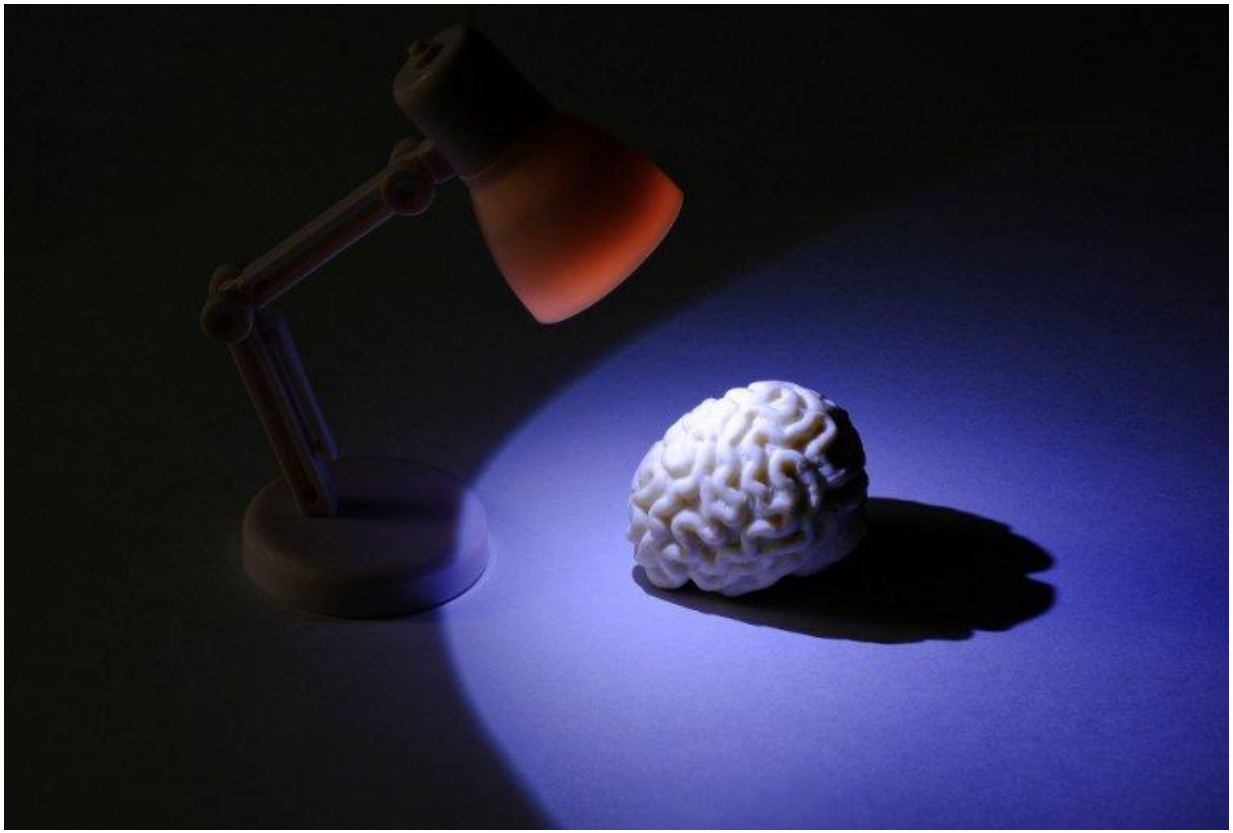
L'importanza dei modelli traslazionali in neuroscienze.
Il punto di vista del neurologo

Università di Roma Tor Vergata



Nicola Biagio Mercuri

La richiesta di competenza neurologica nel prossimo futuro
Sesta edizione
Fortuna Resort, Chianciano Terme (Siena)
13-15 maggio 2022

La ricerca on the Bench

Considerazioni sulle motivazioni che mi hanno spinto a fare RICERCA TRANSLAZIONALE

Vorrei condividere con voi le sensazioni che provo da neurologo attraverso la RICERCA di BASE, che, a mio giudizio, sono interessanti, per cui cerco di trasmetterle a chi interagisce/lavora con me.

Parto da alcune valutazioni sulla ricerca di base e parlerò adducendo note «personali» :

a) In generale penso sia riduttivo diagnosticare e seguire l'inesorabile ed ineluttabile decorso clinico di una malattia (cosa che spesso succede in Neurologia) senza avere la speranza, almeno teorica di poter, adesso o nel prossimo futuro, incidere per prevenirla e/o rallentarne il decorso.

Ciò può essere raggiungibile soprattutto con la ricerca traslazionale.

b) La RICERCA TRASLAZIONALE ci fa capire meglio ciò che vero da ciò che è falso, portandoci ad ottenere capacità autonome di valutazione e di giudizio.

Per quanto mi riguarda proprio da quanto ho appreso in laboratorio, so che, almeno in ambito terapeutico, noi ancora continuiamo ad usare delle sostanze che fanno poco/nulla ai pazienti, o che hanno meccanismi di azione diversi da quelli che ci vengono detti.

Quindi non sappiamo, e a volte usiamo farmaci a sproposito e/o senza cognizione di causa. A ciò si può ovviare con la RICERCA TRASLAZIONALE.

c) Attraverso la RICERCA, si acquisisce una visione diversa degli accadimenti clinici e terapeutici (a mio avviso più completa). Si apprende un metodo di verifica che si basa su controlli e prove guidate dal ragionamento.

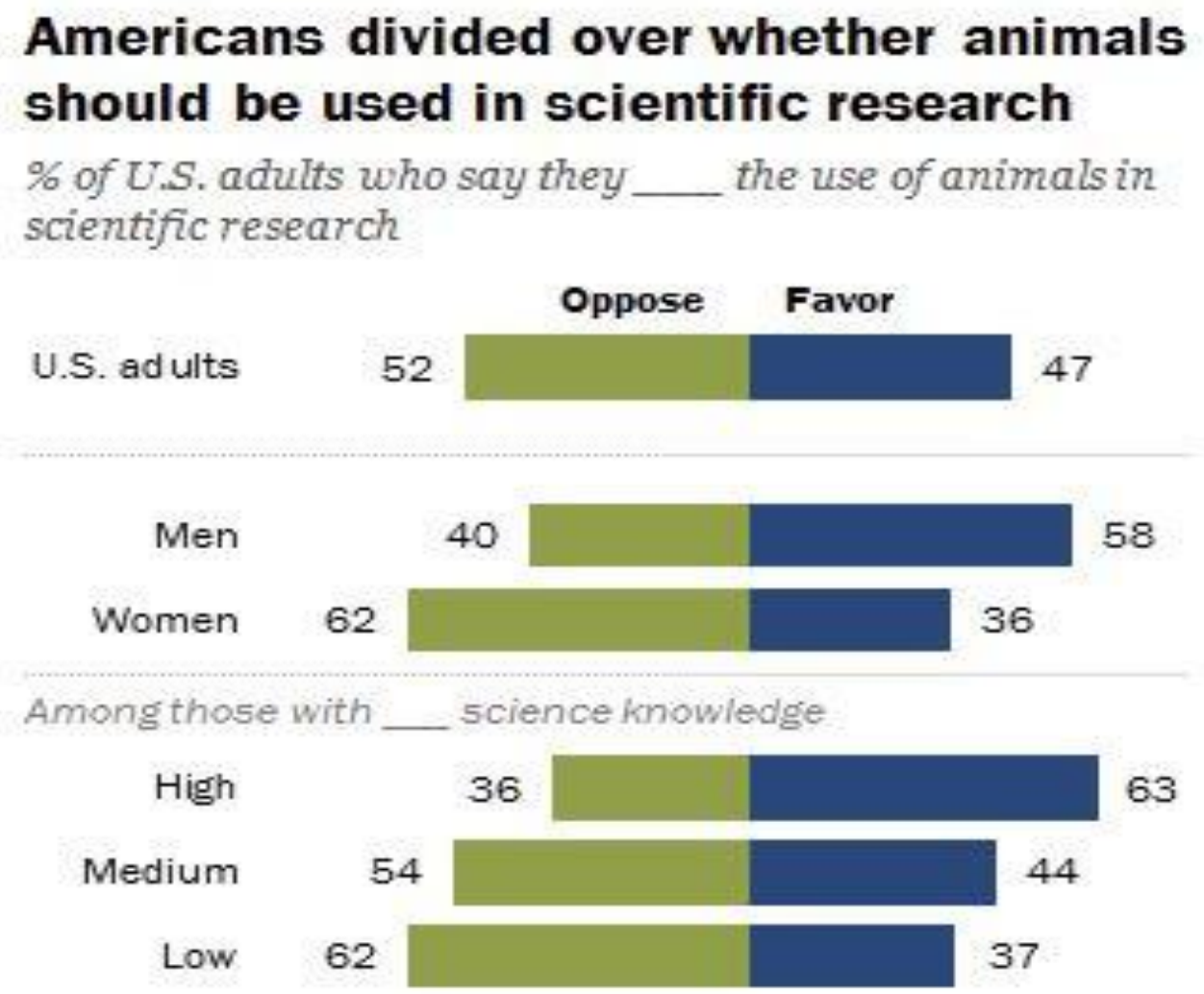
d) Praticando la RICERCA TRASLAZIONALE ci si accorge che si lavora in un’ambiente un po’ diverso da quello clinico. Direi meno paludato, più informale. Basato su rapporti reciproci diretti e rispettosi del valore delle persone.
Sei cosa fai, non cosa rappresenti.

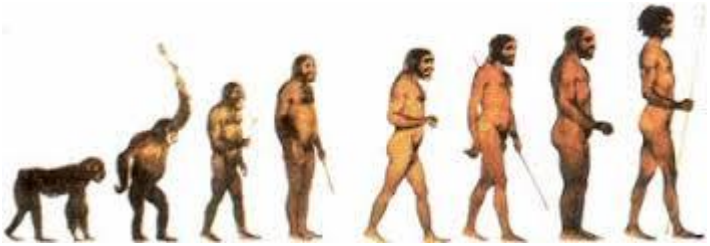
e) Spesso la RICERCA TRASLAZIONALE ti da la soddisfazione di competere per un risultato, di viaggiare, di conoscere altri gruppi.
Diventa quindi una componente importante del tuo lavoro ed una sorgente di entusiasmo.

Attualmente poter fare RICERCA TRASLAZIONALE (DI BASE) è difficile in Italia.
In qualche modo ed in maniera un po' ottusa, la ricerca, specialmente quella su modelli animali, è oberata da pregiudizi e da passaggi burocratici che io ritengo inutili e fine a se stessi.
Diciamolo anche chiaramente, nel nostro paese non è sufficientemente finanziata.

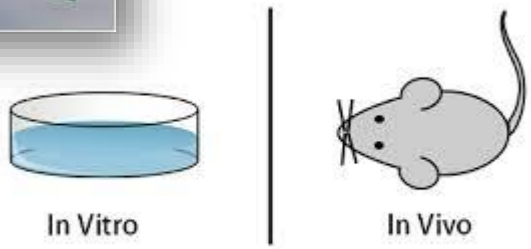
Tuttavia se si è dotati di buona volontà, conoscenza, ed un po' di fortuna, è ancora possibile svolgerla anche come neurologo.
In particolar modo avere in una persona due visioni (sperimentale e clinica) è un notevole vantaggio perché si hanno a disposizione sia le conoscenze biologiche che quelle cliniche del problema che si sta affrontando.
E' sicuramente un vantaggio, ma richiede un maggiore sforzo intellettivo e una maggiore disponibilità di tempo.

Opinione negli USA sulla ricerca animale - 2017





UNEXPECTED RD


In Vitro
In Vivo

Nel mondo scientifico è importante identificare dei modelli che possano in qualche modo mimare la patologia umana.

Per quanto attiene ai modelli animali, questi ci aiutano a capire il complesso funzionamento del Sistema Nervoso, e di conseguenza i meccanismi fisiopatogenetici che producono le malattia neurologiche e psichiatriche.

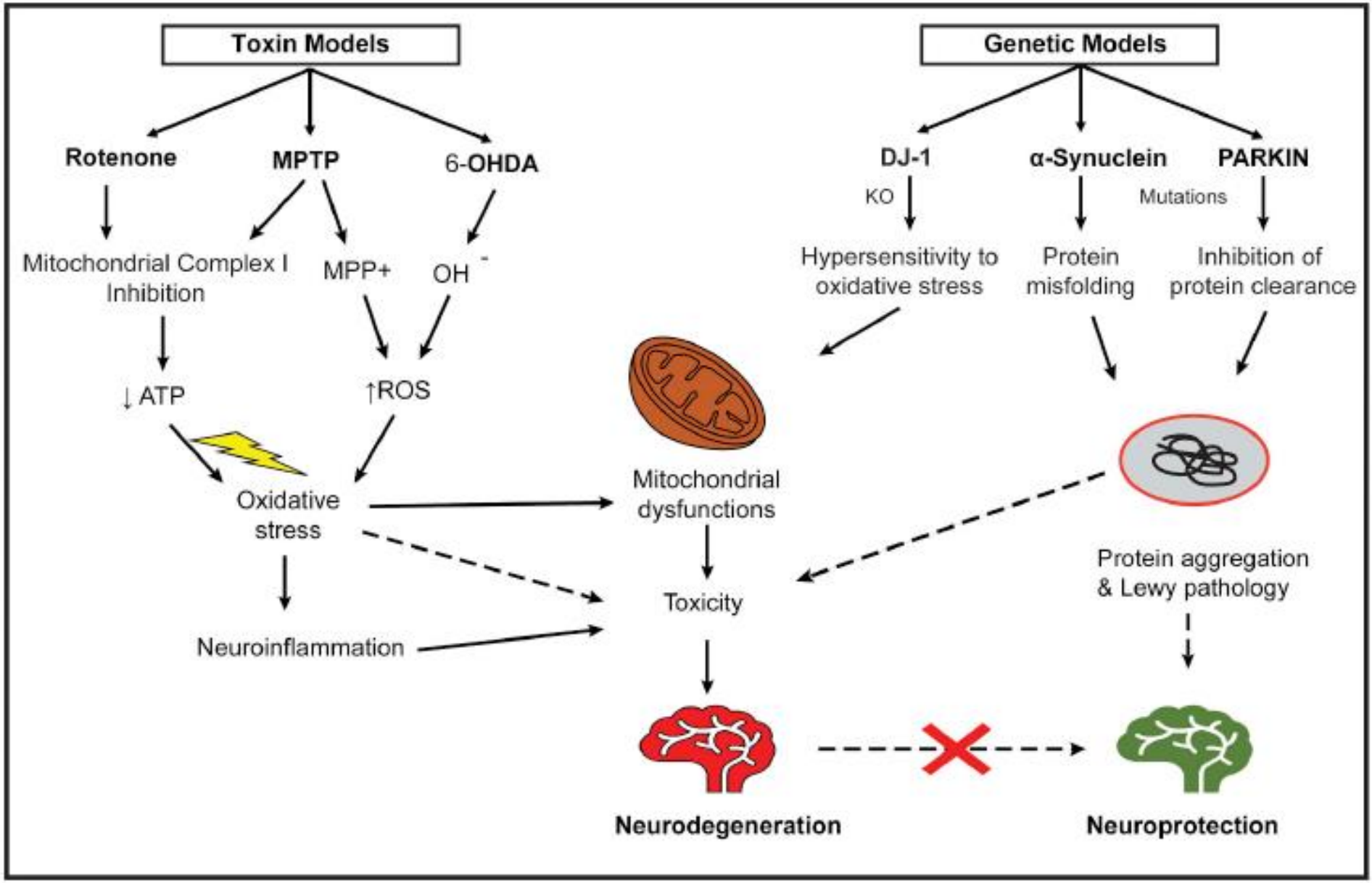
In altre parole, essi sono indispensabili per capire e, possibilmente prevenire e curare le malattie del sistema nervoso centrale e periferico e la patologia neuromuscolare.

- Praticamente tutto ciò che un medico, un veterinario, un farmacista, un’infermiera, un tecnico delle professioni sanitarie, e un paramedico può fare per i malati è stato reso possibile con la ricerca animale

Modelli Animali di Malattia di Parkinson (PD)

Tossine, reserpina/tetrabenazina – modelli di animali modificati geneticamente (esprimenti l'alfa-sinucleina normale o mutata).

Modelli ipermelanergici


Toxin Models
Genetic Models
Rotenone
MPTP
6-OHDA
DJ-1
α-Synuclein
PARKIN
KO
Mutations
Mitochondrial Complex I Inhibition
MPP+
OH -
Hypersensitivity to oxidative stress
Protein misfolding
Inhibition of protein clearance
↓ ATP
↑ROS
Oxidative stress
Mitochondrial dysfunctions
Toxicity
Protein aggregation & Lewy pathology
Neuroinflammation
Neurodegeneration
Neuroprotection

CI SONO SOSTANZE IN GRADO DI CAUSARE UNA DEGENERAZIONE PIU' O MENO SELETTIVA DELLE CELLULE DOPAMINERGICHE CHE VENGONO ANCHE USATE PER PRODURRE MODELLI DI PD

MPTP-MPP+

Paraquat, Rotenone,

6-idrossidopamina

camptocormico

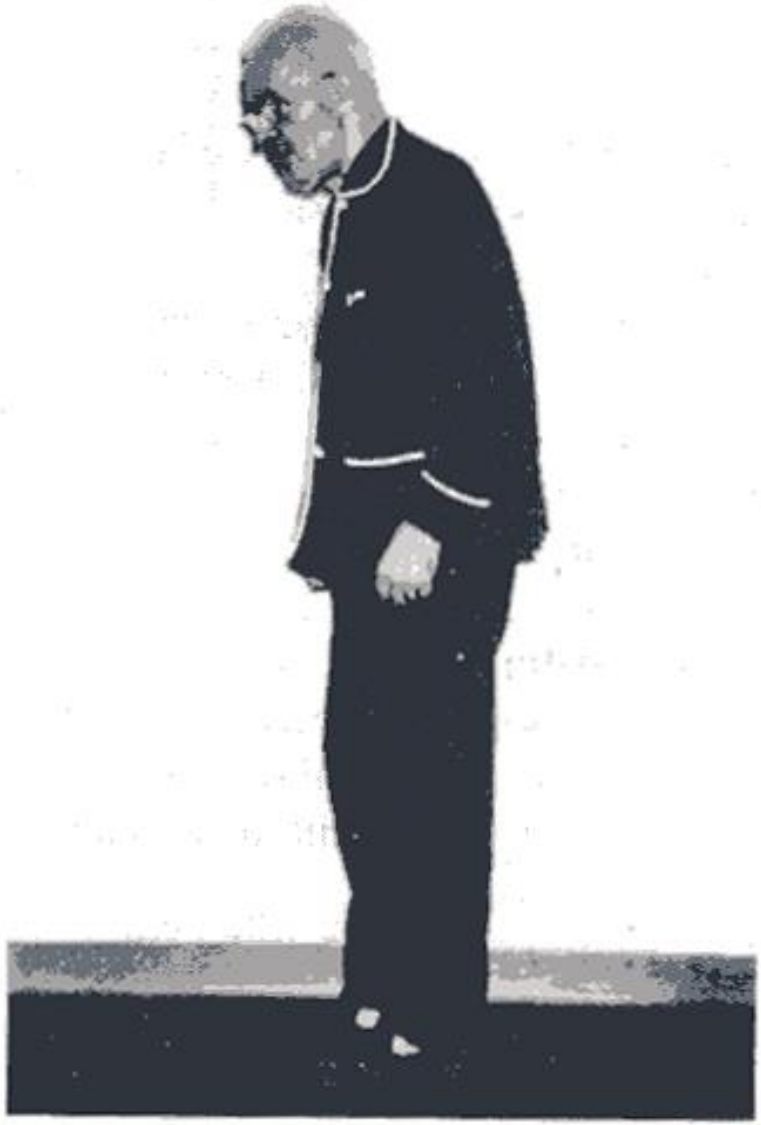


Figura 14.2. *Malattia di Parkinson: atteggiamento generale in flessione.*

Reserpina

Figure 4. Rabbits treated with reserpine (5 mg/kg intravenously) before (top) and after DL-DOPA (200 mg/kg intravenously, bottom). From Carlsson (1960). Photo: Tor Magnusson.

Neuroleptics

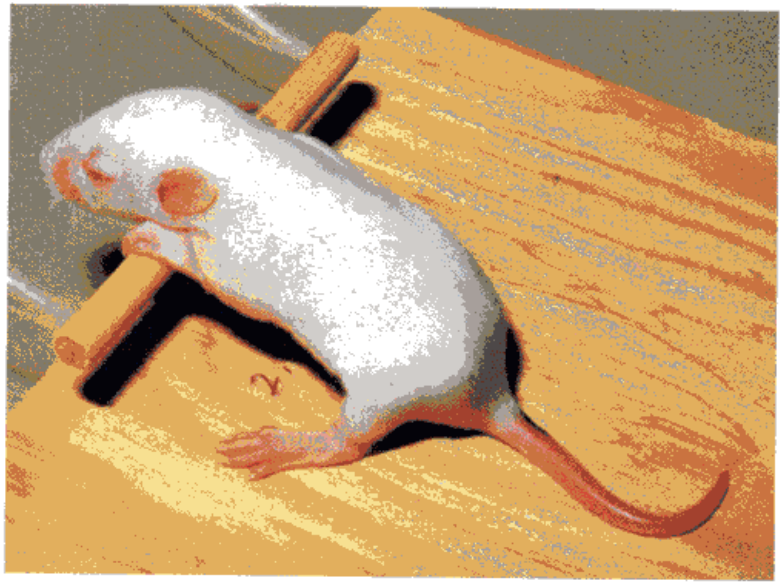
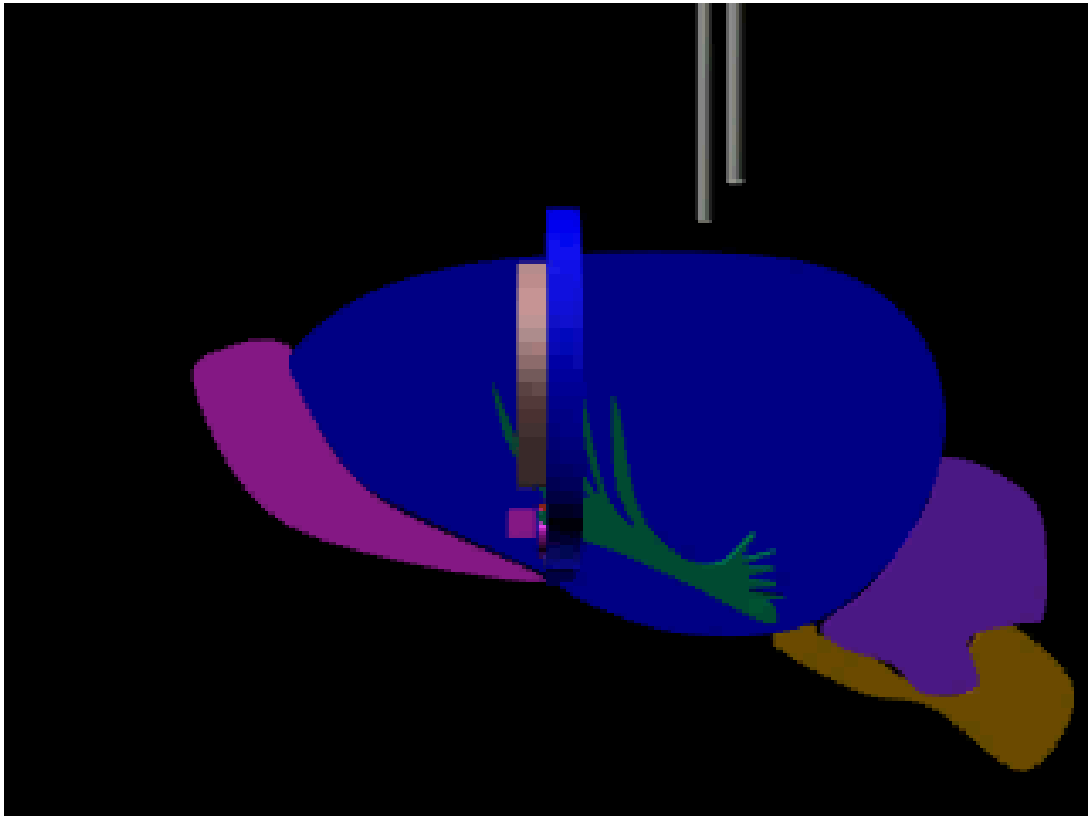


Figure 5.10 Catalepsy can be produced by DA receptor antagonists, particularly drugs that block D_2 receptors. Shown here is a 10-day-old rat pup that had received a subcutaneous injection of the D_2 antagonist haloperidol (1 mg/kg) 1 hour earlier. Pups treated in this manner often spent an entire 3-minute testing period immobile with their forepaws resting on the elevated bar, whereas control pups not given haloperidol got off the bar within a few seconds. (Photograph by Jerrold Meyer.)

Malattia di Parkinson; modello di lesione da 6-idrossi-dopamina



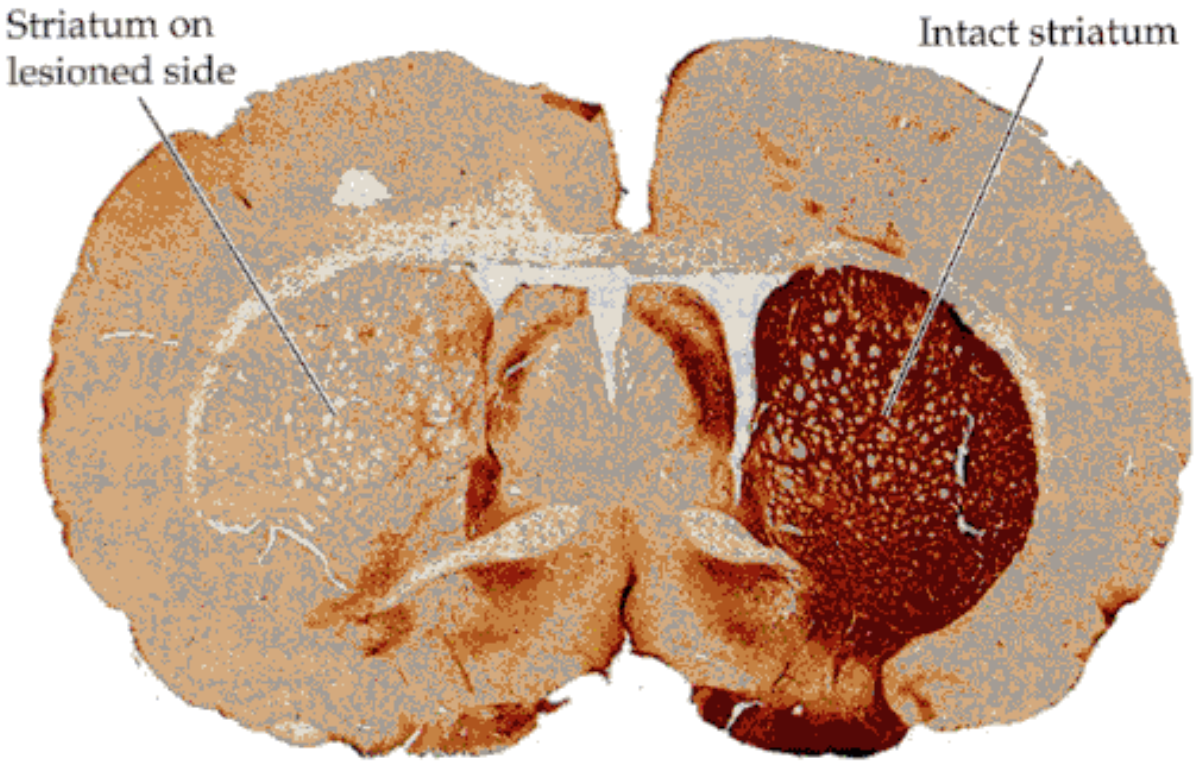


Figure 5.8 Damage to the nigrostriatal pathway on one side of the brain causes degeneration of dopaminergic fibers in the striatum on that side. This is shown in the photomicrograph of a tissue section through the brain of a rat that had received a unilateral 6-OHDA lesion of the medial forebrain bundle, which contains the axons of the nigrostriatal pathway. The section, which was stained using an antibody against tyrosine hydroxylase, depicts the loss of dopaminergic fibers and terminals in the striatum on the side of the lesion. (Photomicrograph courtesy of Michael Zigmond and Annie Cohen.)

Modelli di roditore denervato unilateralmente.

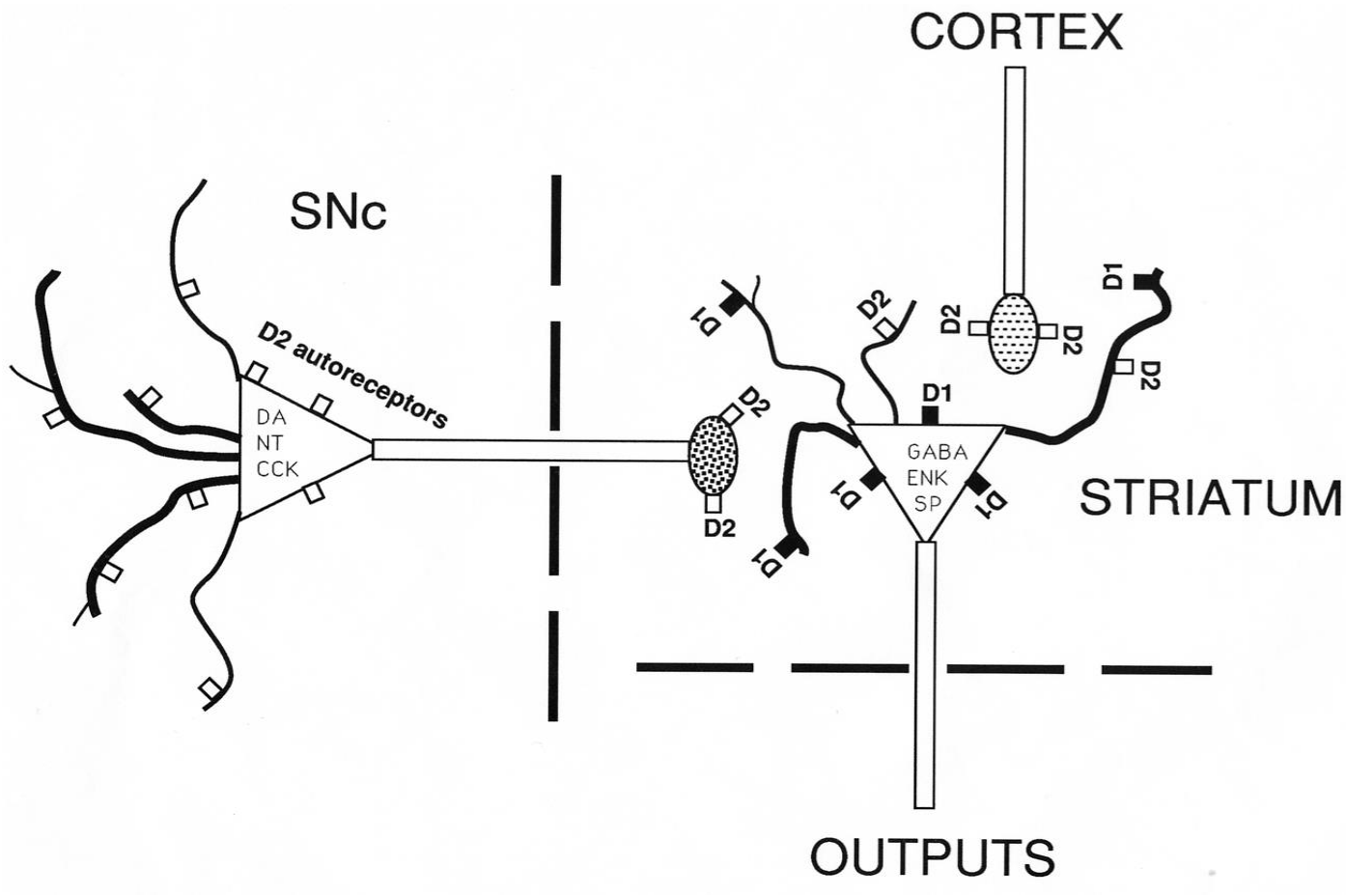
Risposta contraversiva con dopamino agonisti diretti, ipsiversiva per anfetamina e levodopa

Università di Roma Tor Vergata

- We have based our research on the consideration that an investigation of the functioning and dysfunctioning of the dopaminergic cells might be important in the development of preventive and symptomatic therapeutic strategies in Parkinson's disease, and eventually, mood disorders and psychosis.

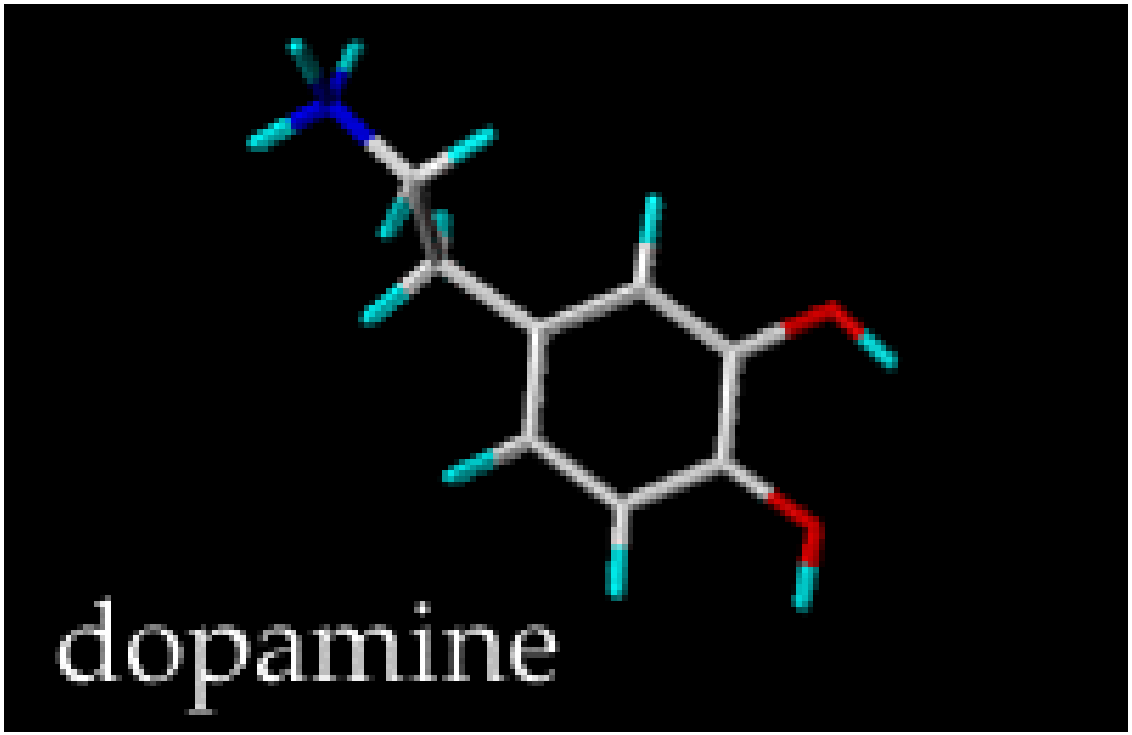
Uno dei nostri principali motivi di ricerca

Our approach is physiological and pharmacological. The **target** is the dopaminergic neuron.

