International Course on Functional Stereotactic Neurosurgery, Beijing, May 2015

- Elements of Basal Ganglia Anatomy
- Physiology of Basal Ganglia
- Physiopathology of Basal Ganglia
- High Frequency Stimulation mechanism hypothesis

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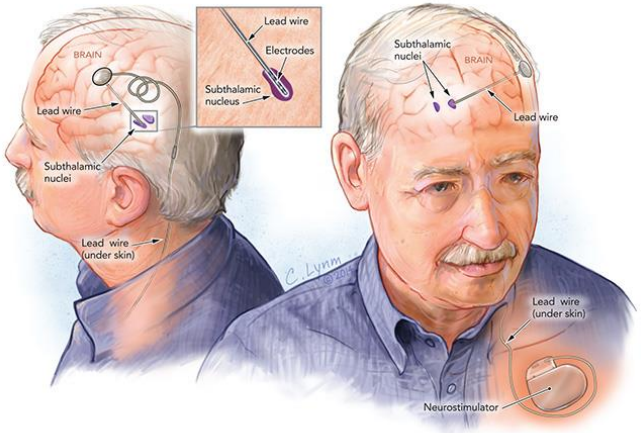
Lasker DeBakey

Clinical Medical Research Award

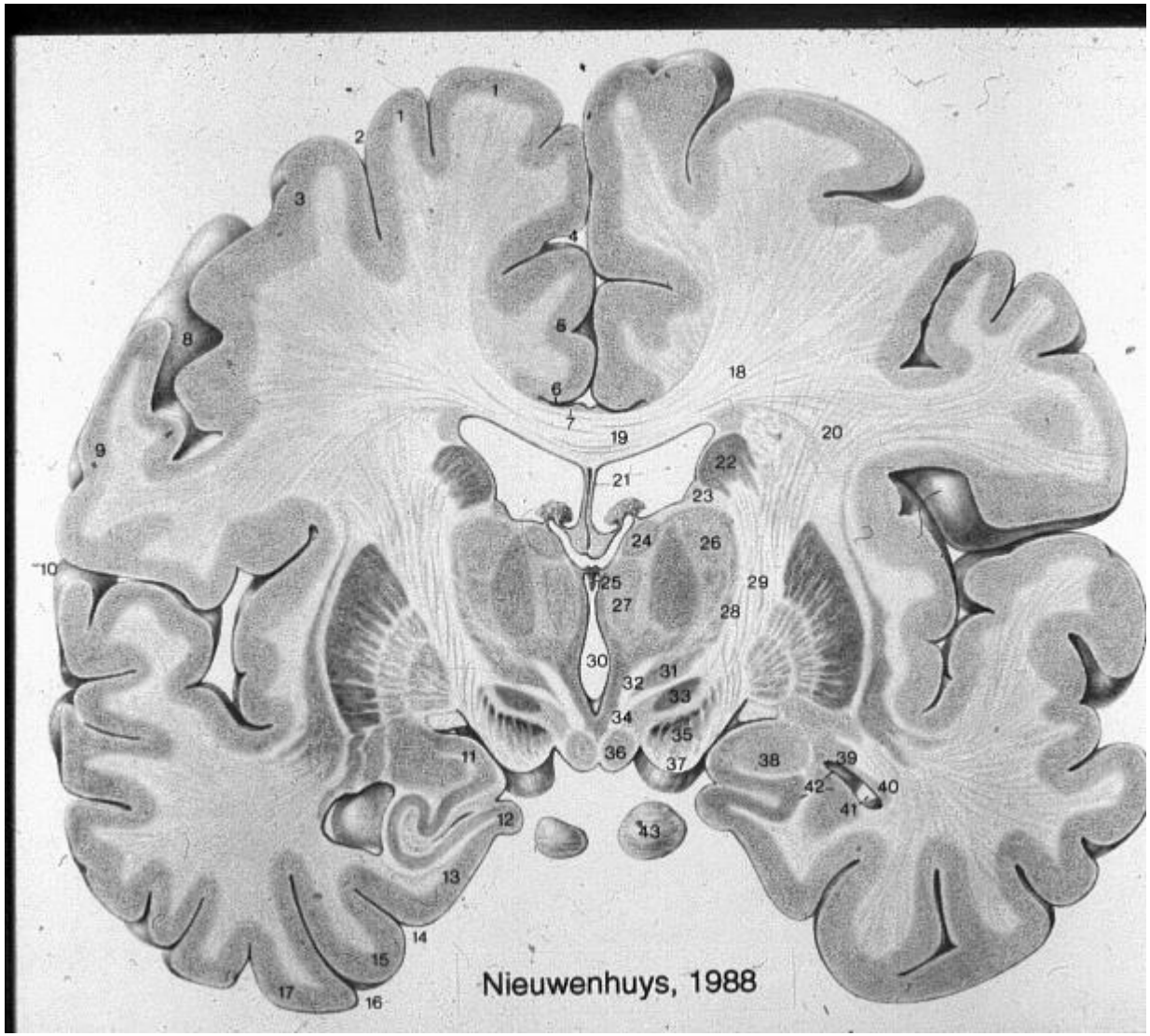
Alim Louis Benabid and **Mahlon DeLong**

For the development of deep brain stimulation of the subthalamic nucleus, a surgical technique that reduces tremors and restores motor function in patients with advanced Parkinson's disease.



Deep Brain Stimulation. Electrodes attached to a lead wire are implanted into the subthalamic nucleus (or another target site) through a small opening in the skull. The insulated wire tunnels to a programmable neurotransmitter that lies under the skin near the collarbone and delivers the therapeutic current.

CREDIT: Illustration by Cassio Lynm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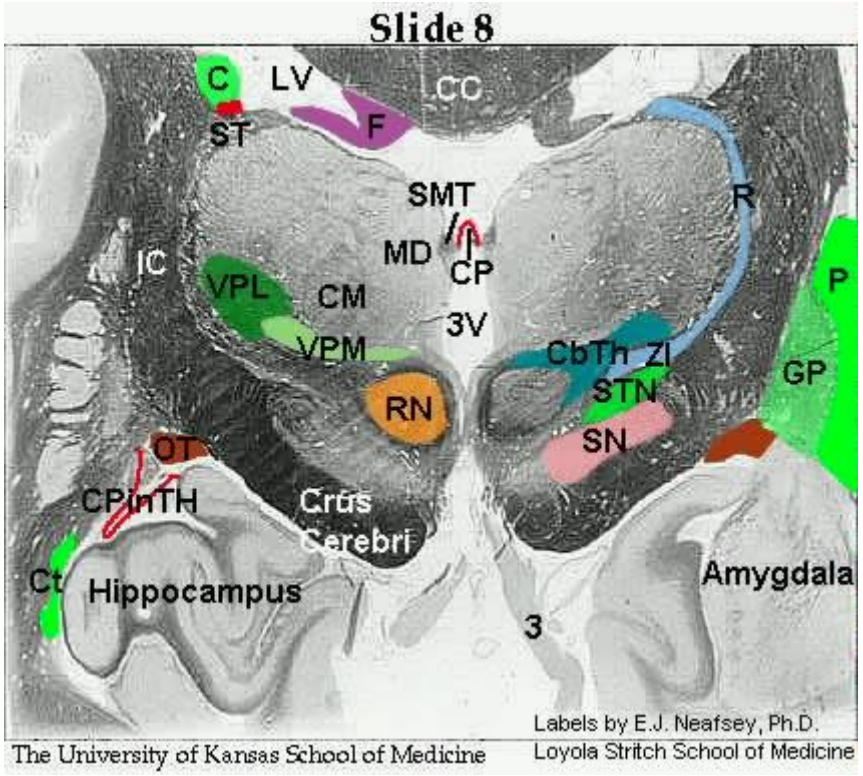
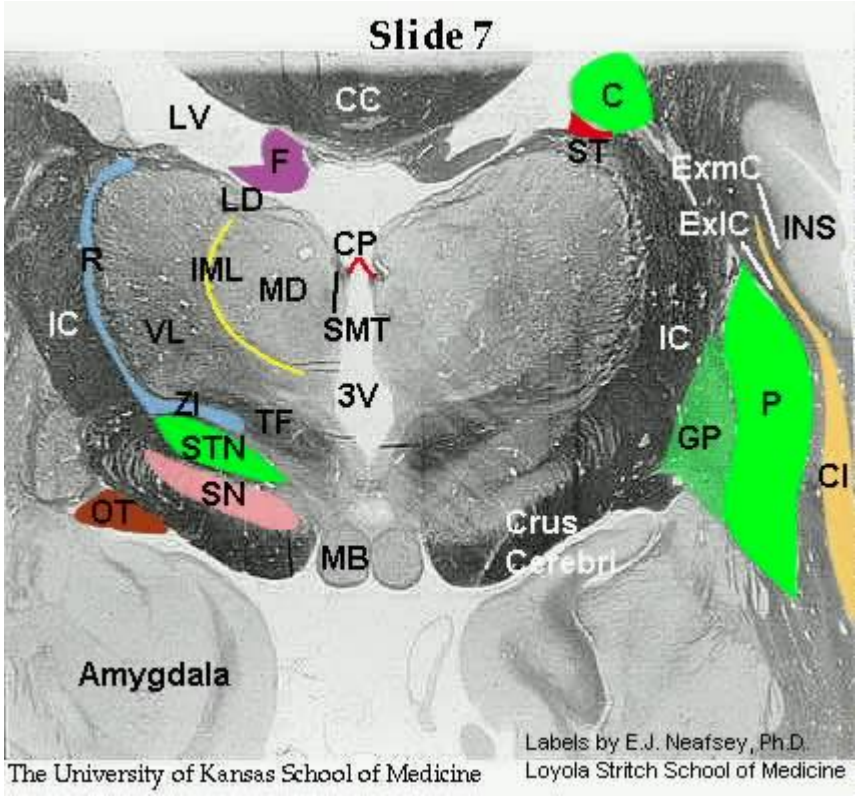
Nieuwenhuys, 1988



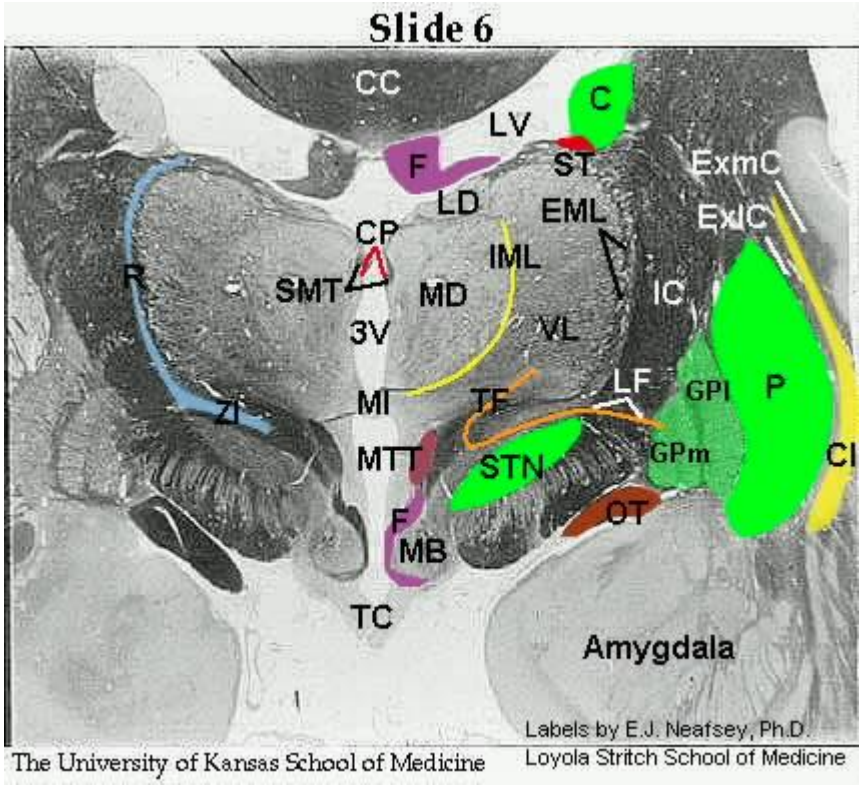
Ventral Posteromedial (VPM) and Ventral Posterolateral (VPL) nuclei
Centromedian nucleus (CM)
Mediodorsal Nucleus (MD)
Stria Medullaris Thalami (SMT)
Choroid Plexus forming roof of third ventricle (3V)
Crus Cerebri
Substantia Nigra (SN)
Red Nucleus (RN)
Reticular nucleus (R) and Zona Incerta (ZI)
Internal Capsule (IC)
Stria Terminalis (ST)
Body of Lateral Ventricle (LV)
Corpus Callosum (CC)
Fornix (F)
Optic Tract (OT)
Subthalamic Nucleus (STN)
Body of Lateral Ventricle (LV)
Body of Caudate (C)
Putamen (P)
Globus Pallidus (GP)
Oculomotor Nerves (3)
Amygdala
Tail of Caudate (Ct)
Temporal Horn of Lateral Ventricle (TH)
Hippocampus
Amygdala

http://www.meddean.luc.edu/lumen/MedEd/Neuro



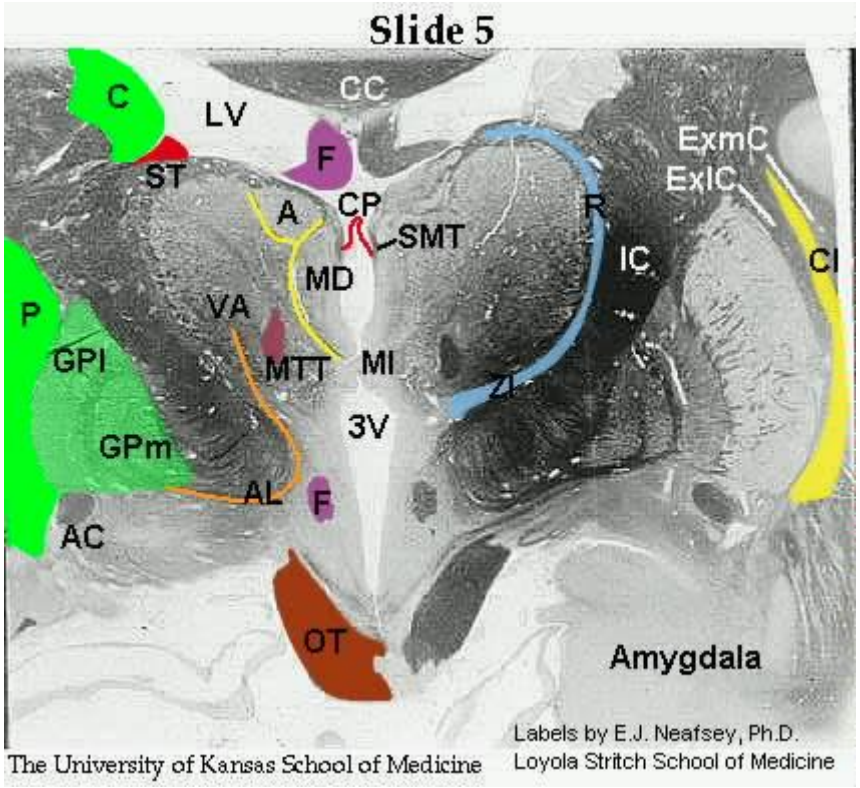
Corpus Callosum (CC)
Fornix (F)
Lateral Ventricle (LV)
Body of Caudate (C)
Stria Terminalis (ST)
Stria Medullaris Thalami (SMT)
Mediodorsal Nucleus (MD)
Lateral Dorsal nucleus (LD)
Choroid Plexus (CP) forming roof of third ventricle (3V)
Internal Medullary Lamina (IML)
Ventral Lateral Nucleus (VL)
Thalamic fasciculus (TF, contains cerebello-thalamic and pallido-thalamic fibers)
Reticular Nucleus (R) and Zona Incerta (ZI)
Internal Capsule (IC)
Subthalamic Nucleus (STN)
Substantia Nigra (SN)
Crus Cerebri
Extreme Capsule (ExmC)
Claustrum (Cl)
External Capsule (ExlC)
Putamen (P)
Globus Pallidus (GPm, GPl)
Amygdala
Mammillary Bodies (MB)

http://www.meddean.luc.edu/lumen/MedEd/Neuro



Corpus Callosum (CC)
Lateral Ventricle (LV)
Fornix (F, both dorsally and ventrally)
Body of Caudate (C)
Stria Terminalis (ST)
Stria Medullaris Thalami (SMT, thin band of white matter on medial surface of MD)
Choroid Plexus forming roof of third ventricle (3V)
Mediodorsal Nucleus (MD)
Lateral Dorsal Nucleus (LD)
Internal Medullary Lamina (IML)
Ventral Lateral Nucleus (VL)
External Medullary Lamina (EML)
Reticular Nucleus (R) and Zona Incerta (ZI)
Subthalamic Nucleus (STN)
Internal Capsule (IC)
Extreme Capsule (ExmC)
Claustrum (Cl)
External Capsule (ExlC)
Putamen (P)
Globus Pallidus (GPm, GPl)
Optic Tract (OT)
Amygdala
Lenticular Fasciculus (LF)
Thalamic Fasciculus (TF, contains pallido-thalamic and cerebello-thalamic fibers)
Mammillothalamic Tract (MTT)
Tuber cinereum (TC, contains median eminence of hypothalamo-hypophyseal portal system)

http://www.meddean.luc.edu/lumen/MedEd/Neuro



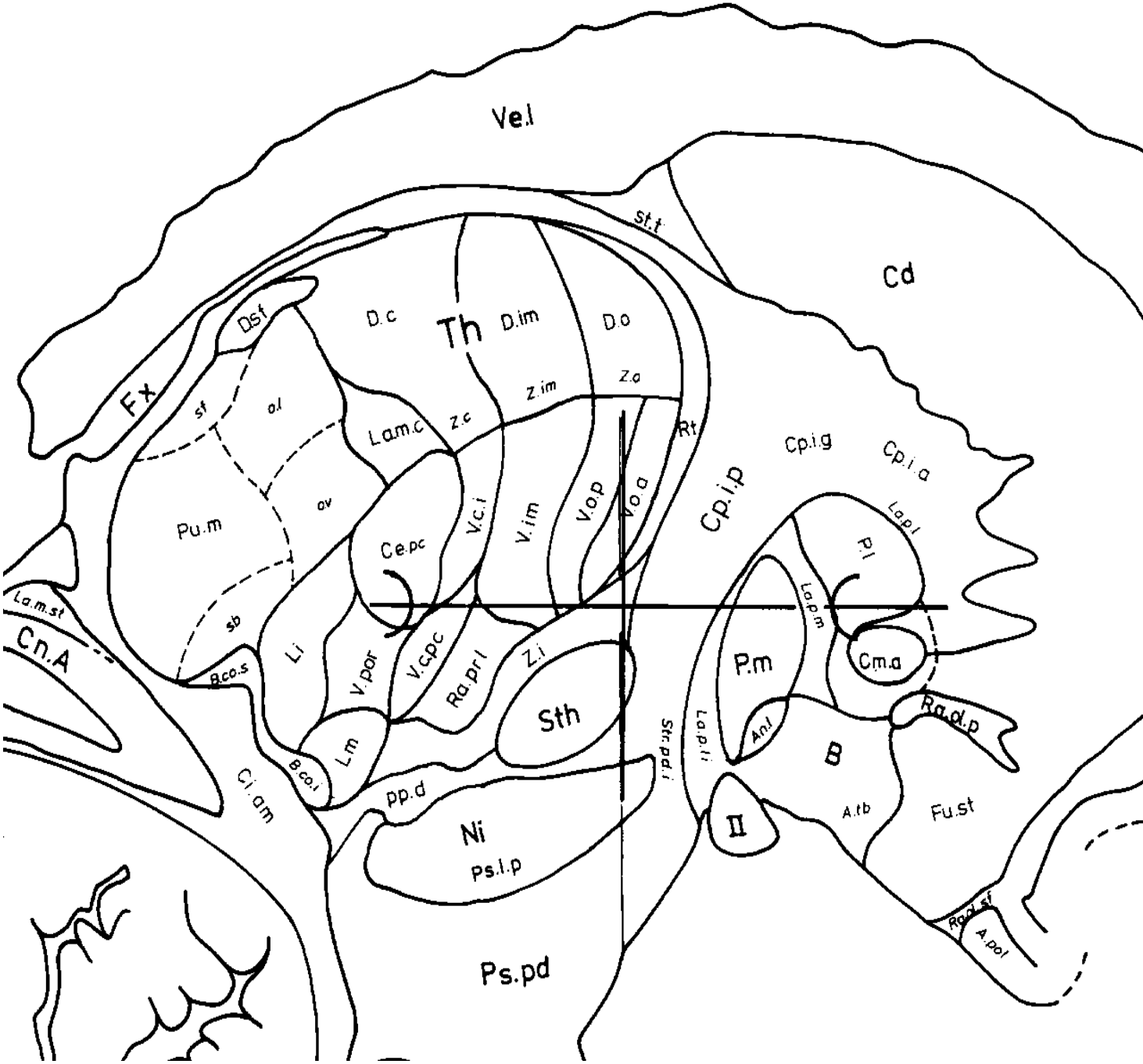
Corpus Callosum (CC)
Lateral Ventricle (LV)
Fornix (F, dorsally and ventrally)
Body of Caudate (C)
Stria Terminalis (ST)
Stria Medullaris Thalami (SMT)
Choroid Plexus (CP) forming roof of third ventricle (3V)
Mediodorsal Nucleus (MD)
Anterior Nucleus (A)
Internal Medullary Lamina (IML)
Ventral Anterior Nucleus (VA)
Reticular Nucleus (R) and Zona Incerta (ZI)
Internal Capsule (IC)
Extreme Capsule (ExmC)
Claustrum (Cl)
External Capsule (ExlC)
Putamen (P)
Globus Pallidus (GPm, GPl)
Optic Tract (OT)
Amygdala
Ansa Lenticularis (AL, pallidothalamic projections to VA)
Anterior Commissure (AC)
Mammillothalamic Tract (MTT)
Massa Intermedia (MI)

