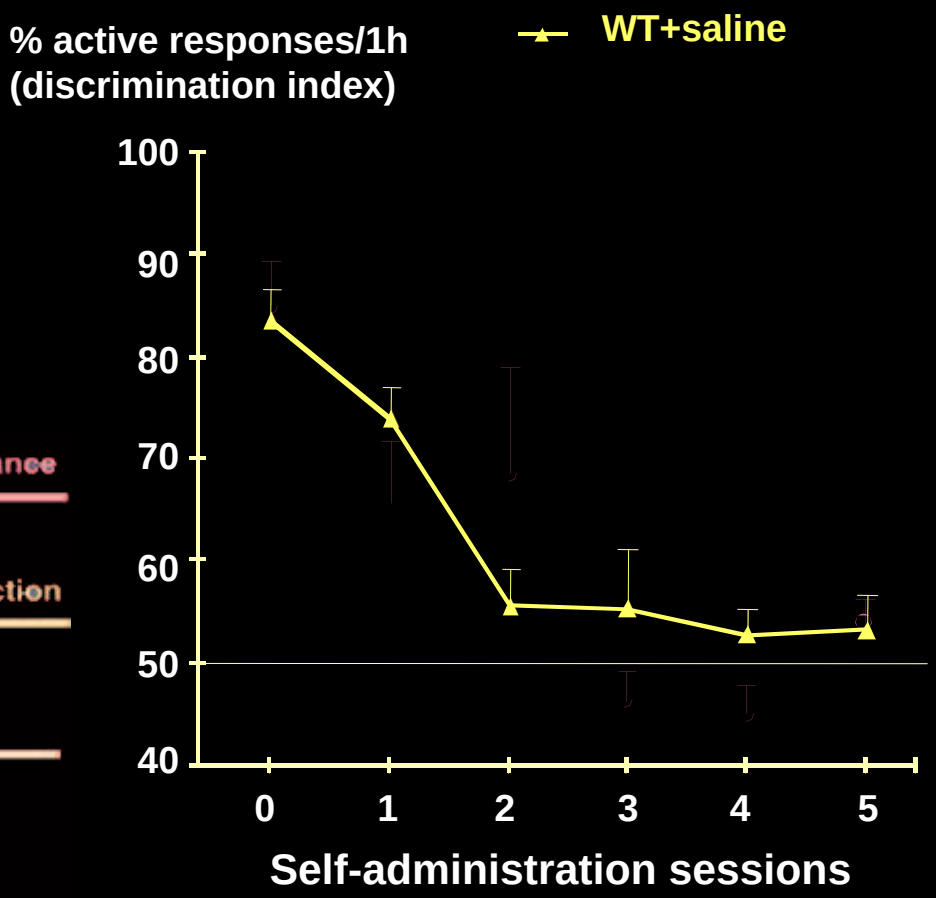




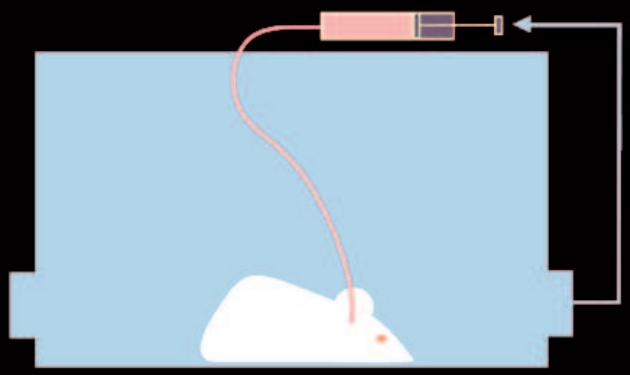
β2 and nicotine self-administration

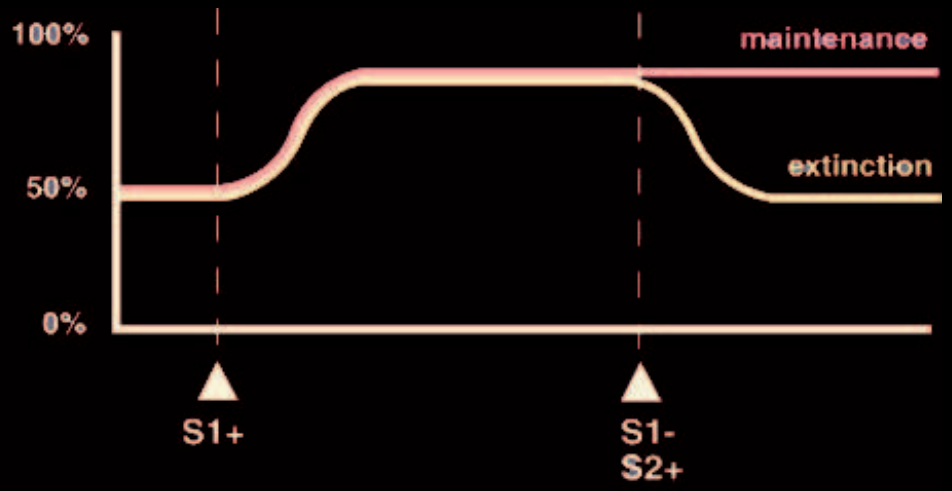