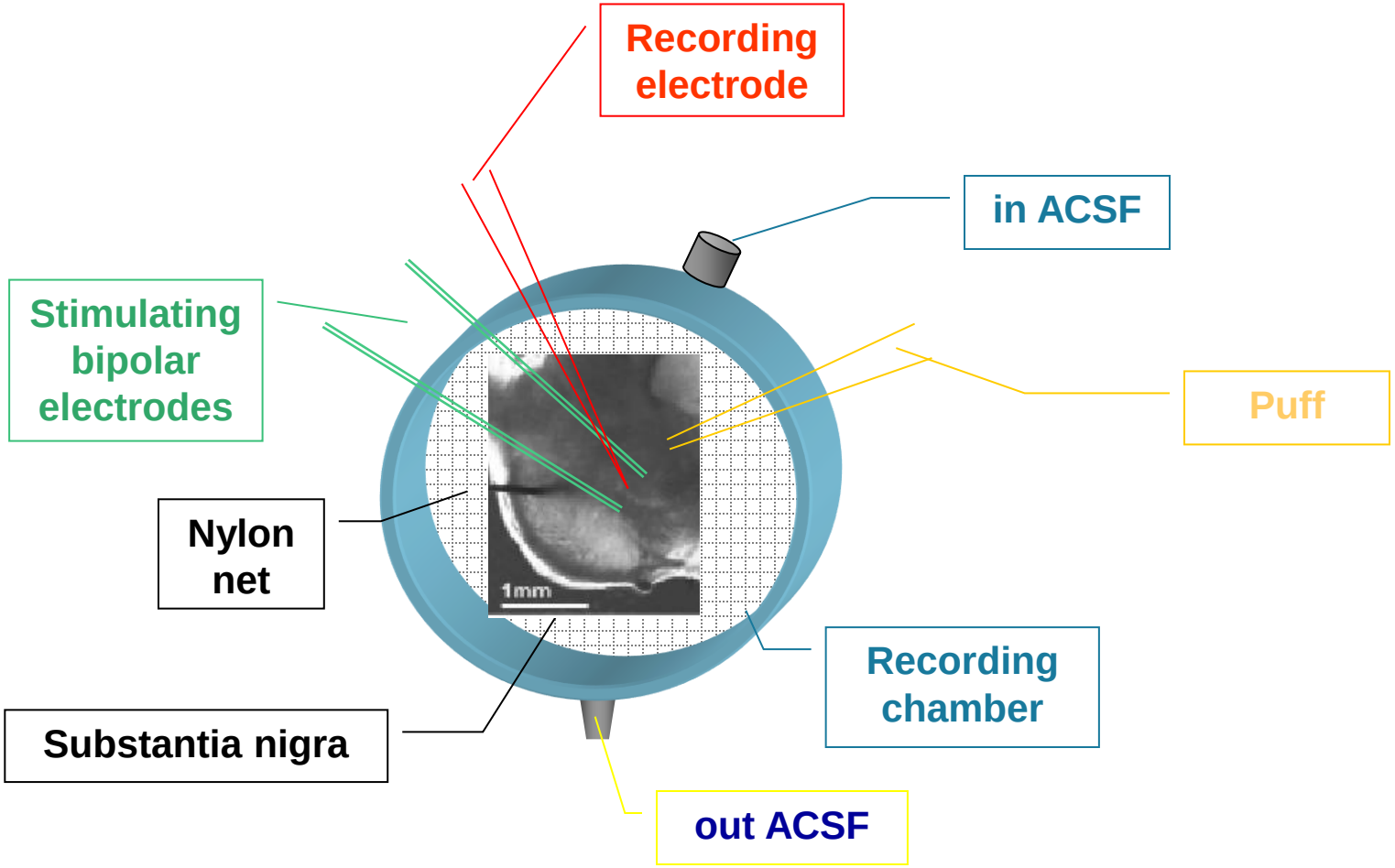


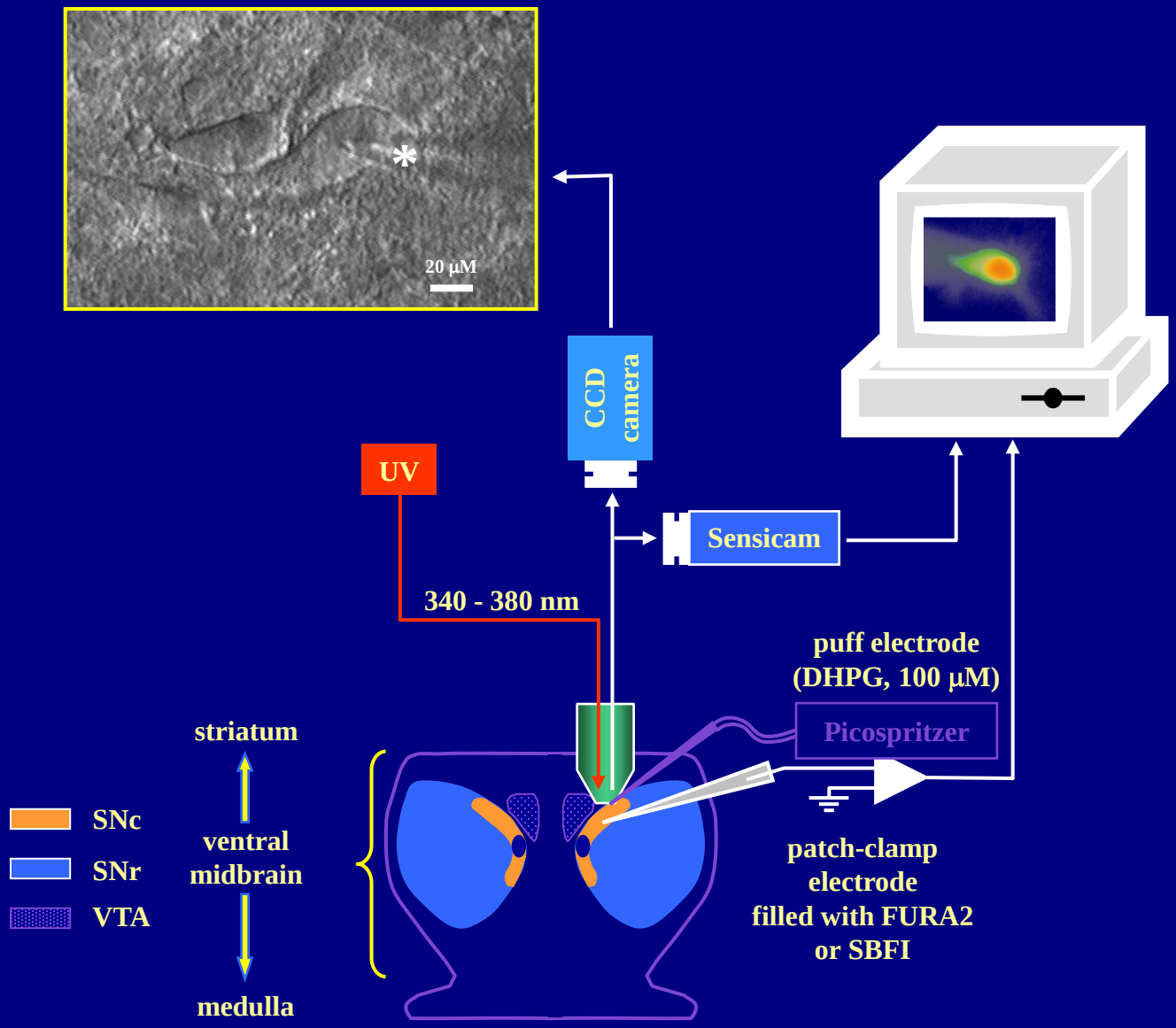
- The dopaminergic cells release DA not only in the terminal fields but also in the ventral midbrain.

  There is a release of DA from dendrites and DA is acting on the dopaminergic neurons by stimulating somato-dendritic autoreceptors.


dopamine

Scheme of the midbrain slice preparation in the chamber for electrophysiological recordings

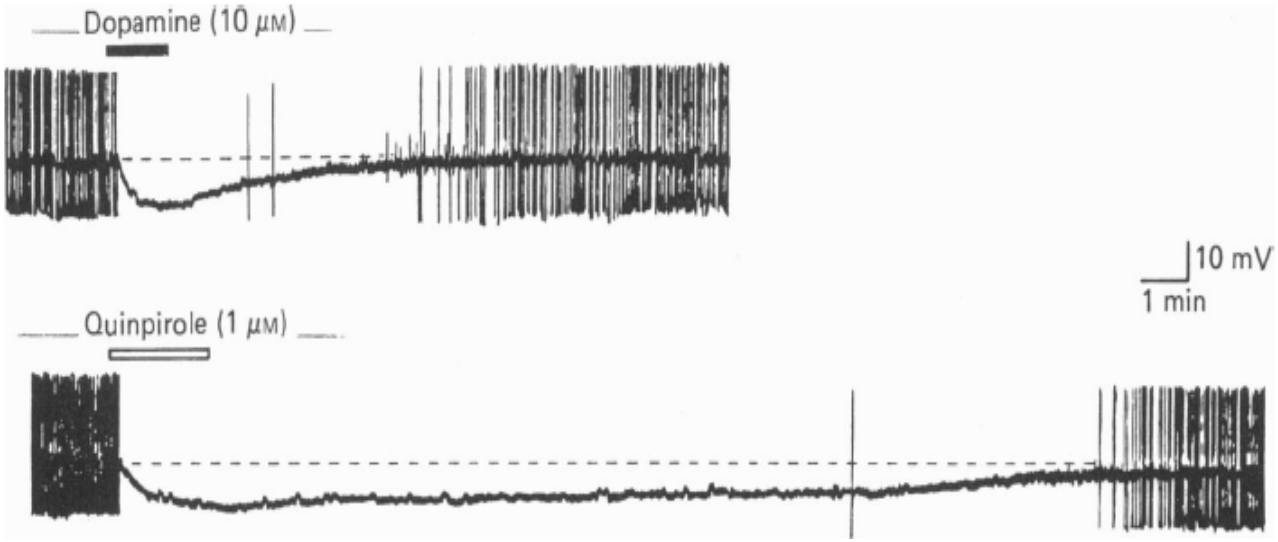



20 µM
CCD camera
UV
Sensicam
340 - 380 nm
puff electrode
(DHPG, 100 µM)
Picospritzer
striatum
ventral
midbrain
medulla
SNc
SNr
VTA
patch-clamp
electrode
filled with FURA2
or SBFI

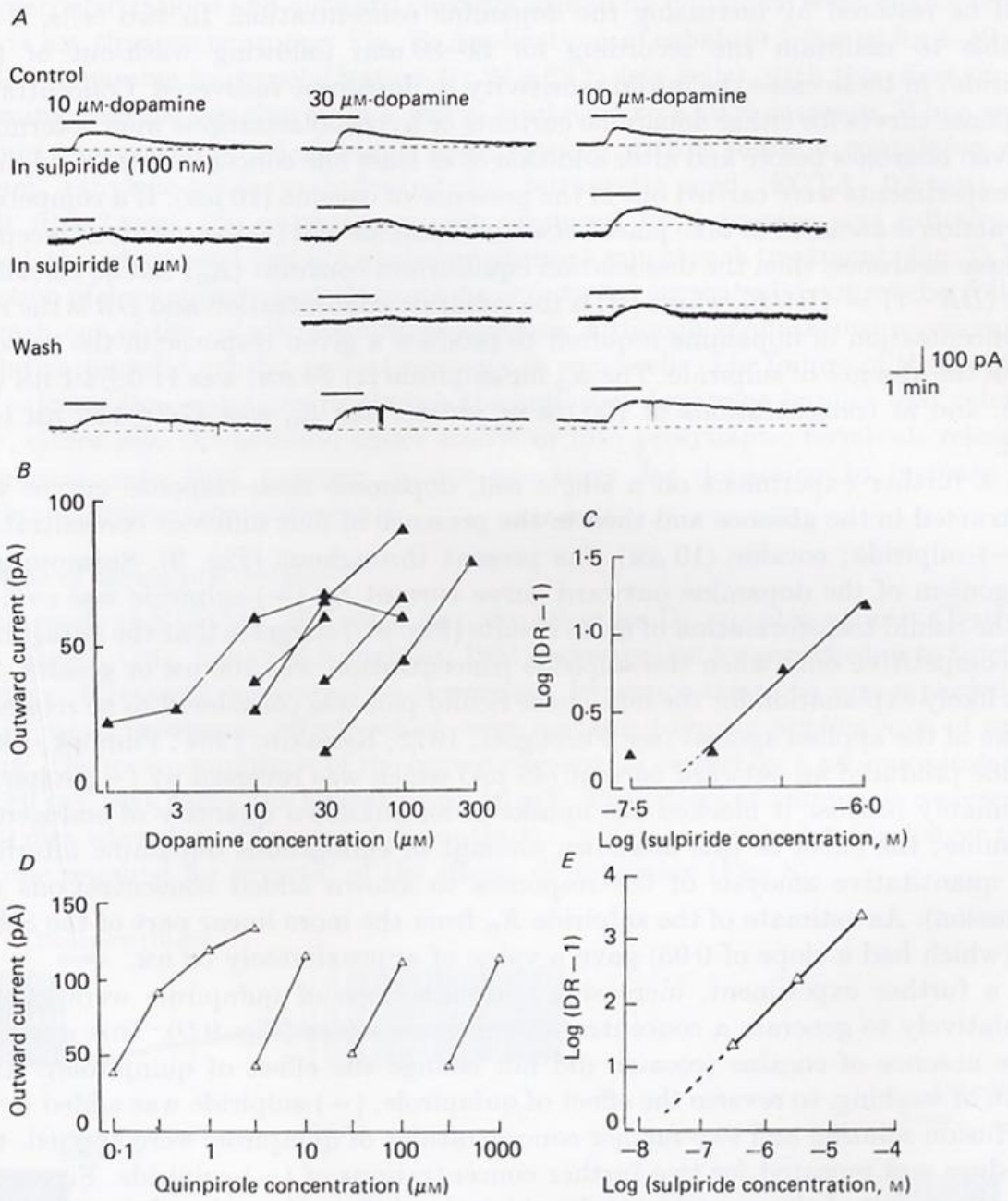
What are the functions of the somato-dendritic receptors?

These receptors are inhibitory

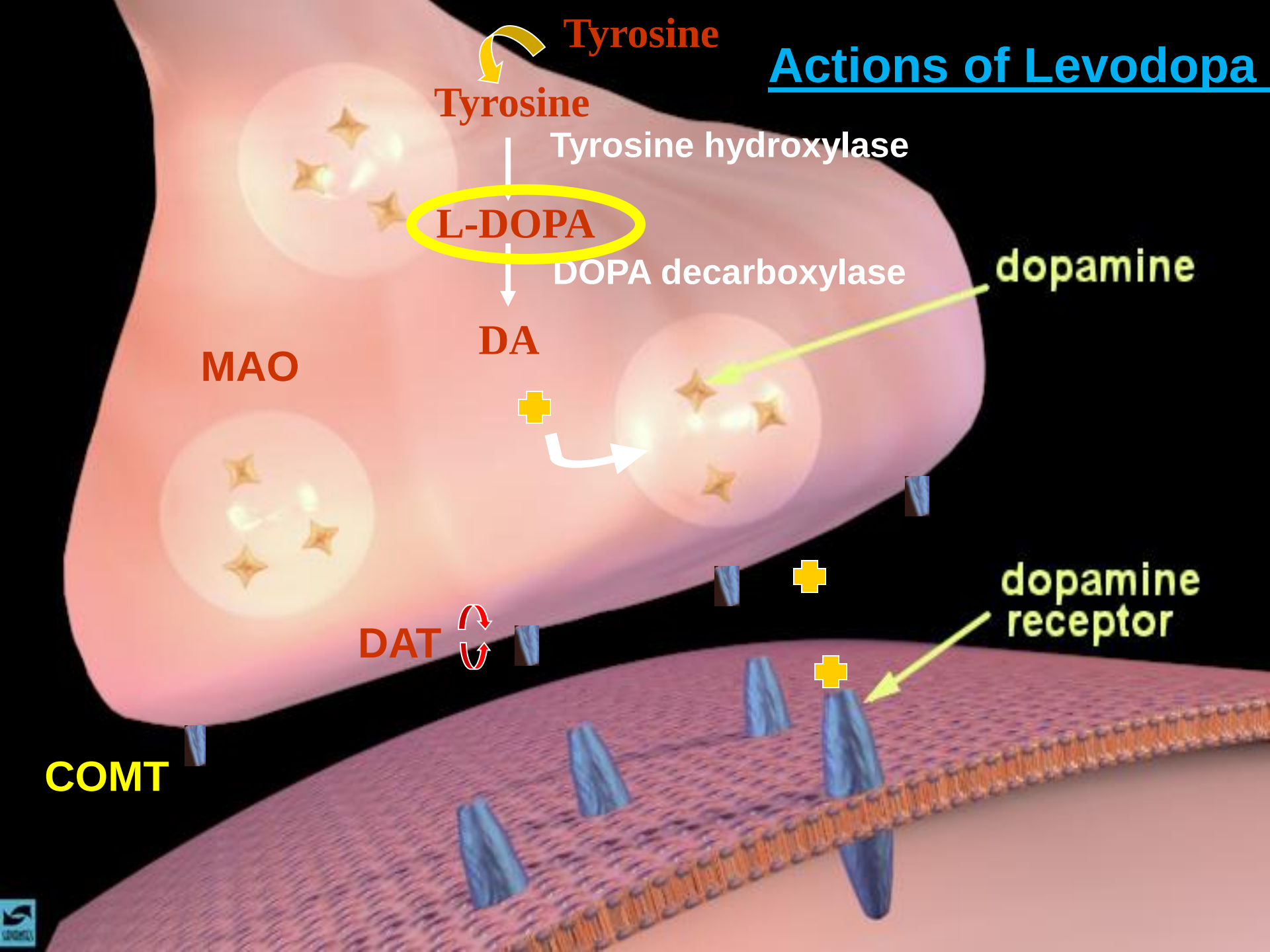
D2 receptor agonist are effective



Lacey, M. G., Mercuri, N. B., & North, R. A. (1987). Dopamine acts on D2 receptors to increase potassium conductance in neurones of the rat substantia nigra zona compacta. *Journal of Physiology, 392*, 397-416.

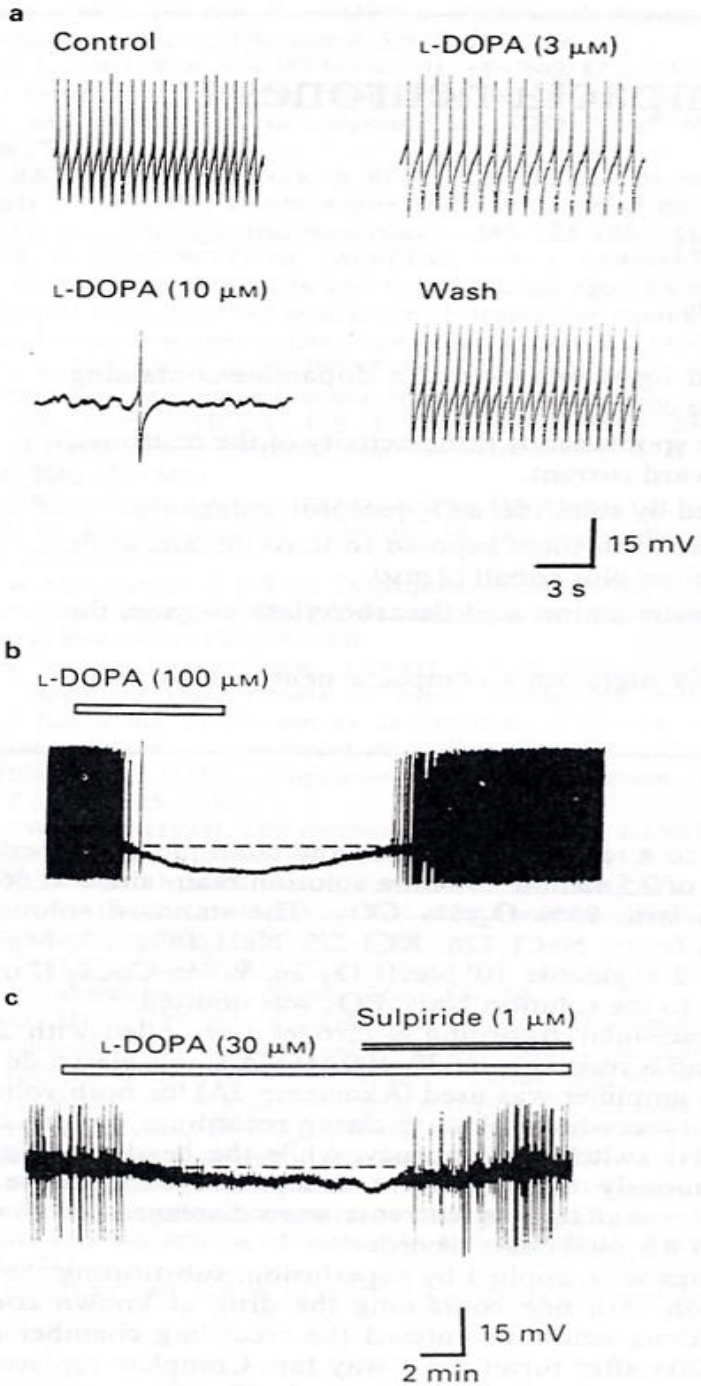

A
Control
10 μM-dopamine
30 μM-dopamine
100 μM-dopamine
In sulpiride (100 nM)
In sulpiride (1 μM)
Wash
100 pA
1 min
B
Outward current (pA)
Dopamine concentration (μM)
C
Log (DR −1)
Log (sulpiride concentration, M)
D
Outward current (pA)
Quinpirole concentration (μM)
E
Log (DR −1)
Log (sulpiride concentration, M)

Actions of Levodopa

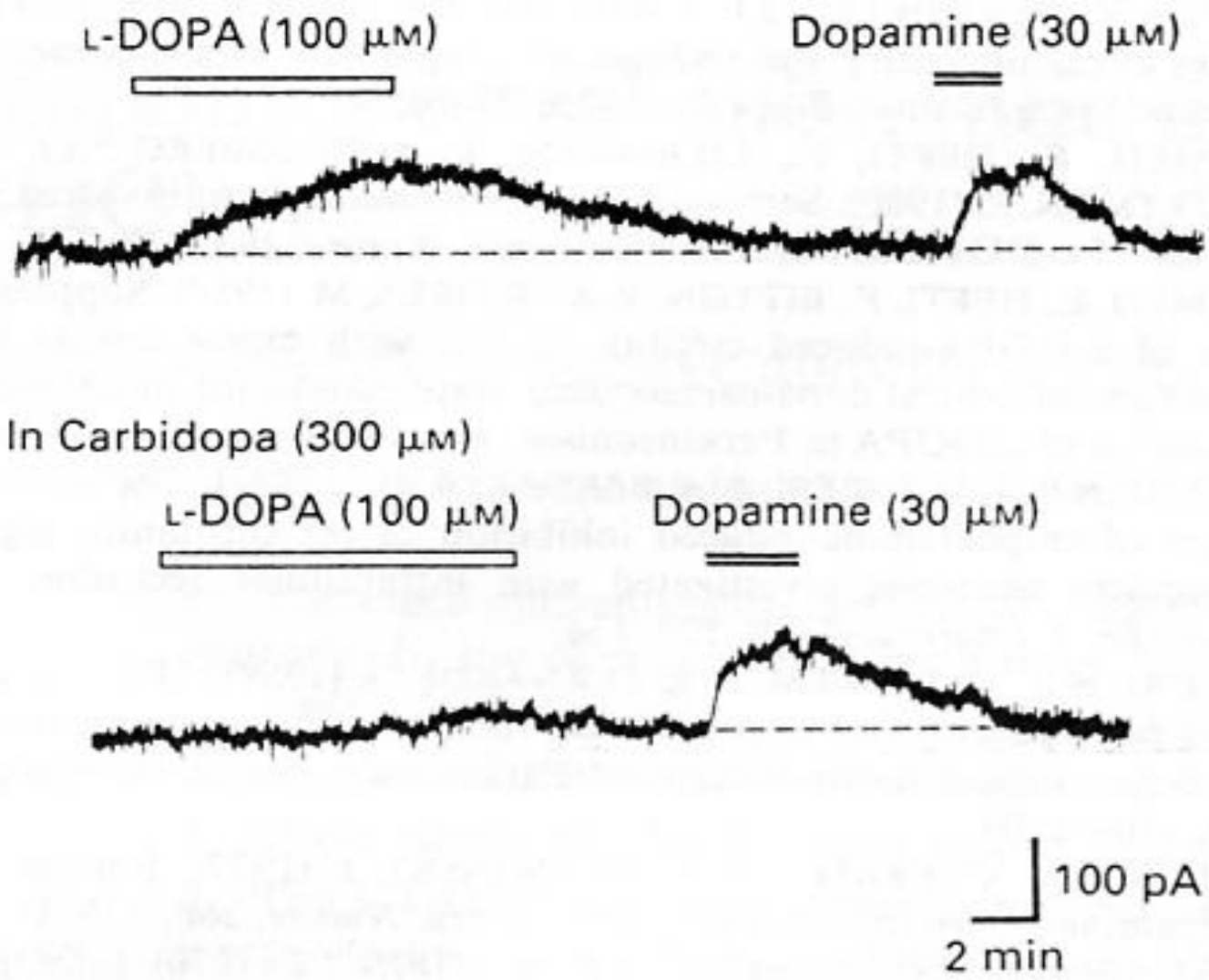


Levodopa

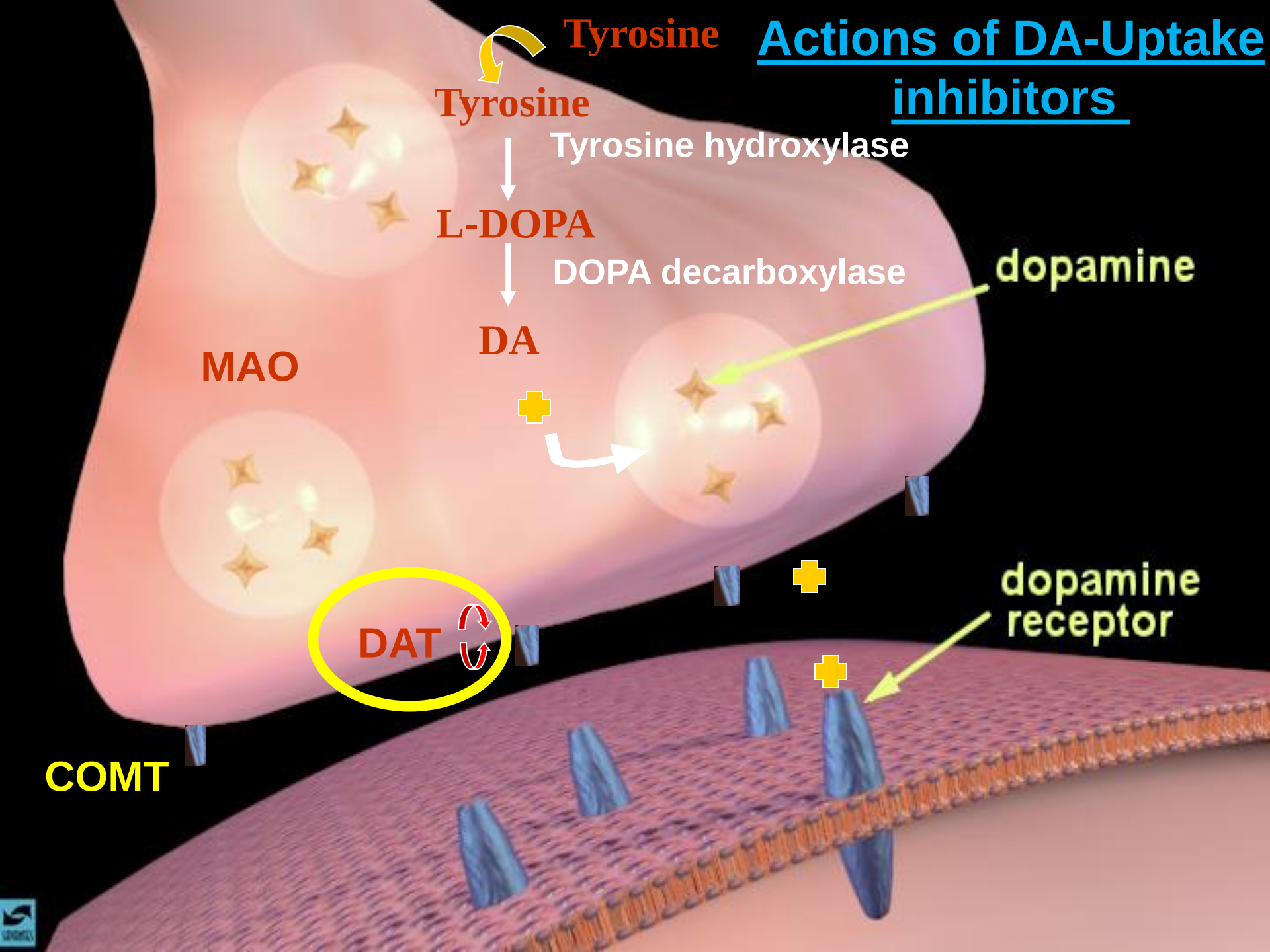
Mercuri NB, Calabresi P, Bernardi G. Responses of rat substantia nigra compacta neurones to L-DOPA. Br J Pharmacol. 1990 100(2):257-60.



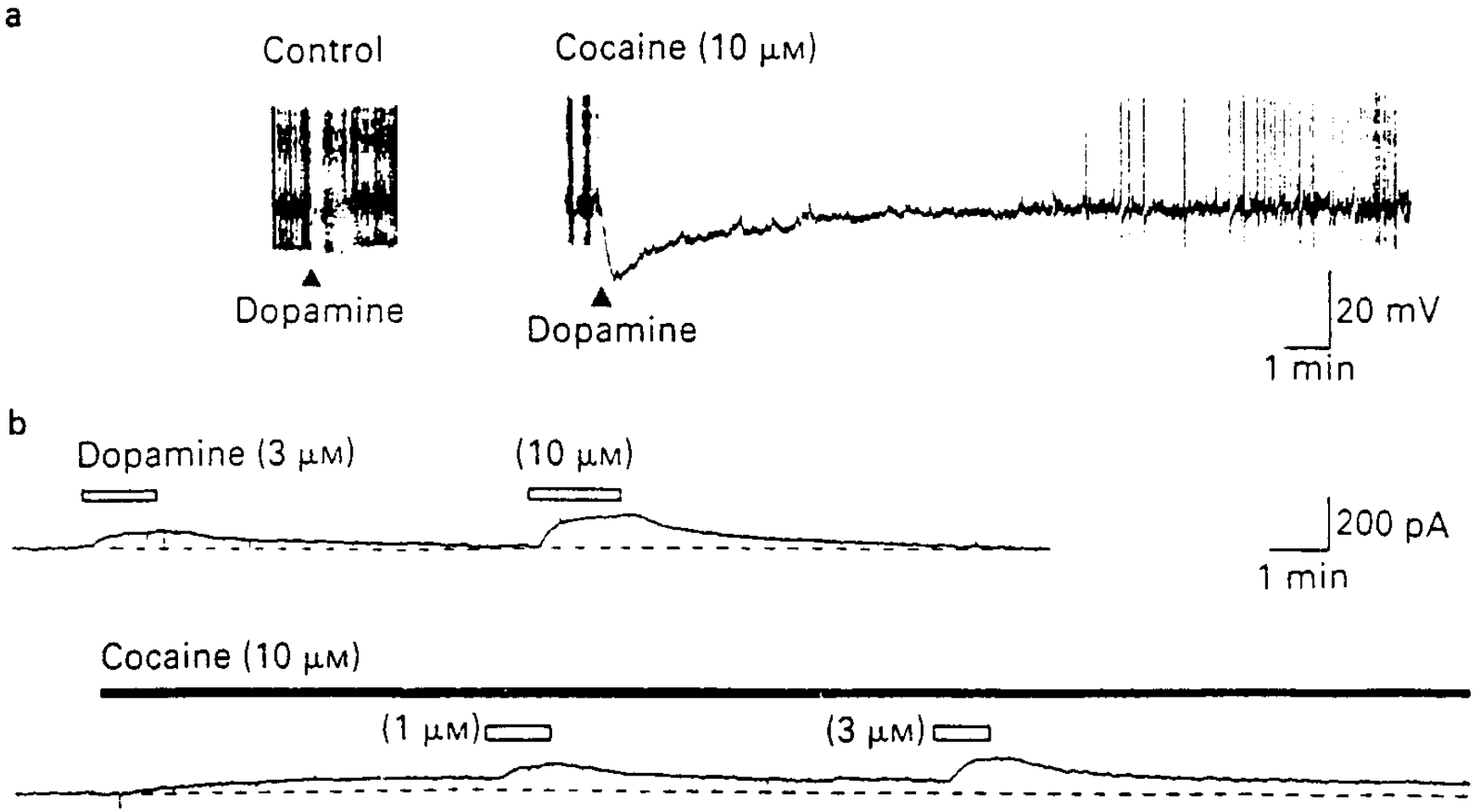
The actions of levodopa are indirect.
They are mediated by its transformation in DA



Actions of DA-Uptake inhibitors



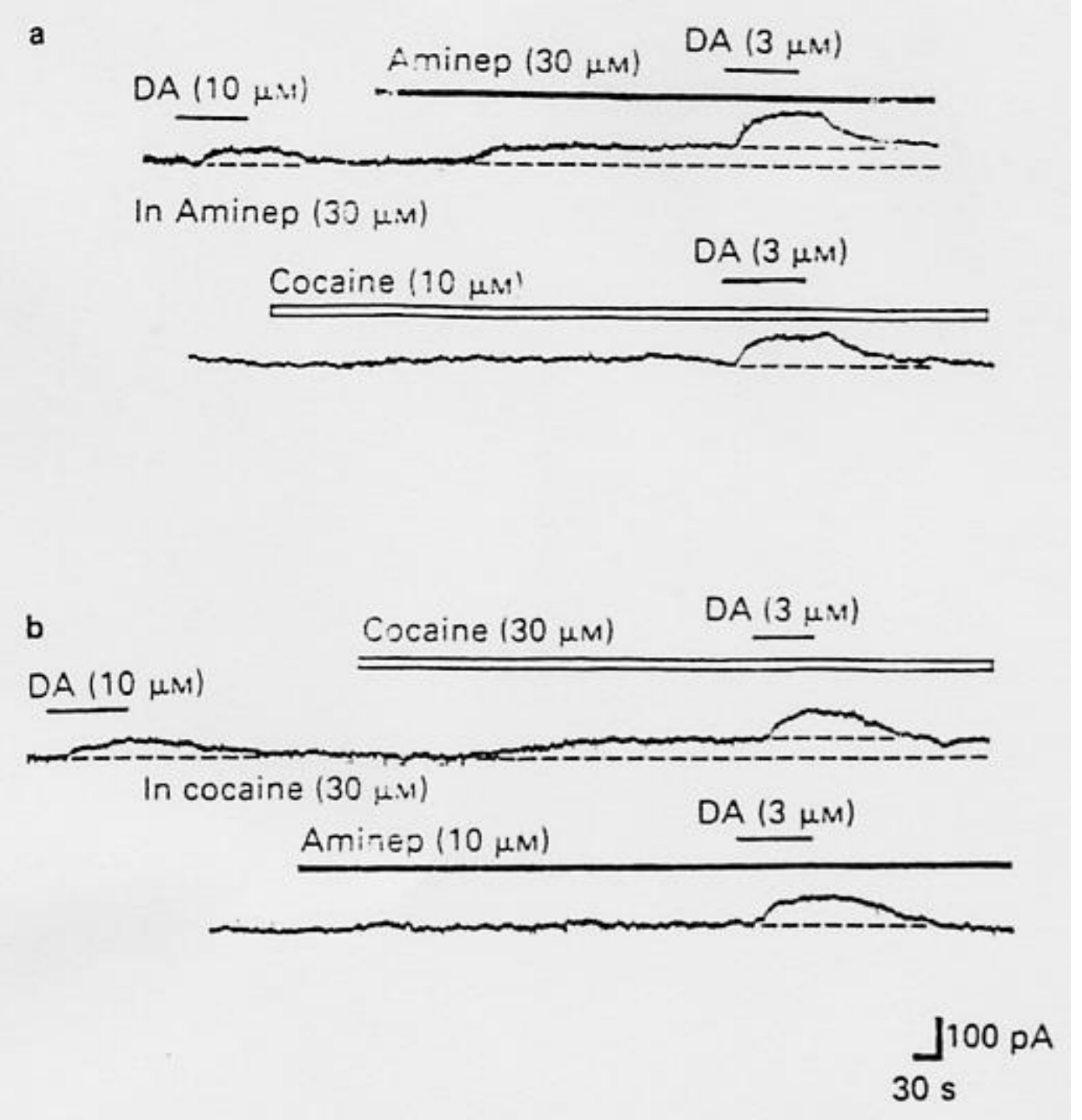
Cocaine



Lacey MG, Mercuri NB, North RA. Actions of cocaine on rat dopaminergic neurones in vitro. Br J Pharmacol. 1990 Apr;99(4):731-5.