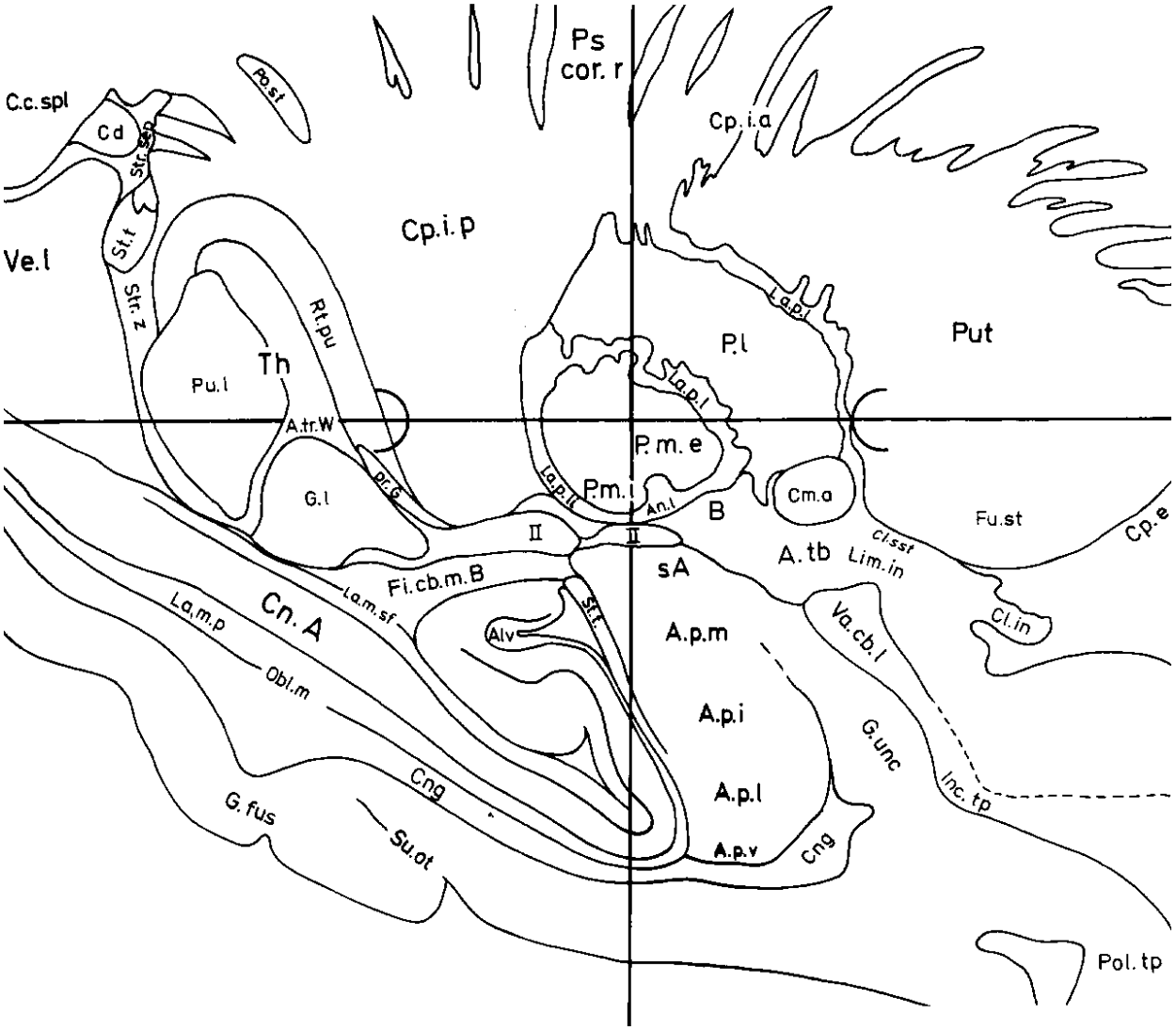
http://www.meddean.luc.edu/lumen/MedEd/Neuro

Schaltenbrand and Wahren stereotactic atlas

Sagittal view AC-PC plane

Swsl12

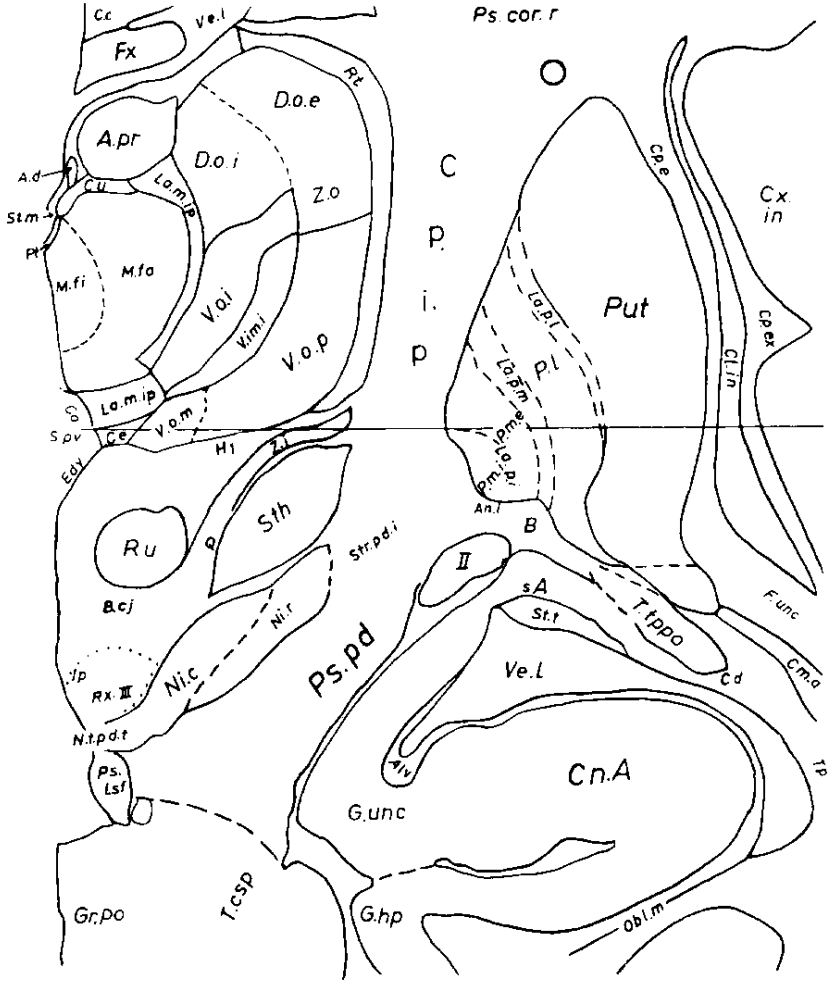




Sagittal view
AC-PC plane

SwSL22

Swfp30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Fx
Ps. cor. r
Rt
D.o.e
A.pr
D.o.i
Z.o
A.d
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La.m.ip
St.m
Pf
M.fi
M.fa
V.a.l
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V.o.p
C
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p
Cp.e
Cx. in
La.p.l
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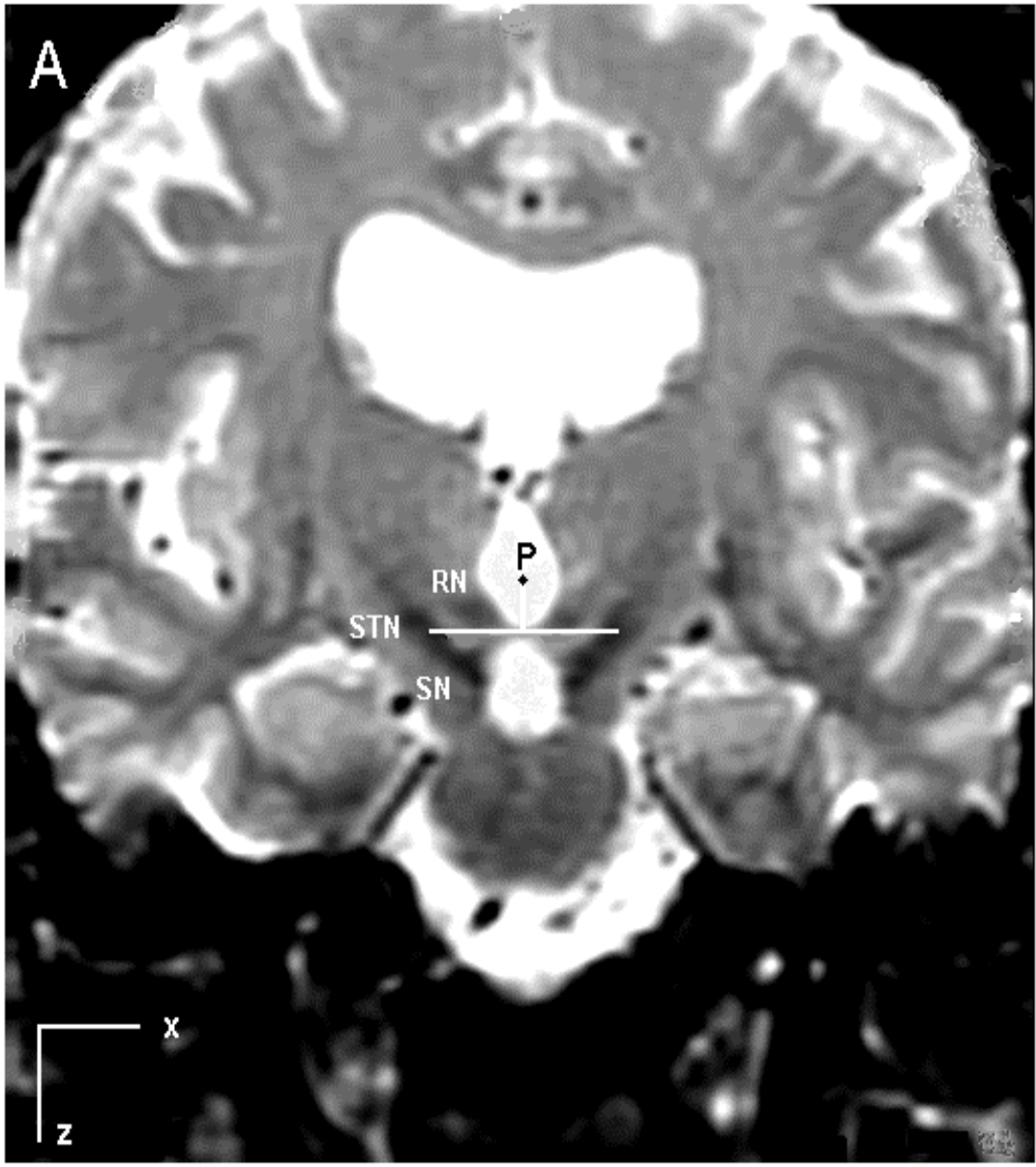
A
P
RN
STN
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X
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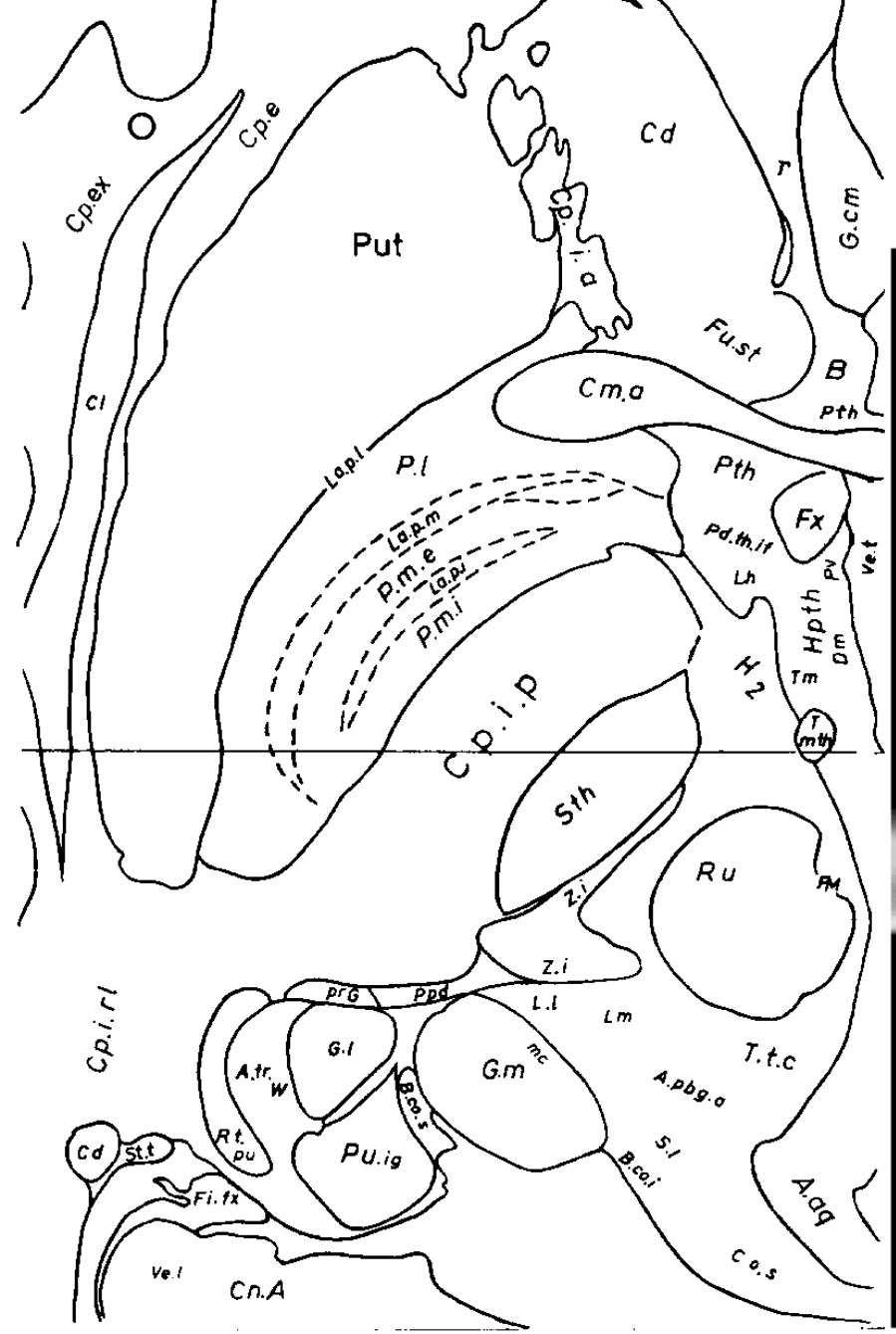
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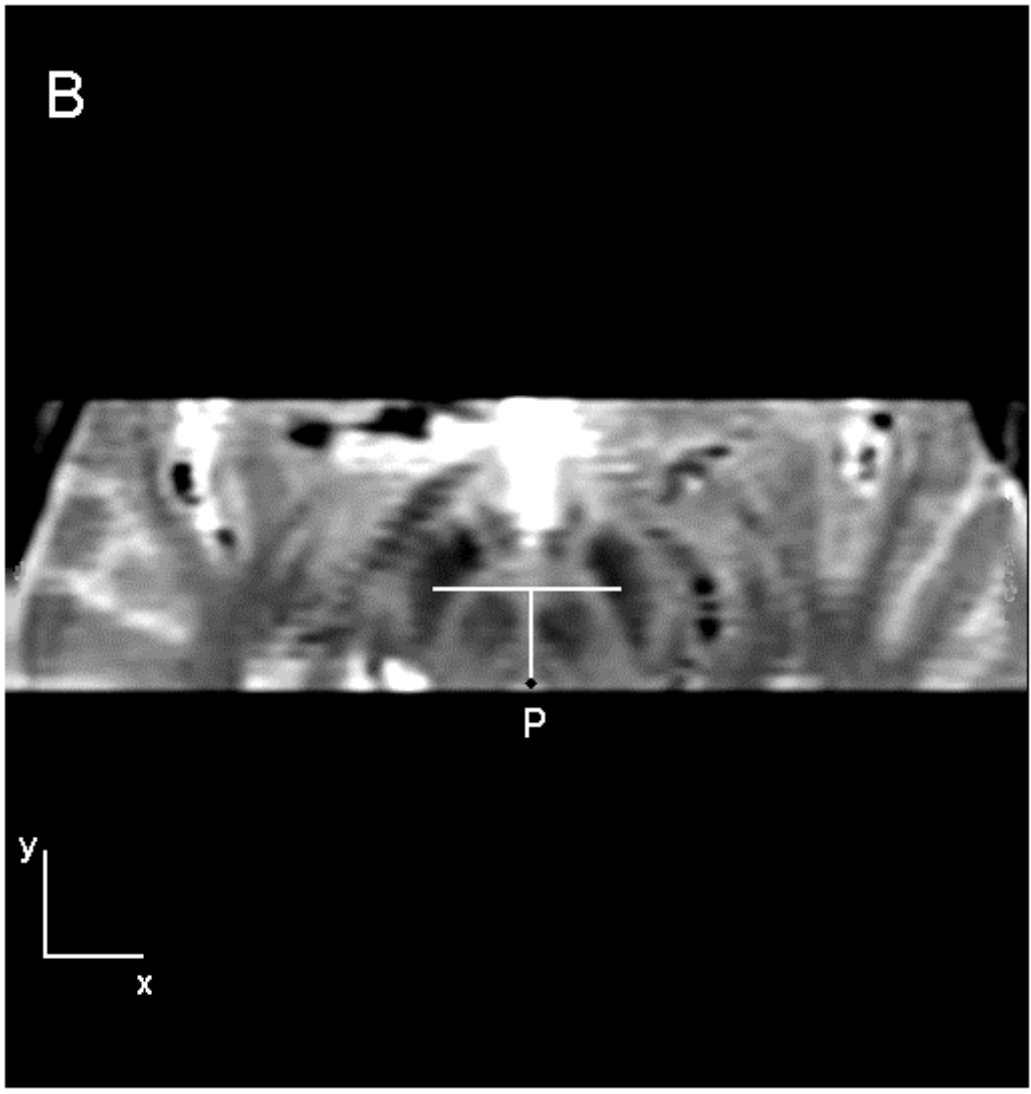
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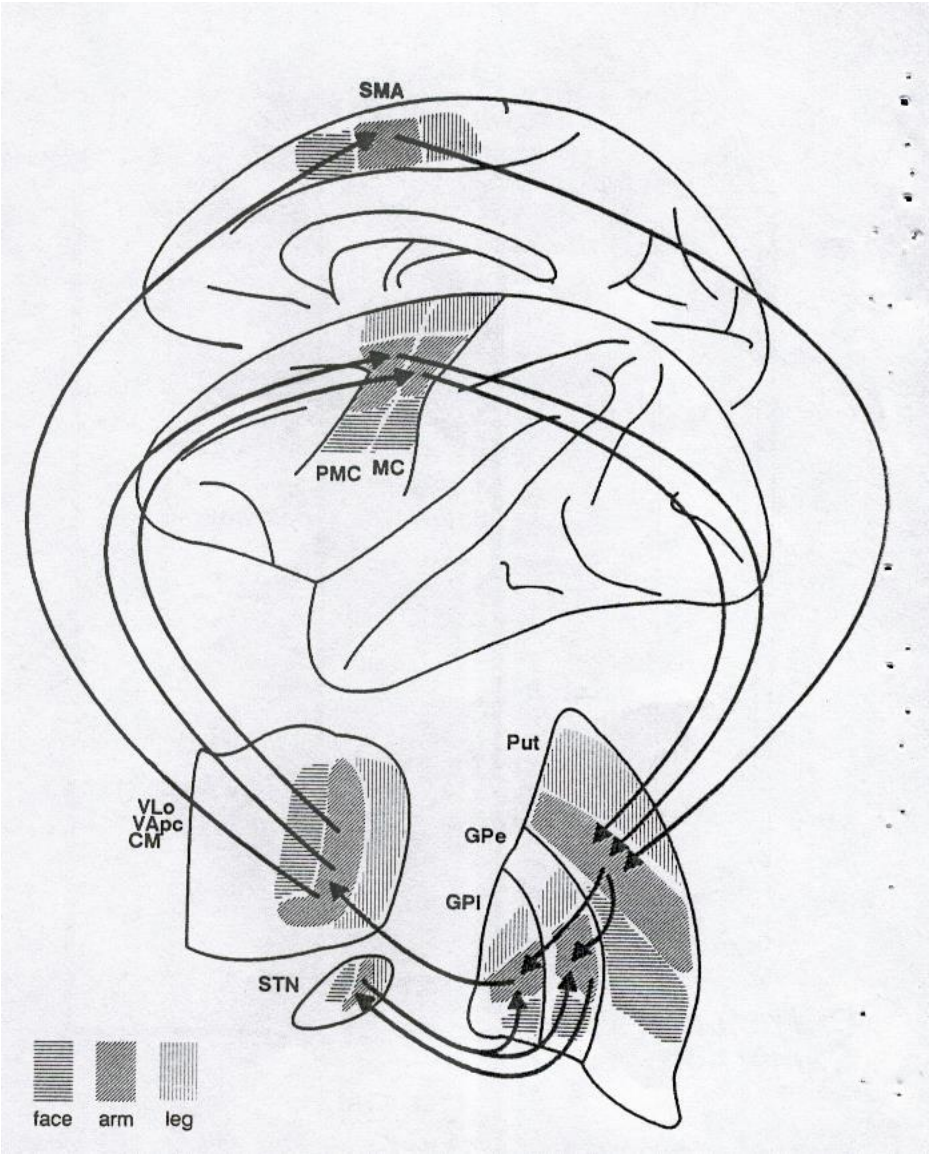
SMA
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face
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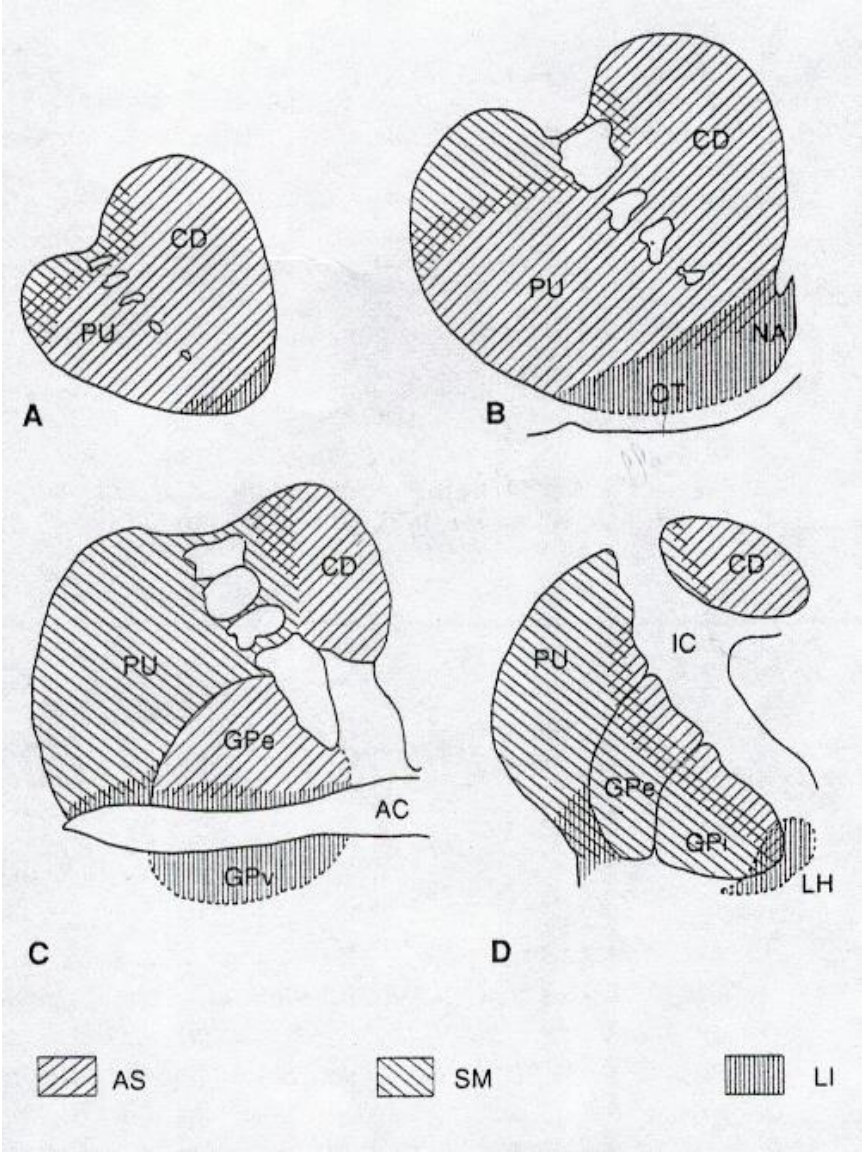
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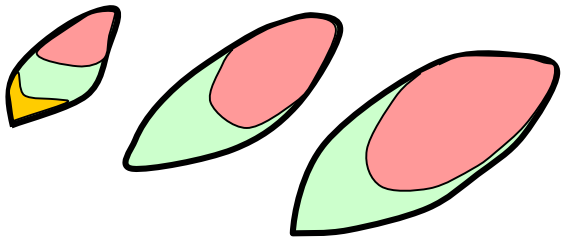