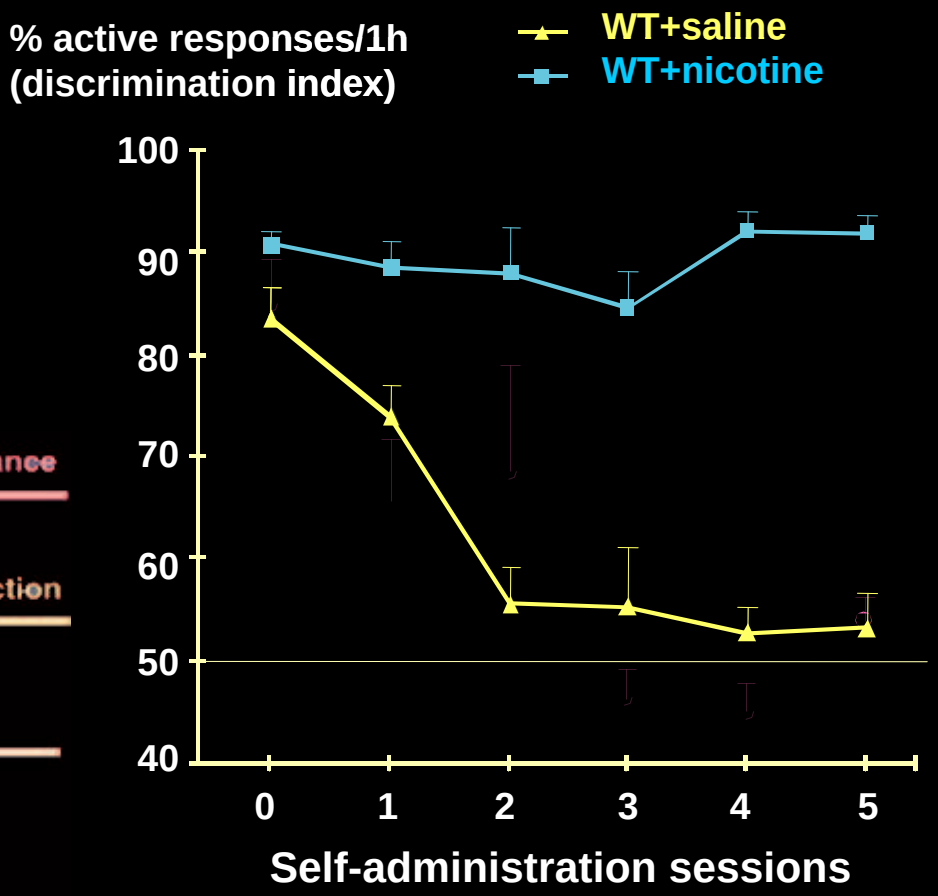




β2 and nicotine self-administration







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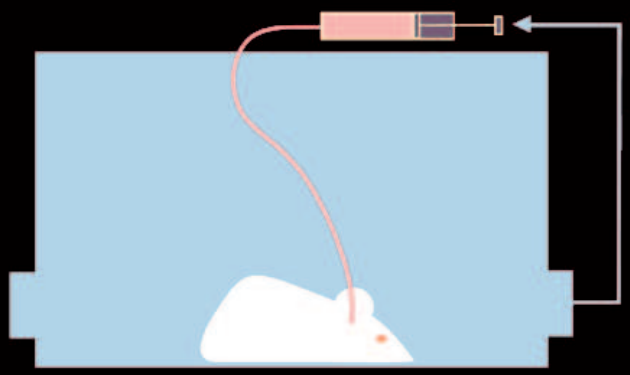