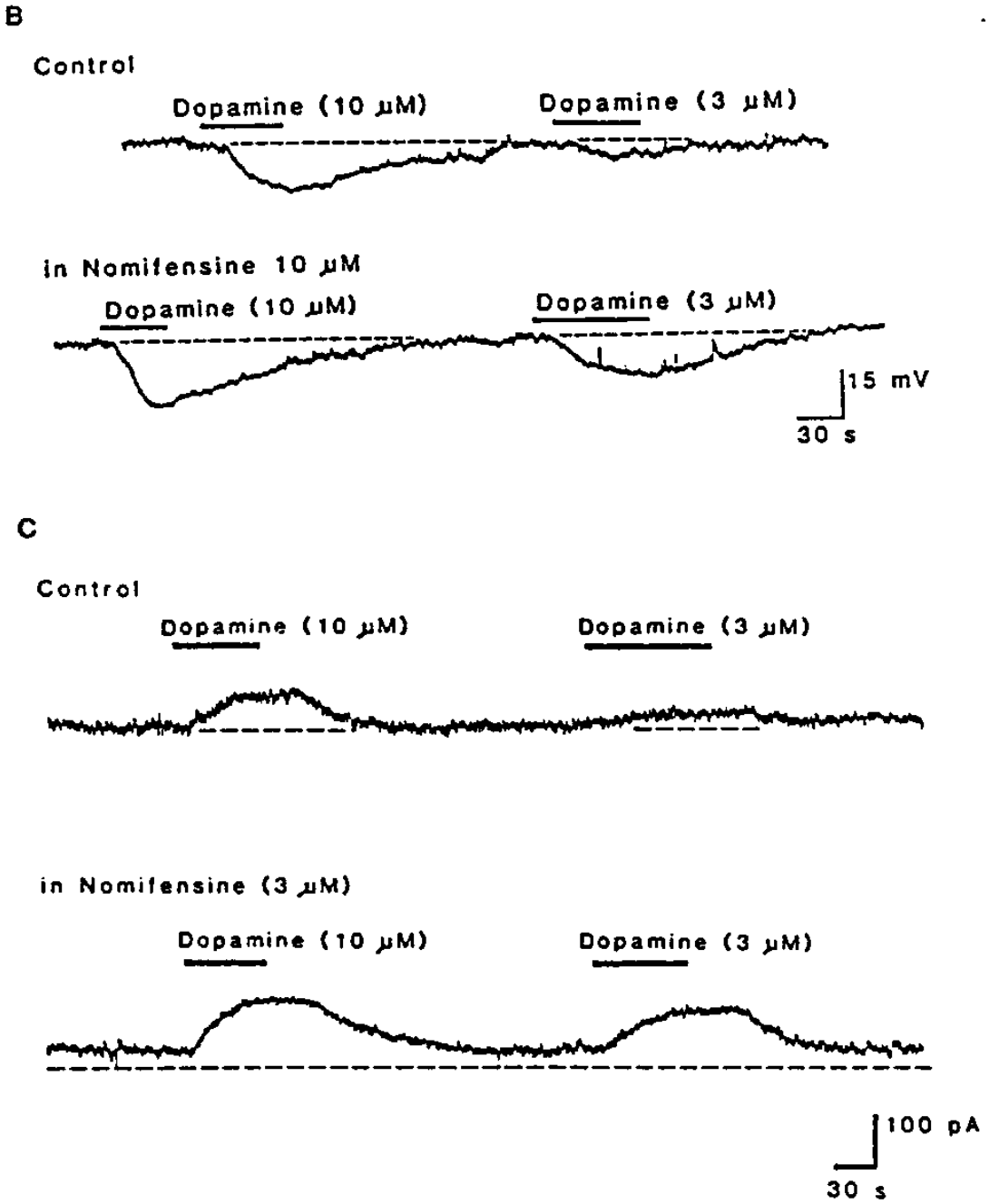
Amineptine and cocaine

Mercuri, et al. *British Journal of Pharmacology* 1991, *104*(3), 700-704



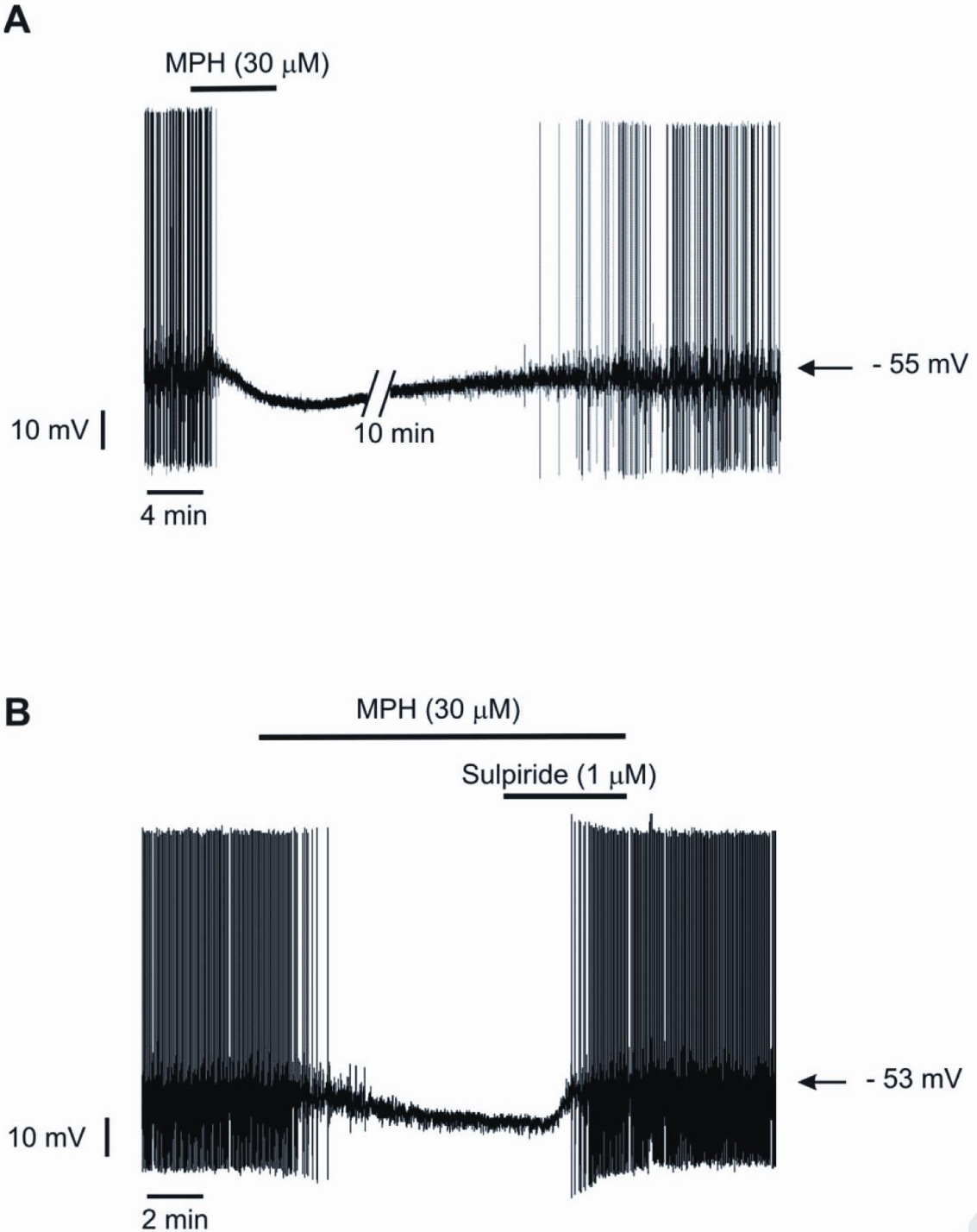
Nomifensine

Mercuri et al., *Neuroscience Letters*, 1991 *131*(2), 145-148.

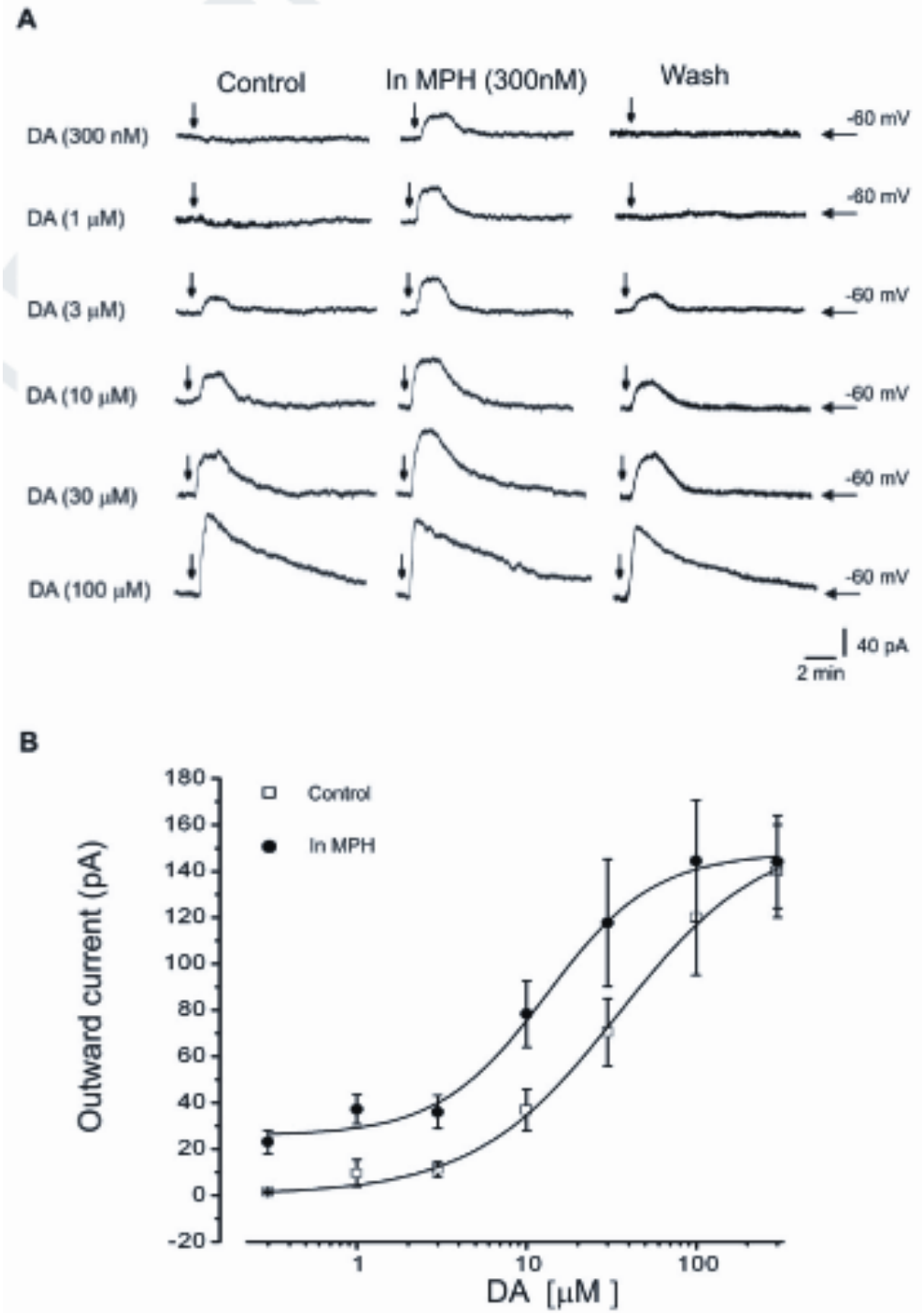


Methylphenidate (MPD)

Federici et al., *Biological Psychiatry, 2005, 57*(4), 361-365.



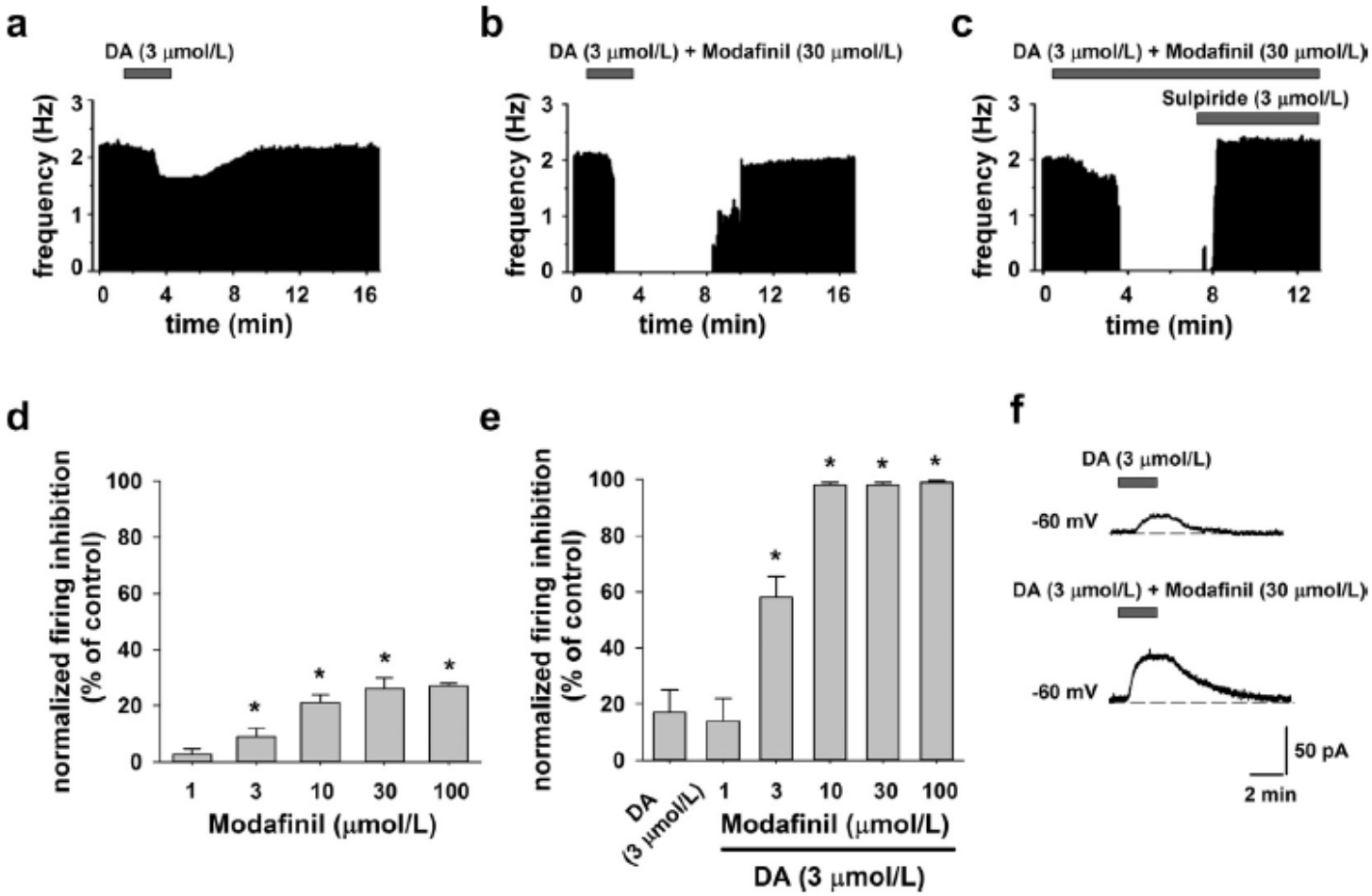
MPD


A
Control
In MPH (300nM)
Wash
DA (300 nM)
DA (1 μM)
DA (3 μM)
DA (10 μM)
DA (30 μM)
DA (100 μM)
-60 mV
40 pA
2 min
B
Control
In MPH
Outward current (pA)
DA [μM]

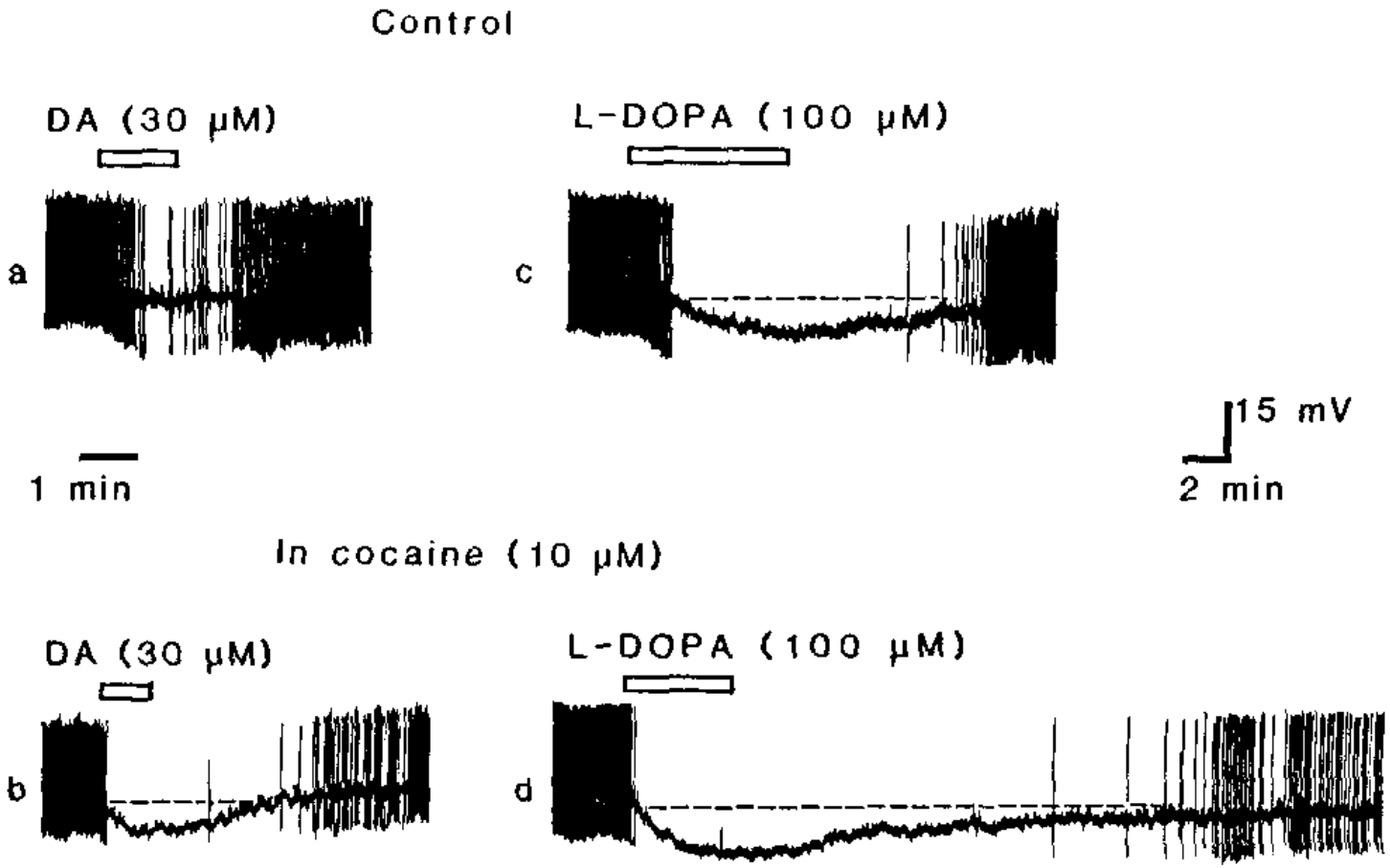
Neuroscience 252 (2013) 118–124

ELECTROPHYSIOLOGICAL AND AMPEROMETRIC EVIDENCE THAT MODAFINIL BLOCKS THE DOPAMINE UPTAKE TRANSPORTER TO INDUCE BEHAVIORAL ACTIVATION

M. FEDERICI,[a] E. C. LATAGLIATA,[a] F. R. RIZZO,[a]
A. LEDONNE,[a] H. H. GU,[b] A. ROMIGI,[c] R. NISTICÒ,[a,d]
S. PUGLISI-ALLEGRA[a,e] AND N. B. MERCURI[a,c*]



DA reuptake blockers and levodopa



Mercuri et al., *Neuroscience Letters,* 1991, *126*(1), 79-82.

Nutt et al., The dopamine transporter: Importance in Parkinson's disease
Annals of Neurology 2004; 55 , 766 – 773

Table 4. Effects of L-Dopa Infusion Rate and Methylphenidate on Percentage of Subjects Responding (N = 14)

		Subjects (%)	
		Placebo	MPD
Tapping (increase >10%)			
L-dopa (mg/kg/hr)	0.5	36	86%
	1.0	86	93
Walking time (decrease >20%)			
L-dopa (mg/kg/hr)	0.5	43	71
	1.0	57	93
Dyskinesia (>0)			
L-dopa (mg/kg/hr)	0.5	43	71
	1.0	93	93

Both experimental results and clinical observations indicate that the residual DAT is functional in PD and is a potential target for therapy.

Neuroscience Letters, 131 (1991) 145–148
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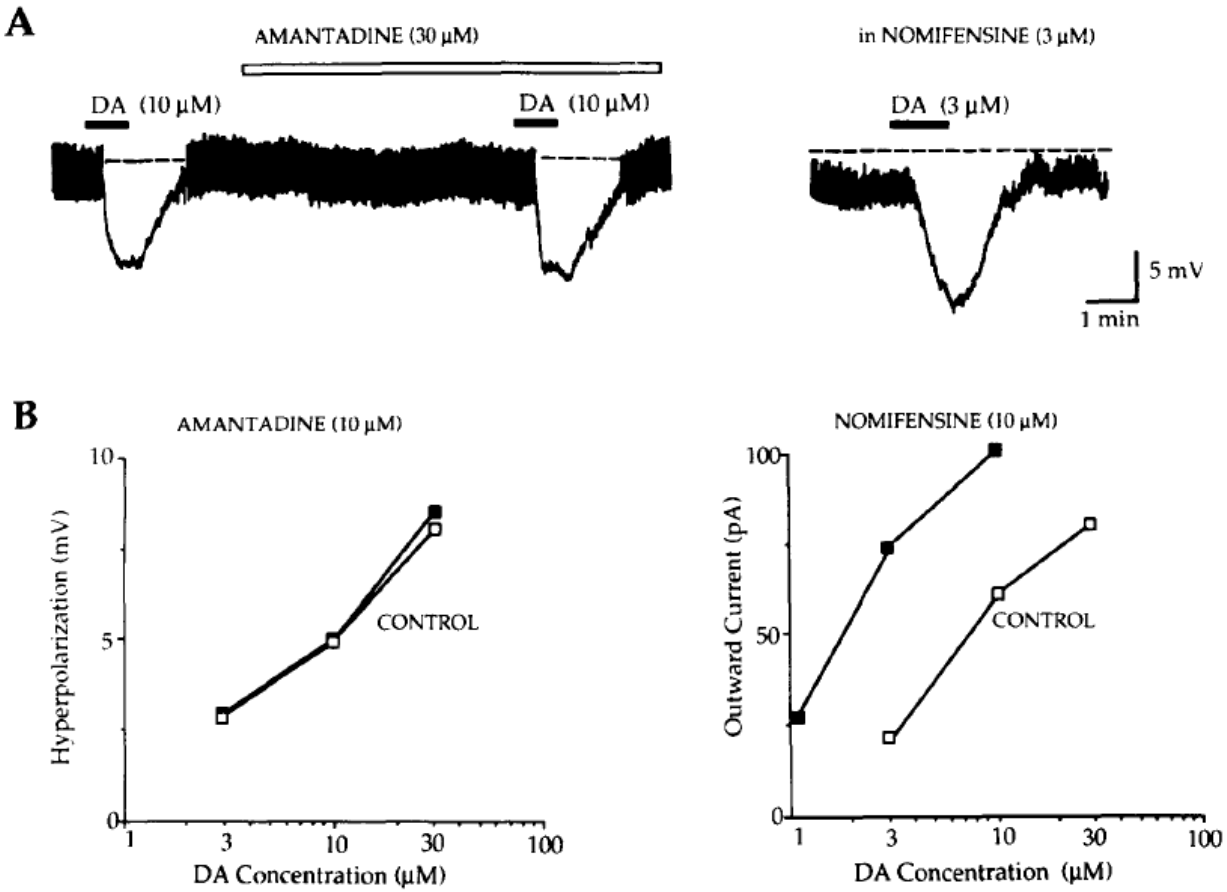
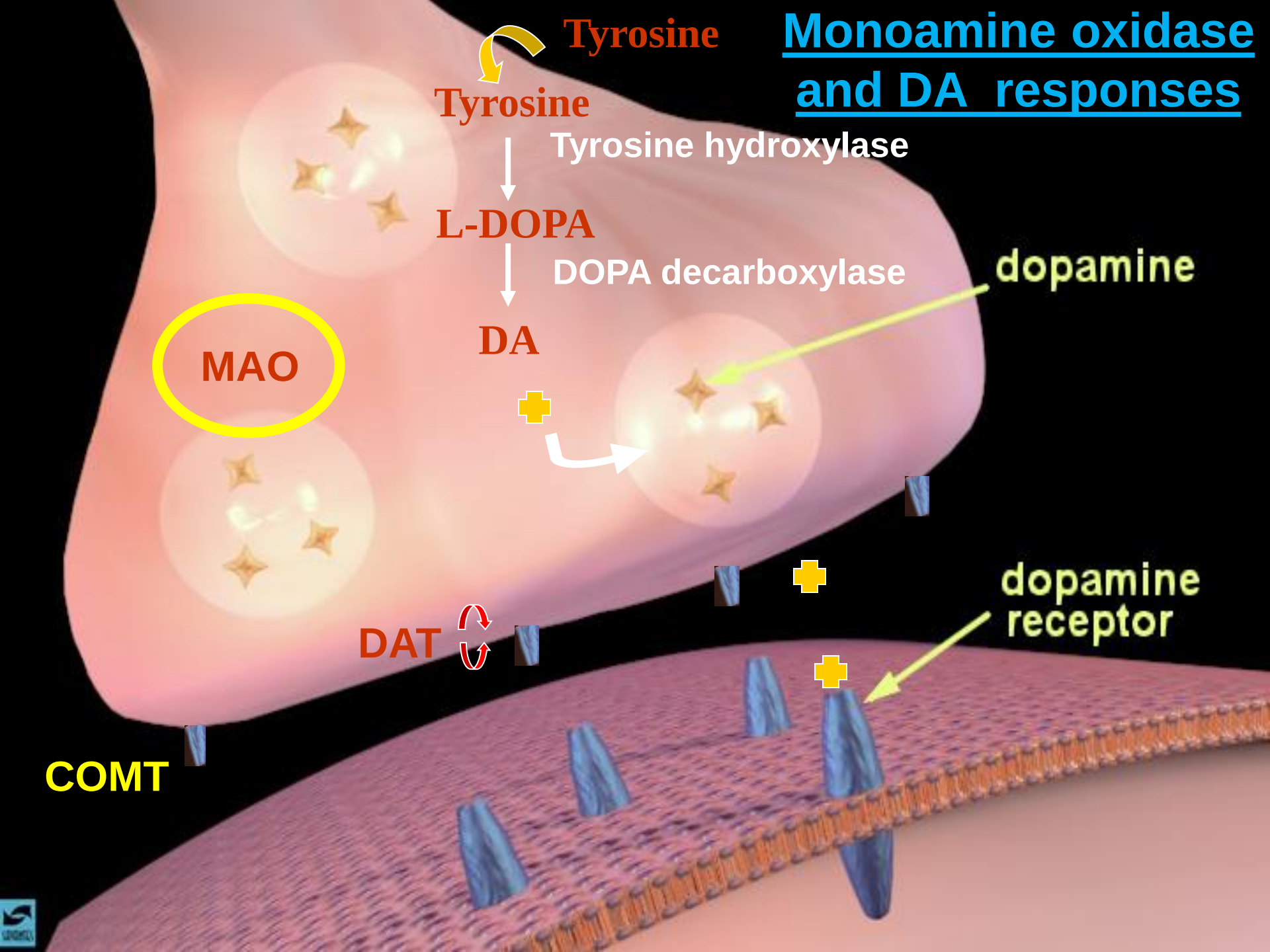
NSL 08078

Nomifensine but not amantadine increases dopamine-induced responses on rat substantia nigra zona compacta neurons

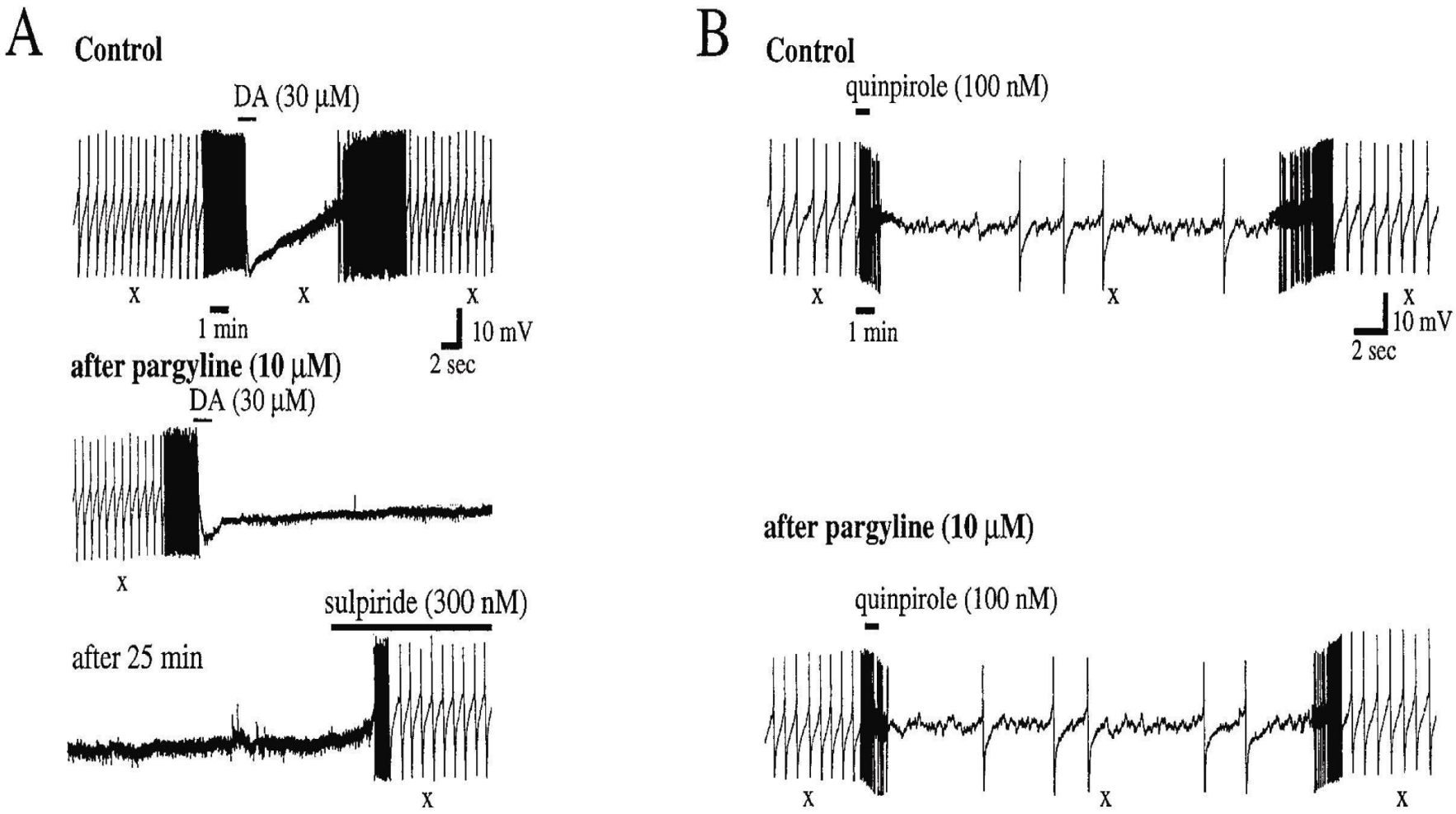
Nicola B. Mercuri, Francesca Stratta, Paolo Calabresi and Giorgio Bernardi