Frontal slices of monkey STN
Levels : Anterior Middle Posterior

D'une manière générale, le territoire sensorimoteur est dorsal et latéral donc plus postérieur que l'associatif. Le limbique s'il est vraiment confirmé serait à la pointe la plus médiale et ventrale, donc antérieur.

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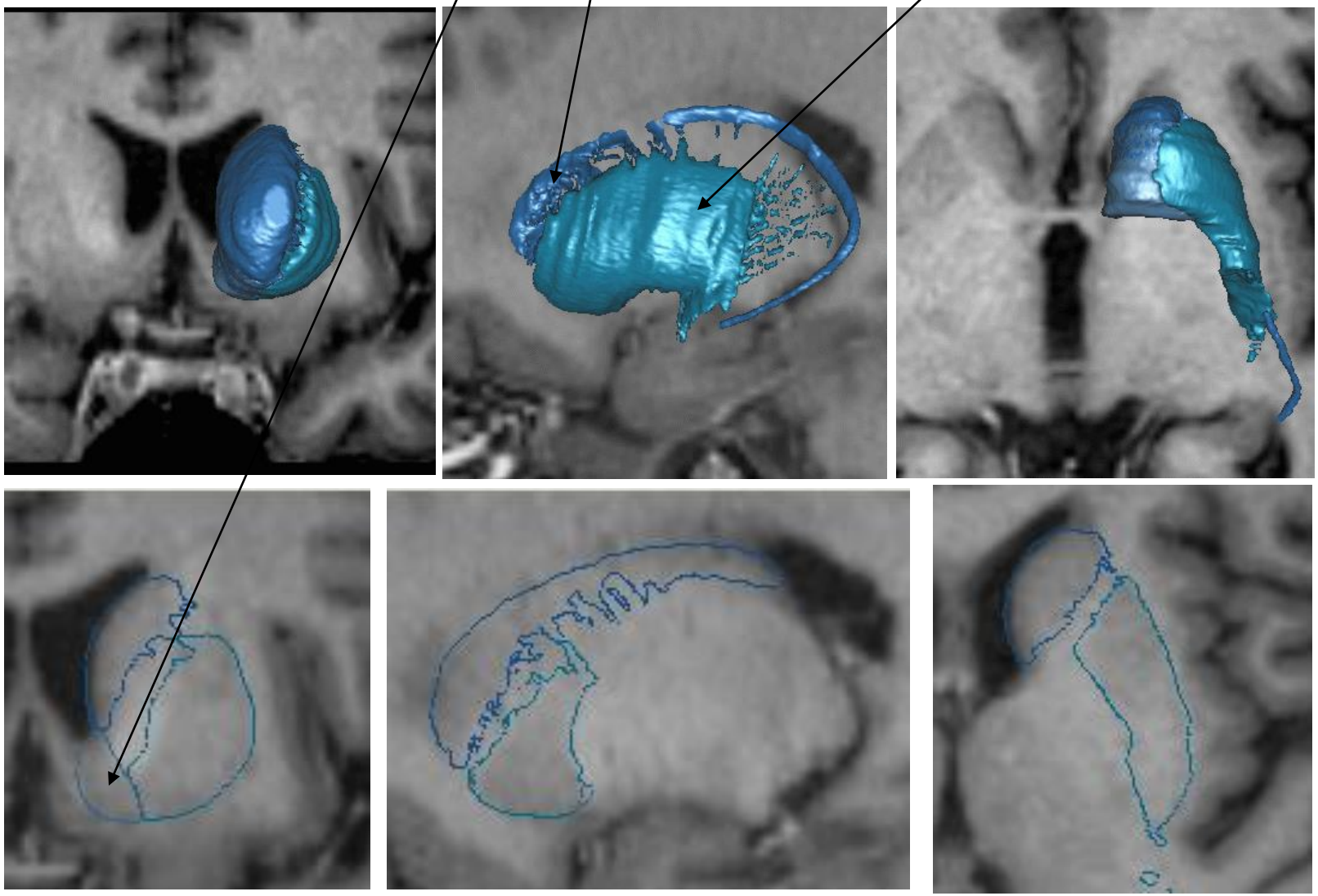
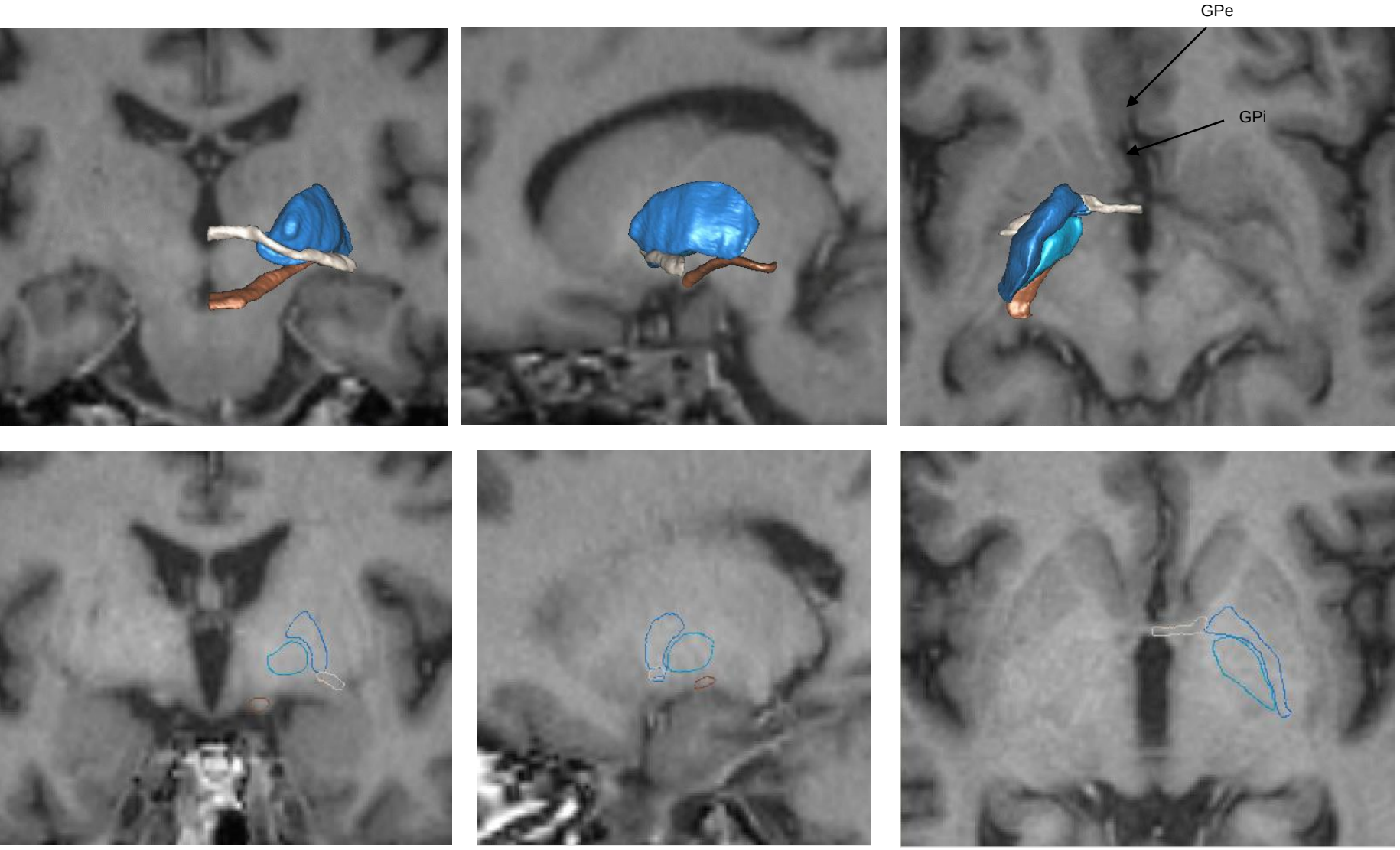
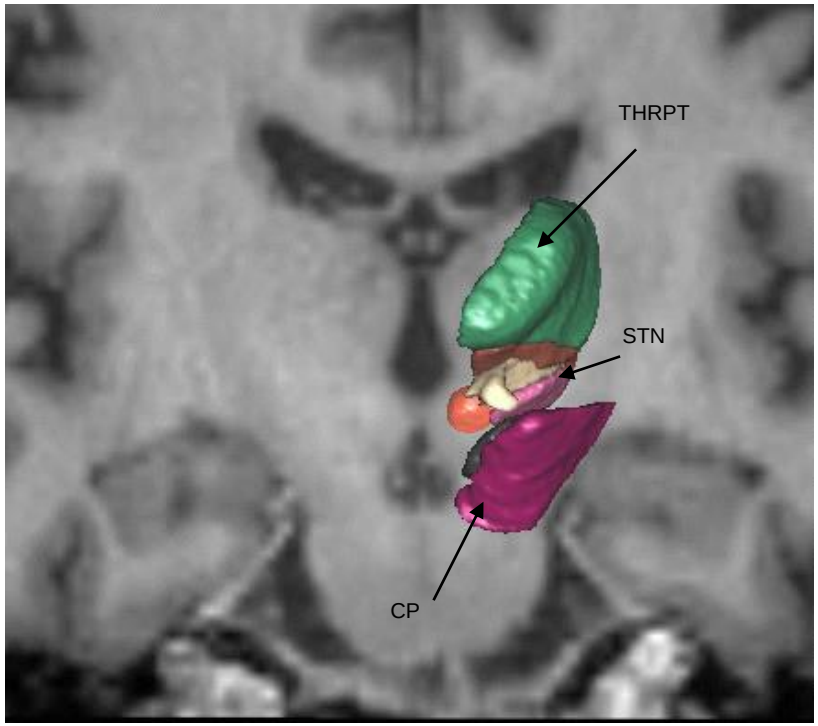
Accumbens, caudate nucleus, putamen