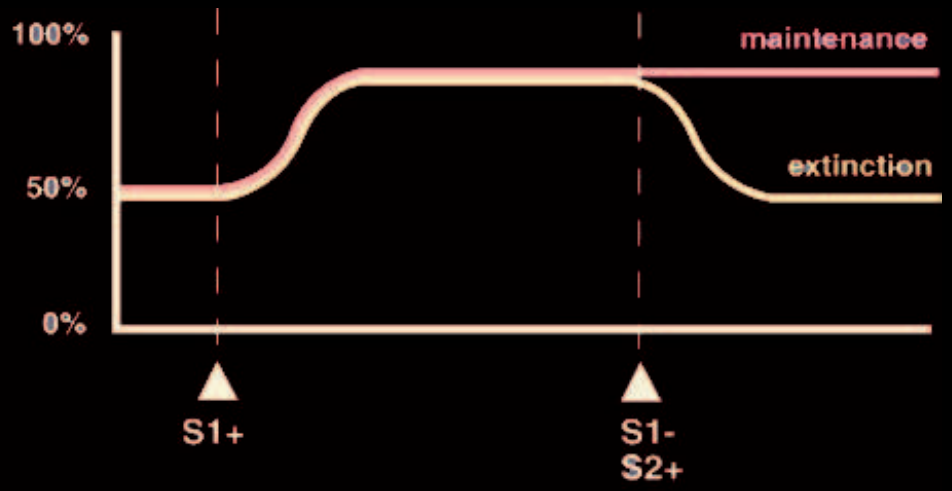

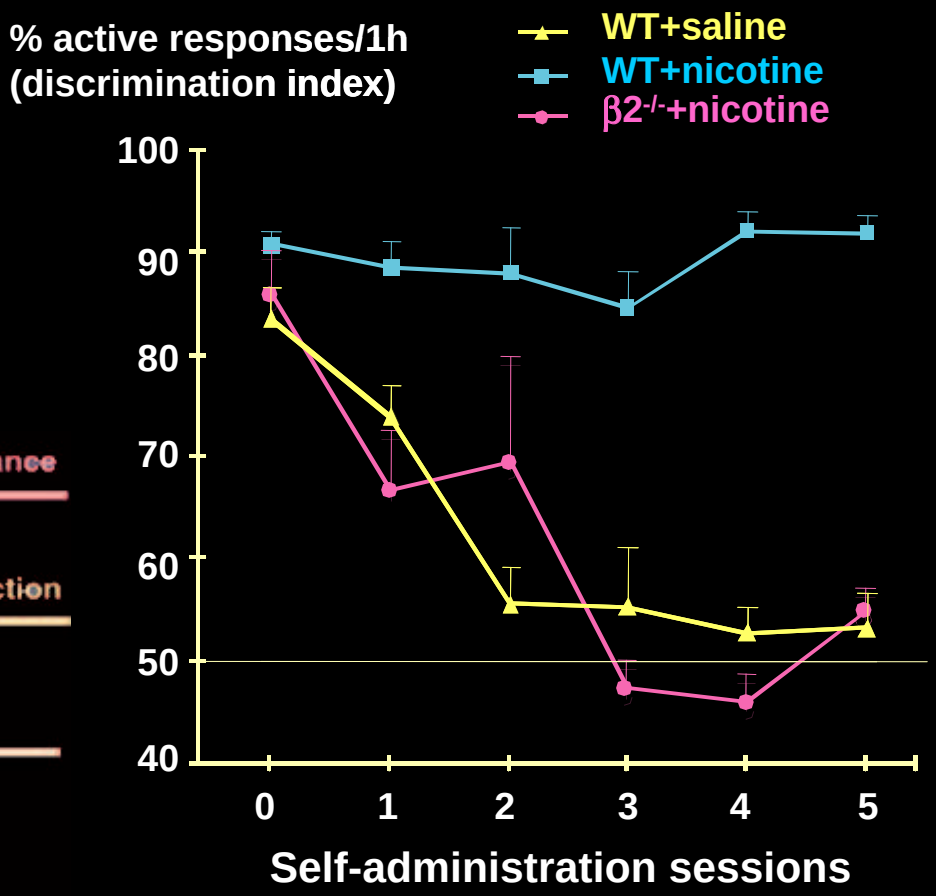

Conclusion

α4, α6 and β2 subunits are involved but:

- A dopaminergic cell contains several kinds of functional nAChRs, which can be located in different subcellular compartments;
- The function of an isotype depends both on the identity of its components and its cellular location;
- The links between receptor biophysics and cell physiology on one part, and cell physiology and behaviour on the other part, are still partially uncovered;

The progression towards a perfect understanding of the biological basis of nicotine addiction is continuous but long is the road.

DopaNet

Pan-european consortium

- Three model cells
  - Mesencephalic dopaminergic cell
  - Striatal GABA medium spiny neuron
  - Prefrontal Glutamate pyramidal cell
- Associated diseases
  - Drug dependance, Huntington chorea
  - Parkinson disease, Schizophrenia, etc.
- Detailled and quantitative data
  - Multiple levels: single molecule, supra-macromolecular apparatus, neuronal cell, neuronal network.
- Creation of a meta-database
  - Genetic, biochemical, functional, and morphological information.
- Accurate models of synapses and of whole interacting neurones

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  - Daniel Bertrand
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  - Thomas Grutter
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  - **Bernard Gilquin**
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  - Denis Servent
- KO generation
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  - Philippe Brûlet
  - **Nicolas Champtiaux**
  - Yvan Lallemand
  - Lisa Marubio
  - **Marina Picciotto**
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  - Rosaria Ferrari
  - Alain Gardier
  - **Cecilia Gotti**
  - Alban de Kerchove d' Exaerde
  - **Clément Léna**
  - Emilio Merlo-Pich
  - R Rimondini
  - Michele Zoli