Monoamine oxidase and DA responses

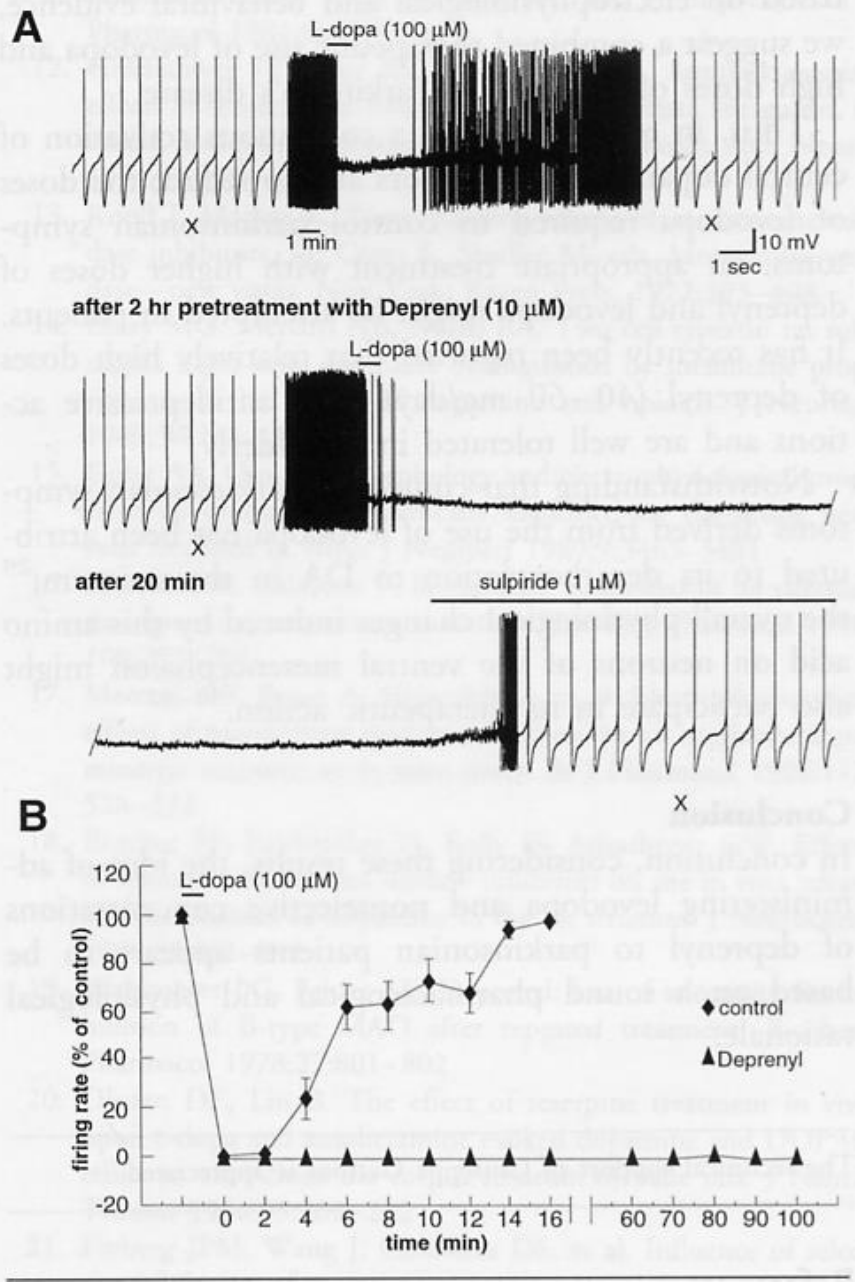


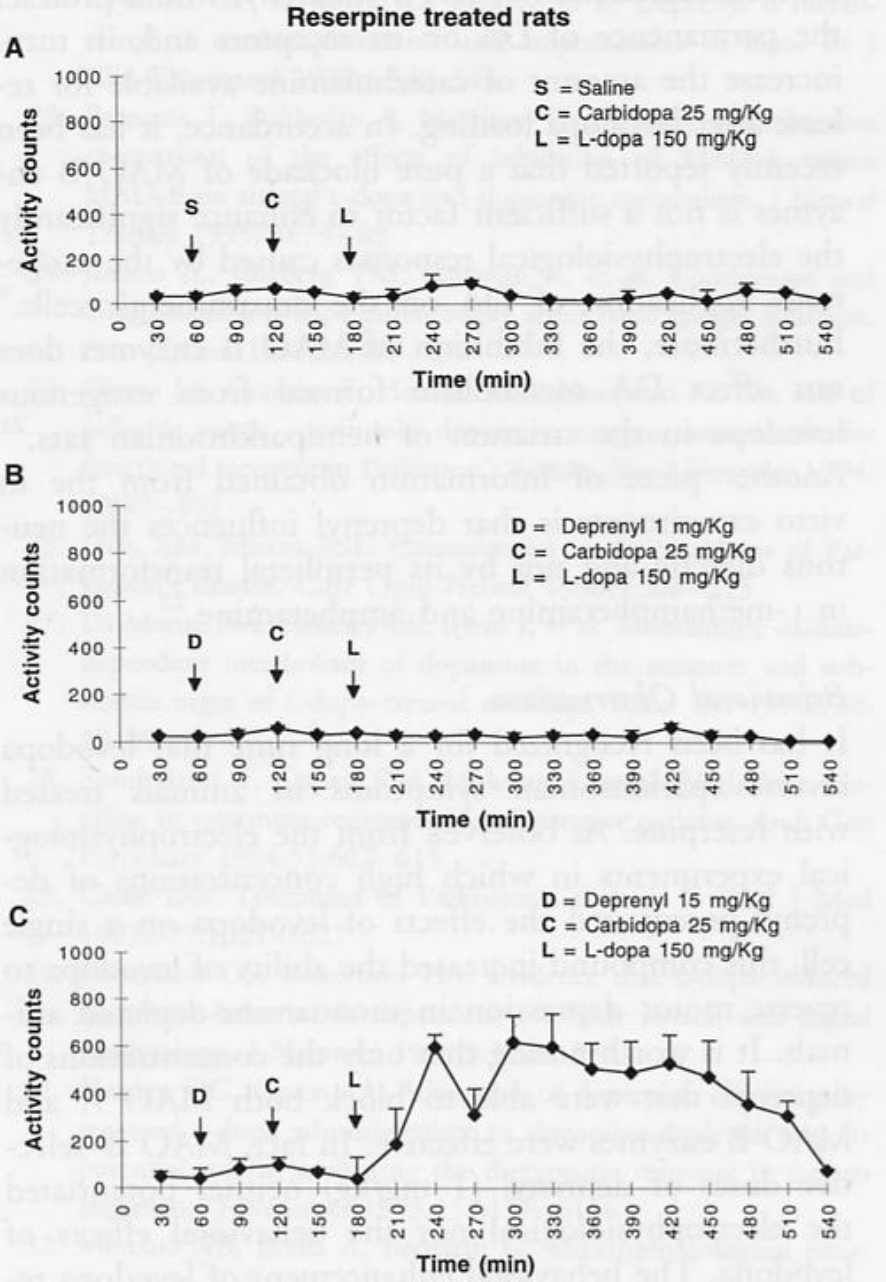
Mercuri et al., Monoamine oxidase inhibition causes a long-term prolongation of the dopamine-induced responses in rat midbrain dopaminergic cells.
J Neurosci. 1997;1 7(7):2267-72.



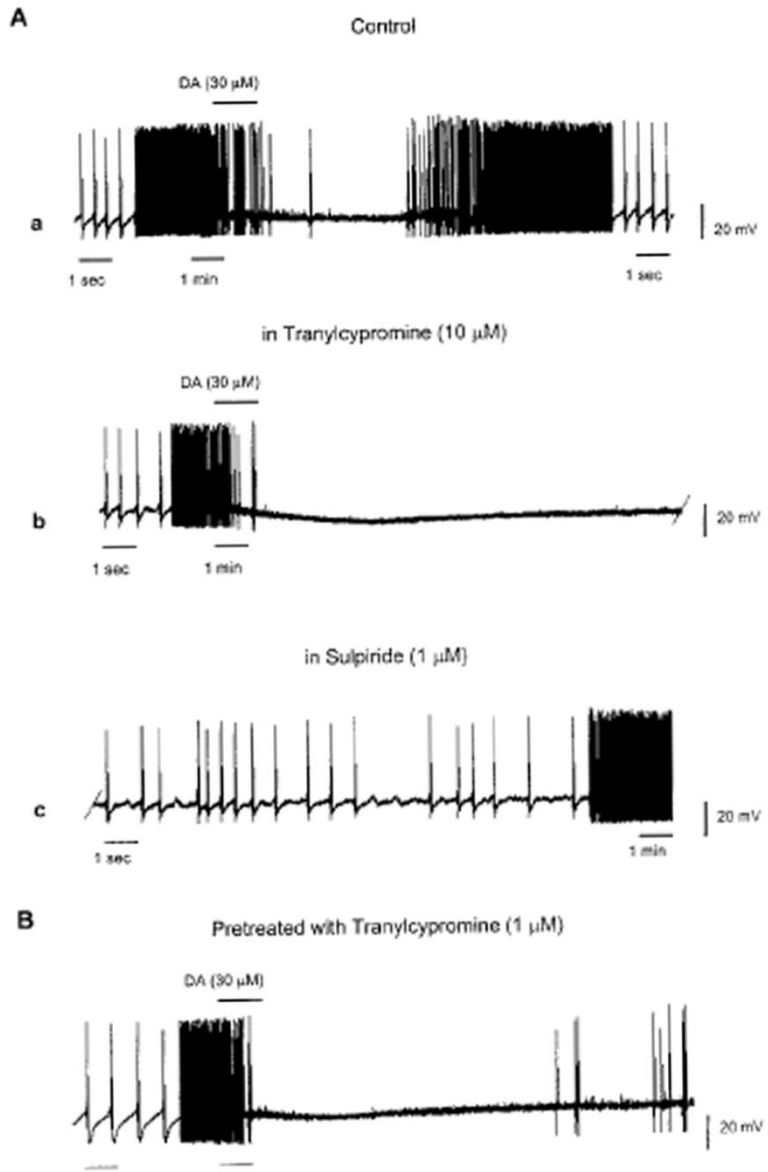
Selegiline

Mercuri et al., Ann. Neurol. 1998; 43: 613-617.

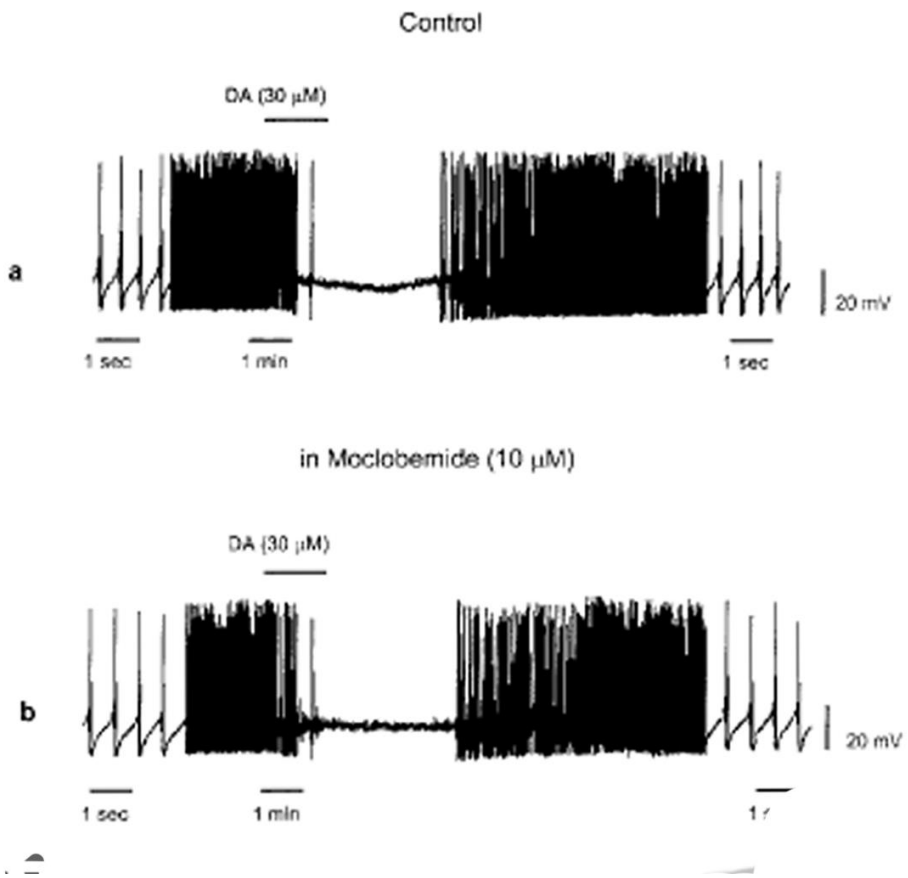




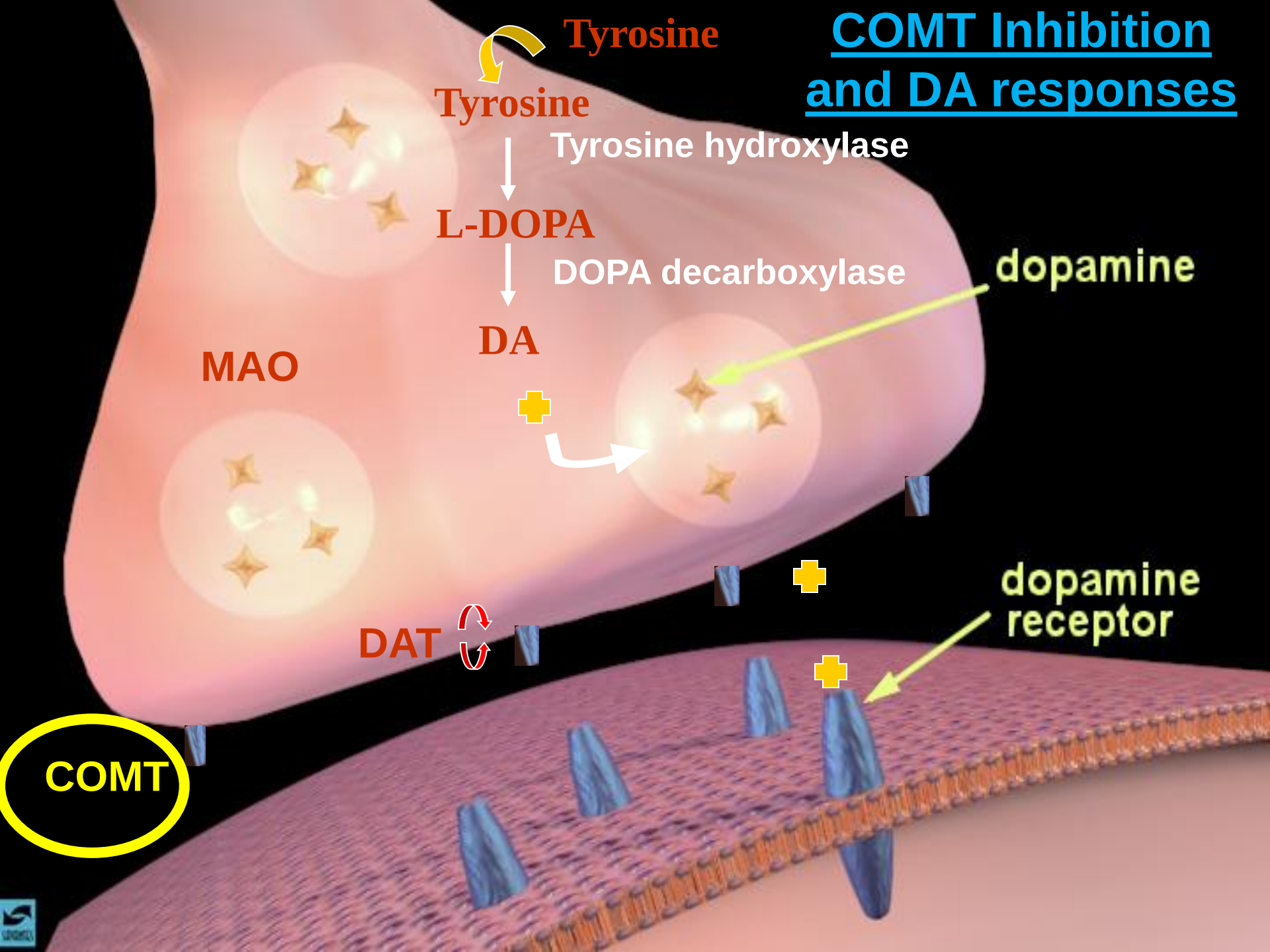
Mercuri et al., 2000. Tranylcypromine, but not moclobemide, prolongs the inhibitory action of dopamine on midbrain dopaminergic neurons: an in vitro electrophysiological study. Synapse 37:216-21.



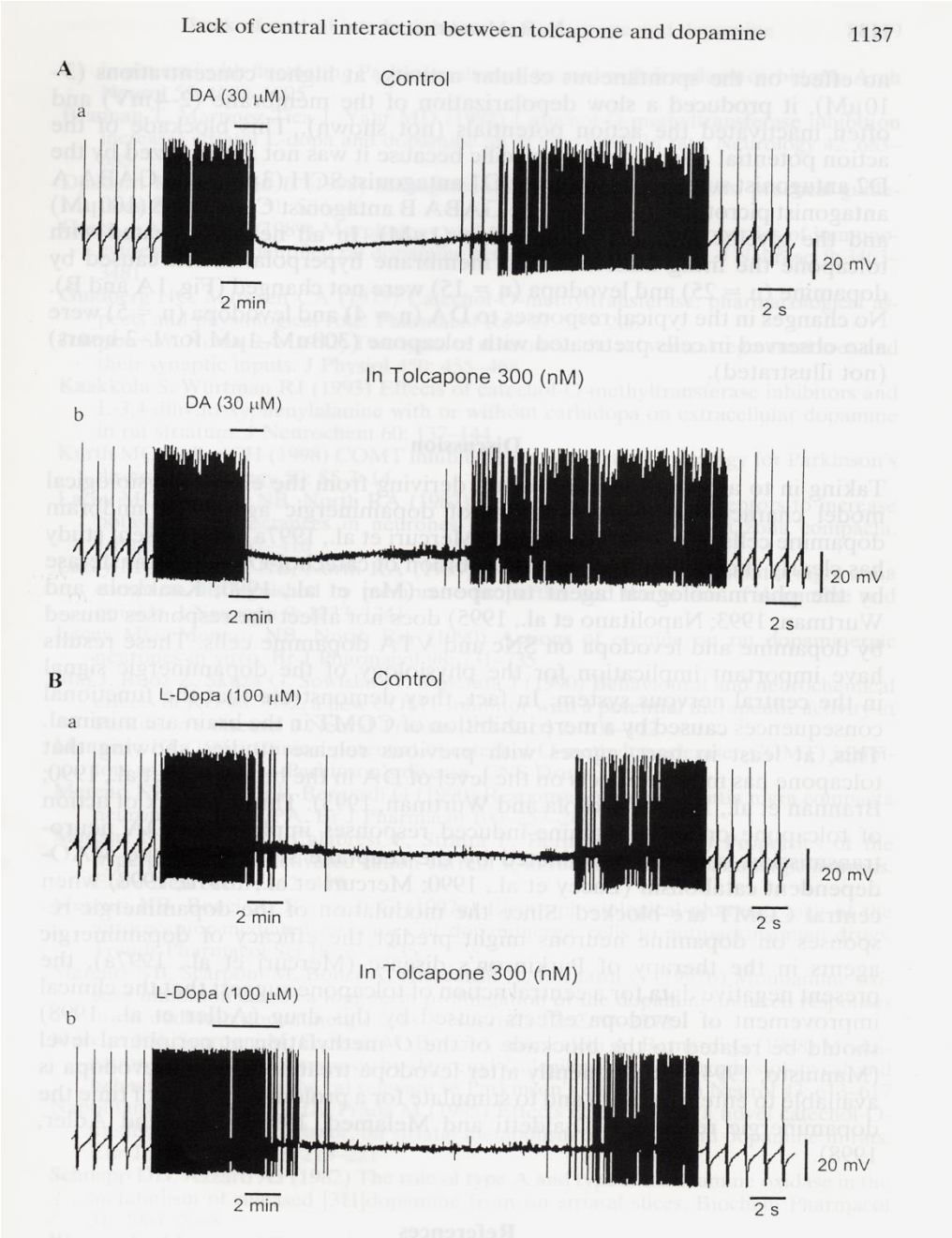
MAO A e B azione combinata



COMT Inhibition and DA responses

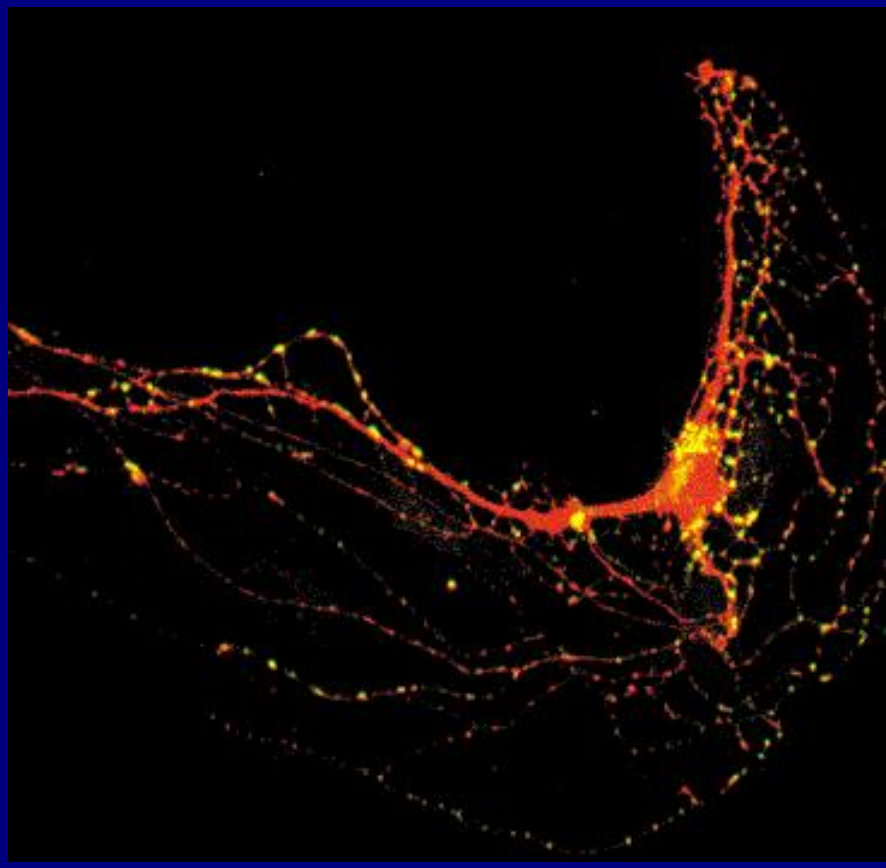


Mercuri et al.,. J Neural Transm. 1999;106, 1135-40.



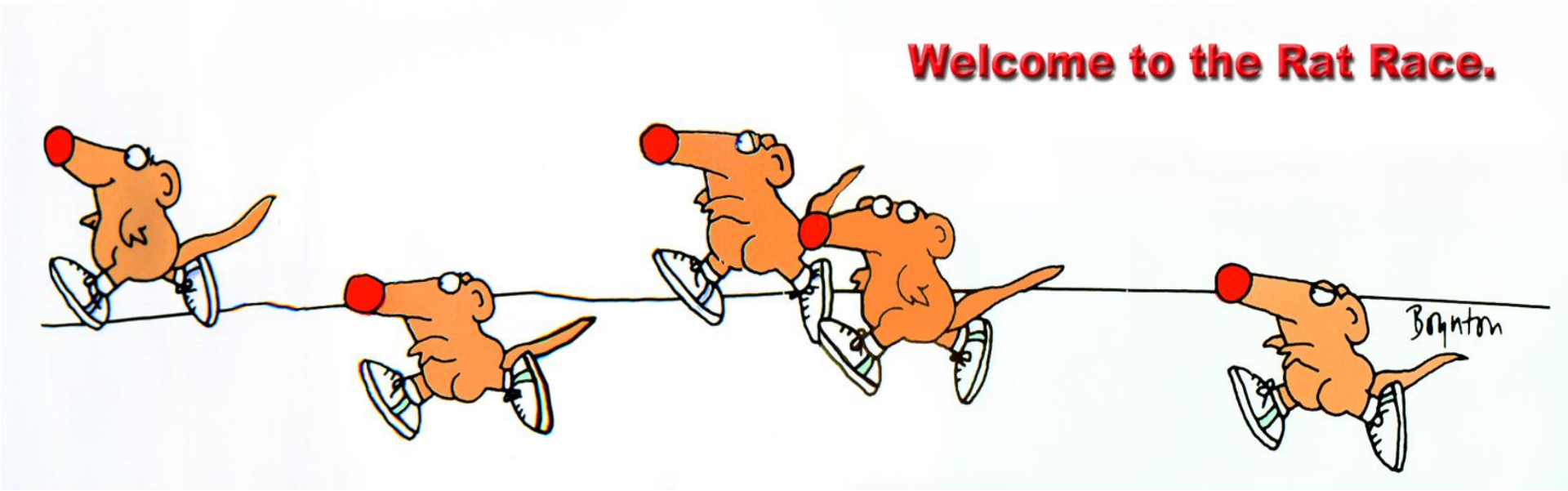
- Alternative electrophysiological *in vitro* model.
- The modalities of the inhibitory responses induced by DA and DA agonists on the dopaminergic cells predict their therapeutic effectiveness in Parkinson's disease.

- **Mercuri NB, et al., Physiology and pharmacology of dopamine D2-receptors: their implications in dopamine-substitute therapy for Parkinson's disease.** Neurology. 1989; 39(8):1106-8.



To test clinically effective drugs

Relatively new PD model in the laboratory



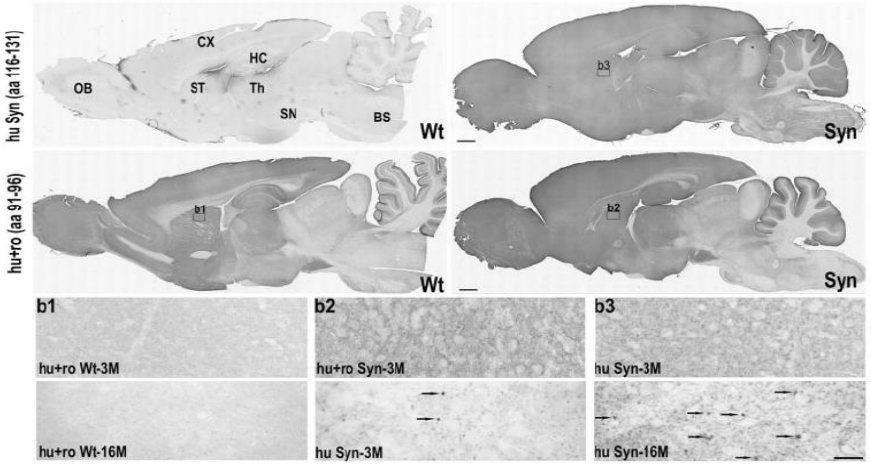
Human α -synuclein overexpression

doi:10.1093/brain/aws358 Brain 2013: 136; 412–432 | 412

BRAIN
A JOURNAL OF NEUROLOGY

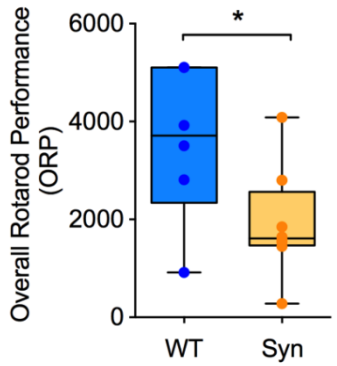
A progressive dopaminergic phenotype associated with neurotoxic conversion of α-synuclein in BAC-transgenic rats

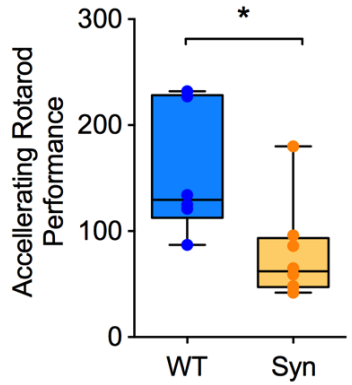
Silke Nuber,[1,2] Florian Harmuth,[2] Zacharias Kohl,[3] Anthony Adame,[1] Margaritha Trejo,[1] Kai Schönig,[4] Frank Zimmermann,[5] Claudia Bauer,[2] Nicolas Casadei,[2] Christiane Giel,[2] Carsten Calaminus,[6] Bernd J. Pichler,[6] Poul H. Jensen,[7] Christian P. Müller,[8] Davide Amato,[8] Johannes Kornhuber,[8] Peter Teismann,[9] Hodaka Yamakado,[10,11] Ryosuke Takahashi,[10,11] Juergen Winkler,[3] Eliezer Masliah[1] and Olaf Riess[2]



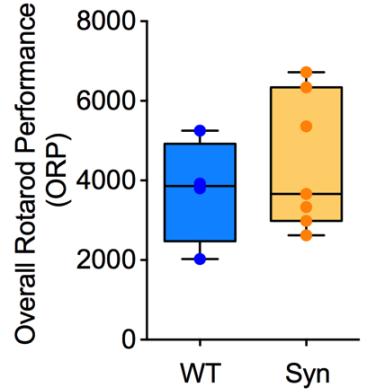
Reduction of motor ability in Syn rats at 4-5 month-old

a

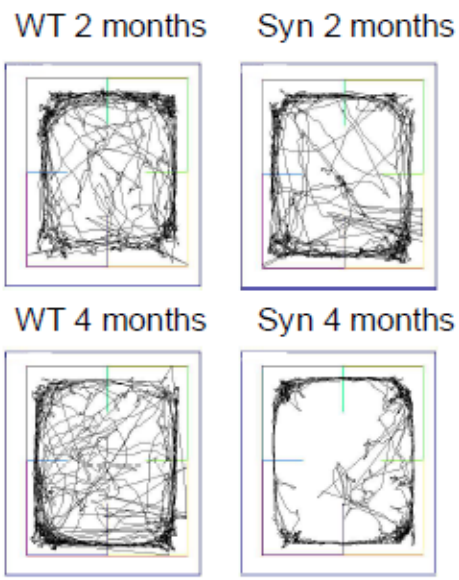




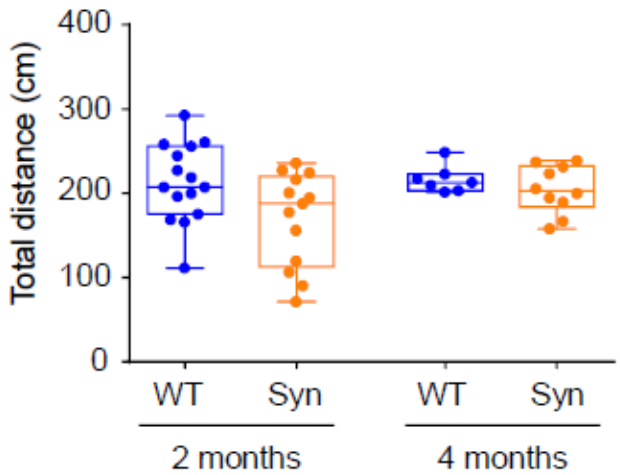
At 2 month-old

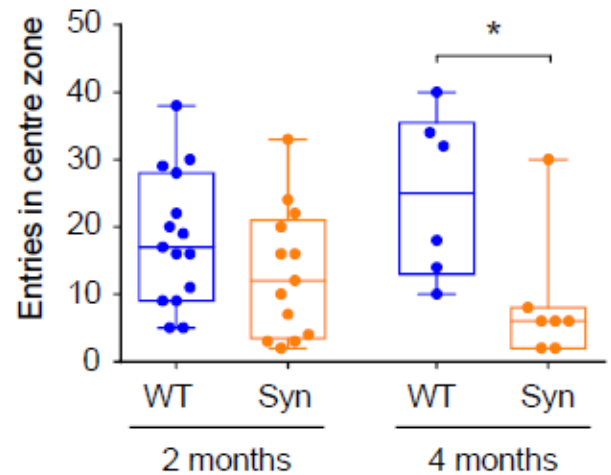


a



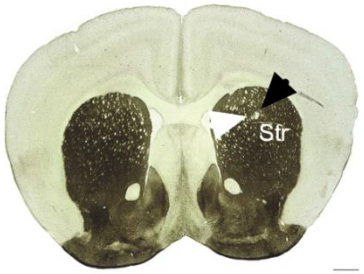
We used motor tests to highlight differences in two genotypes