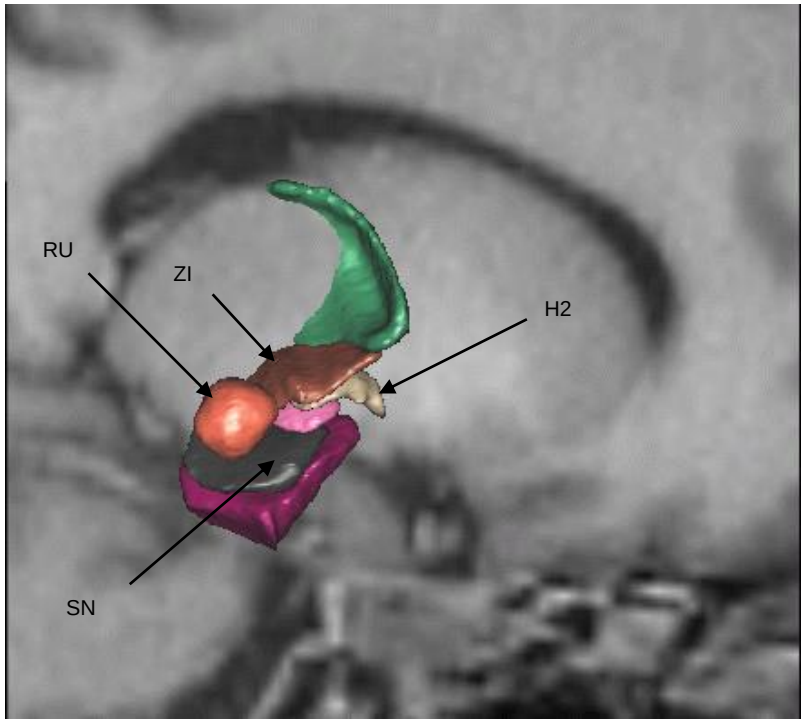


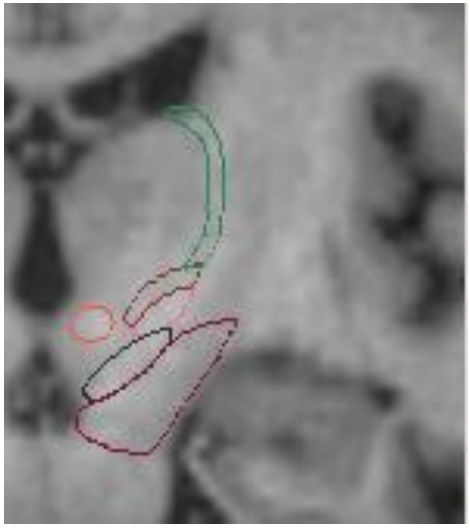
Globus pallidus

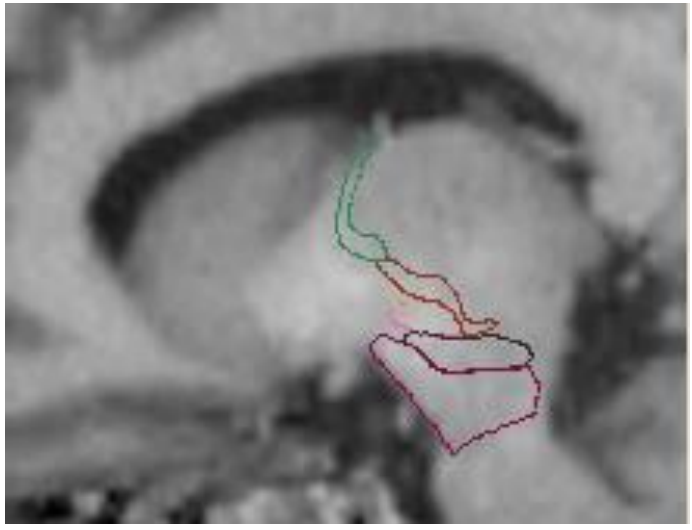


Sub-thalamic nucleus, substancia nigra, red nucleus

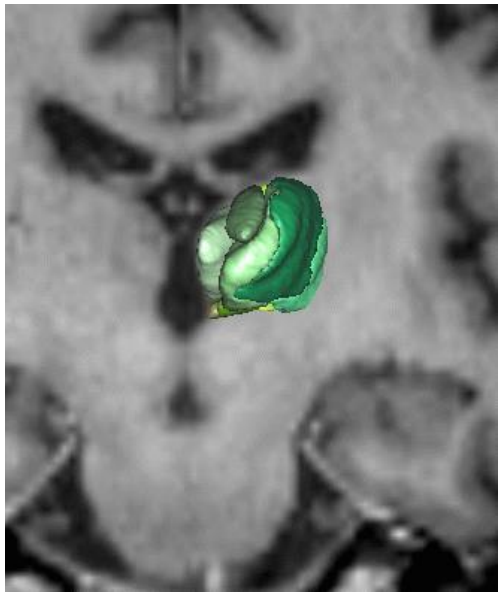


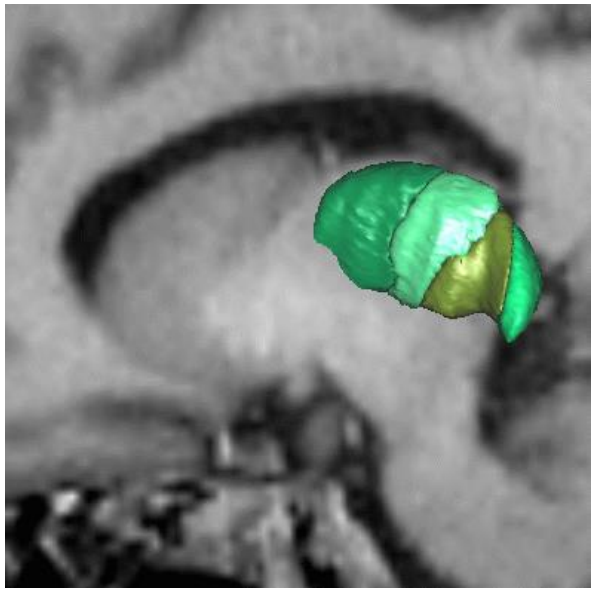


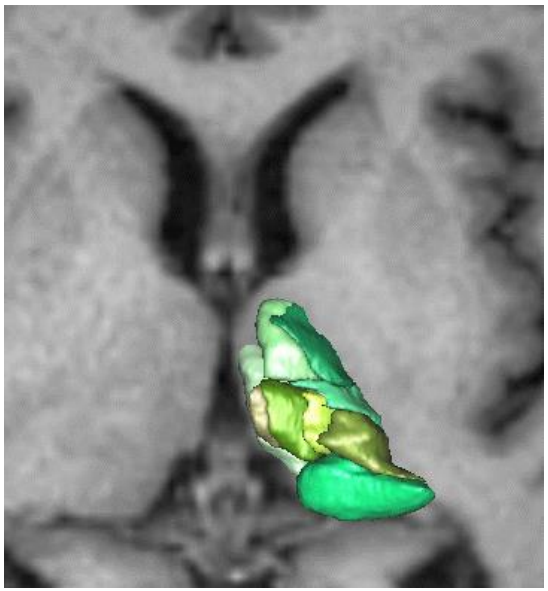


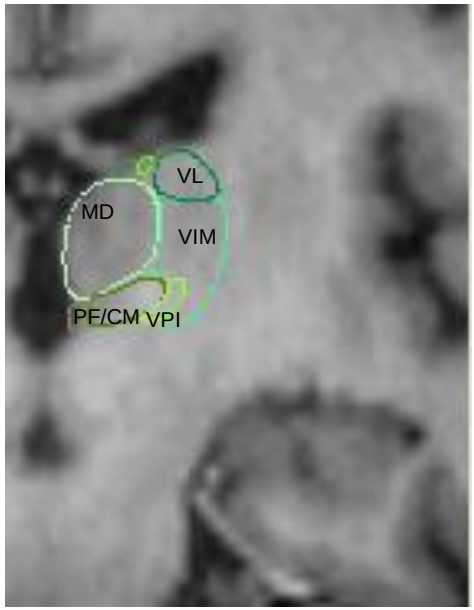


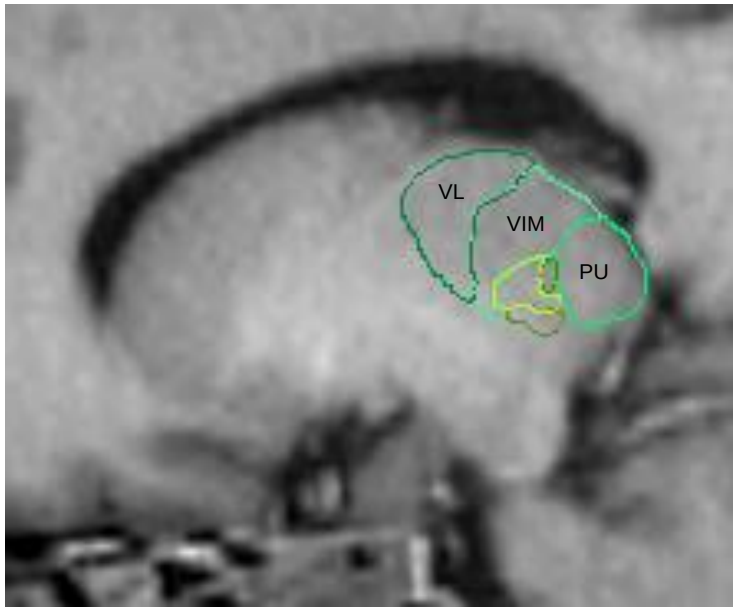
Thalamus

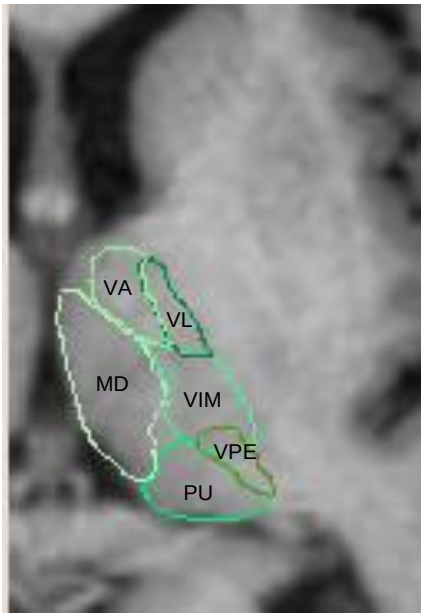




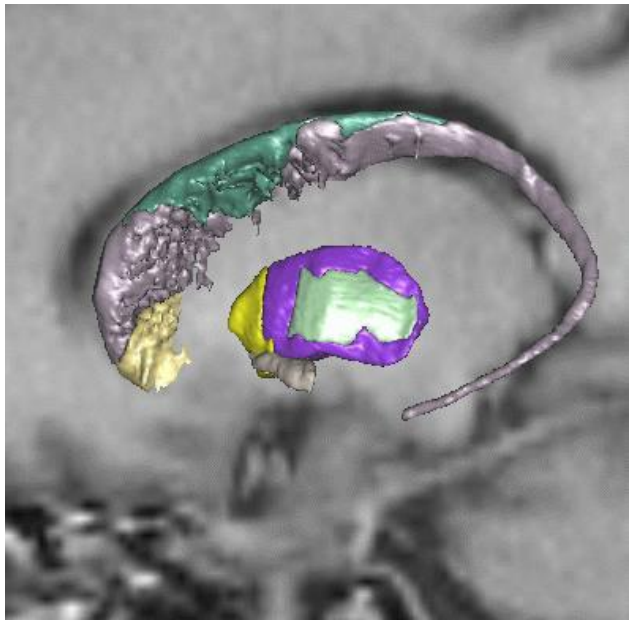


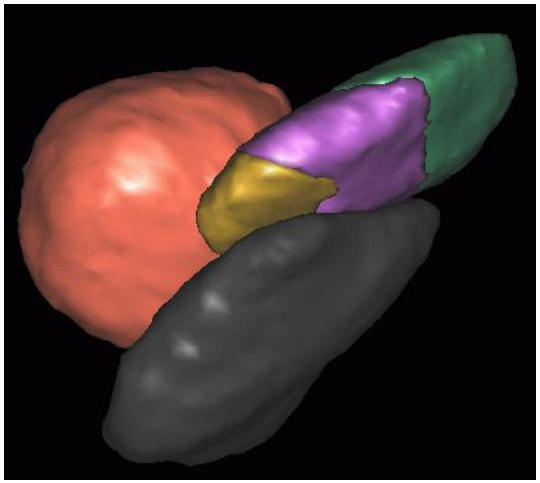
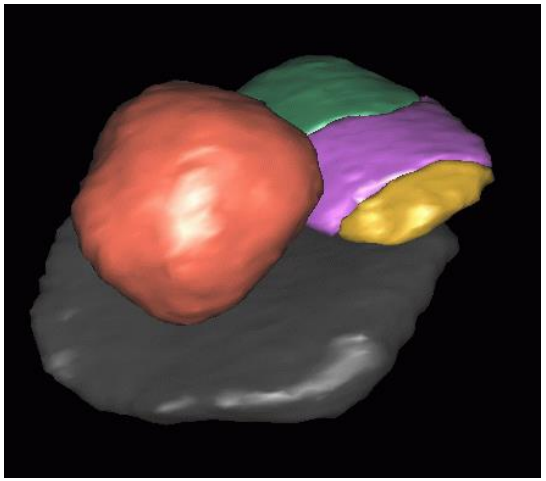
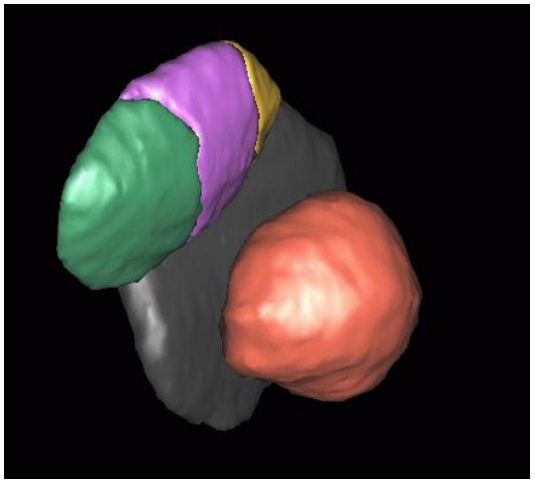


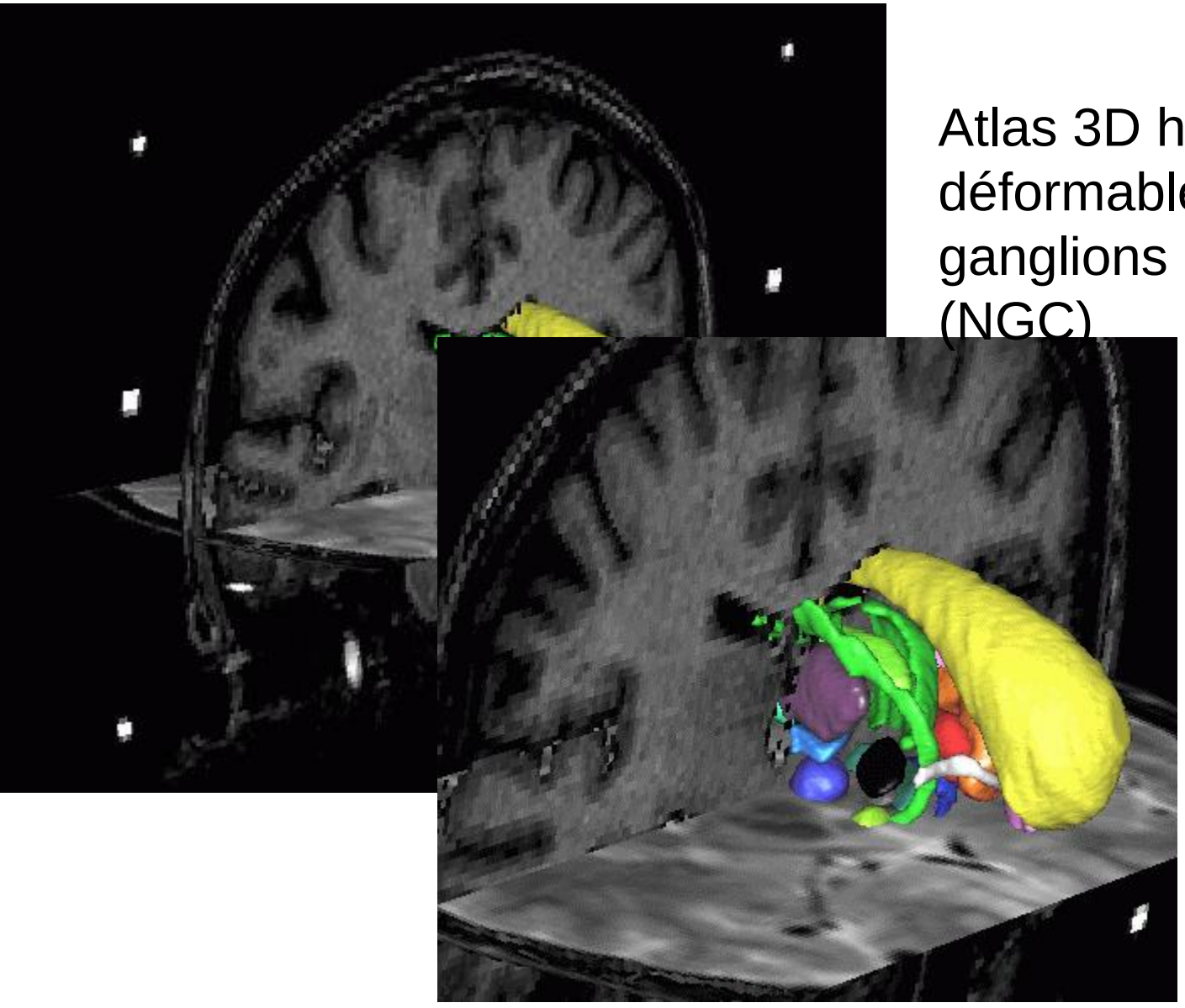




Functional territories

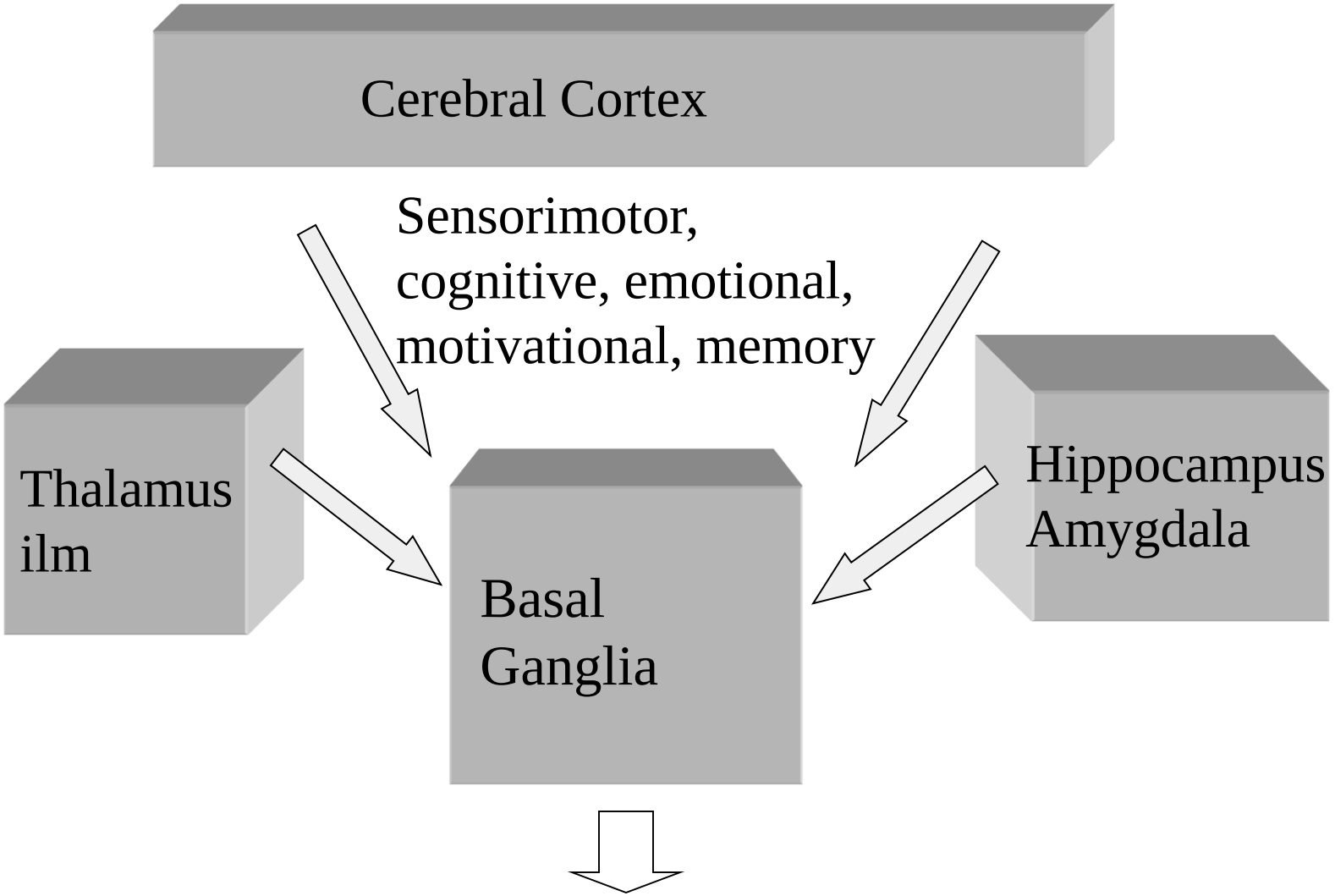






Atlas 3D histologique déformable des ganglions de la base (NGC)

Functions of basal ganglia

from J.M. DENIAU



Environmental contextual analysis and organisation of a contextually adaptated behavior

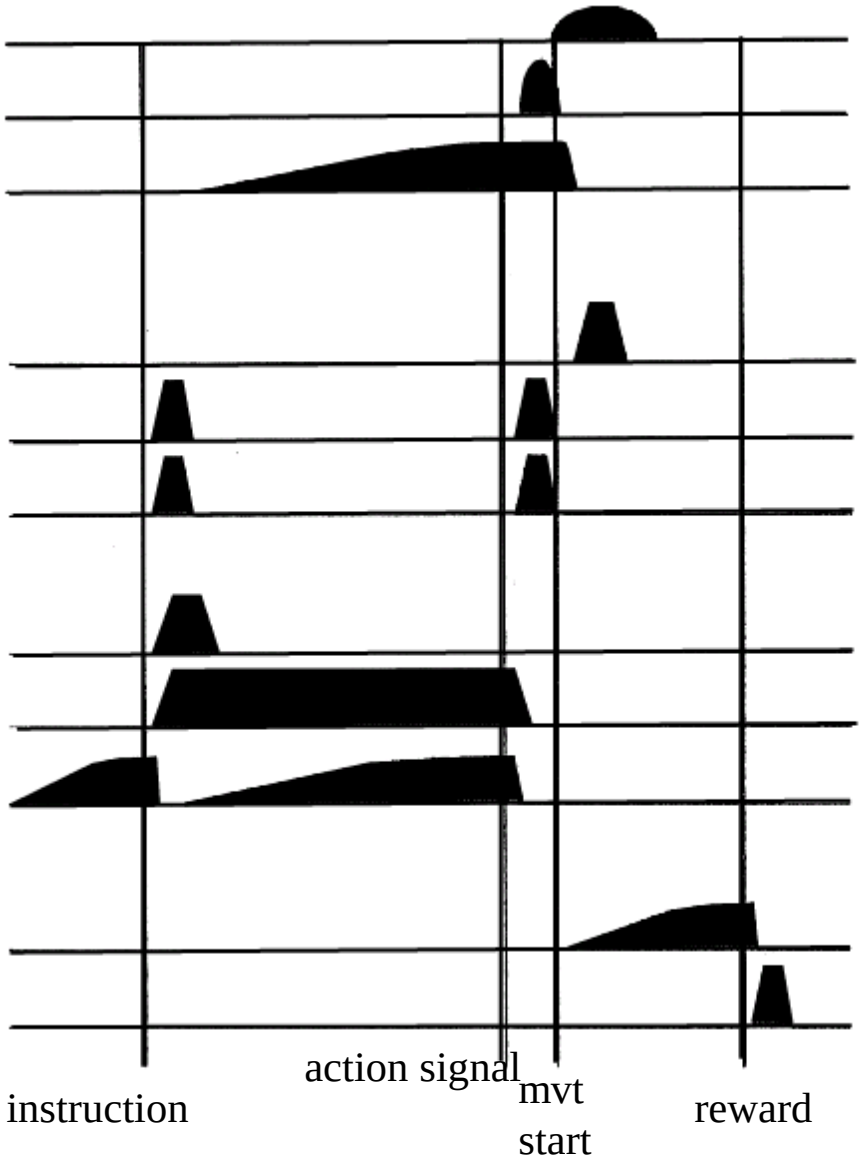
Striatum is active along all key phases of behavior organisation

Movement execution
Movement initiation
Movement preparation

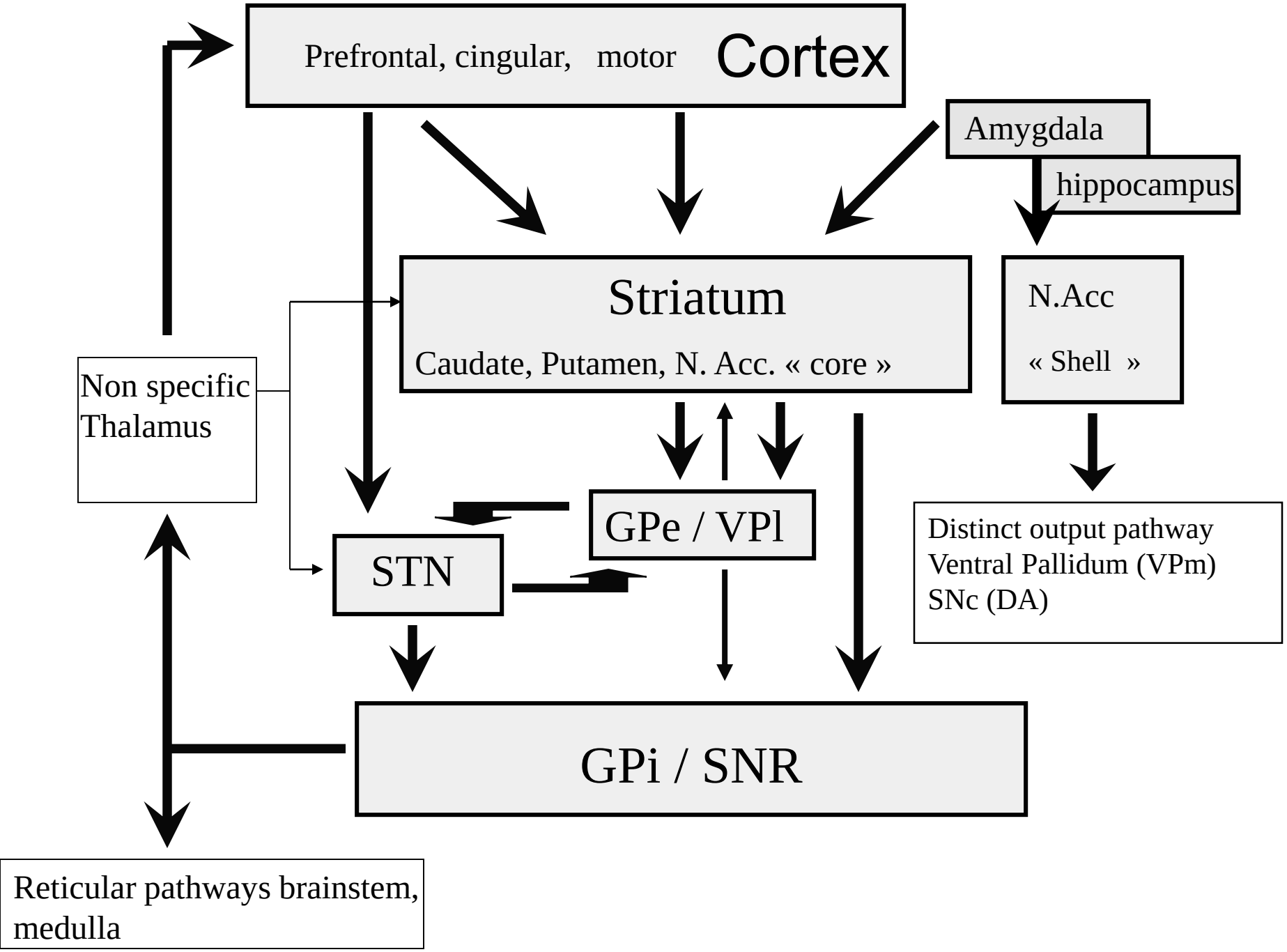
Somatosensoy response
Visual response
Auditory response

Short term memory
Work memory
Prediction, waiting

Waiting for a reward
Reward



From W. Schultz


Prefrontal, cingular, motor Cortex
Amygdala
hippocampus
Striatum
Caudate, Putamen, N. Acc. « core »
N.Acc
« Shell »
Non specific
Thalamus
GPe / VPl
STN
Distinct output pathway
Ventral Pallidum (VPm)
SNc (DA)
GPi / SNR
Reticular pathways brainstem,
medulla

Basal ganglia modulate various
prefrontal cortical areas,

premotor, motor, temporal and parietal cortex

via thalamic projections

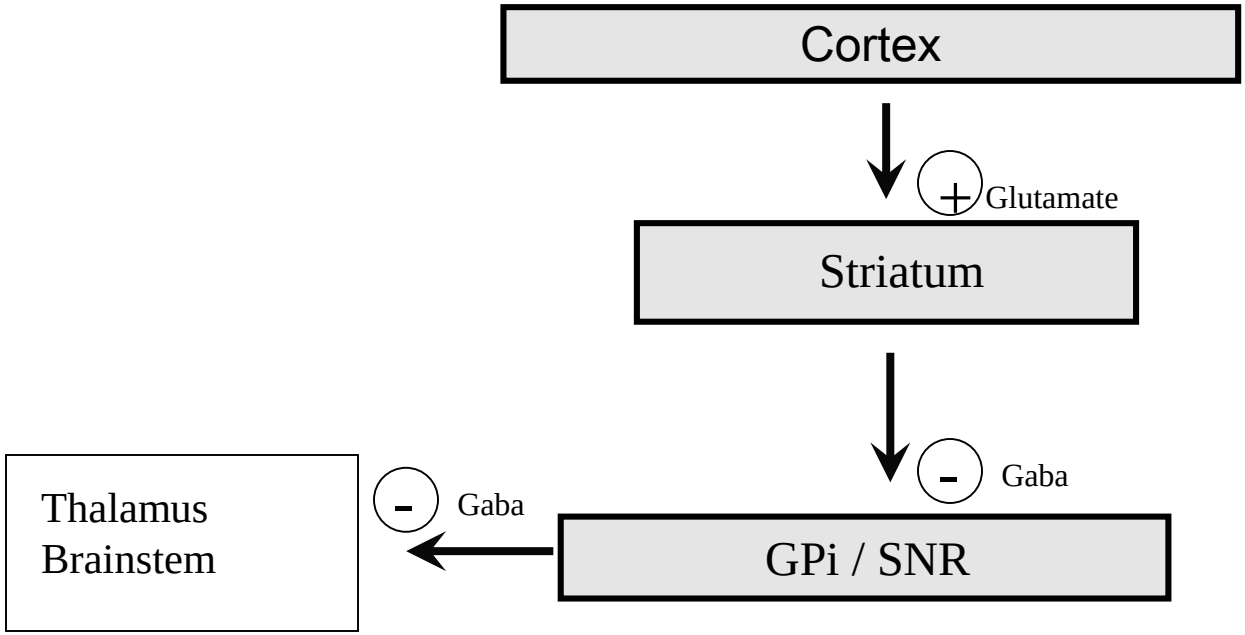
of Substantia Nigra and Globus Pallidus

Informations originating from cortical areas are transmitted to output structures of basal ganglia through three
main pathways:

A direct trans-striatal circuit,

An indirect trans-striatal circuit,

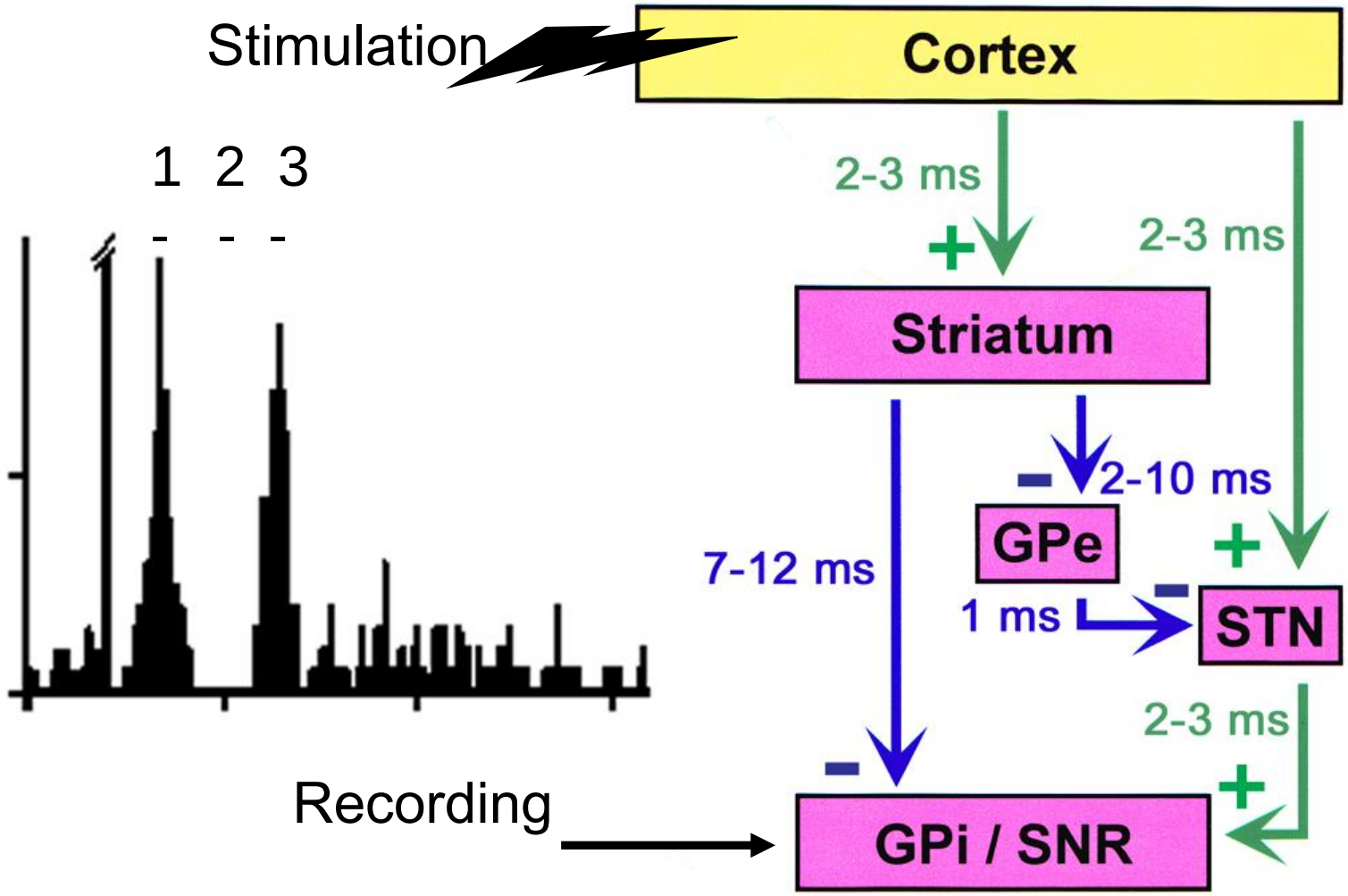
A direct trans-subthalamic circuit



Direct trans-striatal circuit activates target pathways of basal ganglia via a disinhibition mechanism

Trans-subthalamic pathways perform a temporal and spatial configuration of the striatal dis-inhibiting signal

Cortical stimulation evoques a triphasic response (excitation-inhibition-excitation) in SNR neurones.
1- Early excitation results from the activation of direct trans-subthalamic pathway,
2- inhibition results from the activation of direct trans-striatal circuit and
3- late activation from indirect striato-pallido-subthalamo-nigral pathway.



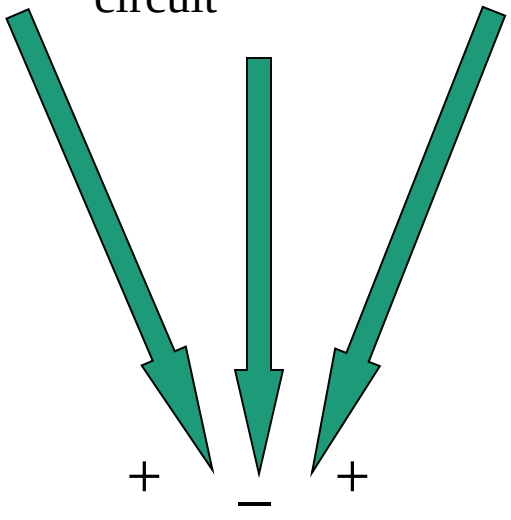
Temporal calibration within a chanel

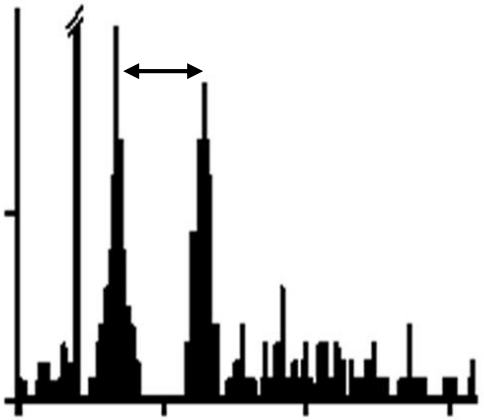
Functionnally associated cortical areas

Direct striatal circuit

Indirect circuit

Direct subthalamic circuit



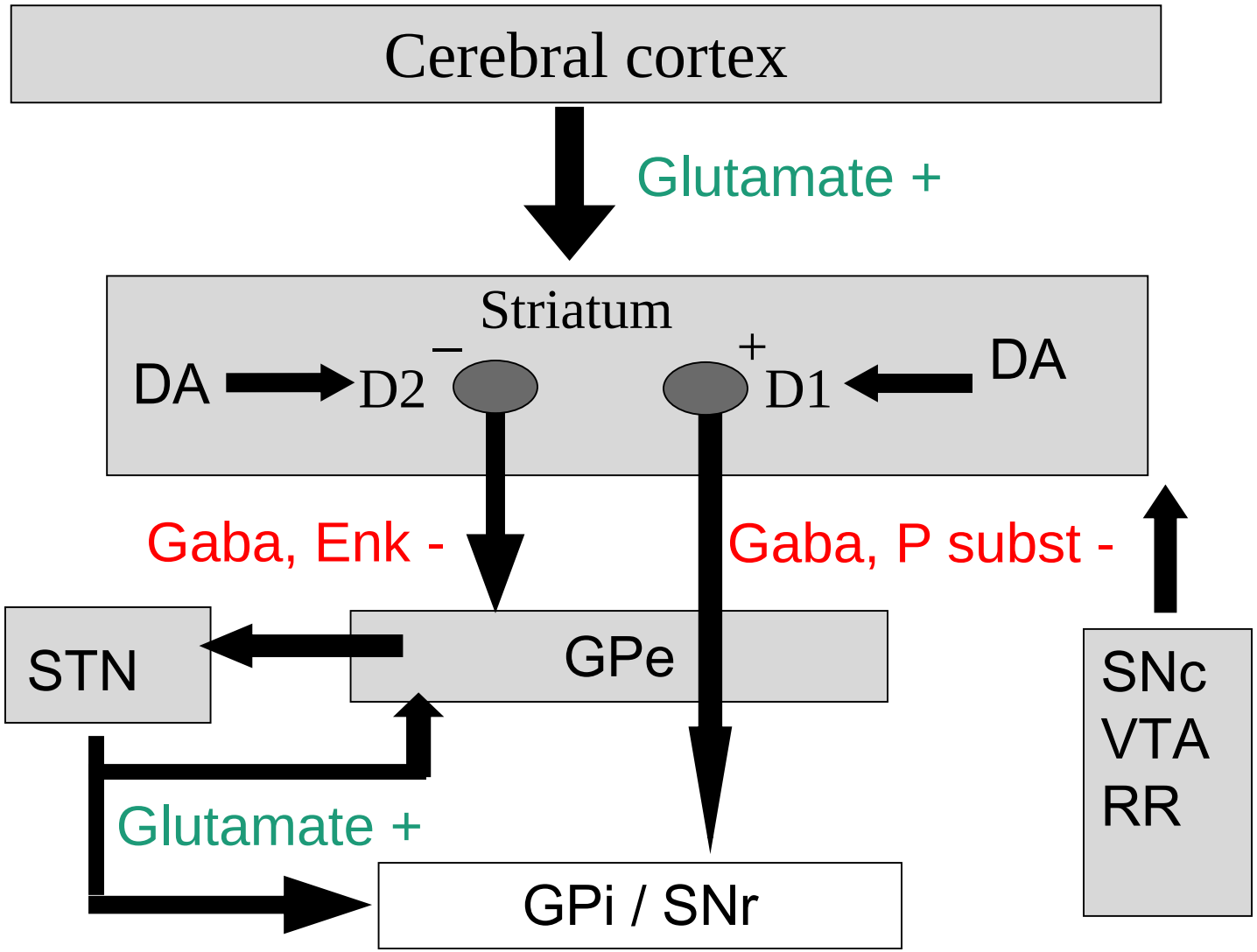


SNR/GPi

Calibration of dis-inhibiting striatal signal duration

Physiopathological models

- hypothesis of a distinct neuronal origine of direct and indirect trans-striatal pathways
- differential control by dopamine on these two sub populations of striatal neurones.