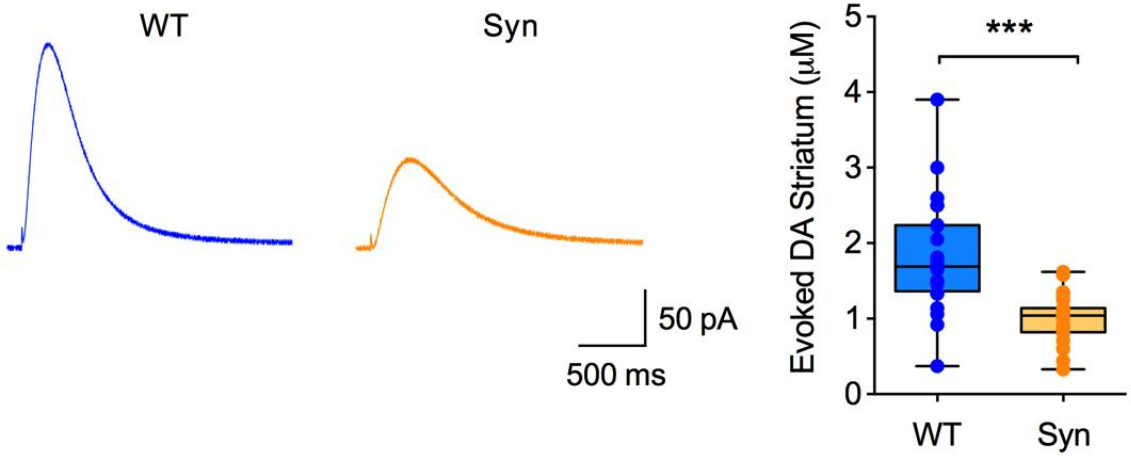


DA release is reduced in dorso-lateral Striatum in Syn rats at 4-5 month-old

a

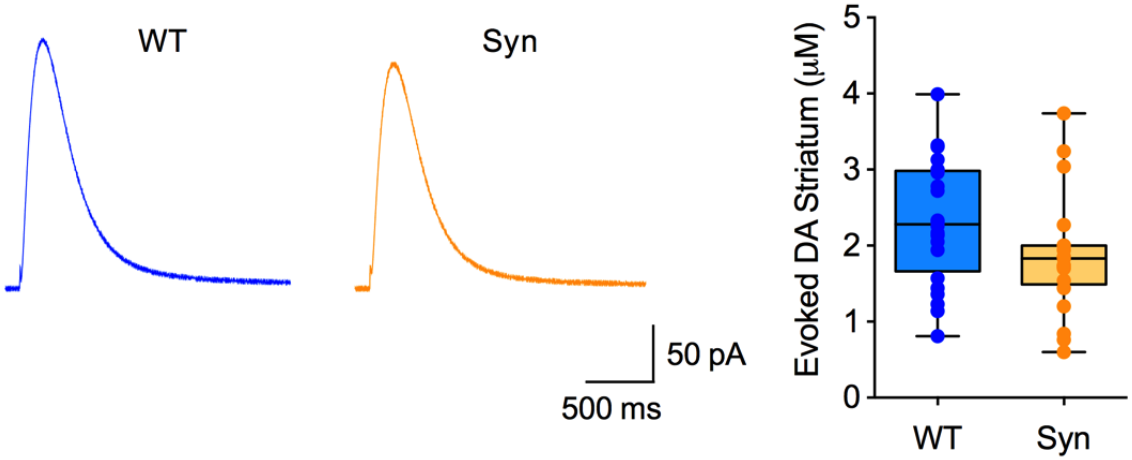


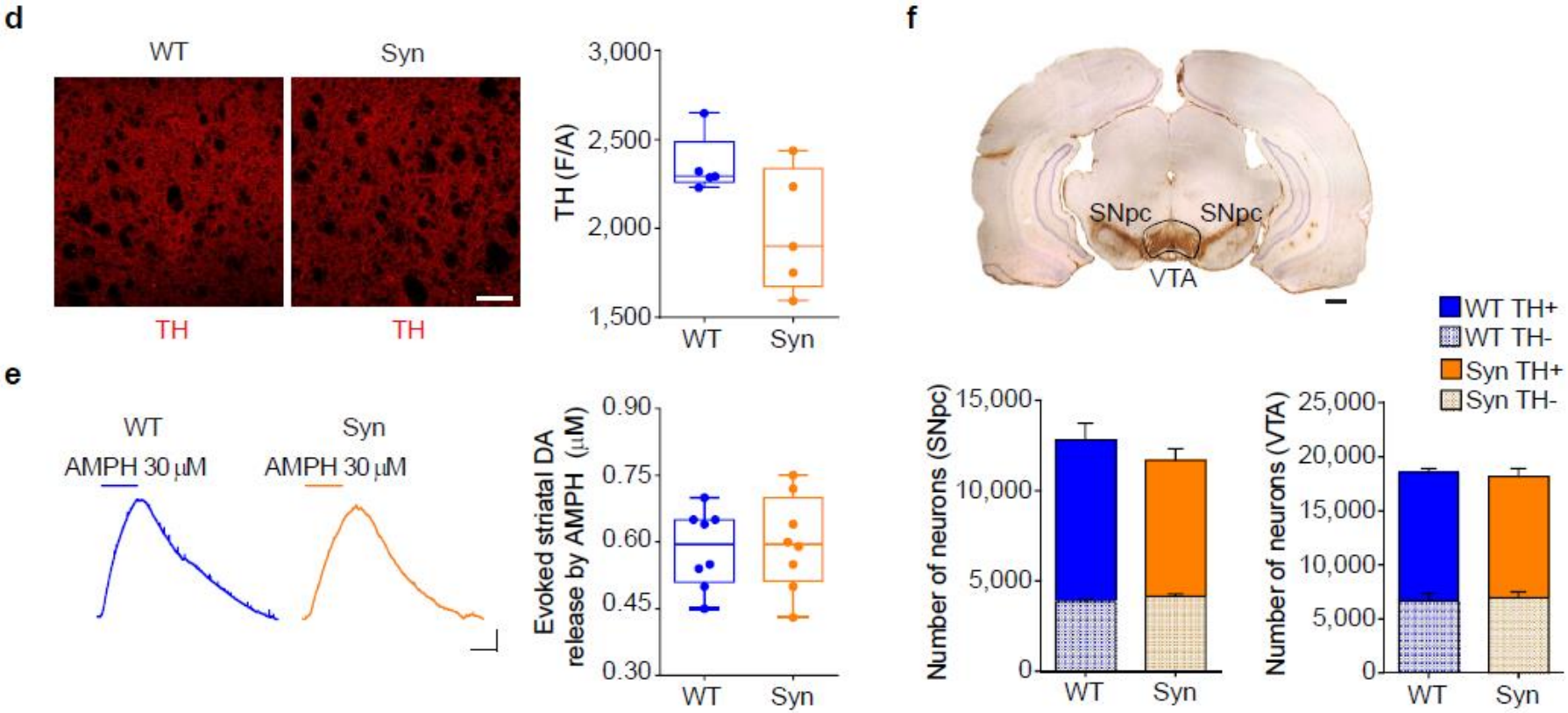
b



But not at 2 month-old…

c

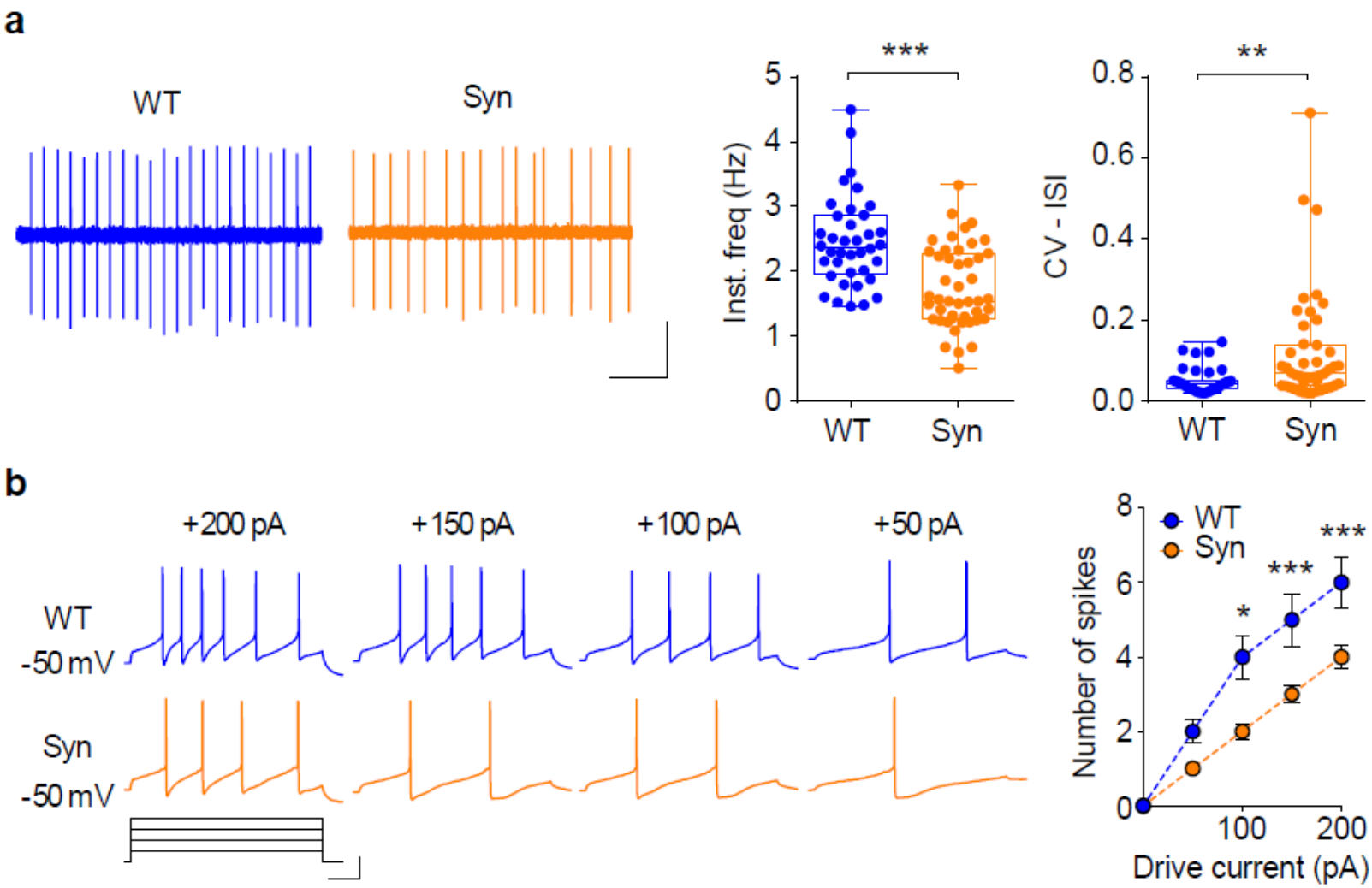




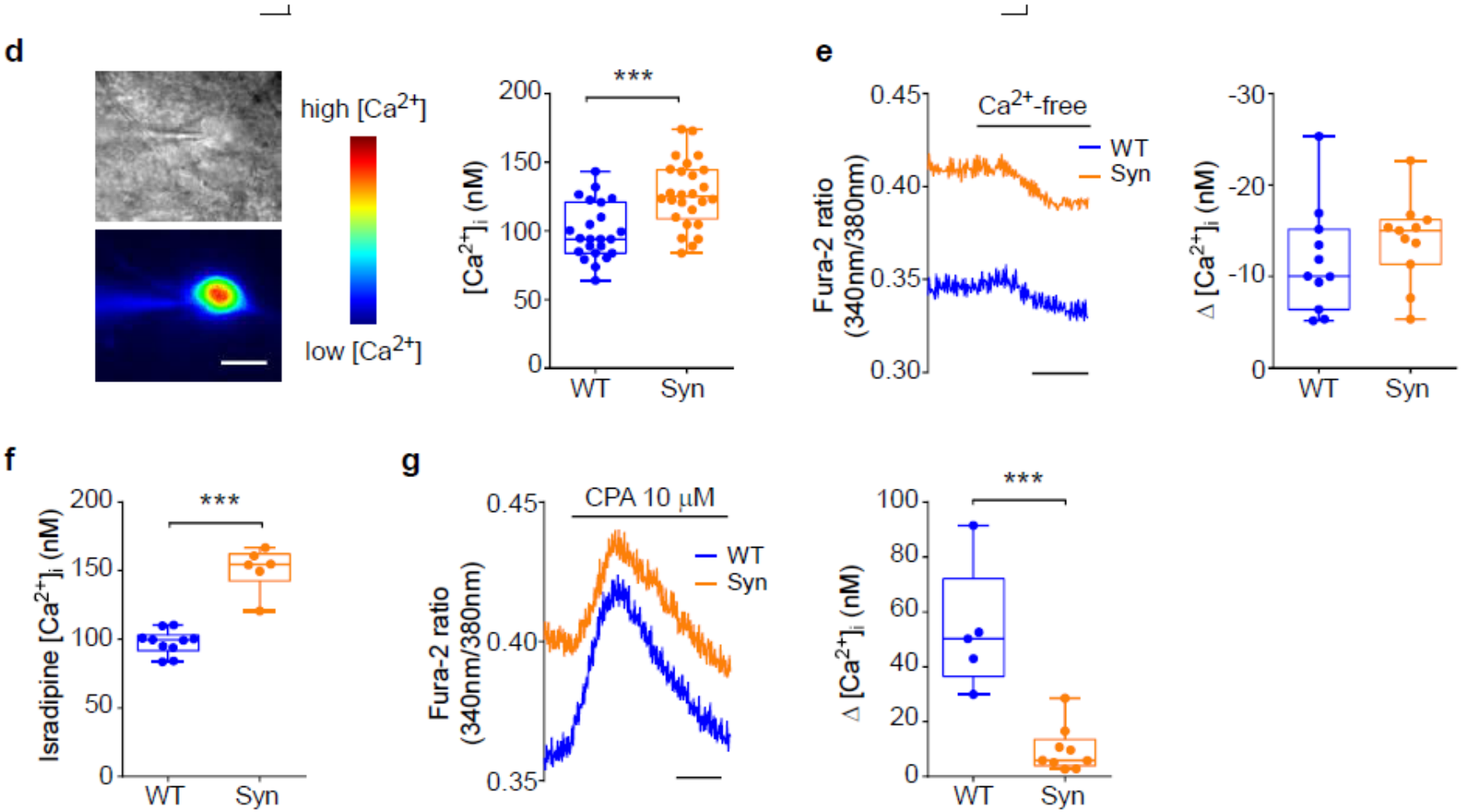
Esclusive alteration of the action potential dependent DA release in the striatum

No changes in TH, cell number and pharmacologically-induced DA release

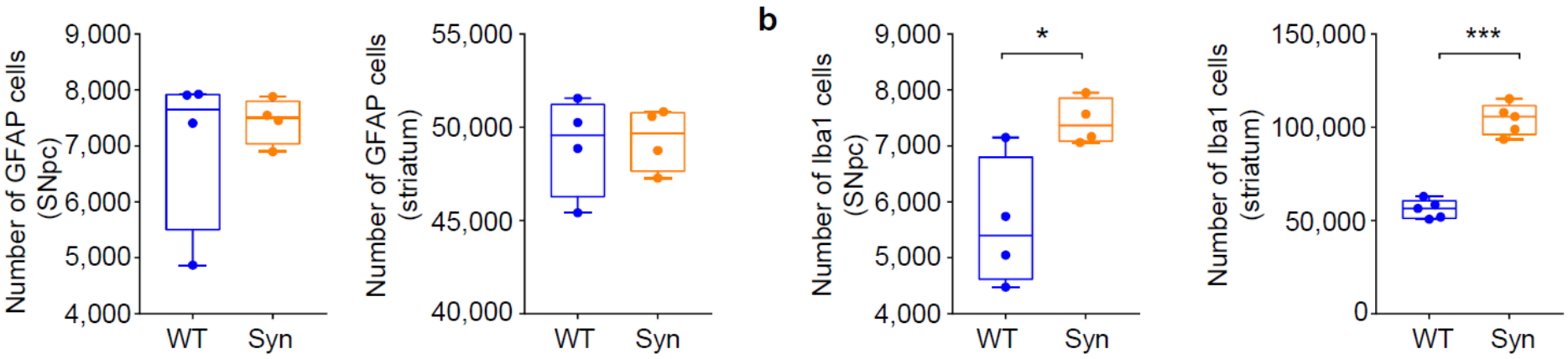
Reduction of excitability in SNpc DAergic cells in Syn rats at 4-5 month-old



Intracellular [Ca2+] is altered in 4-month-old Syn DA neurons



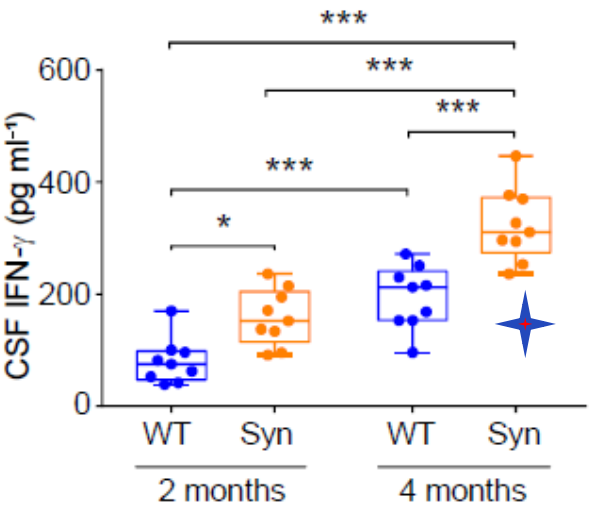
Early neuroinflammatory responses in 4-month-old Syn rats

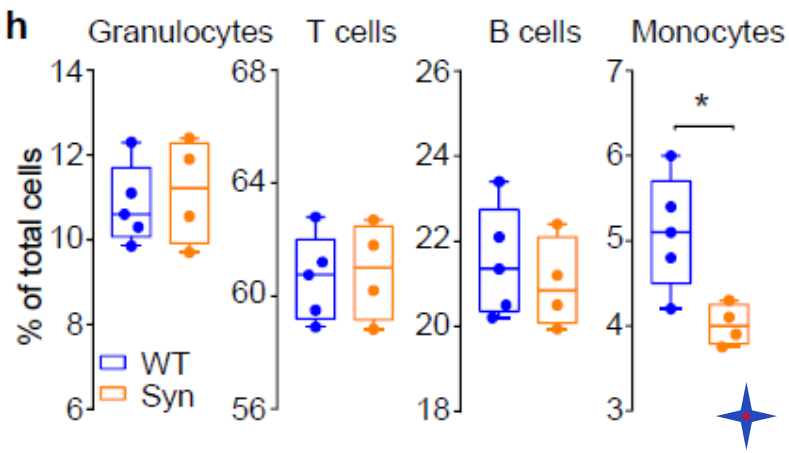


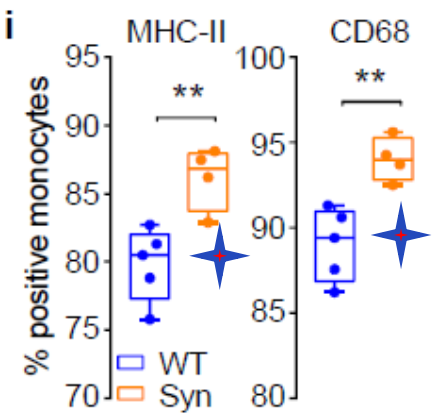
glial fibrillary acidic protein-positive (GFAP$^+$) - astrocytes

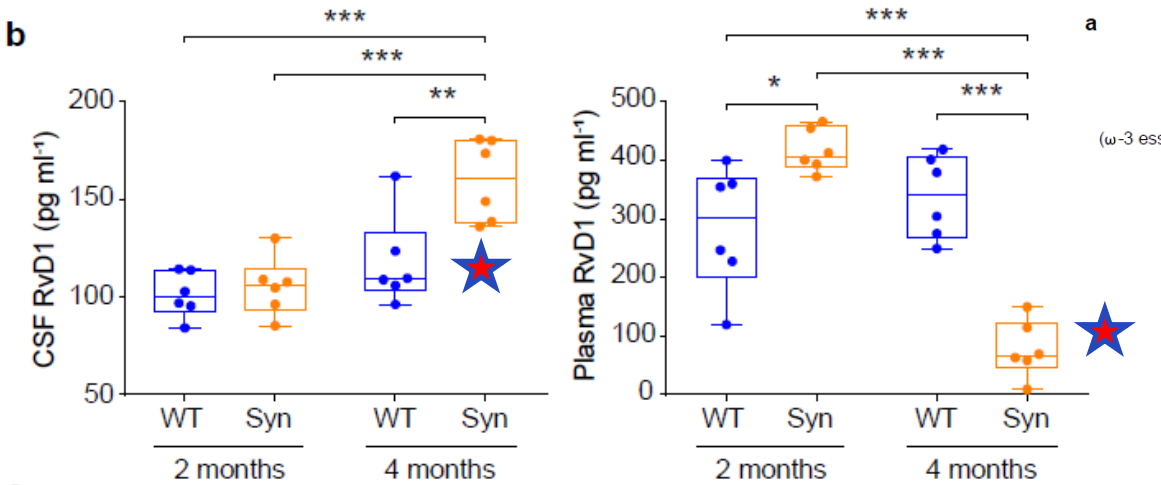
calcium binding adaptor protein-positive (Iba1$^+$) -microglia

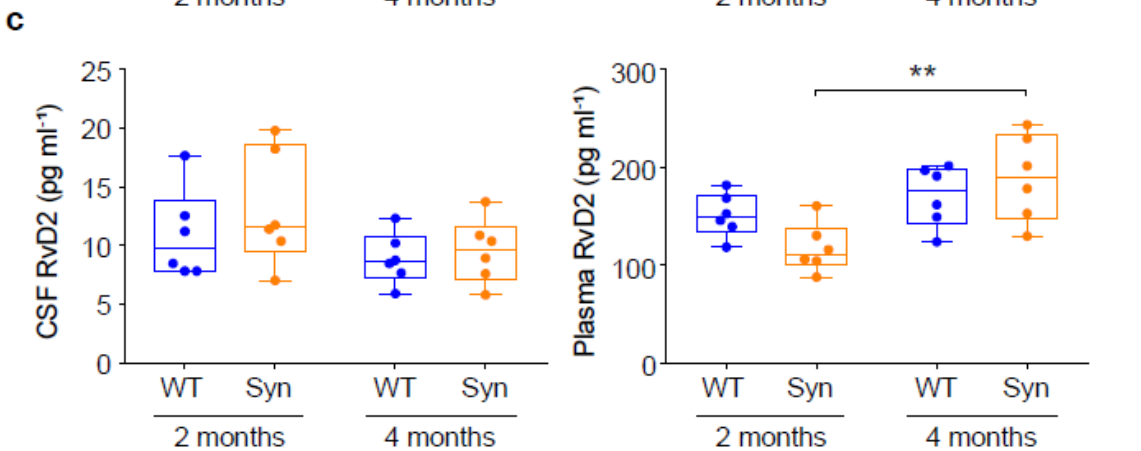
Quantification of IFN-γ levels in the CSF and percentage of peripheral blood cells

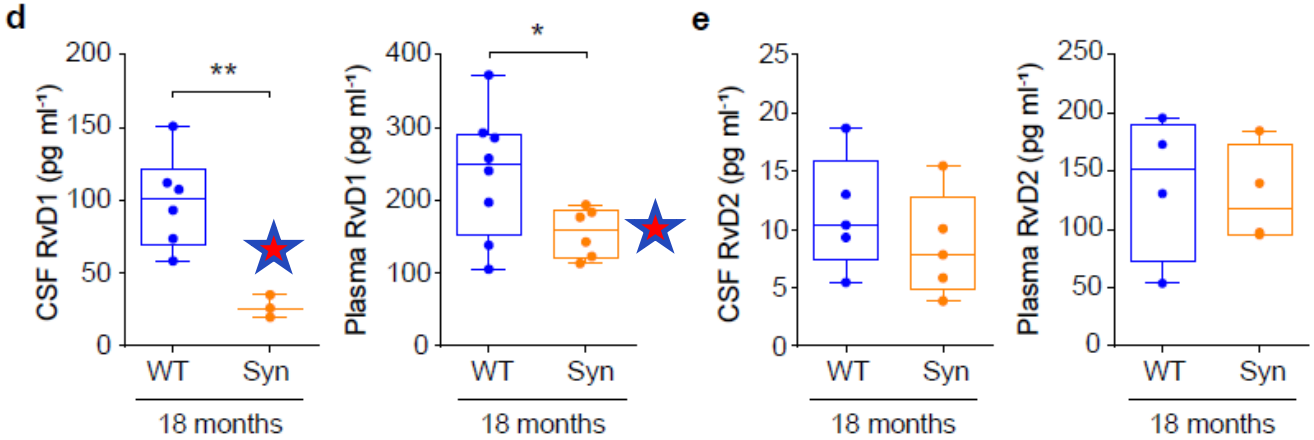


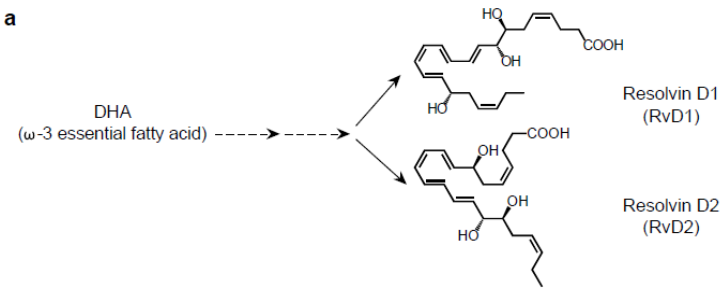








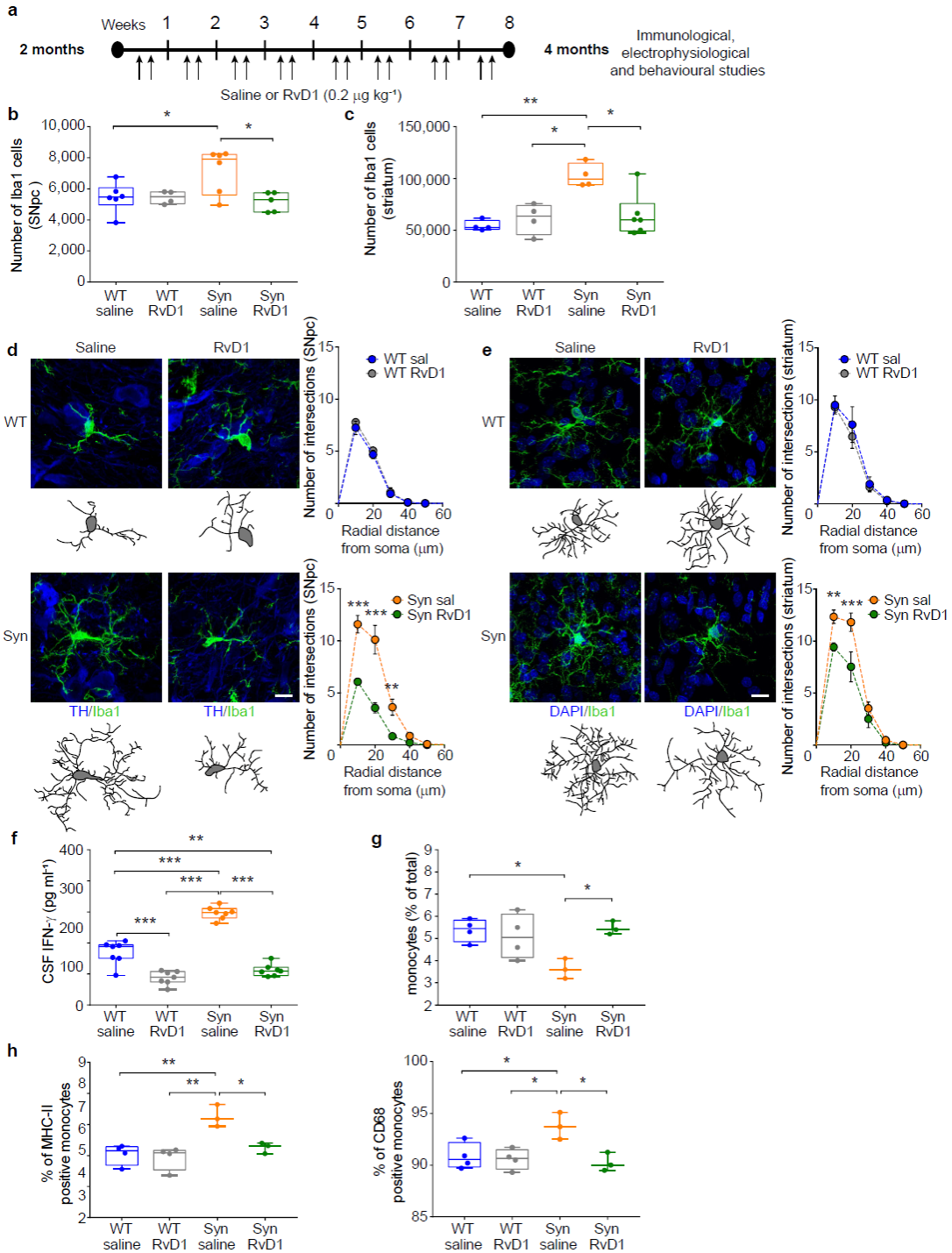


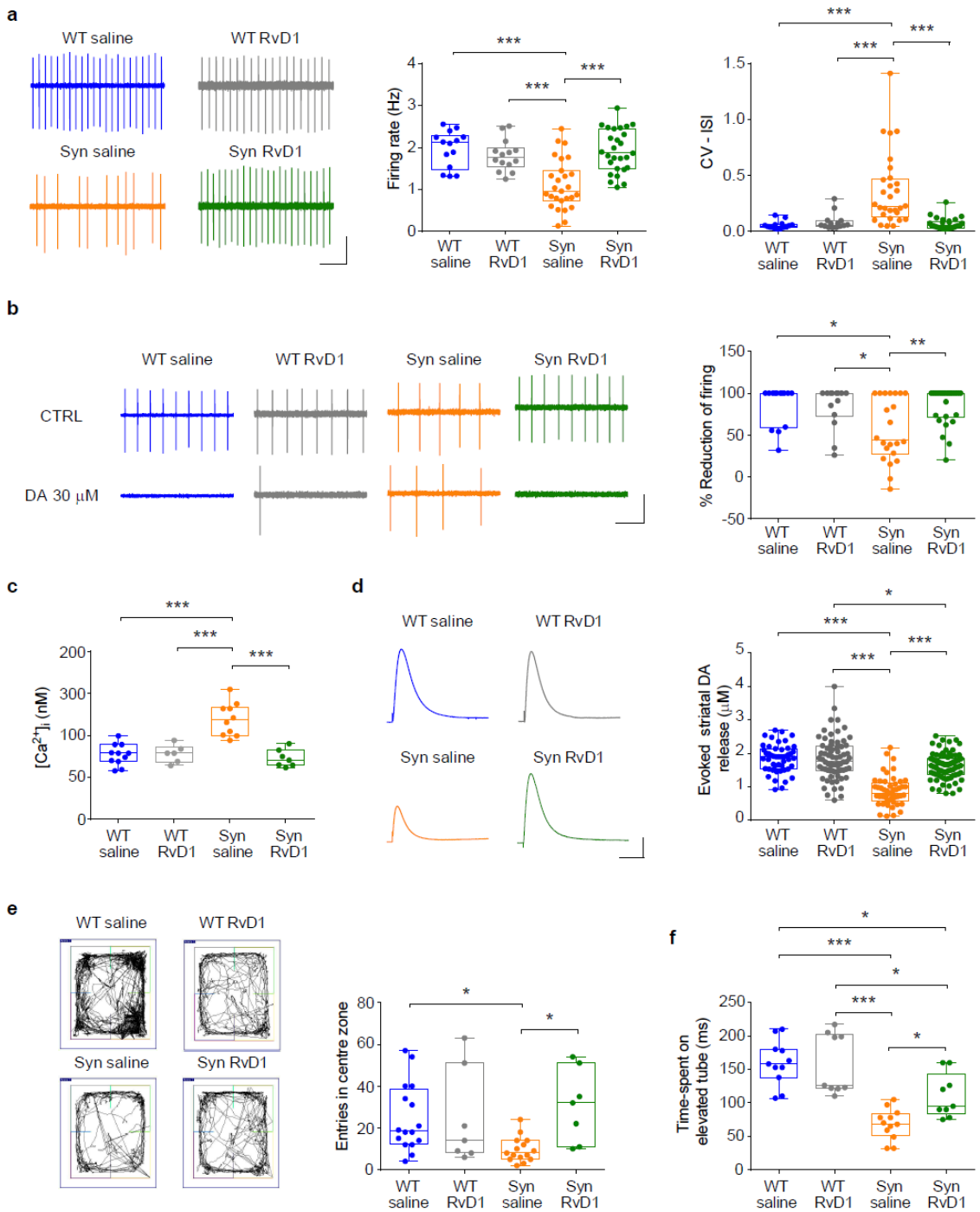


Newly discovered family of omega 3 fatty acids-derived specialized pro-resolving mediators that include resolvins change with age in CFS and plasma of Syn Rats.

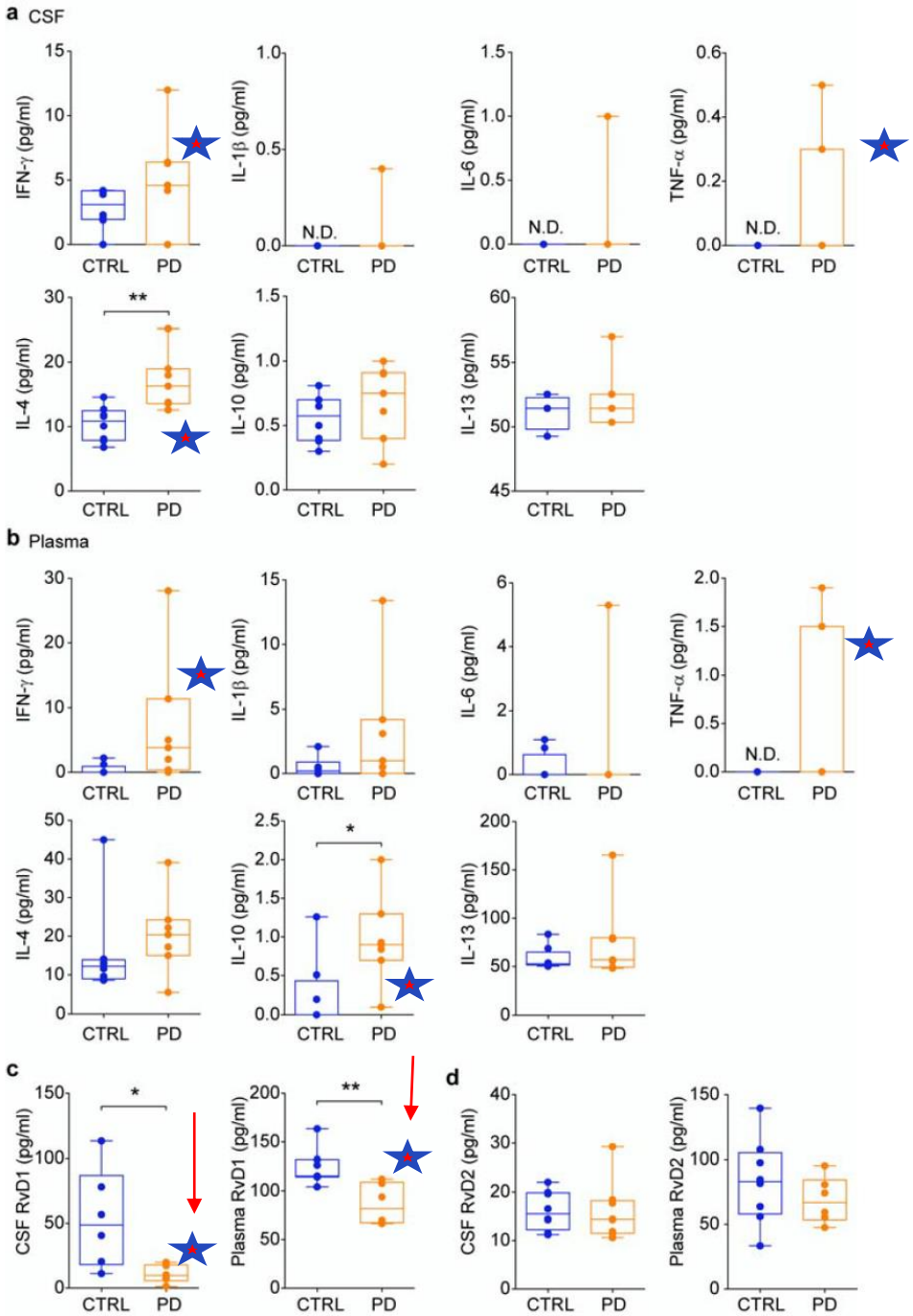
Resolvin 1 (RvD1) is reduced in plasma and increased in CSF

Resolvin 1 i.p. injections, 0.2 µg/kg twice a week, for 2 months, reduces microglia activation, CSF Interferon Y and normalizes monocytes in Syn rats





Rescue of the phenotype



DATA FROM PD PATIENTS

CSF and plasma profiles of cytokines and resolvins in PD patients and control subjects

CSF e plasma IFN-y and TNF-alpha elevation in PD

CSF e plasma RvD 1 reduction in PD

RvD 2 is not affected

Considerazioni

Poiché le alterazioni riportate, sono prevenute nel modello animale da una terapia basata su RvD1, un uso precoce di questa sostanza potrebbe essere sfruttato terapeuticamente nel PD umano. Inoltre, se il basso livello di resolvina 1 sarà confermato in più pazienti con PD, potrebbe essere utilizzato come biomarcatore di malattia.

nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-019-11928-w OPEN

Blunting neuroinflammation with resolvin D1 prevents early pathology in a rat model of Parkinson's disease

Paraskevi Krashia[1,2,11], Alberto Cordella[1,3,11], Annalisa Nobili[1,2,11], Livia La Barbera[1,3], Mauro Federici[1], Alessandro Leuti[1,2], Federica Campanelli[1], Giuseppina Natale[1], Gioia Marino[1], Valeria Calabrese[1], Francescangelo Vedele[1,3], Veronica Ghiglieri[1,4], Barbara Picconi[1], Giulia Di Lazzaro[3], Tommaso Schirinzi[3], Giulia Sancesario[5], Nicolas Casadei[6], Olaf Riess[6], Sergio Bernardini[7], Antonio Pisani[1,3], Paolo Calabresi[1,8], Maria Teresa Viscomi[9], Charles Nicholas Serhan[10], Valerio Chiurchiù[1,2,12], Marcello D'Amelio[1,2,12] & Nicola Biagio Mercuri[1,3,12]

International Journal of
Molecular Sciences

MDPI

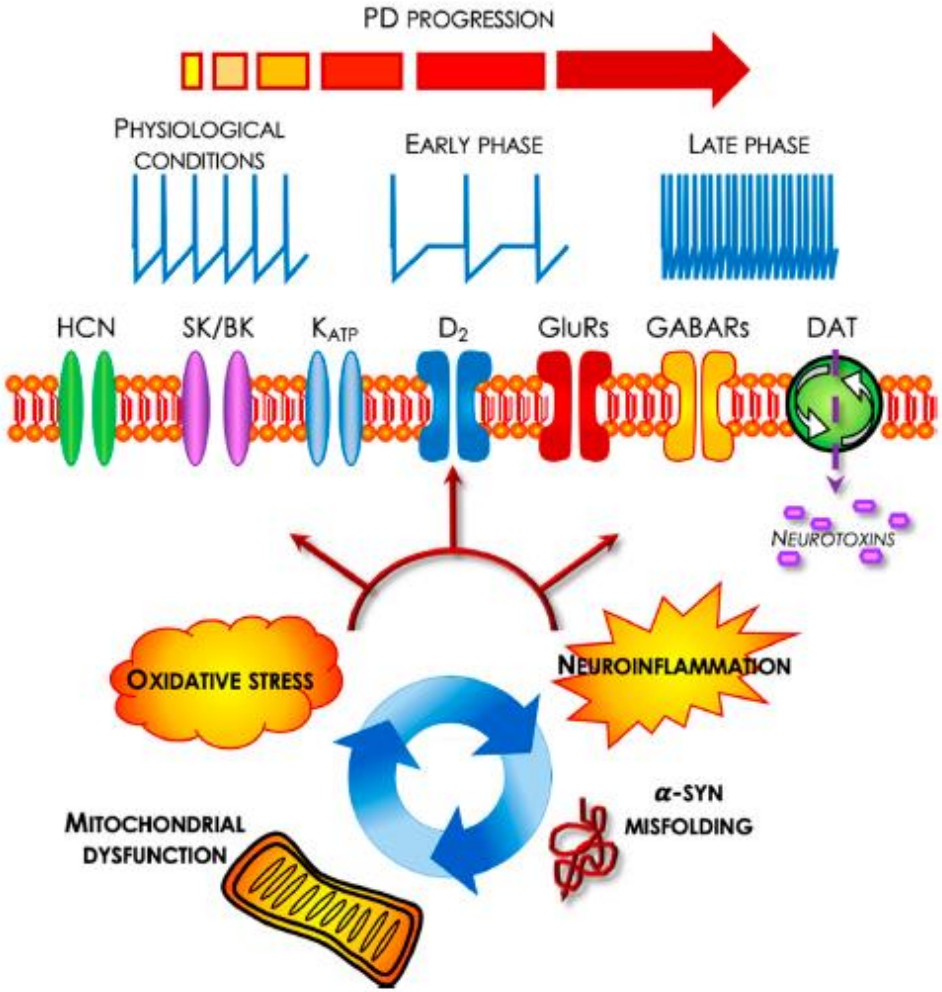
Review

Pathophysiological Features of Nigral Dopaminergic Neurons in Animal Models of Parkinson's Disease

Ezia Guatteo [1,2,†], Nicola Berretta [2,†], V
and Nicola Biagio Mercuri [2,3,*,‡]

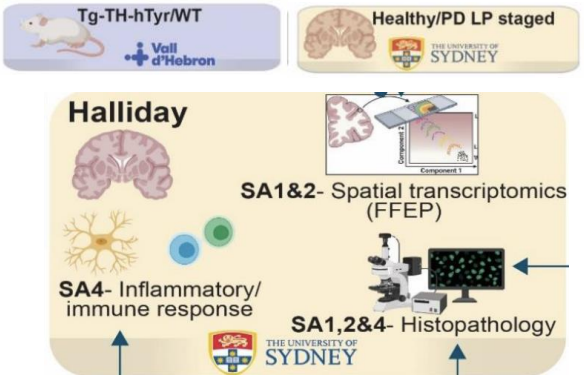
(2022)

We have rewieved the properties of the properties of the DAergic neurons in the different animal models of PD



Obiettivi di un progetto appena finanziato

Miquel Vila's Team
Glenda Halliday, Jose Obeso
Matthias Prigge, Nicola Mercuri



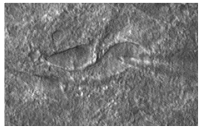
ASAP- Allied Science Against Parkinson

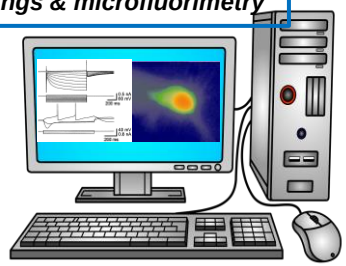
Circuiti cerebrali specifici che sono altamente melanizzati sono colpiti all'inizio del PD.
Questo può essere riprodotto in modelli animali.

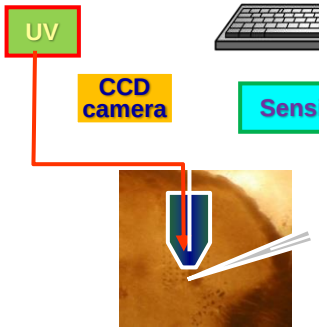
Risponderemo alla domanda fondamentale irrisolta sul perché i circuiti cerebrali altamente melanizzati sono preferenzialmente vulnerabili alla disfunzione/degenerazione nel PD, con conseguenti sintomi motori e non motori.
Identificheremo le associazioni tra neuromelanina, infiammazione e neurodegenerazione nel cervello nelle fasi di malattia e se le immunoterapie a lungo termine avranno un impatto sul PD.

Single-cell and multi-unit characterization of the cellular properties and calcium dynamics of selective neuronal SNpc/VTA

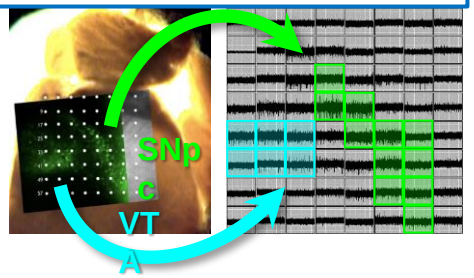
Patch-clamp recordings & microfluorimetry

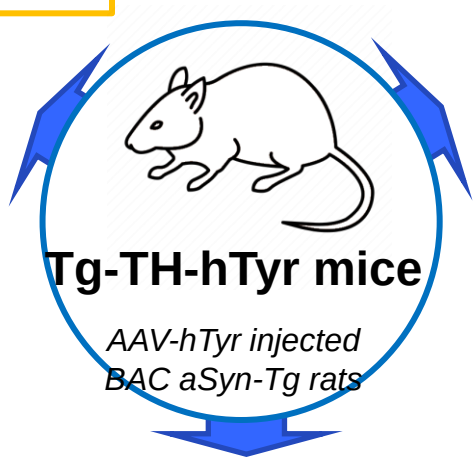




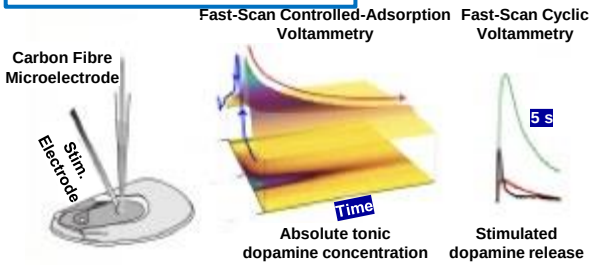


Multi-electrode array (MEA) recordings

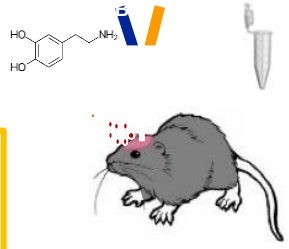




Voltammetry/Amperometry

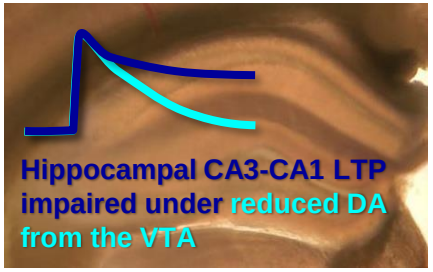


Microdialysis



Functional alterations in brain circuitries associated to regionally-selective DA deprivation

Synaptic plasticity



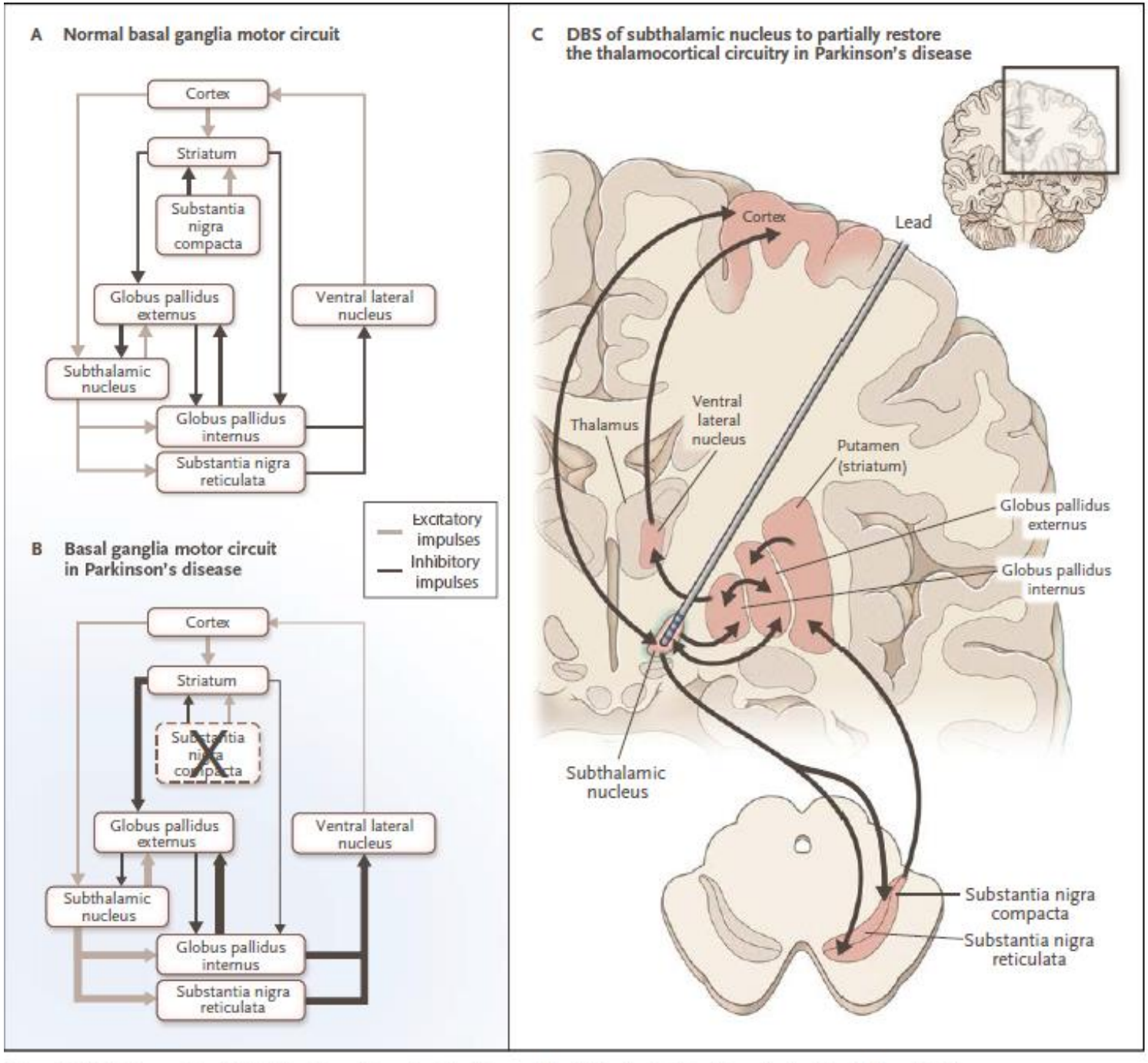
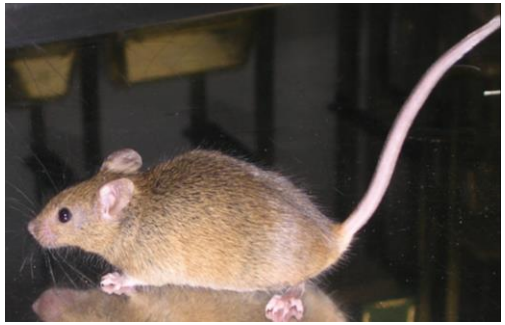


Figure 1. The DeLong "Box" Models of Basal Ganglia Circuitry and Their Use in Guiding Deep-Brain Stimulation (DBS).

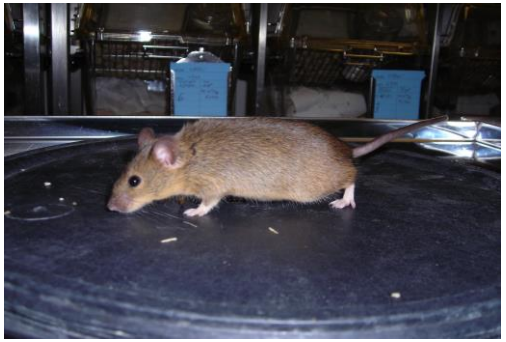
Modelli animali di Sclerosi Laterale amiotrofica

Controllo



Esprime la SOD1 murina

SOD1

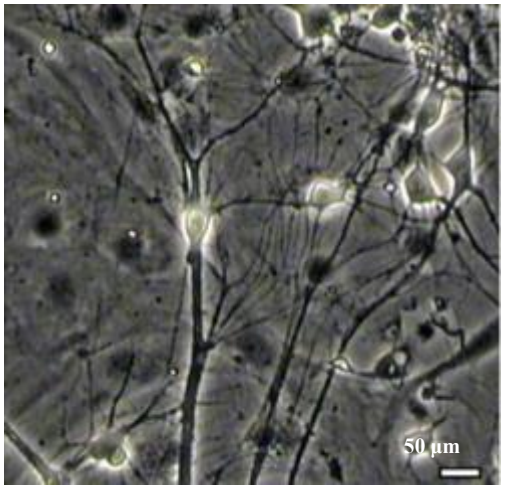


Esprime la SOD1 murina
Sovraesprime la SOD1 umana

G93A

Esprime la SOD1 murina
Sovraesprime la SOD1 umana mutata

Grande speranza per scoprire terapie valide è riposta nella ricerca scientifica.

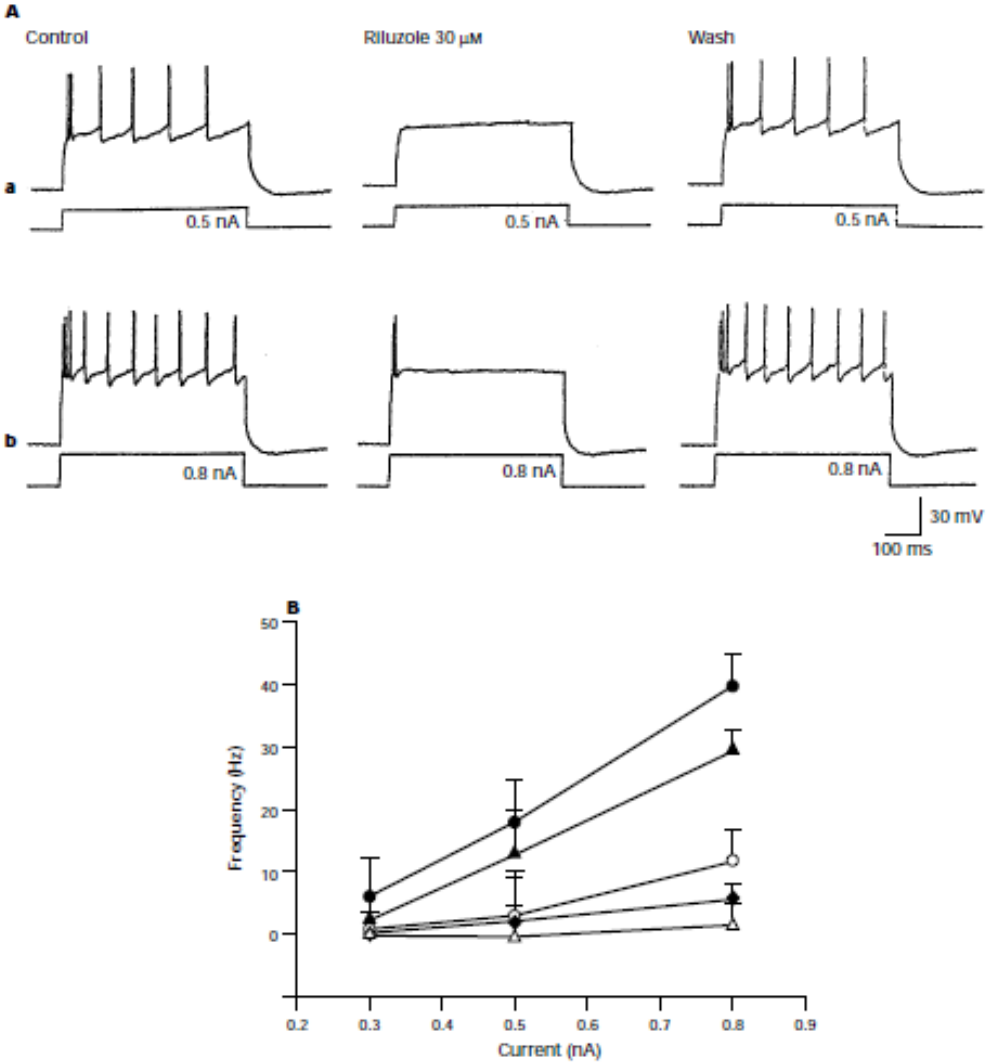


Modelli cellulari

British Journal of Pharmacology (1997) 120, 225–230 © 1997 Stockton Press All rights reserved 0007–1188/97 $12.00

Effects of riluzole on rat cortical neurones: an *in vitro* electrophysiological study

Antonio Siniscalchi, Antonello Bonci, [1]Nicola B. Mercuri & Giorgio Bernardi



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Experimental Neurology

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Increased persistent sodium current determines cortical hyperexcitability in a genetic model of amyotrophic lateral sclerosis

Massimo Pieri, Irene Carunchio, Livia Curcio, Nicola Biagio Mercuri, Cristina Zona *

Department of Neuroscience, University of Rome "Tor Vergata", Via Montpellier 1, 00133 Rome, Italy
Fondazione S. Lucia, I.R.C.C.S., Via del Fosso di Fiorano, 00143 Rome, Italy

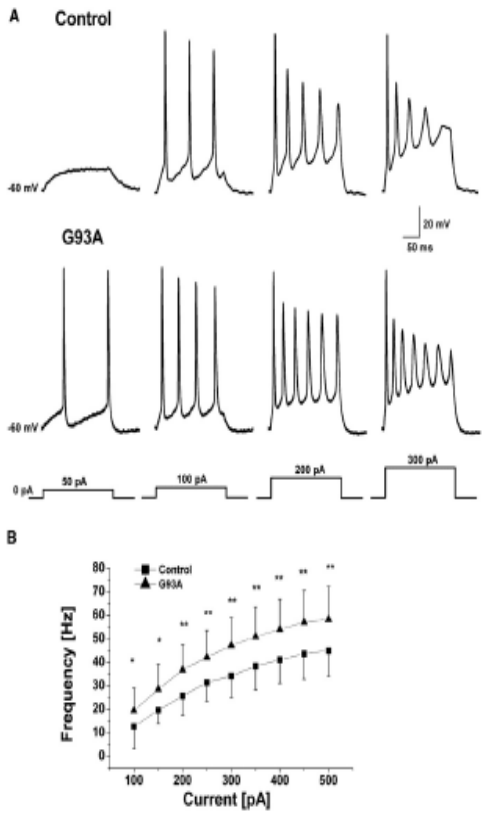
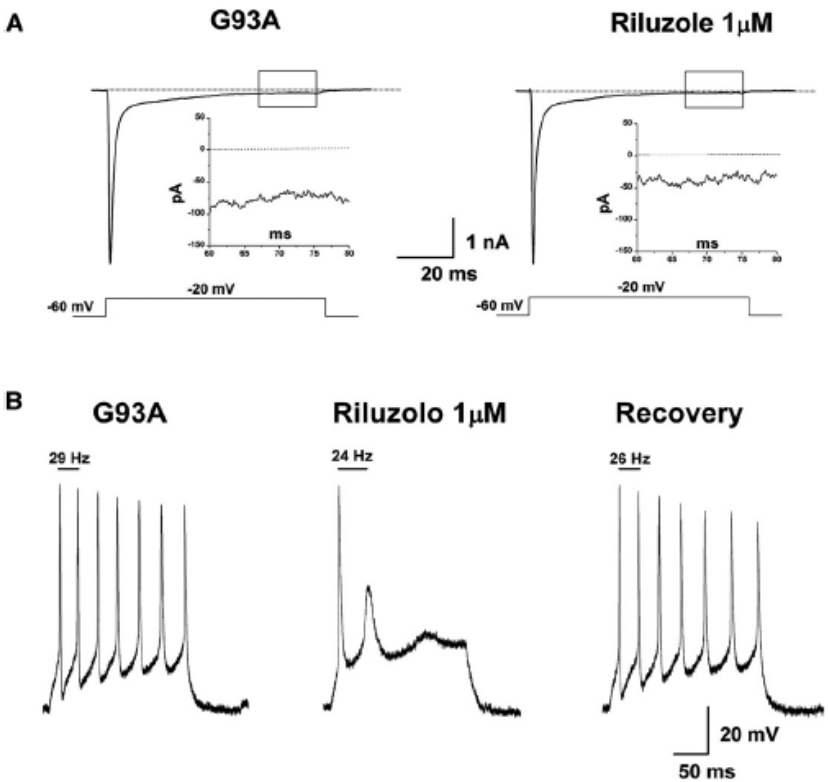


Fig. 3. Repetitive firing properties for Control and G93A neurons. (A) Representative membrane potential responses evoked by +50, +100, +200 and +300 pA current injections (200 ms) in Control and G93A cortical neurons under the current clamp condition. The holding potential was restored to −60 mV and the neurons shown were 11 days old in culture. (B) Mean and standard deviation of repetitive firing frequency in the range of 100–500 pA of current in Control (n = 36) and G93A (n = 15) cortical neurons. The frequency in G93A neurons was significantly higher for all the injected current values compared to those in Control (*P < 0.05, **P < 0.01).



Terapia

- Non esiste una terapia riconosciuta efficace
- E' correntemente usato un agente, il riluzolo, che dicono in grado di bloccare la trasmissione glutammatergica. Effetti molto scarsi.

- Non ha effetti antiglutammatergici

Blocca i canali del sodio
non il rilascio di glutammato

International Journal of
Molecular Sciences

MDPI

Article

Impact of Pharmacological Inhibition of Hydrogen Sulphide Production in the SOD1G93A-ALS Mouse Model

Alida Spalloni [1,†], Viviana Greco [2,3,†], Giulia Ciriminna [1], Victor Corasolla Carregari [2,3], Federica Marini [2,3], Luisa Pieroni [4], Nicola B. Mercuri [5,6], Andrea Urbani [2,3,‡] and Patrizia Longone [1,*,‡]

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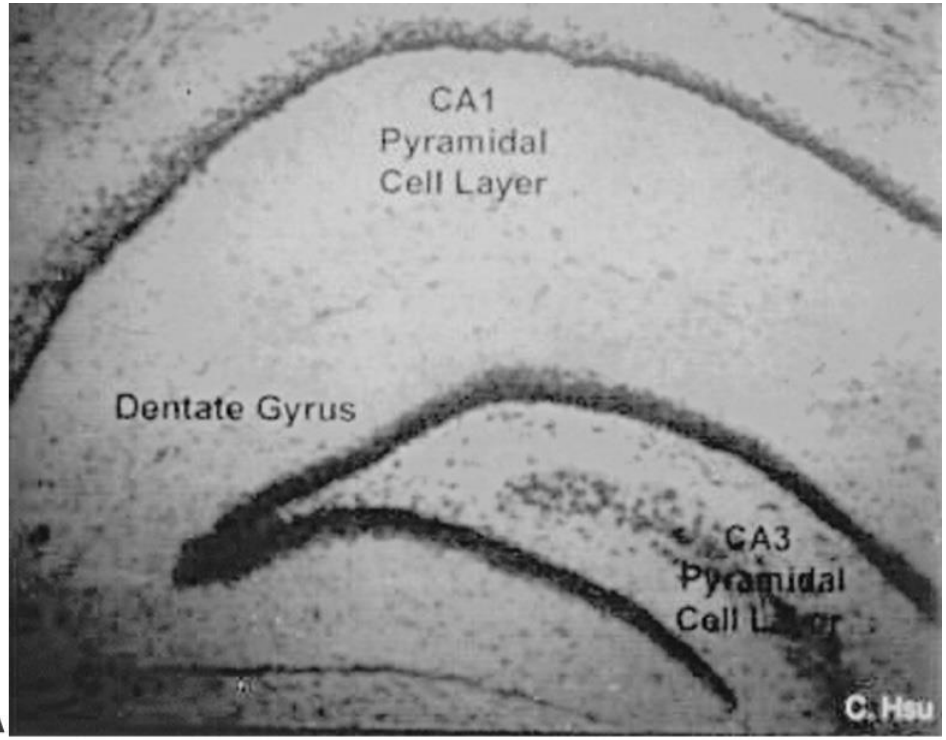
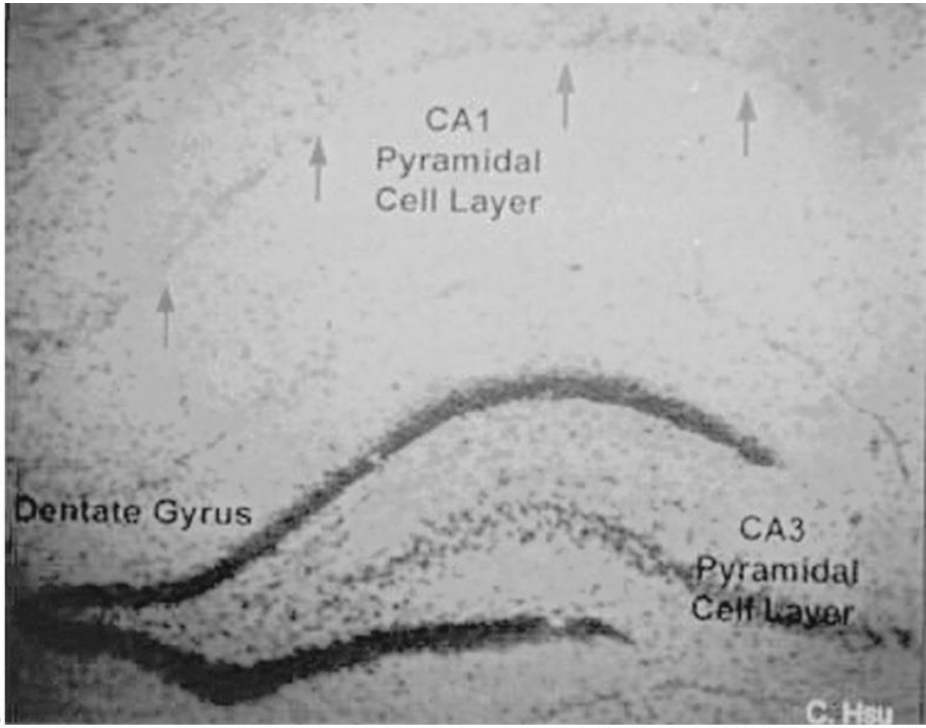
Models of ischemia



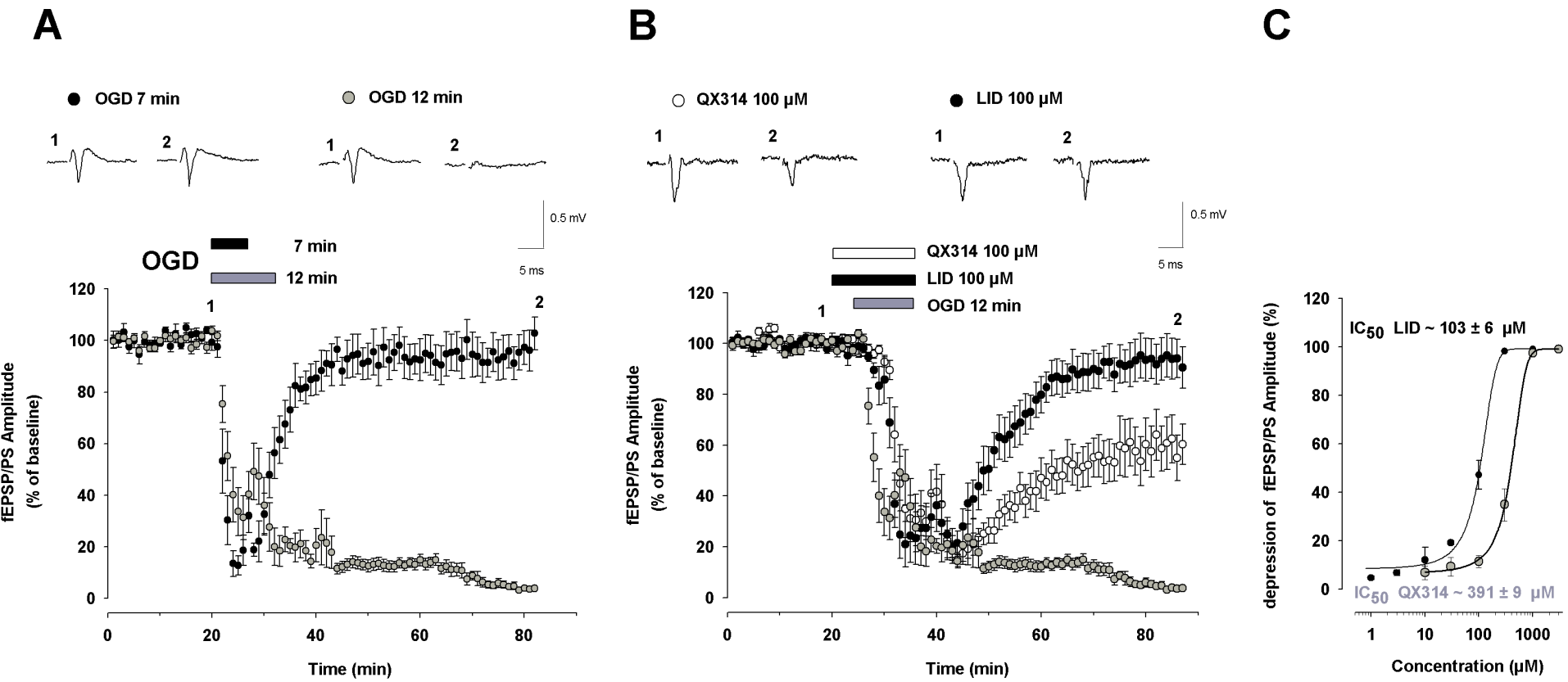
A

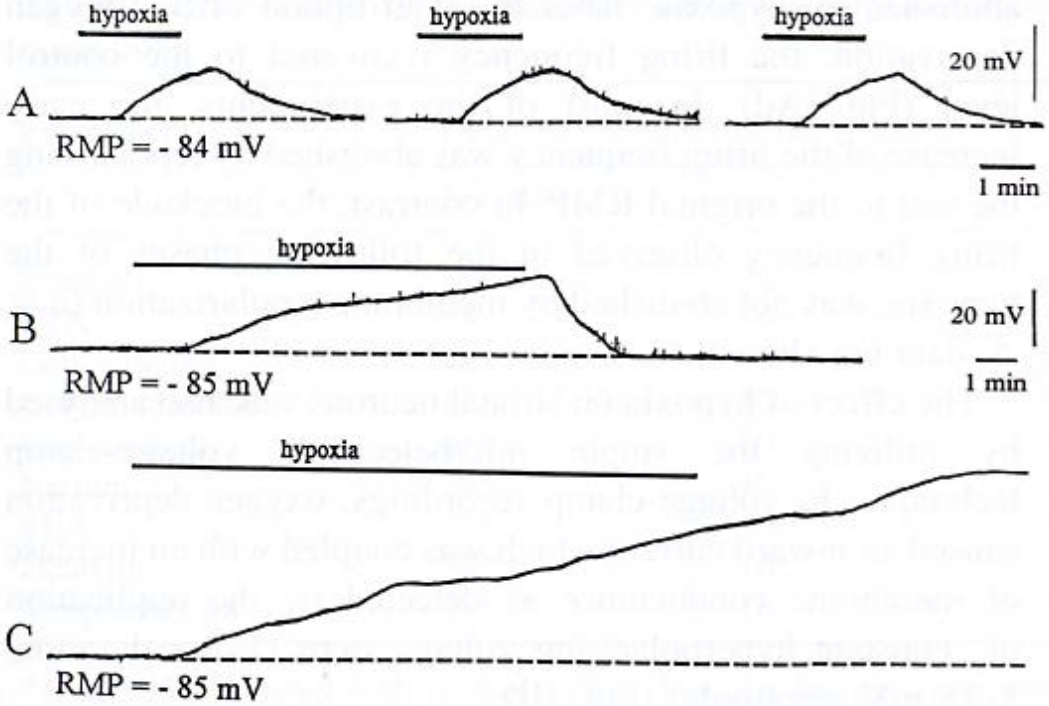
(Courtesy of Dr Chung Y. Hsu, Washington University School of Medicine.)

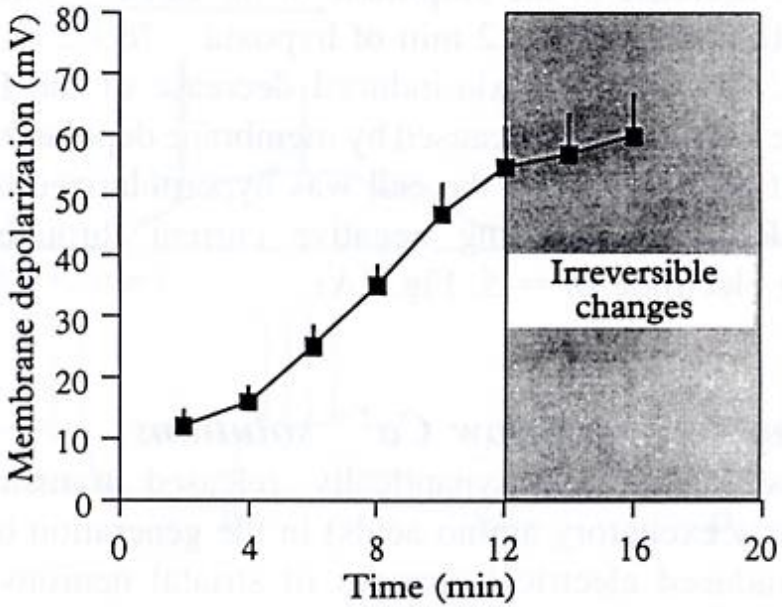


B

(Courtesy of Dr Chung Y. Hsu, Washington University School of Medicine.)