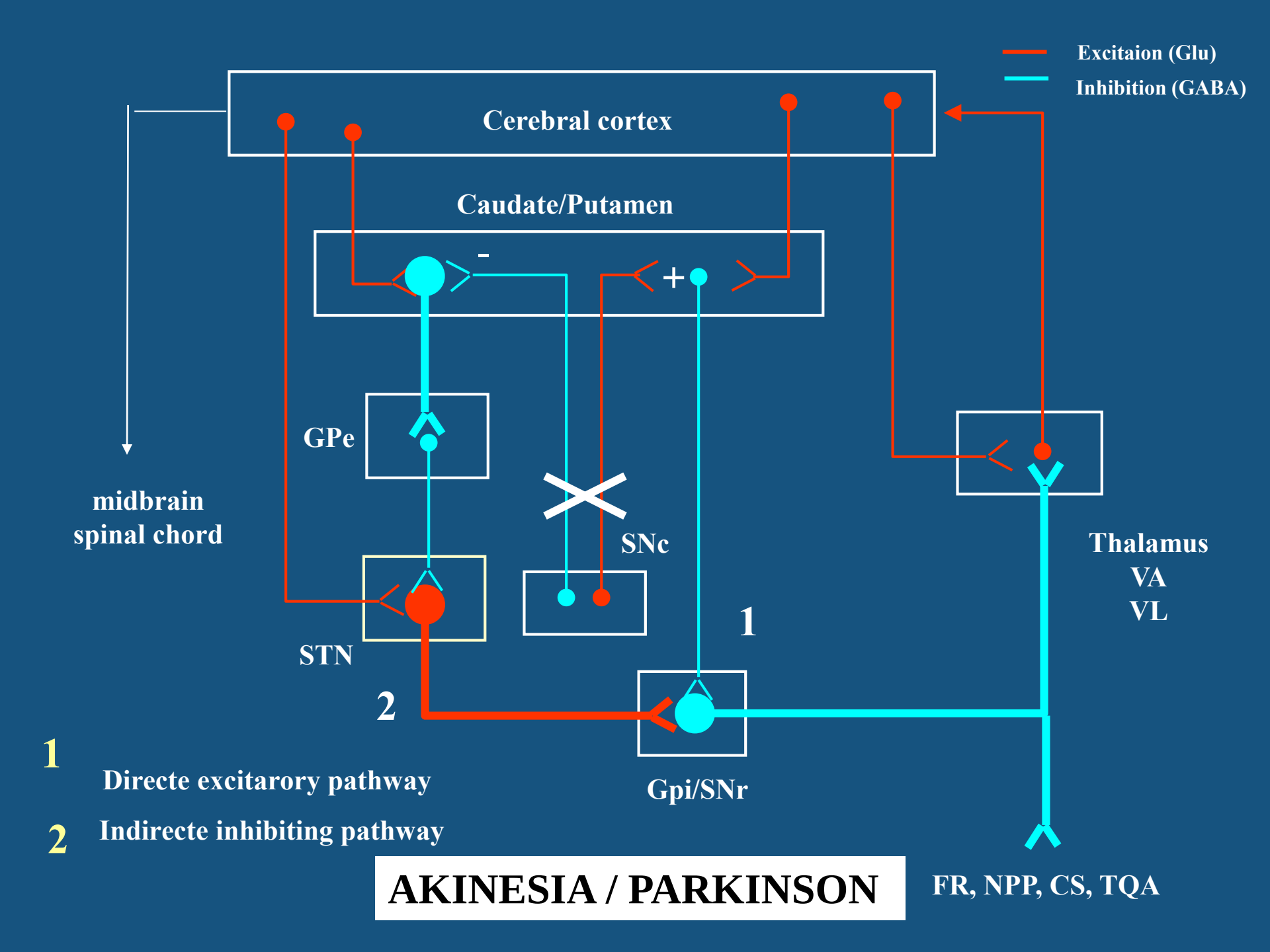


Hypokinetic disorders

Parkinson's disease
neuroleptics parkinsonian syndrom
MPTP monkey parkinsonism model

Parkinson’s disease

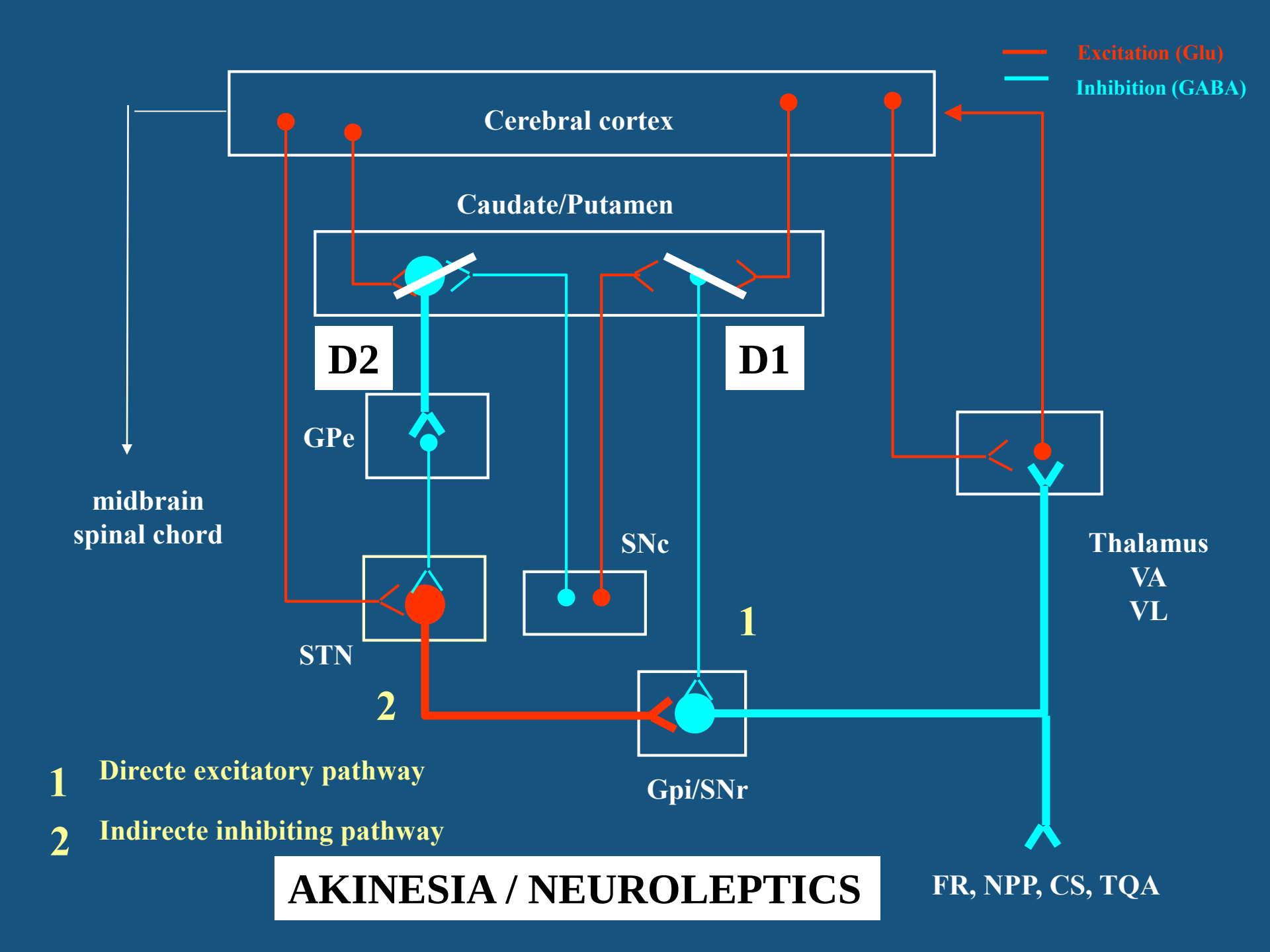
- Akinésia
- Rigidity
- Resting tremor 4-6 Hz



1 Directe excitarory pathway

2 Indirecte inhibiting pathway

AKINESIA / PARKINSON



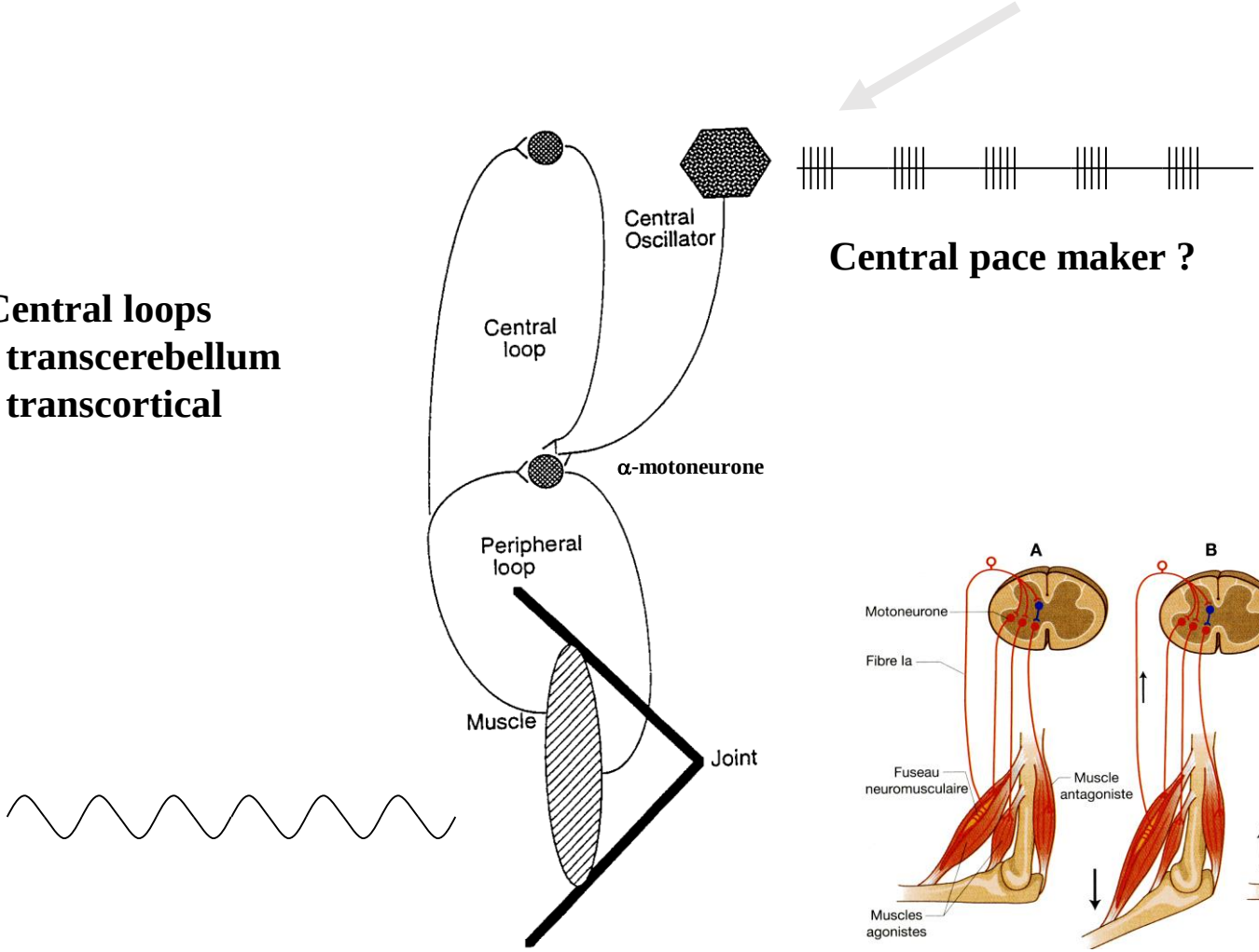
1 Directe excitatory pathway

2 Indirecte inhibiting pathway

AKINESIA / NEUROLEPTICS

Tremor

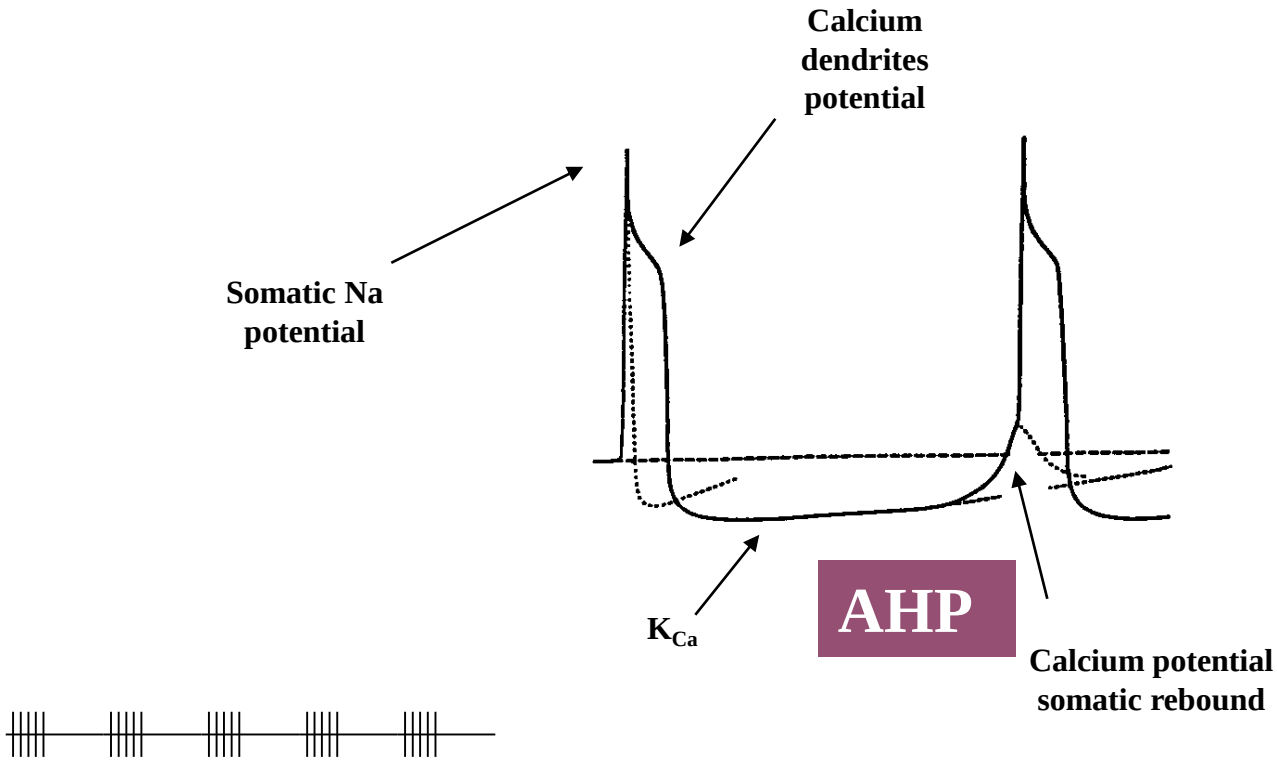
Central loops
- transcerebellum
- transcortical



Central pace maker ?

Peripheral reflex loop

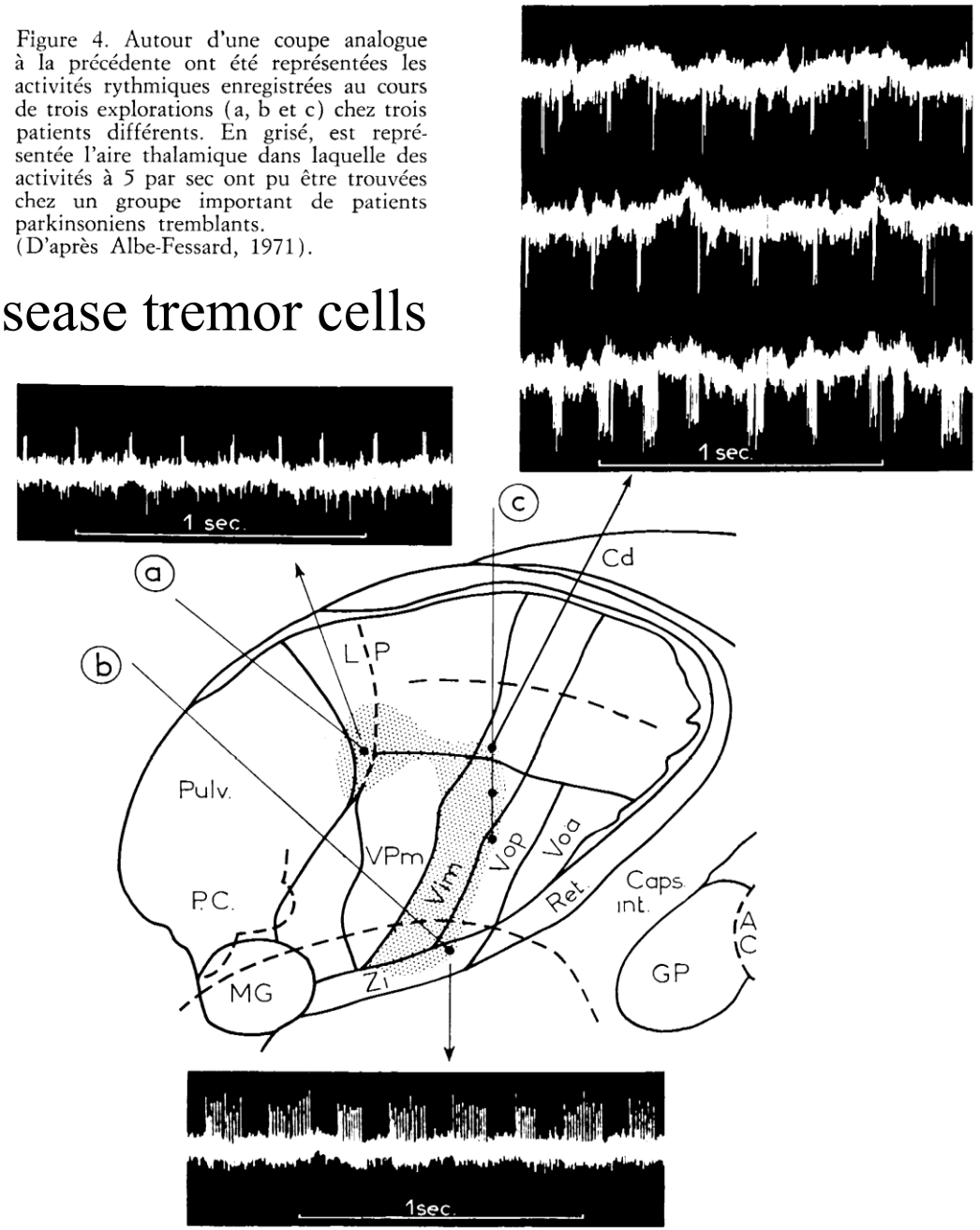
Neuronal pace-maker



Burst phenomenon facilitated by hyperpolarisation

Figure 4. Autour d'une coupe analogue à la précédente ont été représentées les activités rythmiques enregistrées au cours de trois explorations (a, b et c) chez trois patients différents. En grisé, est représentée l'aire thalamique dans laquelle des activités à 5 par sec ont pu être trouvées chez un groupe important de patients parkinsoniens tremblants.
(D'après Albe-Fessard, 1971).