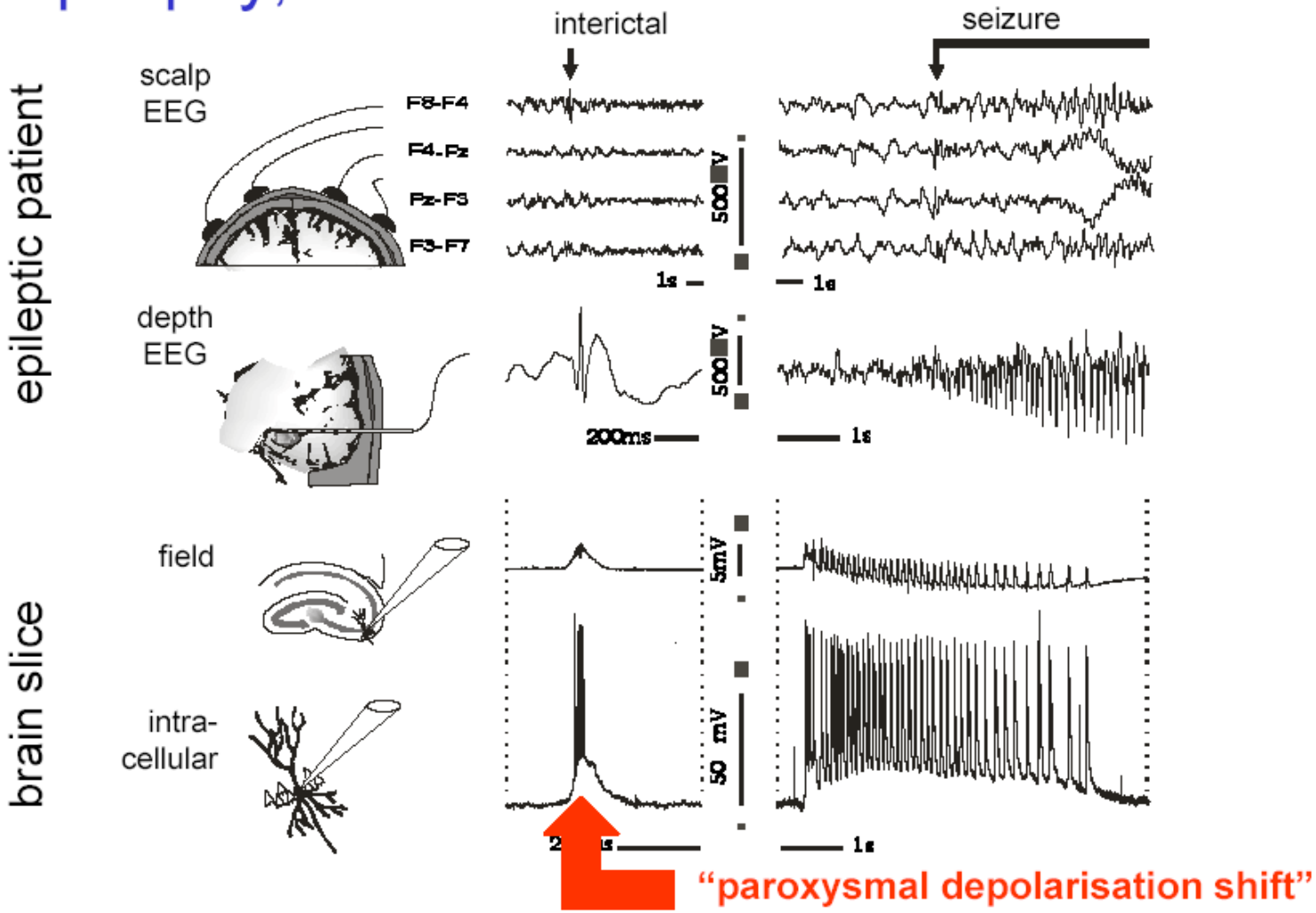

A
OGD 7 min
OGD 12 min
1
2
1
2
0.5 mV
5 ms
OGD
7 min
12 min
fEPSP/PS Amplitude
(% of baseline)
Time (min)
B
QX314 100 µM
LID 100 µM
QX314 100 µM
LID 100 µM
OGD 12 min
C
IC50 LID ~ 103 ± 6 µM
IC50 QX314 ~ 391 ± 9 µM
depression of fEPSP/PS Amplitude (%)
Concentration (µM)





EFFECTS OF HYPOXIA ON MEDIUM SPINY NEURONS

Epilepsy, Models and Basic Mechanisms



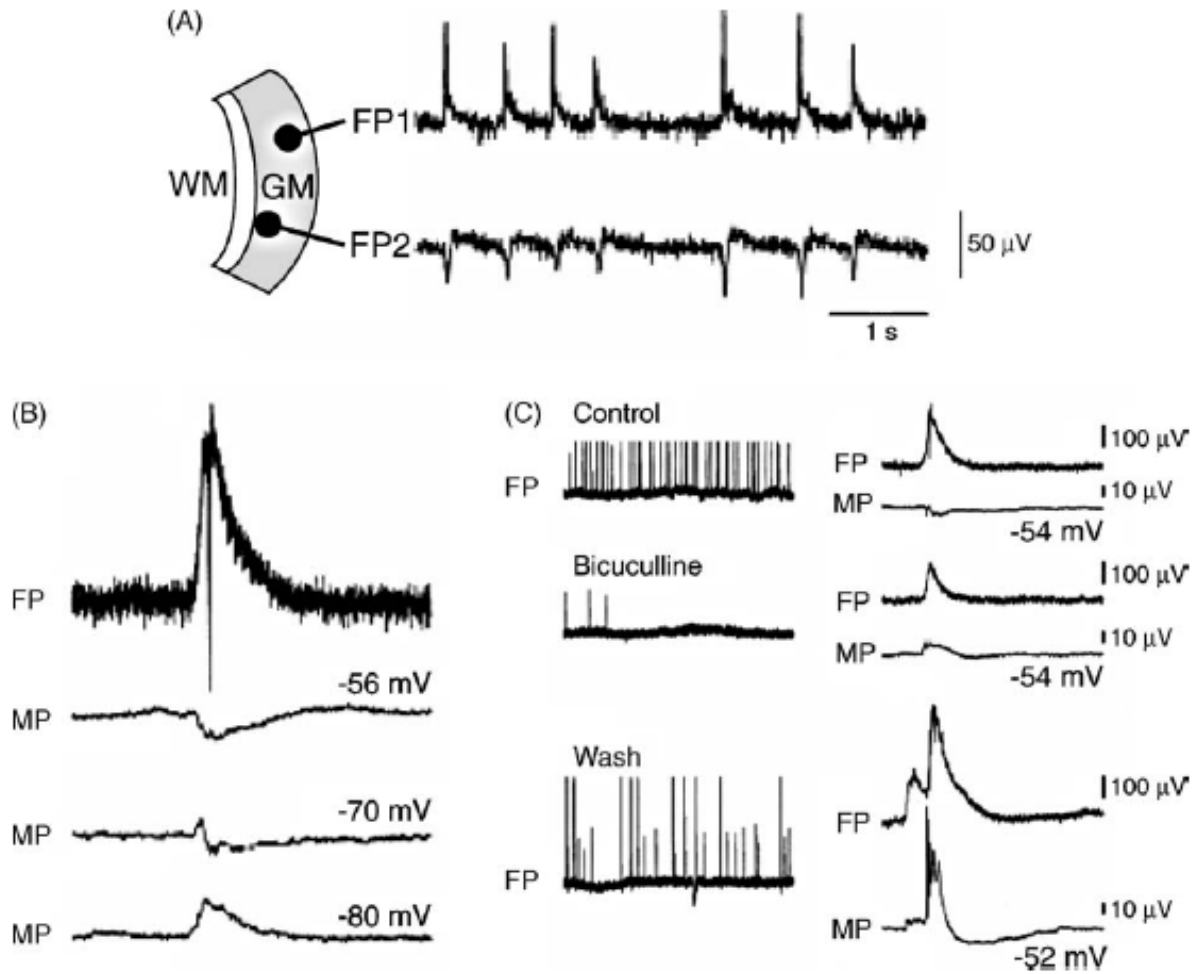
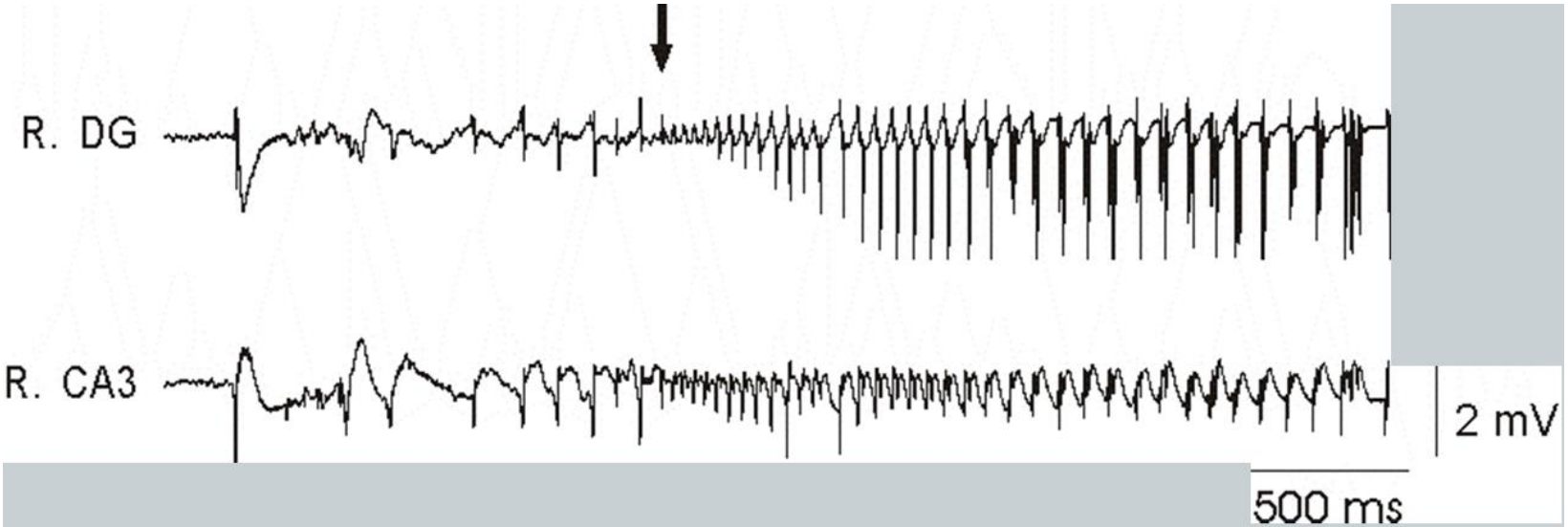


Fig. 4. Spontaneous network discharges in human neocortical slices from epileptic patients. (A) Synchronous network discharges monitored by field potential (FP) recordings from two sites in the slice (FP1 and FP2). In this experiment, the spontaneous activity ecompassed the entire slice. (B) Intracellular (MP) events obtained from a presumed pyramidal neuron during spontaneous field potential discharges (with population spike superimposed) at different membrane potential levels as indicated on the right of each trace. Note that the intracellular events are mainly hyperpolarizing at −56 and −70 mV and become depolarizing at membrane potential >75 mV. (C) The occurrence of network discharges are dependent on GABA receptor-mediated transmission and can be abolished by the $GABA_A$-receptor antagonist bicuculline. Modified from Köhling et al. (1998), with permission.

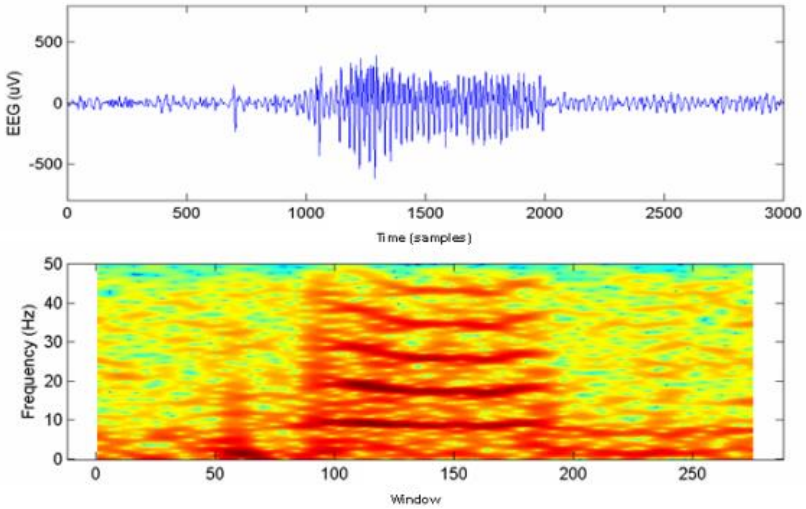
In vivo models of epilepsy

Gerbil

In vivo



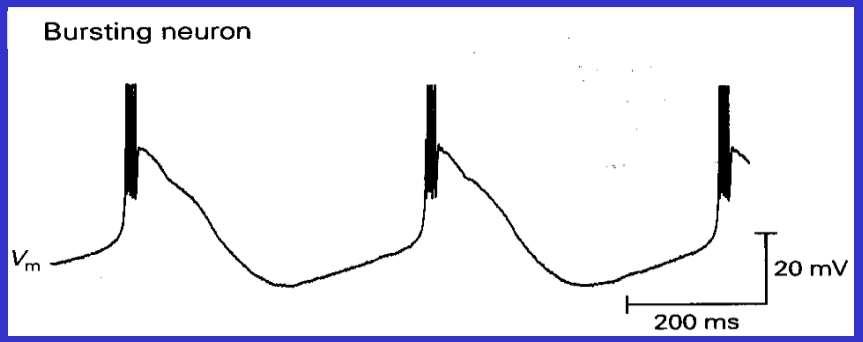
GAERS (Genetic Absence Epilepsy Rats from Strasbourg) are a strain of Wistar rats in which all animals present generalized non-convulsive epileptic seizures.



During these epileptic episodes, the cortical EEG displays the occurrence of bilateral and synchronous Spike and Wave Discharges all over the cortex. Because SWD in GAERS share many clinical characteristics with typical human absence epilepsy and exhibit a similar pharmacological reactivity to drugs, GAERS are generally accepted as a valid experimental animal model of human absence epilepsy.

CANALI DEL CALCIO DI TIPO T ED EPILESSIA

- I canali del Calcio di tipo T regolano il firing neuronale partecipando al controllo dell'attività oscillatoria intrinseca neuronale
- Nel talamo, tali canali partecipano nelle oscillazioni aberranti che sottendono le assenze
- Modelli murini:
  - Topi KO per a1G sono resistenti ad agenti epilettogeni
  - Topi GAERS (Genetic Absence Seizures from Strasbourg)
  - hanno un'aumentata espressione di Canali di tipo T



- Patologie umane → mutazioni in a1H riscontrate in pz con assenze epilettiche dell'infanzia (CAE) *(Chen et al., Ann. Neurol. 2003)*

Importanza dell’approccio elettrofisiologico nella comprensione della fisiopatologia dell’epilessia e nella valutazione d’efficacia dei farmaci antiepilettici

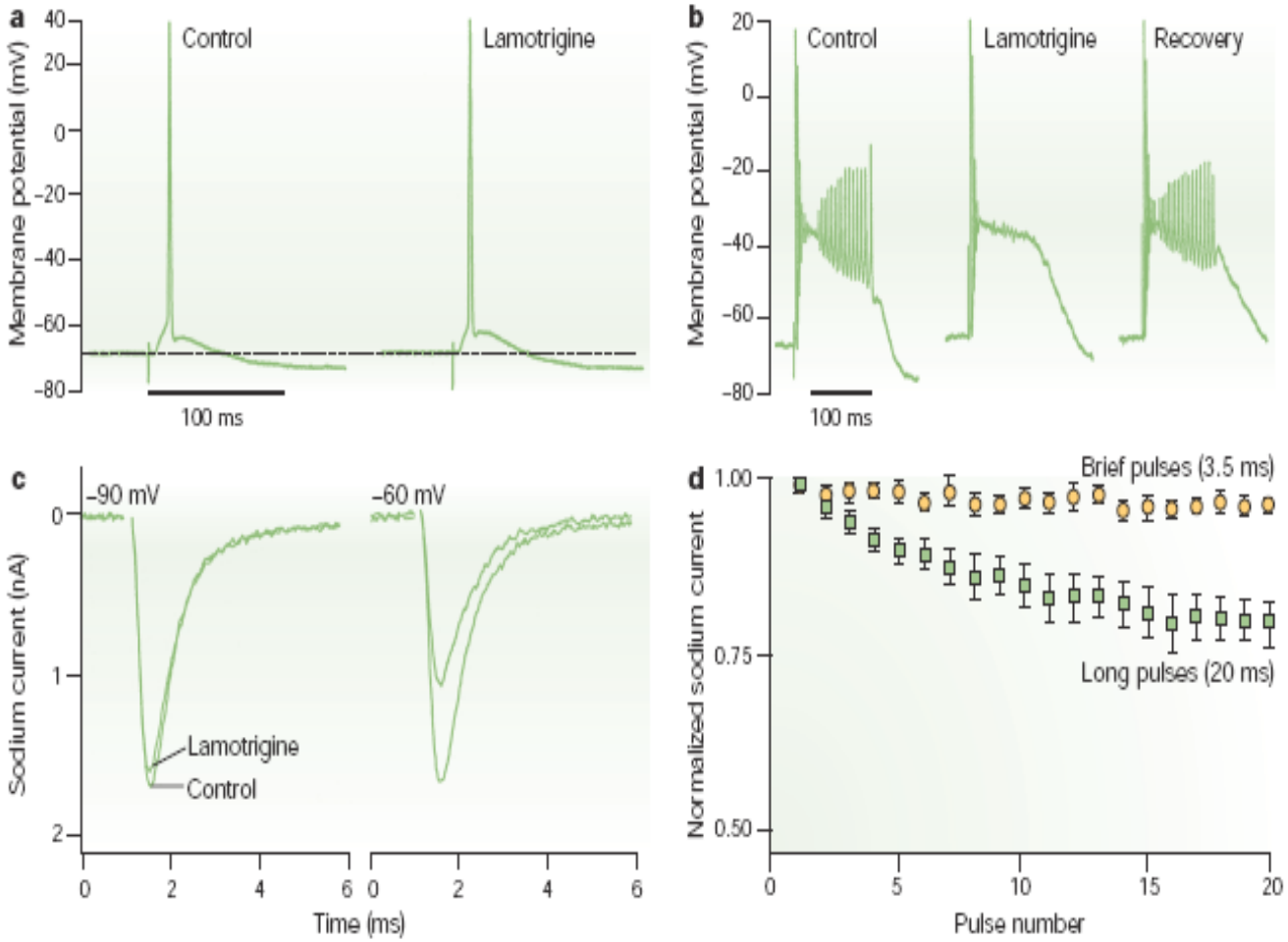
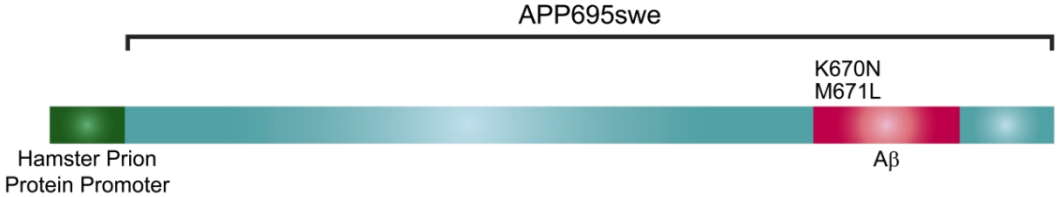
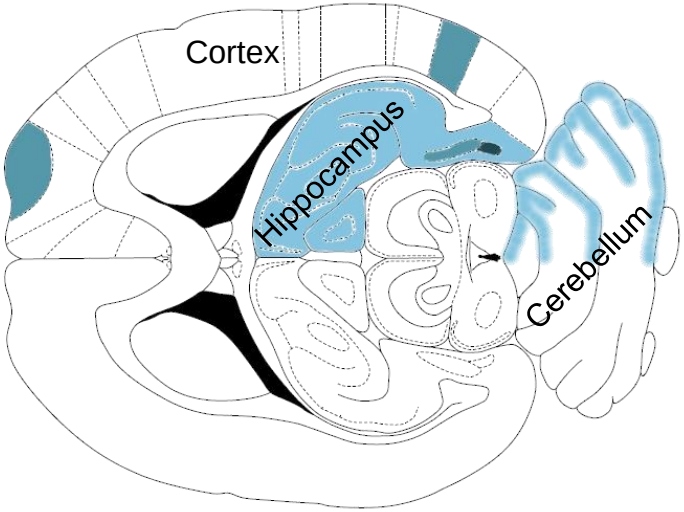


Figure 1 | **Lamotrigine selectively blocks epileptiform discharges without affecting ordinary action potential firing.** **a** | Intracellular recording showing lack of effect of lamotrigine (50 μM) on evoked excitatory synaptic response with superimposed sodium-dependent action potentials. **b** | Recording under magnesium-free conditions (to enhance NMDA (*N*-methyl-D-aspartate) receptor responses) and in the presence of 20 μM bicuculline (to block $GABA_A$ (γ-aminobutyric acid, type A) receptors) showing that lamotrigine selectively inhibits late epileptiform after-discharges without affecting initial action potential responses. Intracellular recordings are from rat CA1 hippocampal neurons evoked with Schaffer collateral/commissural fibre stimulation. **c** | Whole-cell voltage-clamp recording from CNaIIA-1 cells (CHO-K1 cells stably transfected with cDNA encoding rat brain type IIA sodium channels) illustrating voltage-dependent inhibition of sodium current by lamotrigine (50 μM). Currents were activated by step-depolarization to 0 mV from a 30 s conditioning prepulse at the indicated membrane potentials. **d** | Accumulation of block of sodium current with repetitive depolarization (11 Hz) from −90 to 0 mV with pulses of two durations illustrating use-dependence. Modified, with permission, from REF. 17 © (1995) Springer-Verlag.

Animal models of Alzheimer's disease

Tg2576 mouse model





Long-Term Potentiation

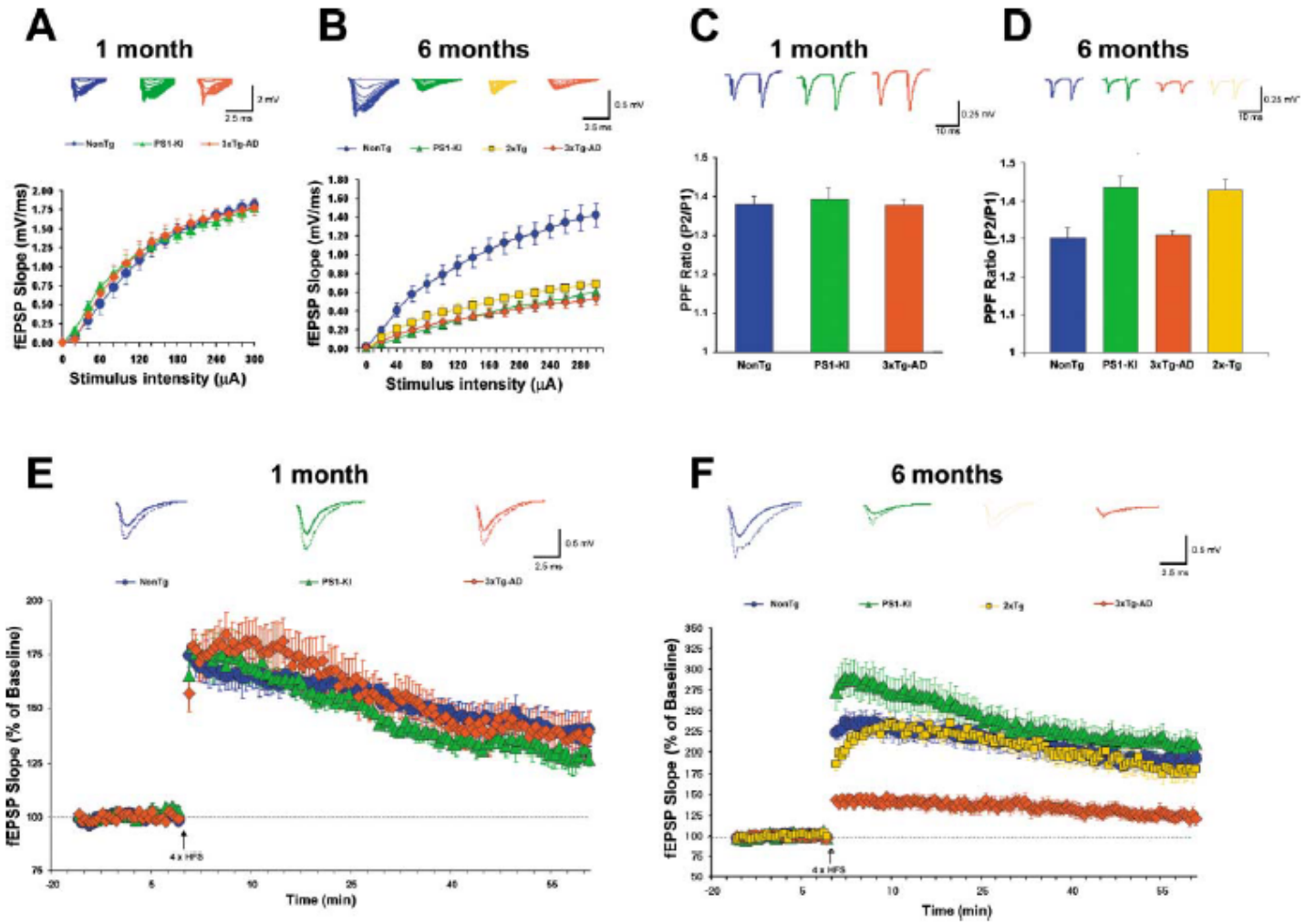
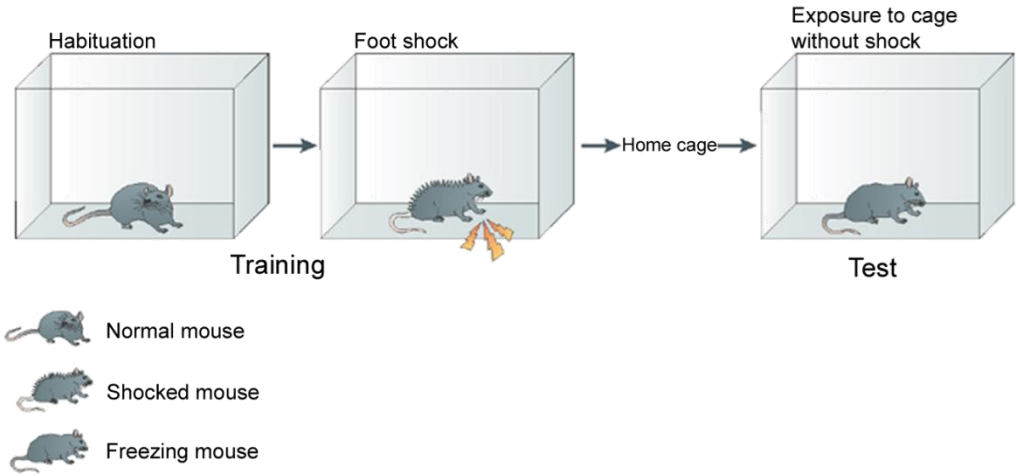


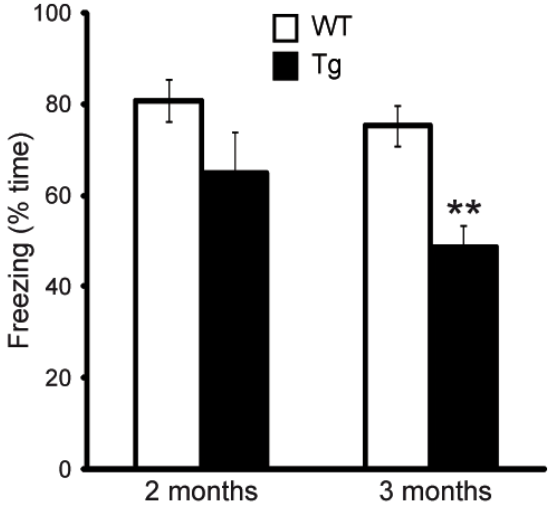
Figure 6. Age-Related Synaptic Dysfunction in 3×Tg-AD Mice

(A) Input/output (I/O) curves and representative fEPSPs at increasing stimulus strengths are shown for NonTg, PS1-KI, and 3×Tg-AD mice, showing no differences at 1 month of age.

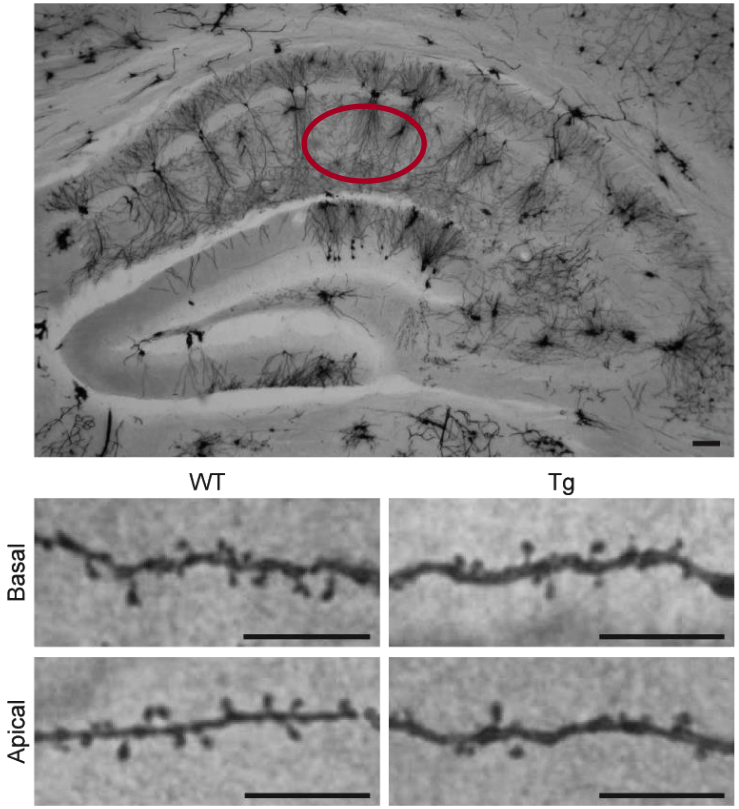
Onset of memory decline in Tg2576 mice

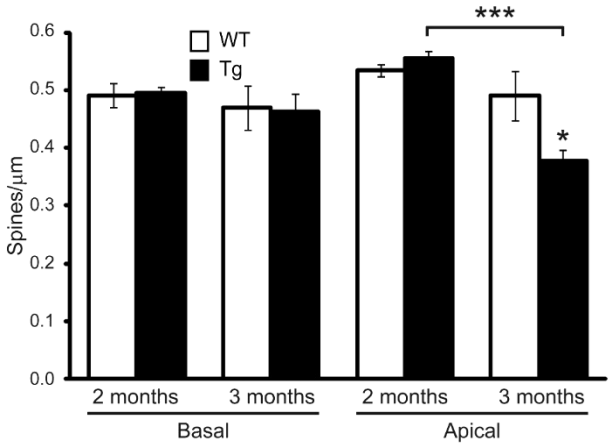
Contextual fear conditioning (CFC) test

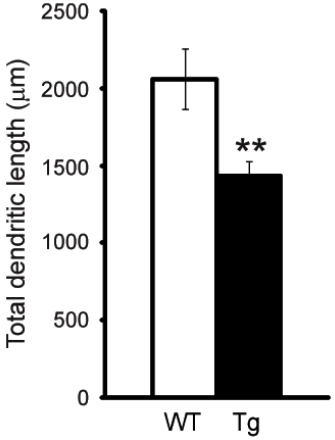


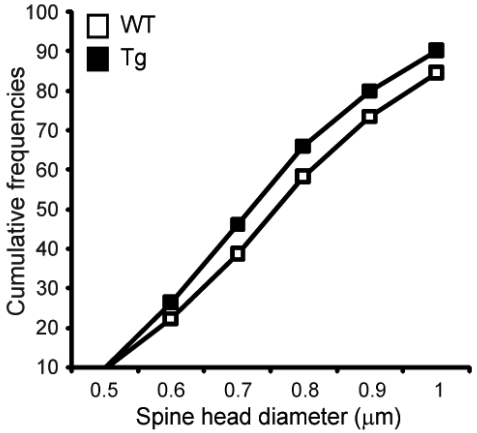


Spine density and spine morphology alteration in 3-month-old Tg2576 hippocampus









nature COMMUNICATIONS

ARTICLE

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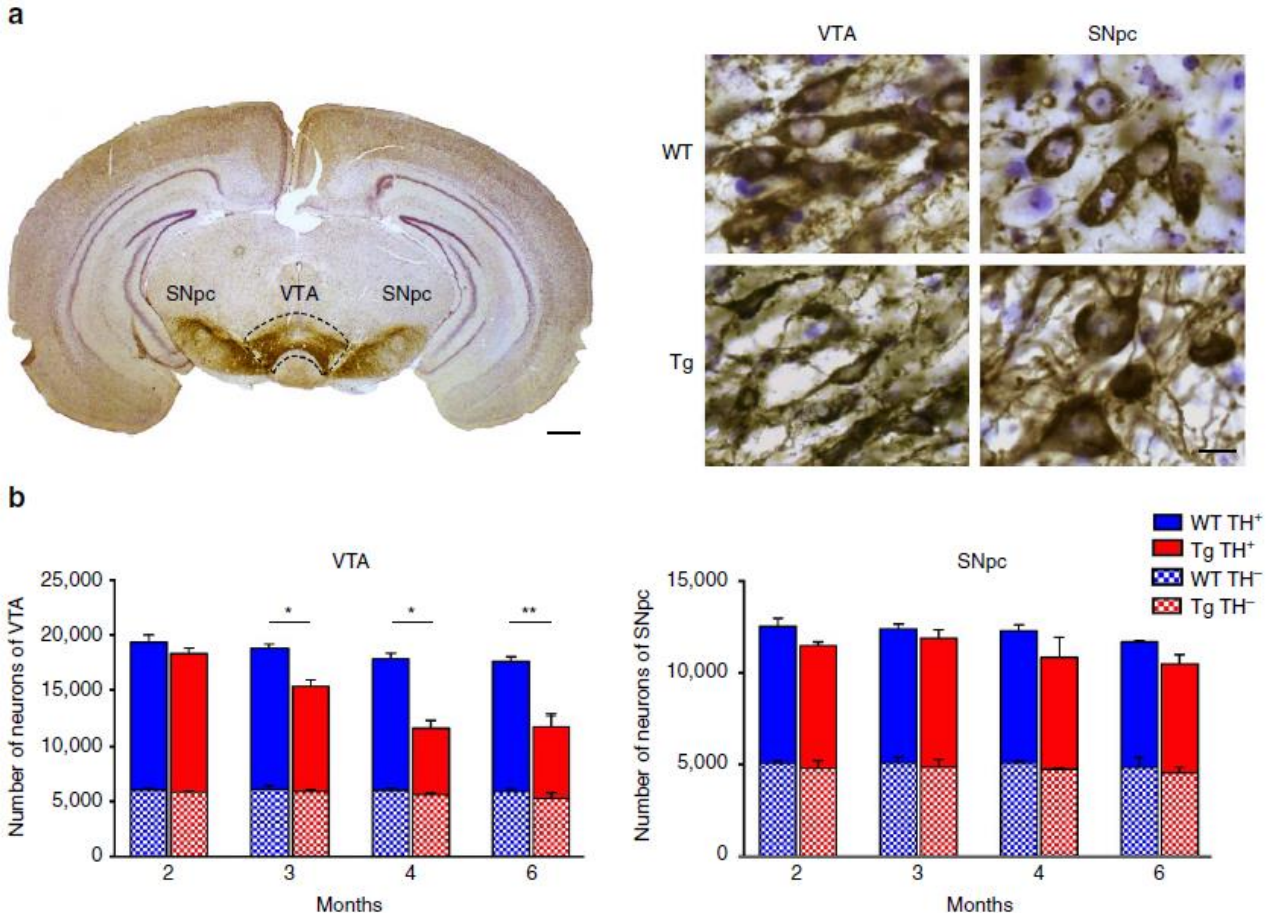
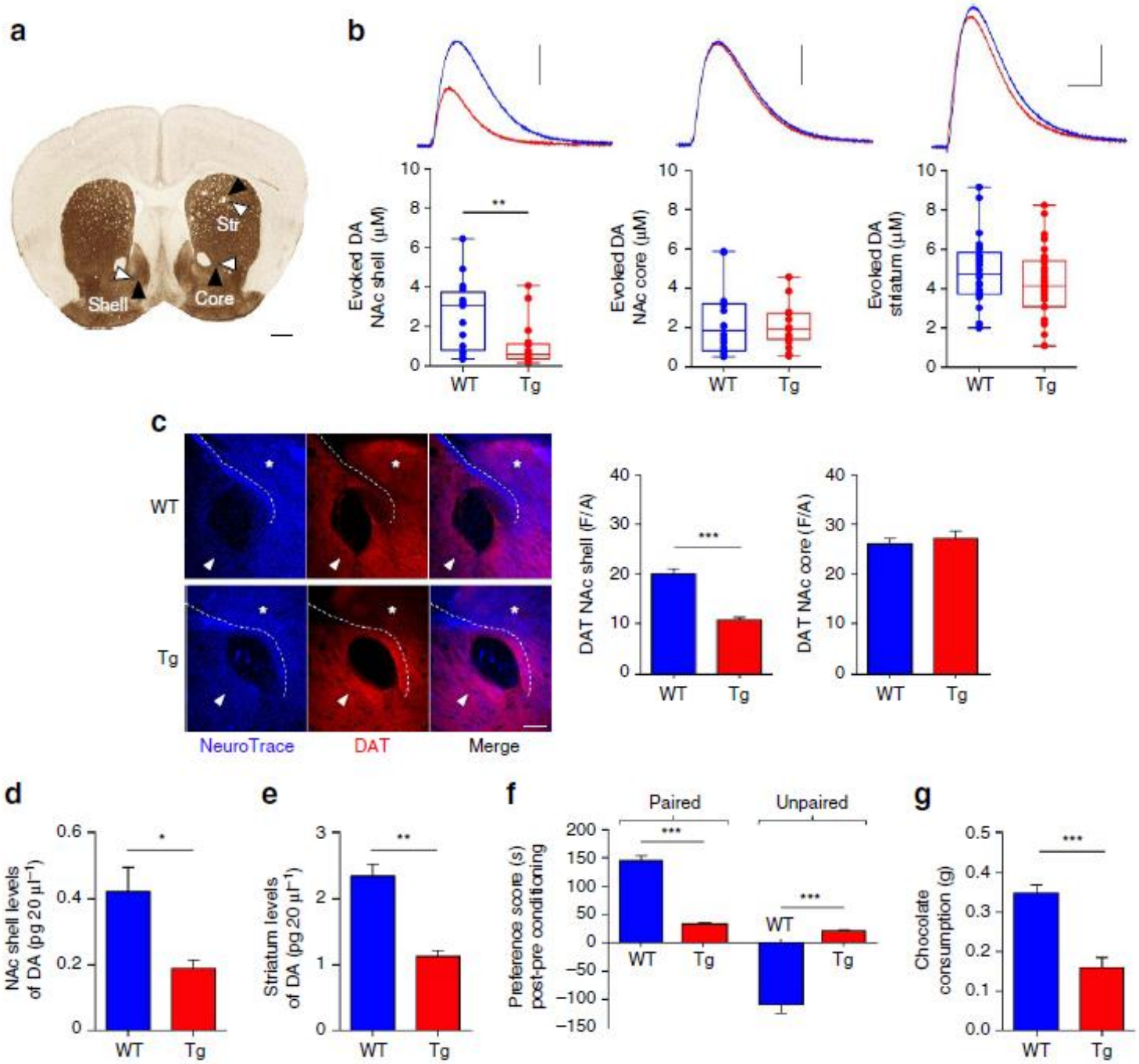
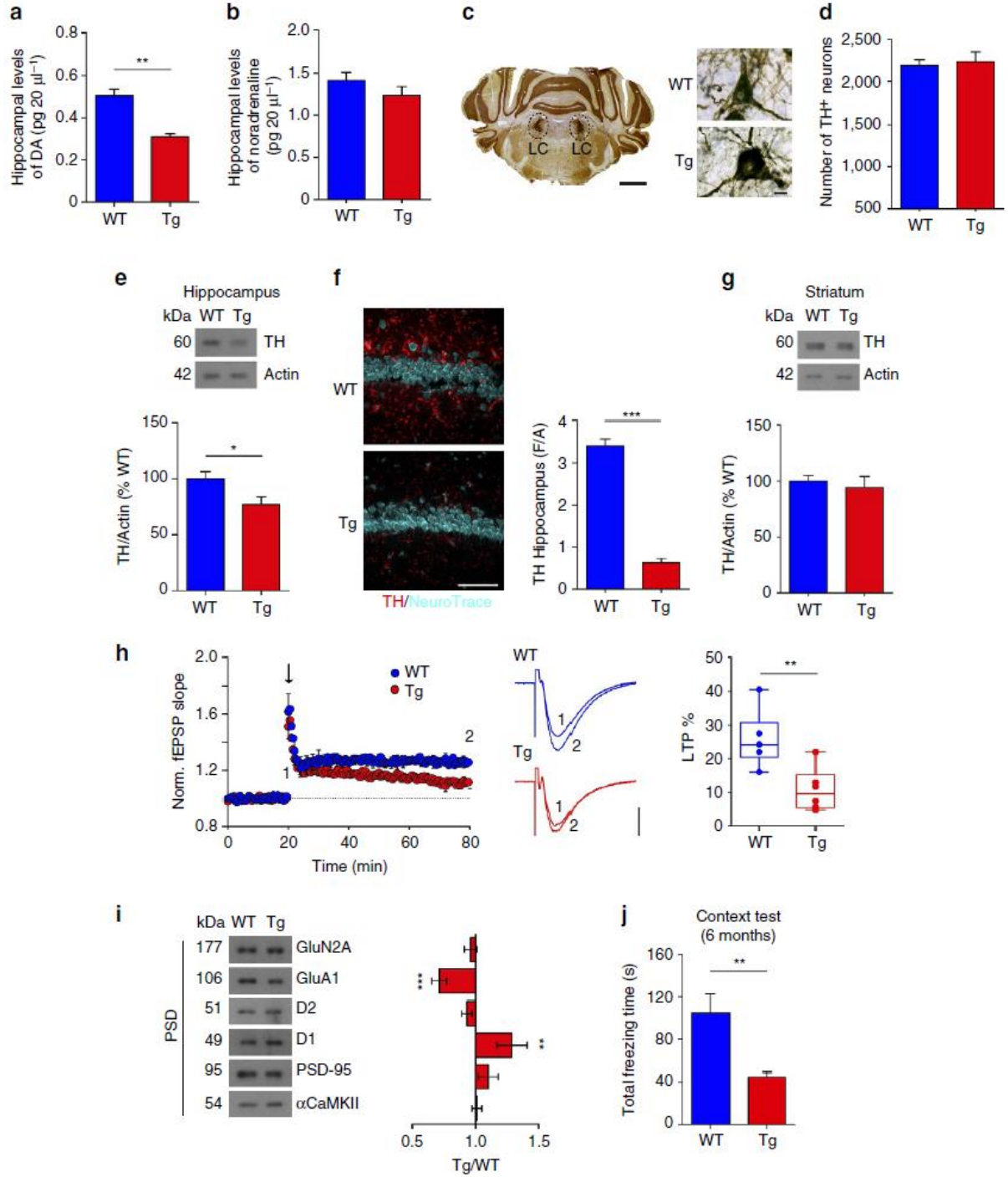
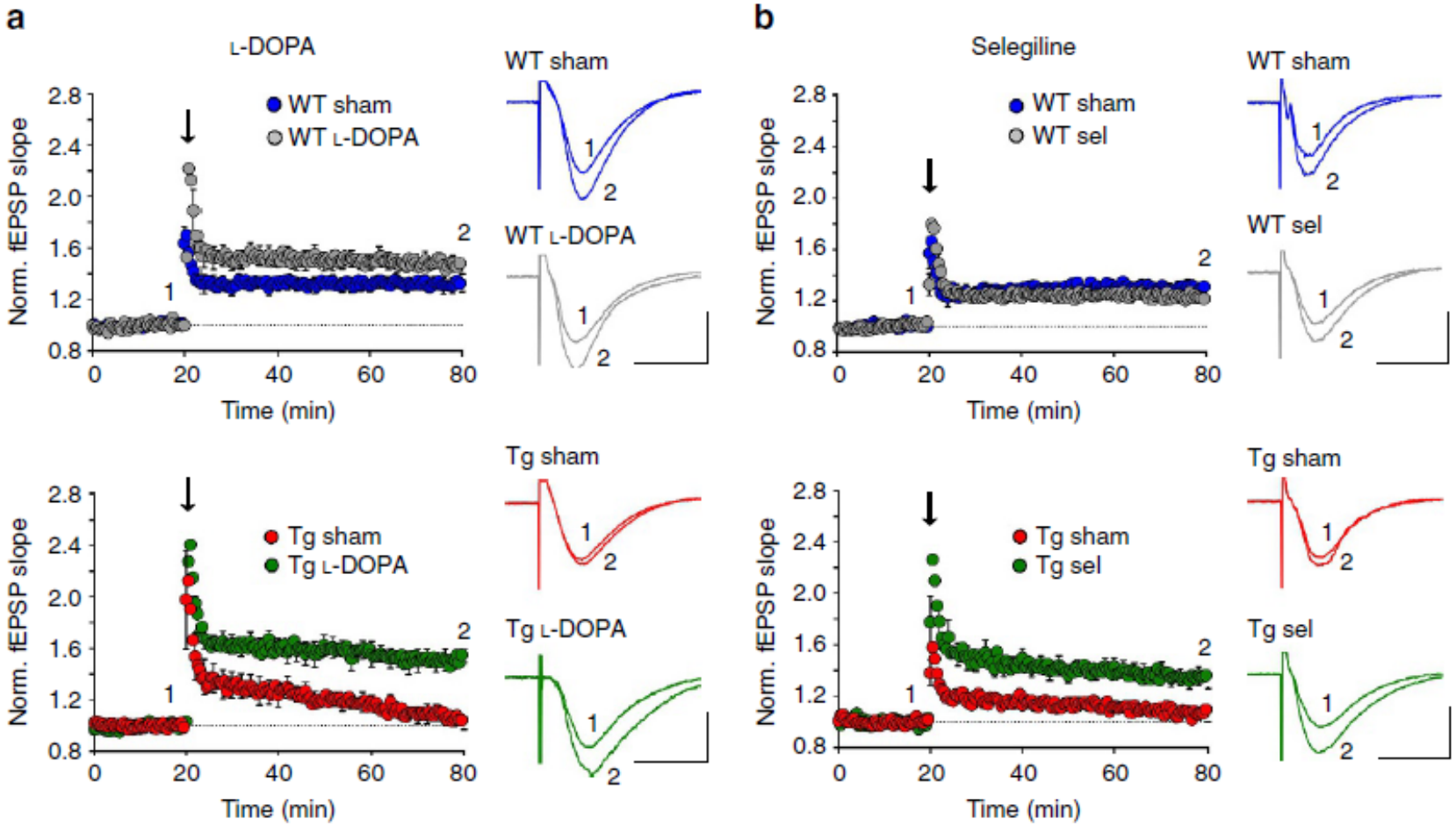
Dopamine neuronal loss contributes to memory and reward dysfunction in a model of Alzheimer's disease

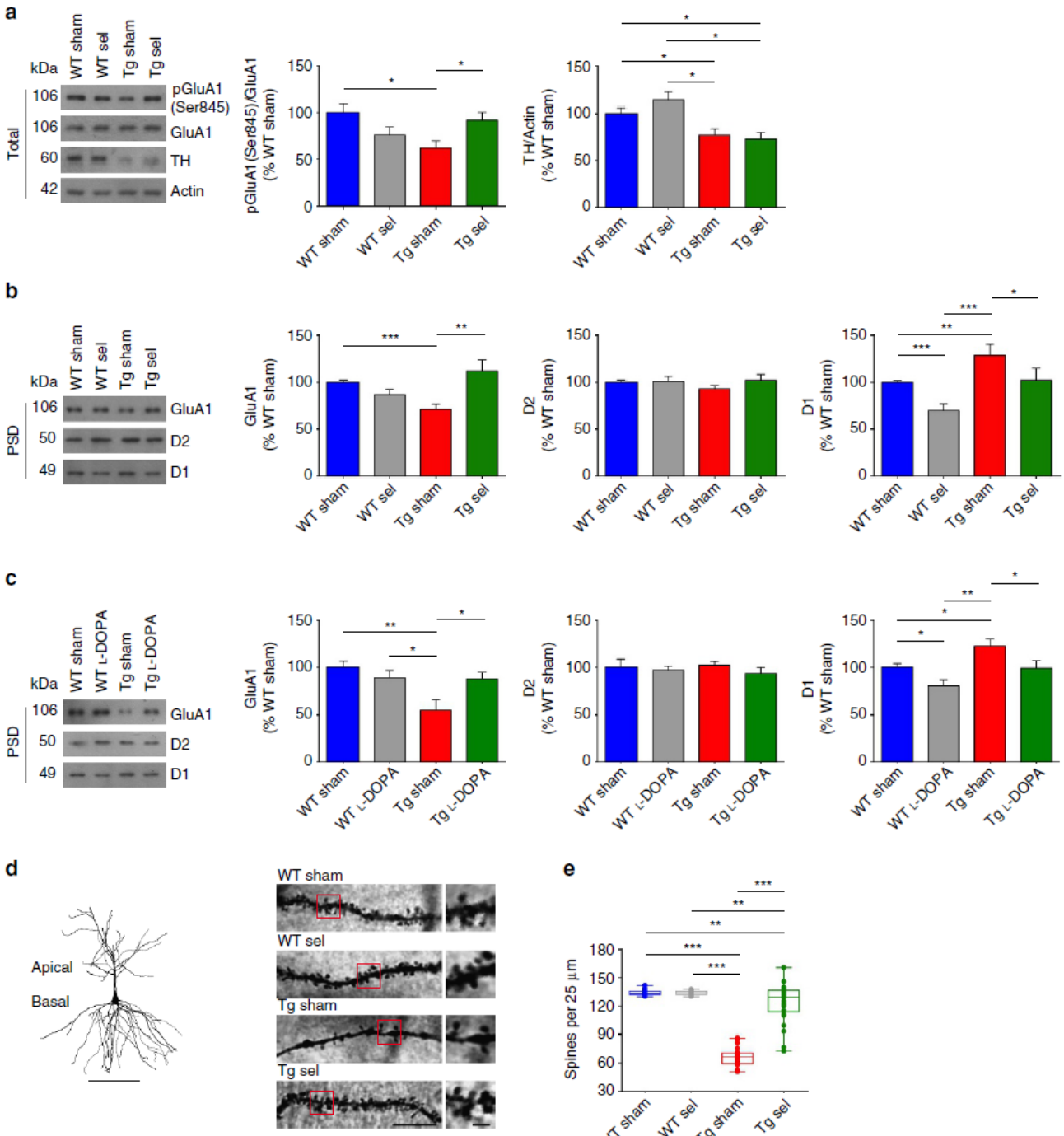
Annalisa Nobili[1,2], Emanuele Claudio Latagliata[1], Maria Teresa Viscomi[1], Virve Cavallucci[1,2,†], Debora Cutuli[1], Giacomo Giacovazzo[1,3], Paraskevi Krashia[1,4], Francesca Romana Rizzo[1,4], Ramona Marino[2,5], Mauro Federici[1], Paola De Bartolo[1,6], Daniela Aversa[1,4], Maria Concetta Dell'Acqua[1,2], Alberto Cordella[1,4], Marco Sancandi[7], Flavio Keller[5], Laura Petrosini[1,7], Stefano Puglisi-Allegra[1,7], Nicola Biagio Mercuri[1,4], Roberto Coccurello[1,3], Nicola Berretta[1] & Marcello D'Amelio[1,2]

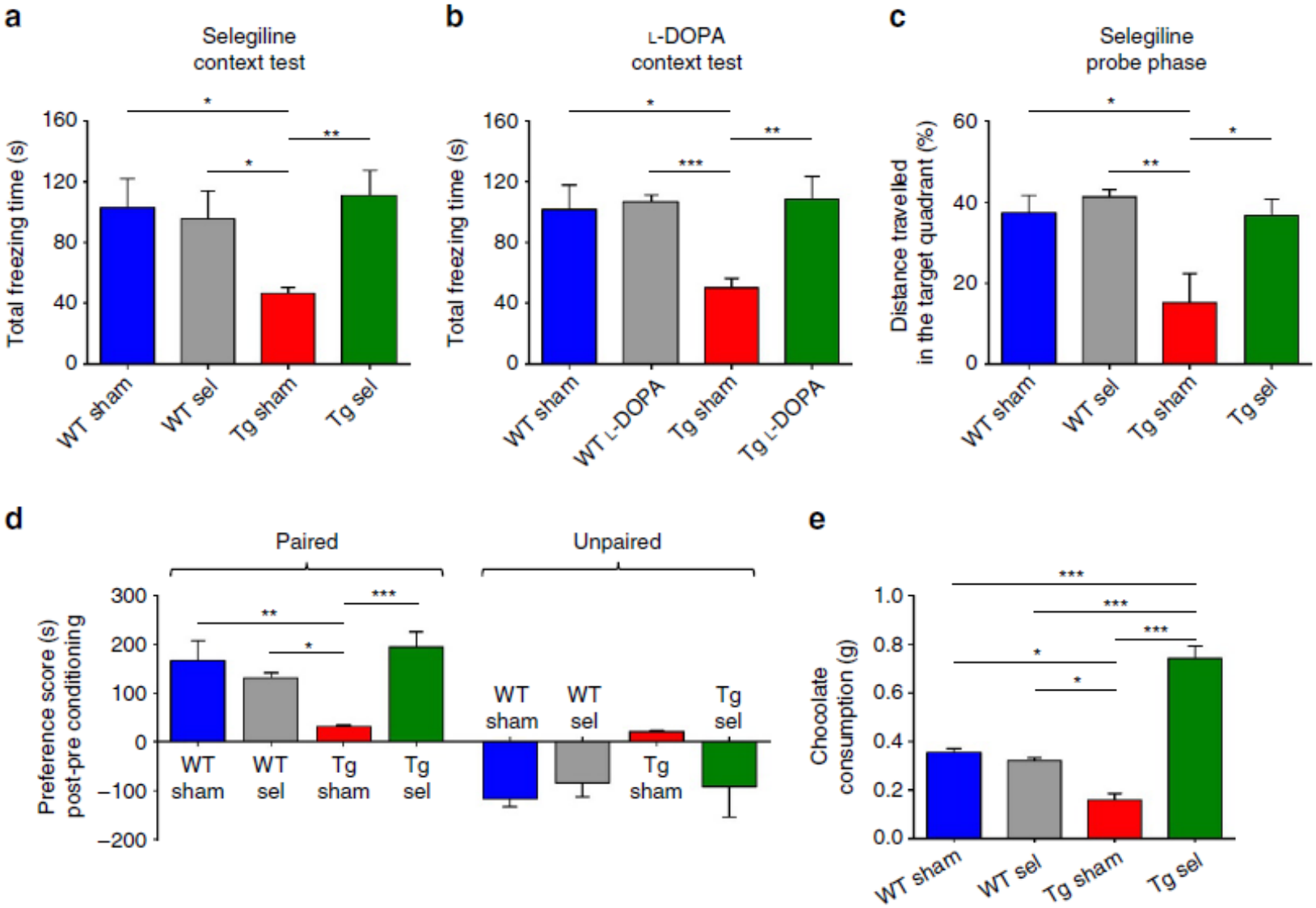



a
Str
Shell
Core
b
Evoked DA NAc shell (μM)
Evoked DA NAc core (μM)
Evoked DA striatum (μM)
**
WT
Tg
c
WT
Tg
NeuroTrace
DAT
Merge
DAT NAc shell (F/A)
DAT NAc core (F/A)
***
d
NAc shell levels of DA (pg 20 μl⁻¹)
*
e
Striatum levels of DA (pg 20 μl⁻¹)
**
f
Paired
Unpaired
Preference score (s) post-pre conditioning
***
g
Chocolate consumption (g)
***


a
Hippocampal levels of DA (pg 20 µl⁻¹)
0.8
0.6
0.4
0.2
0
**
WT
Tg
b
Hippocampal levels of noradrenaline (pg 20 µl⁻¹)
2.0
1.5
1.0
0.5
0
WT
Tg
c
LC
LC
WT
Tg
d
Number of TH+ neurons
2,500
2,000
1,500
1,000
500
WT
Tg
e
Hippocampus
kDa WT Tg
60 TH
42 Actin
TH/Actin (% WT)
150
100
50
0
*
WT
Tg
f
WT
Tg
TH/NeuroTrace
TH Hippocampus (F/A)
4
3
2
1
0
***
WT
Tg
g
Striatum
kDa WT Tg
60 TH
42 Actin
TH/Actin (% WT)
150
100
50
0
WT
Tg
h
Norm. fEPSP slope
2.0
1.6
1.2
0.8
WT
Tg
1
2
0
20
40
60
80
Time (min)
WT
Tg
1
2
LTP %
50
40
30
20
10
0
**
WT
Tg
i
kDa WT Tg
PSD
177 GluN2A
106 GluA1
51 D2
49 D1
95 PSD-95
54 αCaMKII
0.5
1.0
1.5
Tg/WT
j
Context test
(6 months)
Total freezing time (s)
160
120
80
40
0
**
WT
Tg


a
L-DOPA
WT sham
WT L-DOPA
Norm. fEPSP slope
Time (min)
Tg sham
Tg L-DOPA
b
Selegiline
WT sel
Tg sel


a
kDa
WT sham
WT sel
Tg sham
Tg sel
Total
106
pGluA1 (Ser845)
106
GluA1
60
TH
42
Actin
pGluA1 (Ser845)/GluA1 (% WT sham)
TH/Actin (% WT sham)
b
PSD
106
GluA1
50
D2
49
D1
GluA1 (% WT sham)
D2 (% WT sham)
D1 (% WT sham)
c
WT L-DOPA
Tg L-DOPA
d
Apical
Basal
WT sham
WT sel
Tg sham
Tg sel
e
Spines per 25 µm


a
Selegiline
context test
Total freezing time (s)
160
120
80
40
0
*
*
**
WT sham
WT sel
Tg sham
Tg sel
b
L-DOPA
context test
Total freezing time (s)
160
120
80
40
0
*
***
**
WT sham
WT L-DOPA
Tg sham
Tg L-DOPA
c
Selegiline
probe phase
Distance travelled
in the target quadrant (%)
60
40
20
0
*
**
*
WT sham
WT sel
Tg sham
Tg sel
d
Paired
Unpaired
Preference score (s)
post-pre conditioning
300
200
100
0
−100
−200
**
*
***
WT
sham
WT
sel
Tg
sham
Tg
sel
WT
sham
WT
sel
Tg
sham
Tg
sel
e
Chocolate
consumption (g)
1.0
0.8
0.6
0.4
0.2
0.0
***
***
***
*
*
WT sham
WT sel
Tg sham
Tg sel

Neurobiology of Aging 72 (2018) 72–82

Contents lists available at ScienceDirect

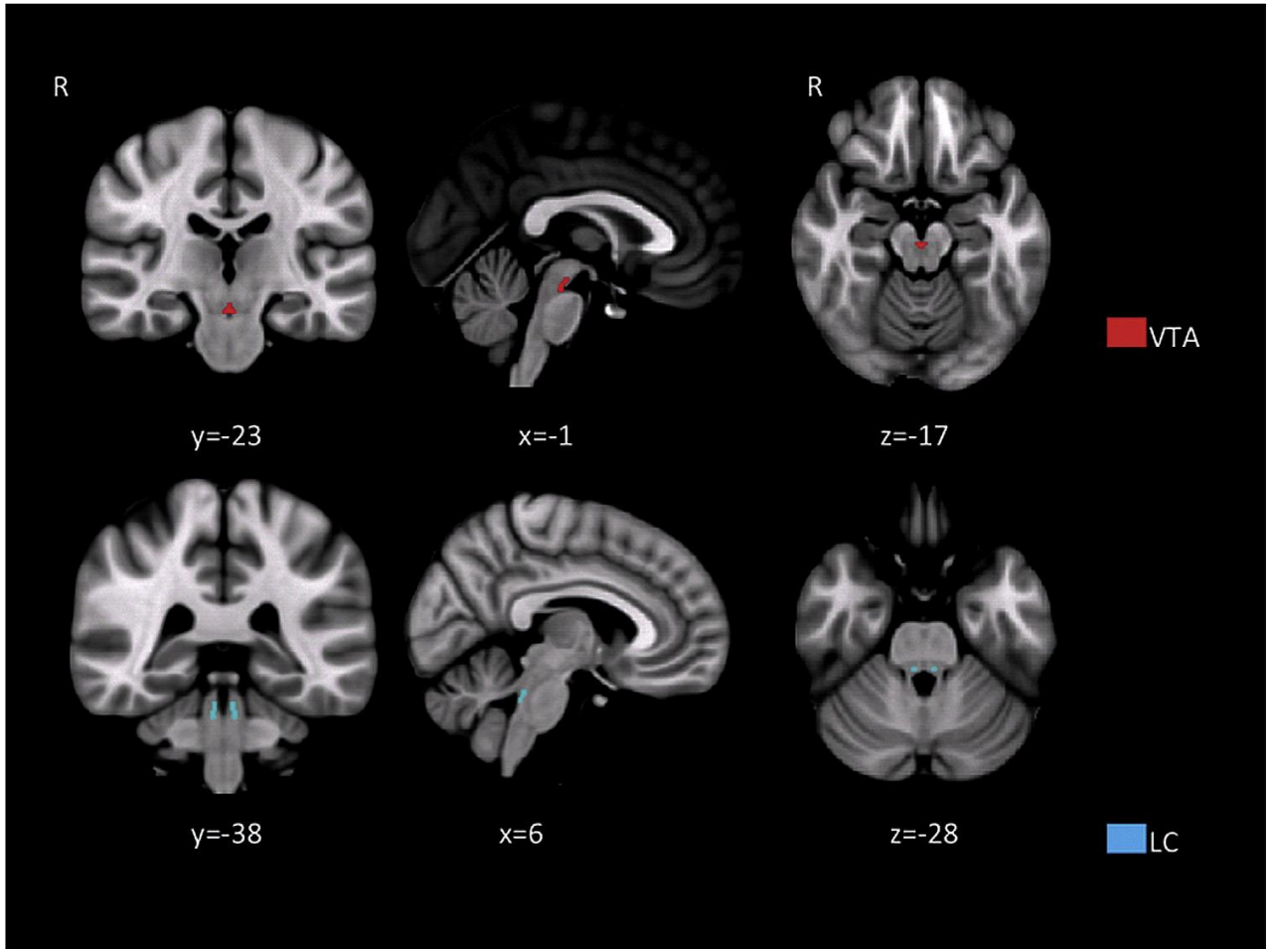
Neurobiology of Aging

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

In vivo mapping of brainstem nuclei functional connectivity disruption in Alzheimer's disease

Laura Serra [a,1], Marcello D'Amelio [b,c,1], Carlotta Di Domenico [a], Ottavia Dipasquale [d], Camillo Marra [e], Nicola Biagio Mercuri [f,g], Carlo Caltagirone [g,h], Mara Cercignani [a,i], Marco Bozzali [a,i,*]

Dati fRMN



Sala et al. Alzheimer's Research & Therapy (2021) 13:187
https://doi.org/10.1186/s13195-021-00925-1

Alzheimer's
Research & Therapy

RESEARCH Open Access

In vivo human molecular neuroimaging of dopaminergic vulnerability along the Alzheimer's disease phases

Arianna Sala[1,2†], Silvia Paola Caminiti[1,2†], Luca Presotto[3], Andrea Pilotto[4,5], Claudio Liguori[6], Agostino Chiaravalloti[7,8], Valentina Garibotto[9], Giovanni Battista Frisoni[9,10], Marcello D'Amelio[11,12], Barbara Paghera[13], Orazio Schillaci[7,8], Nicola Mercuri[6,11], Alessandro Padovani[4] and Daniela Perani[1,2,3*]

Dati SPECT

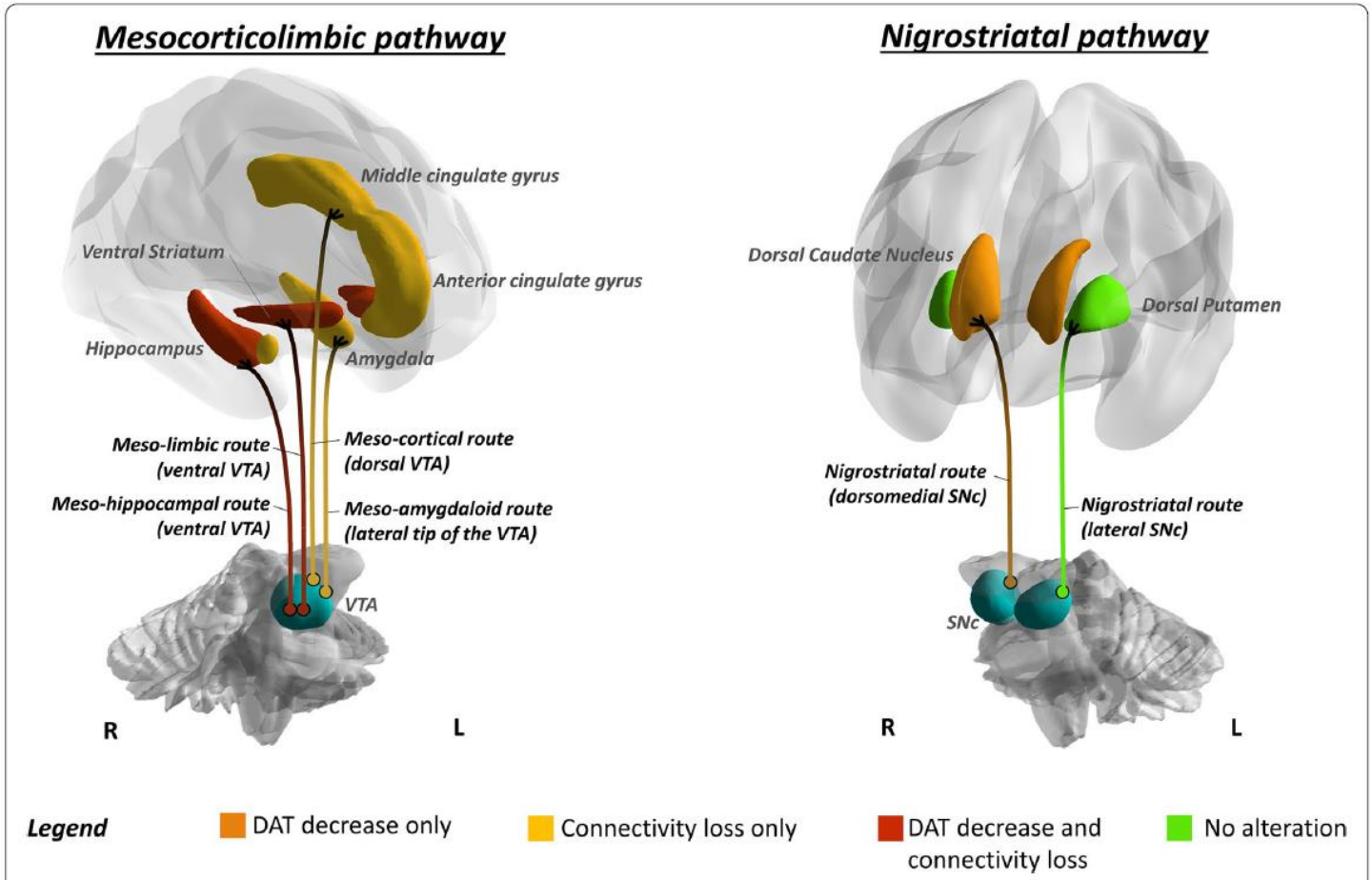
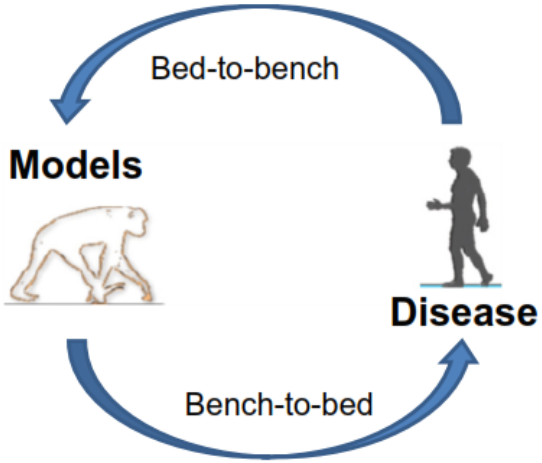


Fig. 5 Summary representation of dopaminergic dysfunction in early AD. Brain renderings show dopaminergic targets presenting with decreased DAT activity (orange), loss of molecular connectivity (yellow), or both (red) in prodromal AD. Alterations in these target regions can be deemed indicative of pre-synaptic dopaminergic dysfunction in specific afferents from the ventral and dorsal VTA and from the medial SN, pars compacta. For the purpose of ensuring a clear visualization, dopaminergic projections are represented only for each target region on the ipsilateral side. Brain renderings were obtained from the BrainNet Viewer toolbox [35]. Abbreviations: SNc, substantia nigra pars compacta; VTA, ventral tegmental area

Conclusioni

La ricerca traslazionale è quel tipo di ricerca che aiuta a trovare dati scientifici di base che siano utili per applicazioni pratiche che migliorino la salute dell'uomo nelle malattie (neurologiche).

Rappresenta, dunque, la reale integrazione tra l'attività di ricerca sperimentale e la pratica clinica.

La Ricerca Traslazionale serve in definitiva
a capire, prevenire, trattare, far regredire le malattie