Parkinson's disease tremor cells



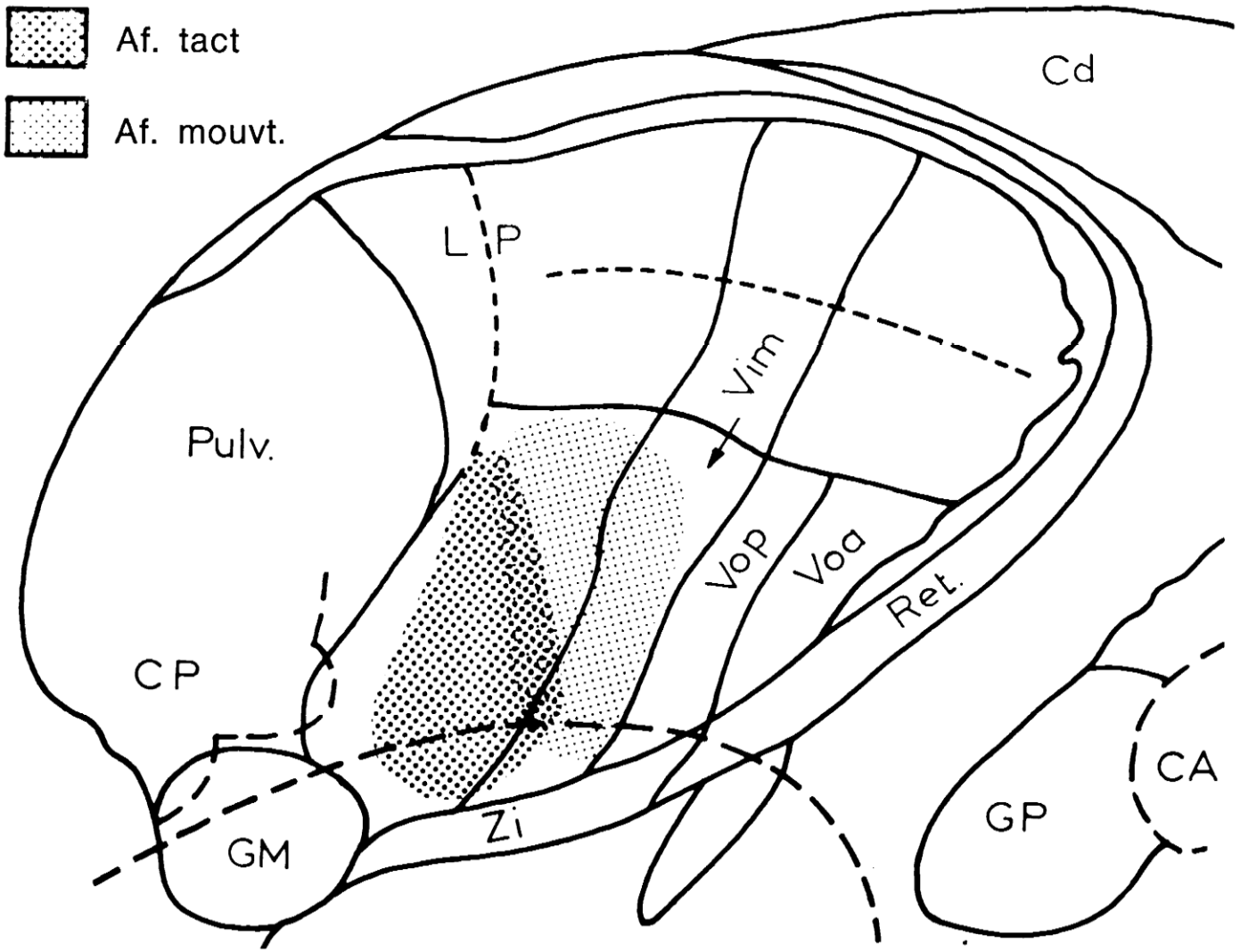


Figure 3. Coupe du thalamus humain dans un plan sagittal se trouvant à 15 mm de la ligne

D. Albe – Fessard, 1967

Hyperkinetic disorders

Huntington’s chorea
Ballism
L-dopa Induced Dyskinesia (LID)
Tardive dyskinesia (neuroleptics)
Tics / Syndrome de Gilles de la Tourette

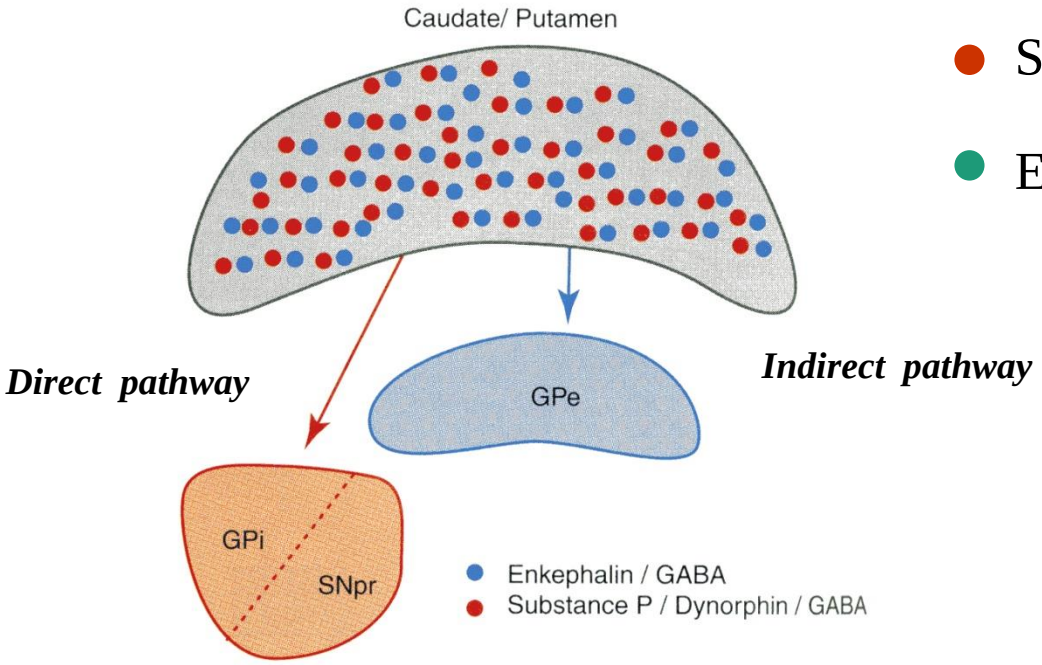
Chorea

- Huntington chorea
  progressive neurodegenerative
  Hereditary
  - Loss of enkephalinergic

  « medium spiny neurons »

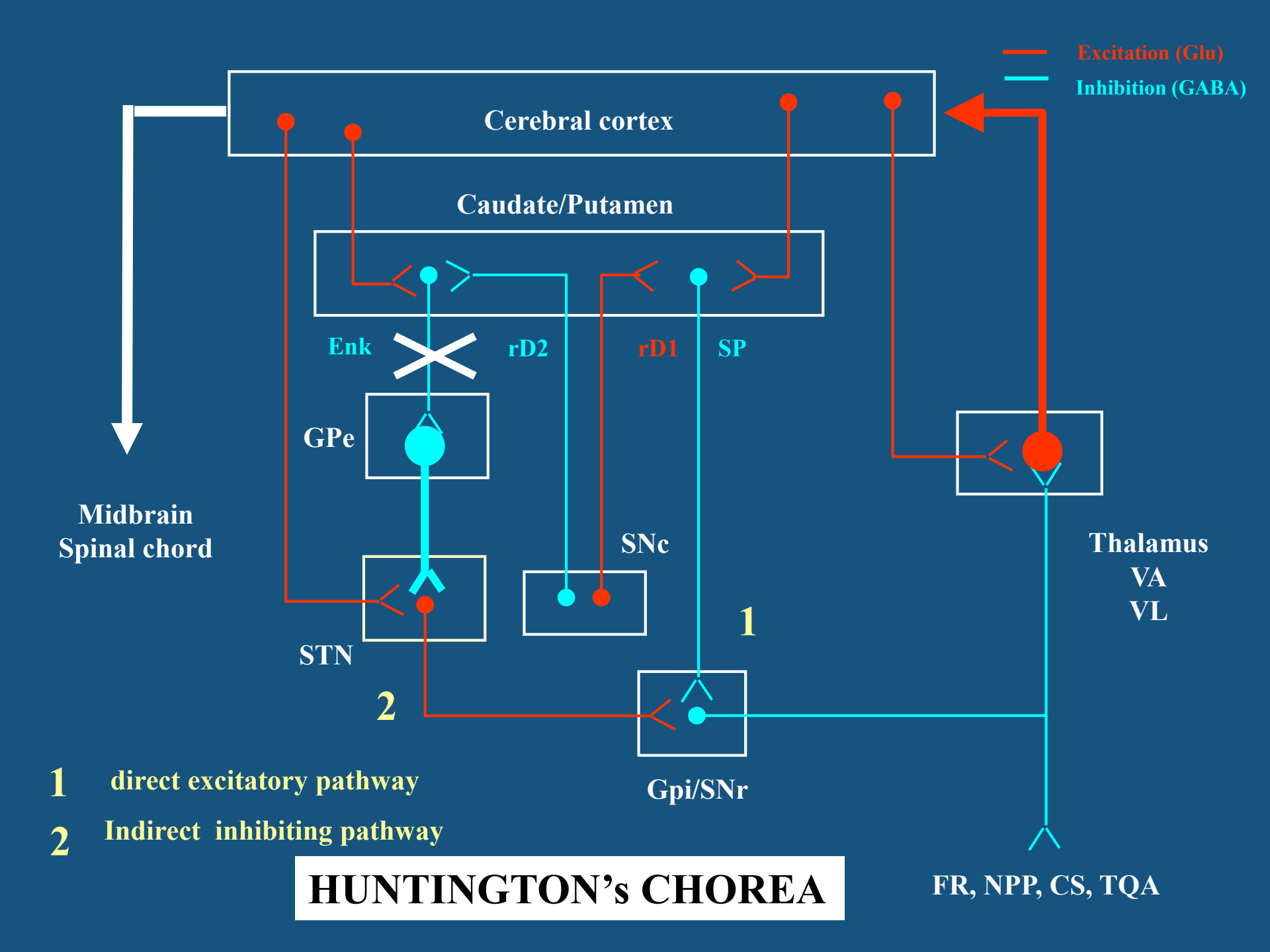
  Chorea, depression, cognitive decline
- Other causes

Two sub-population of striatal « medium spiny neurons »



- Substance P / Dynorphine, D1 recept
- Enképhalines, D2 receptors

From Squire, 2003



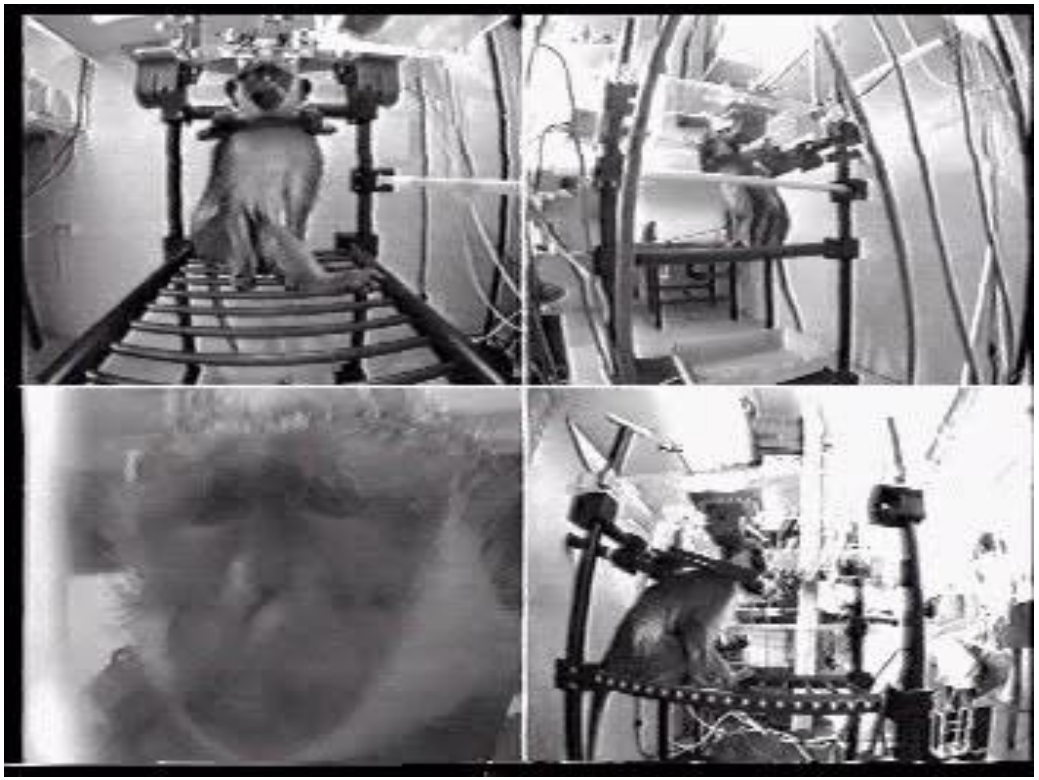
1 direct excitatory pathway

2 Indirect inhibiting pathway

HUNTINGTON's CHOREA

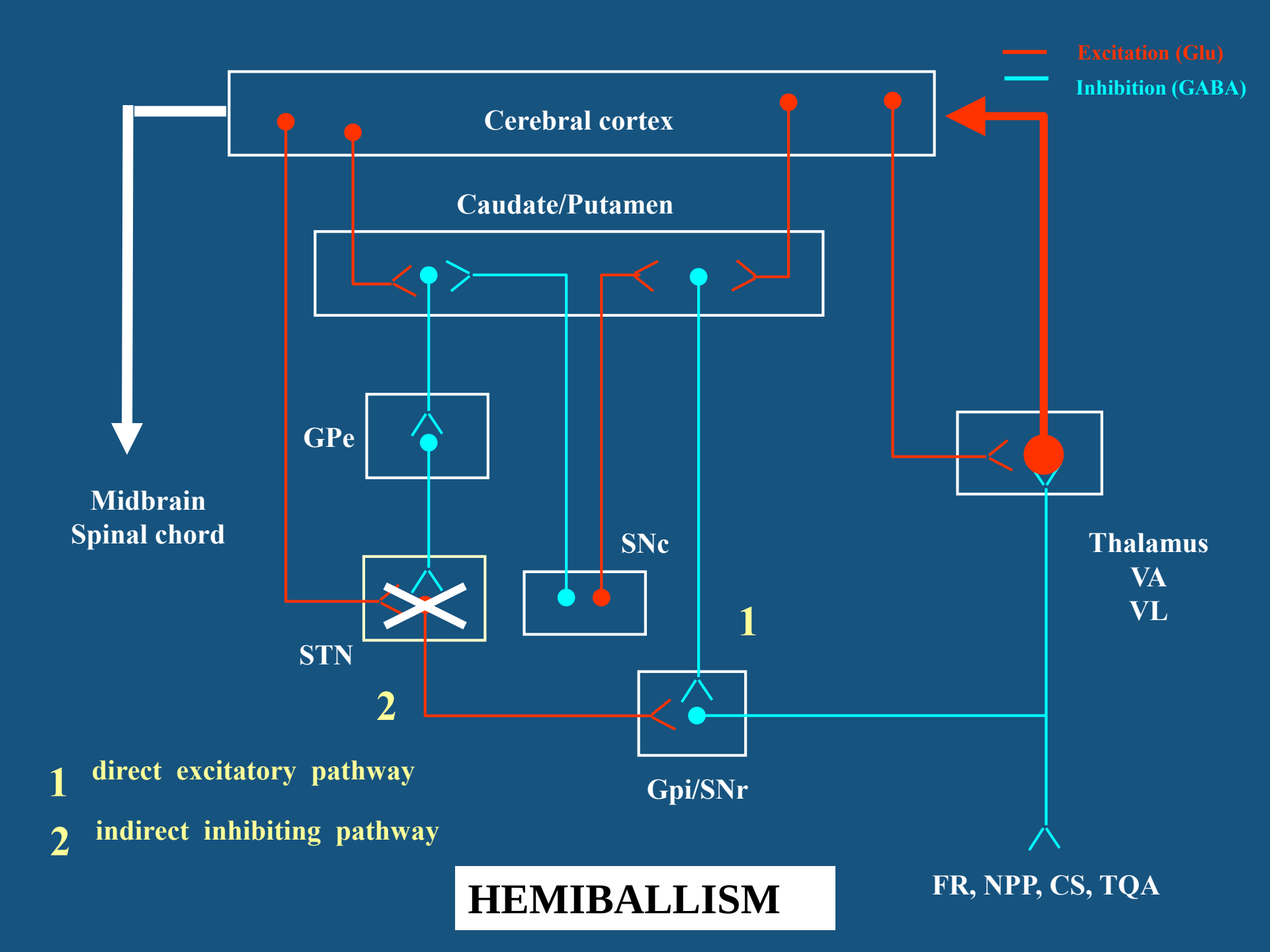
Ballism

Focal lesion of right STN
(cerebral toxoplasmose)



bicucculine STN perfusion
(L Tremblay et D Grabli, U679)

Bicucculine: GABA-A antagonist
Depolarisation bloc with high dosage

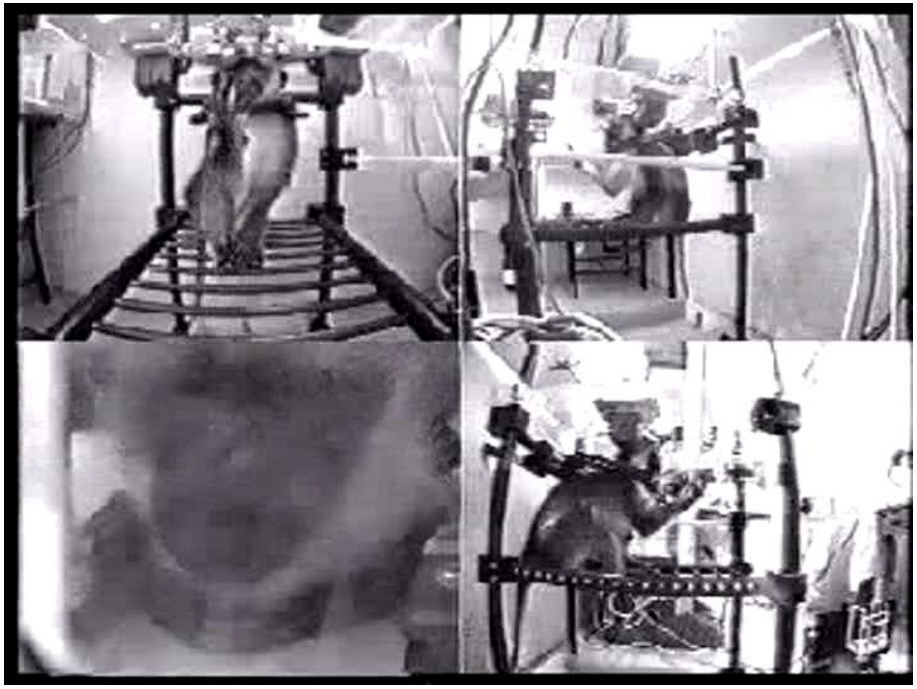

Excitation (Glu)
Inhibition (GABA)
Cerebral cortex
Caudate/Putamen
GPe
Midbrain
Spinal chord
SNc
Thalamus
VA
VL
STN
1
2
Gpi/SNr
1 direct excitatory pathway
2 indirect inhibiting pathway
FR, NPP, CS, TQA
HEMIBALLISM

Tourette's Syndrom

- Simple motor tics
- Normal but inappropriate motor sequences
- Simple or complexe vocal tics

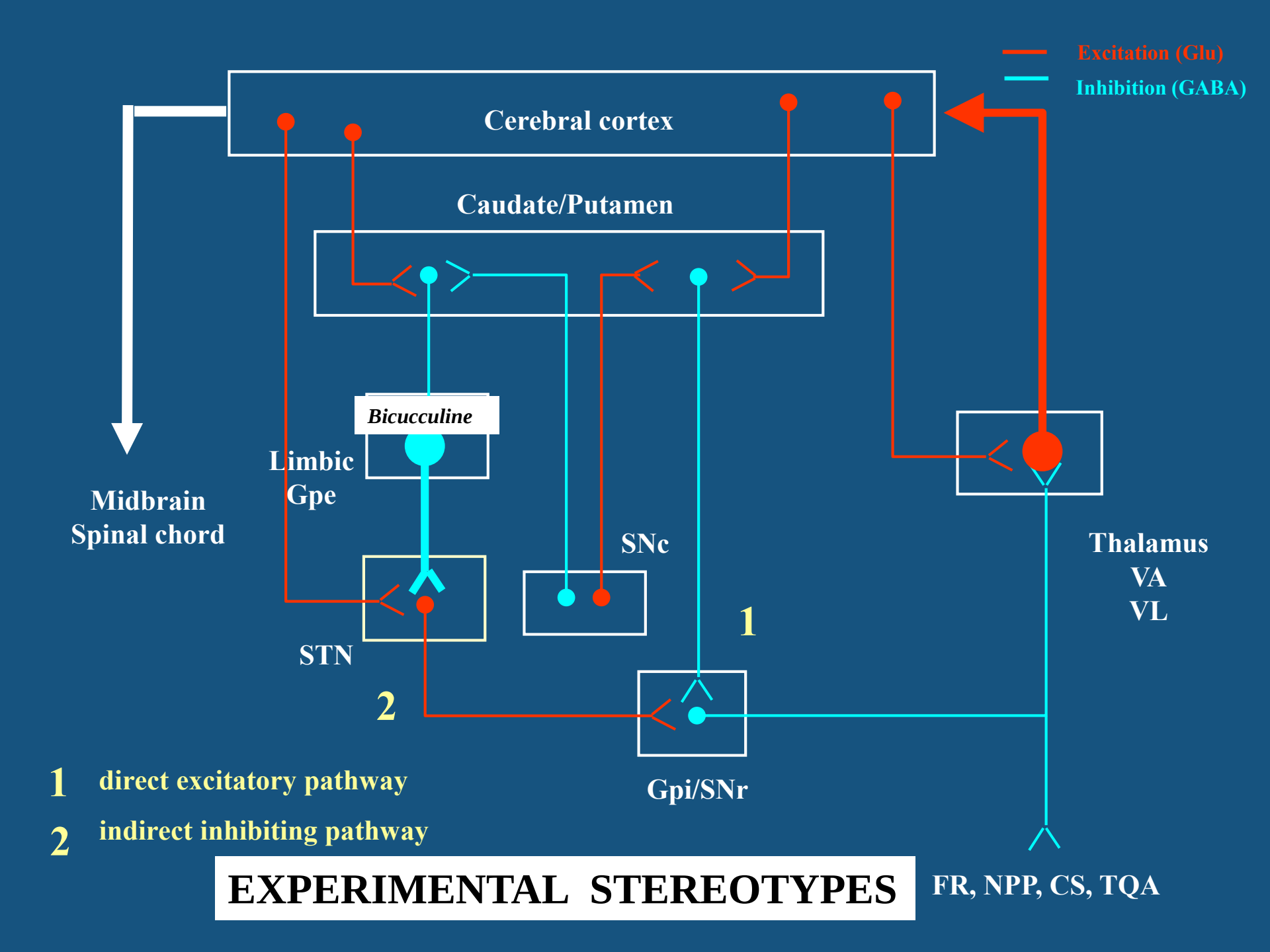
« Urge to move » and rebound effects after a voluntary control

bicucculine injection into limbic GPe



- Stereotypes
- Leaking
- « Touching »

Bicucculine: GABA-A antagonist
GABA-A Inhibiting effect with moderate dosages


Excitation (Glu)
Inhibition (GABA)
Cerebral cortex
Caudate/Putamen
Bicucculine
Limbic
Gpe
Midbrain
Spinal chord
SNc
Thalamus
VA
VL
1
STN
2
Gpi/SNr
1 direct excitatory pathway
2 indirect inhibiting pathway
EXPERIMENTAL STEREOTYPES
FR, NPP, CS, TQA

Deep Brain Stimulation : excitation or inhibition ?

How is it that High Frequency Stimulation mimics the effects of lesion of the target structure ?

- Vim HFS → tremor suppression like thalamotomy

- GPi HFS → removes Levodopa Induced Dyskinesia like pallidotomy

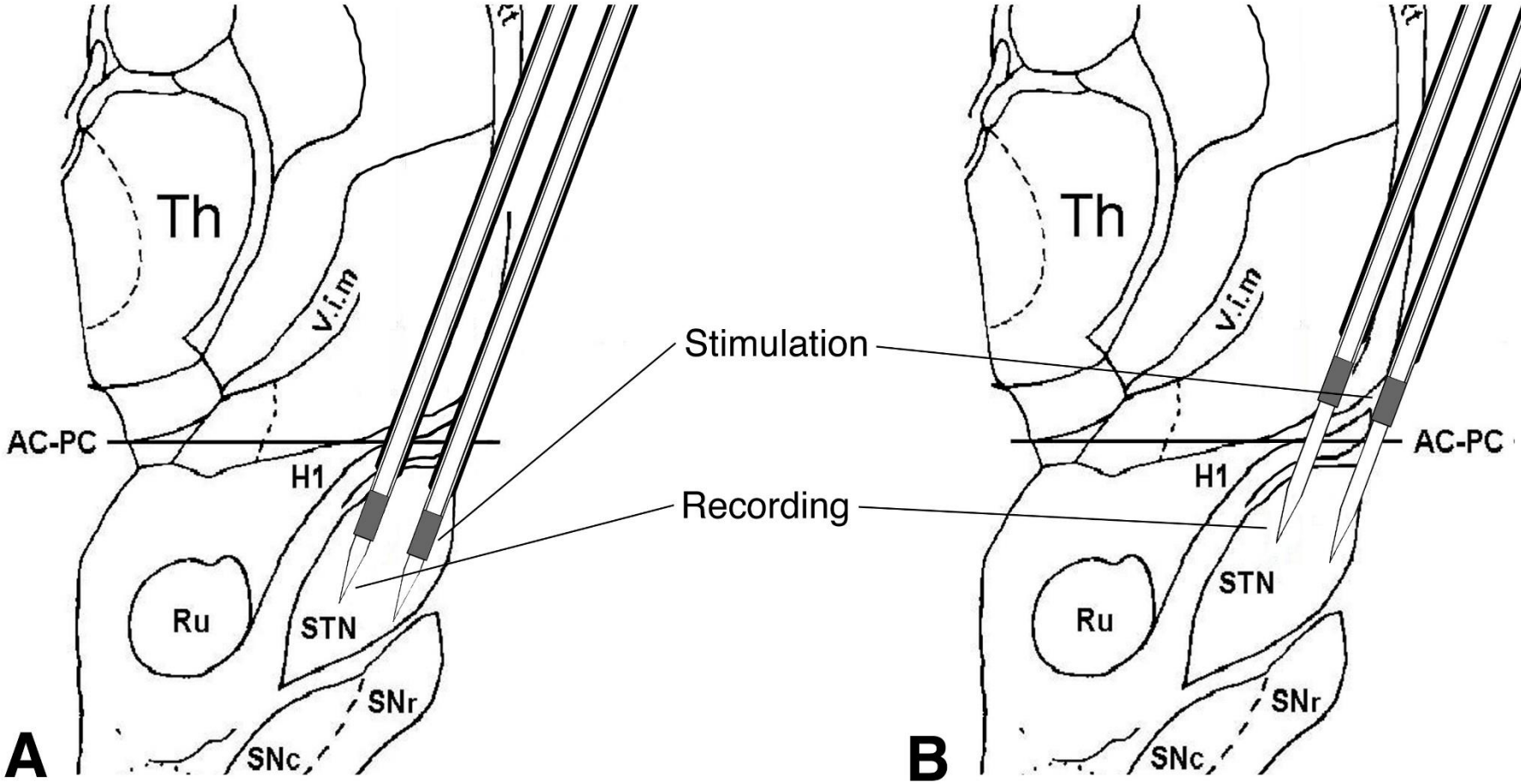
- STN HFS → suppress PD symptoms like STN coagulation.

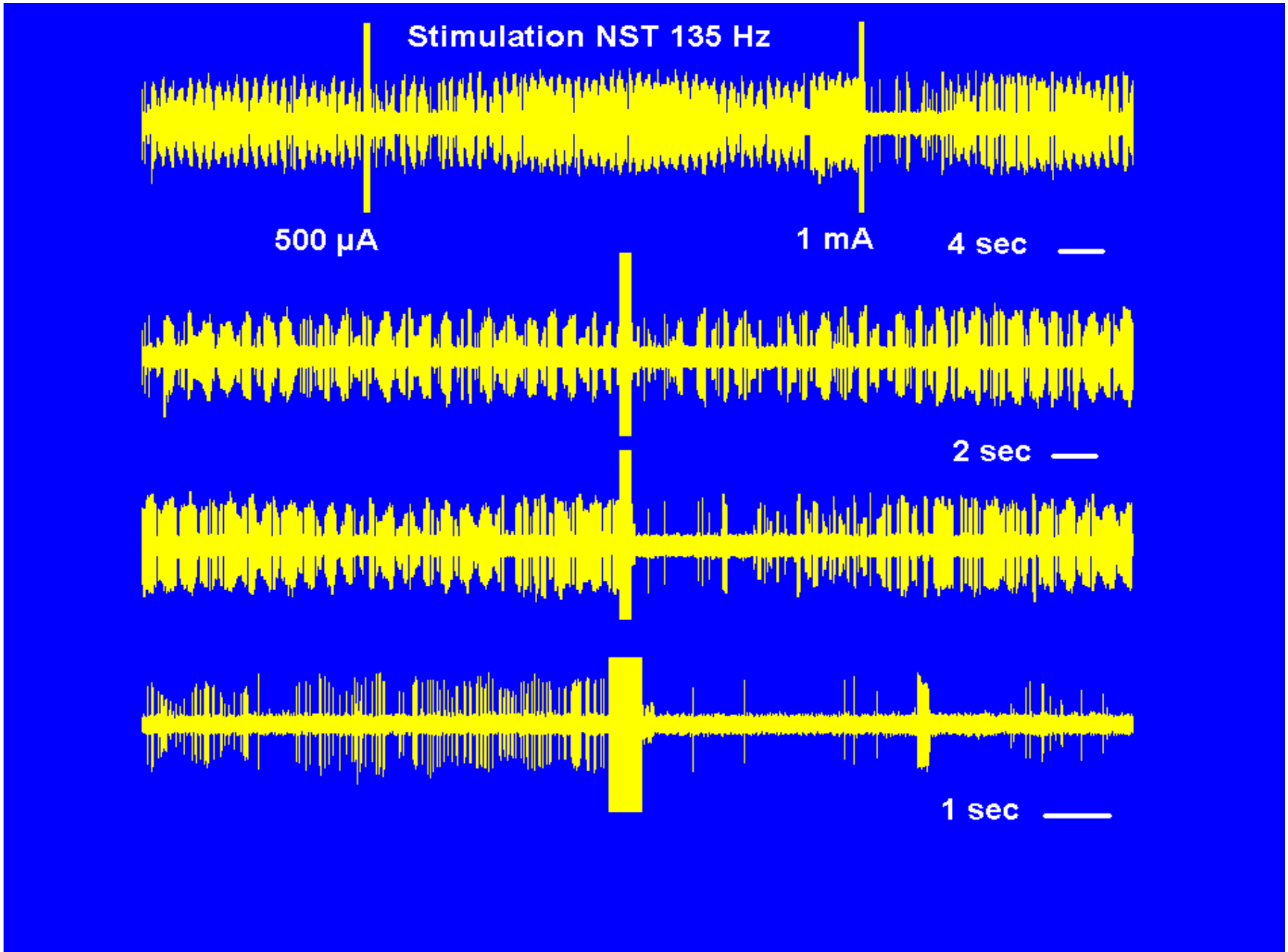
Deep Brain Stimulation : excitation or inhibition ?

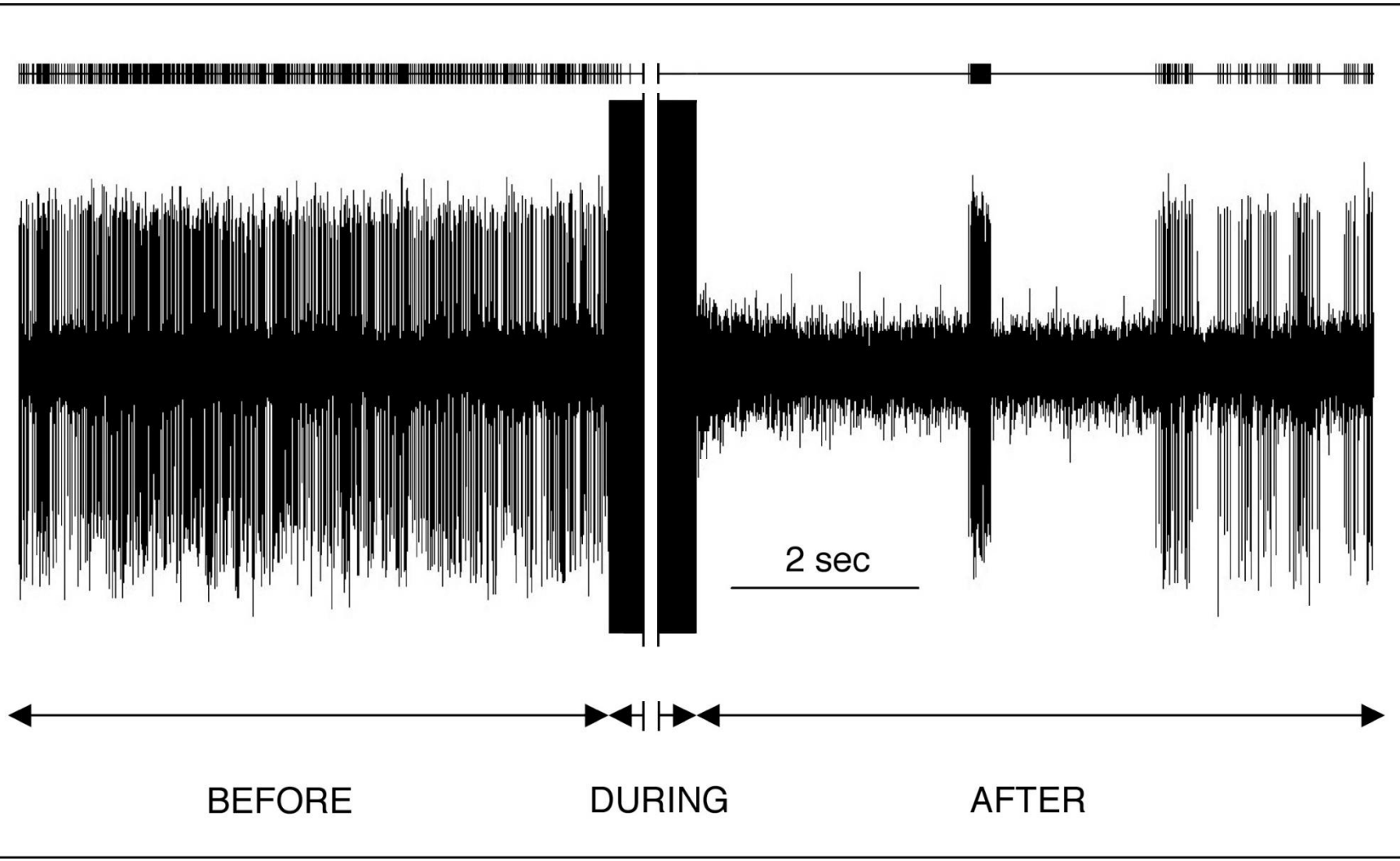
Two opposite hypothesis :

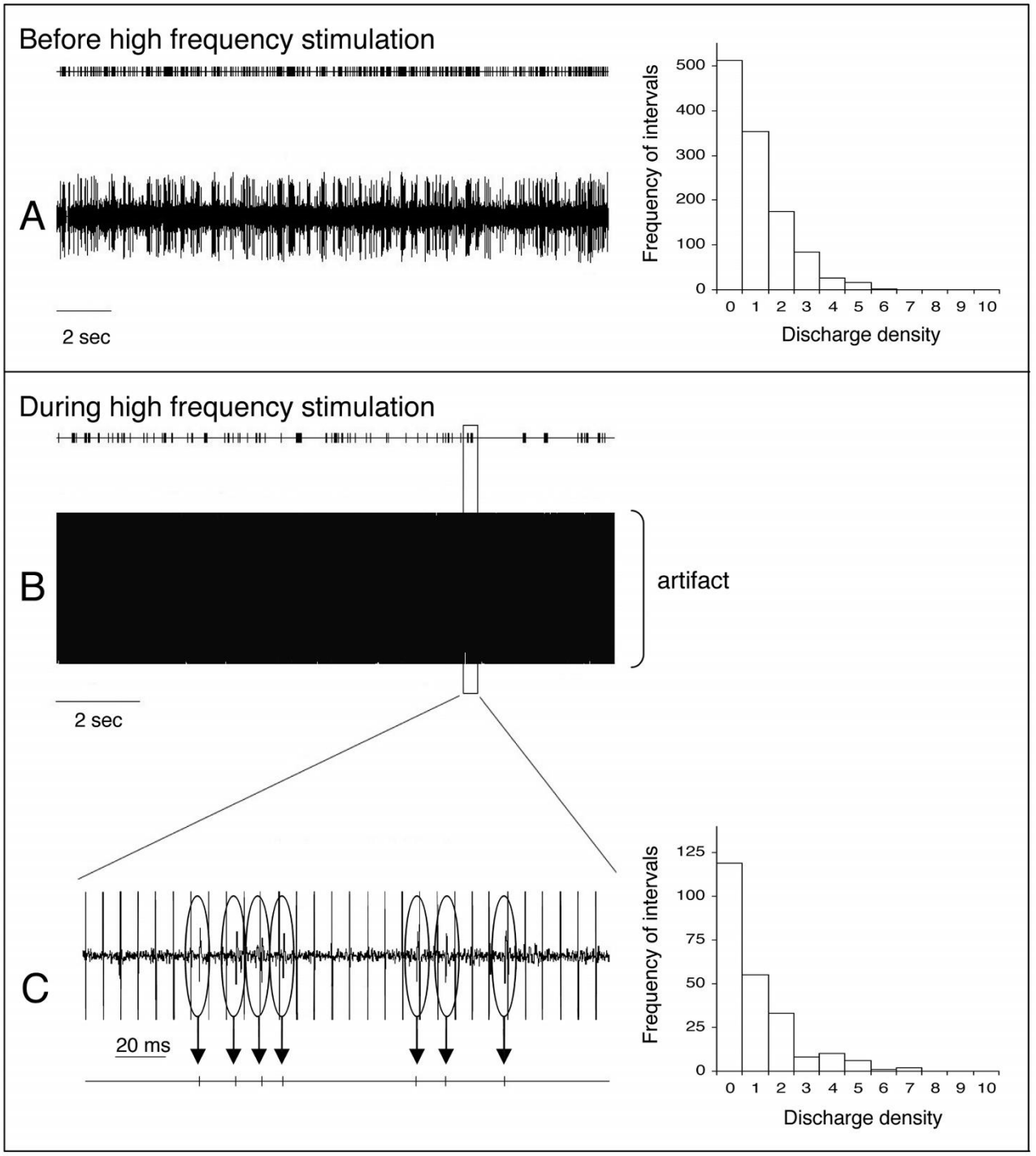
- DBS generates a functional ablation by suppressing or inhibiting the stimulated nucleus

- DBS results in activation of the stimulated nucleus that is transmitted throughout the network


Th
V.i.m
AC-PC
H1
Ru
STN
SNr
SNc
A
Stimulation
Recording
Th
V.i.m
AC-PC
H1
STN
Ru
SNr
SNc
B

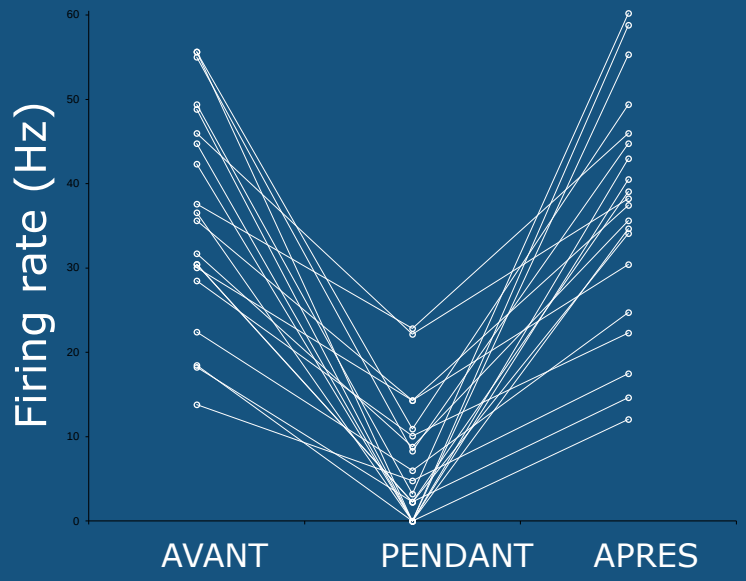

Stimulation NST 135 Hz
500 µA
1 mA
4 sec
2 sec
1 sec

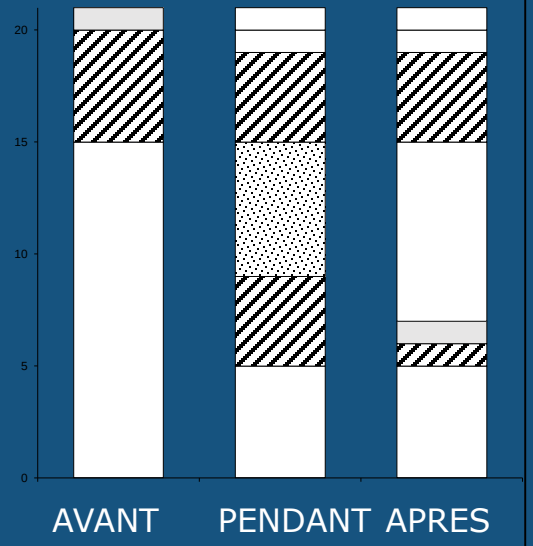

2 sec
BEFORE
DURING
AFTER

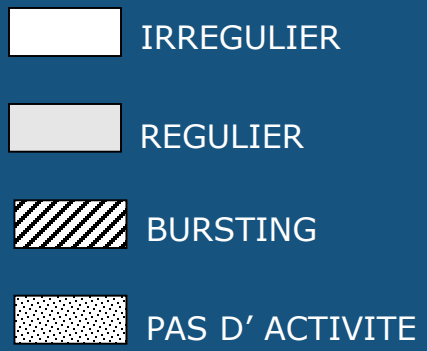

Before high frequency stimulation
A
2 sec
Frequency of intervals
500
400
300
200
100
0
0 1 2 3 4 5 6 7 8 9 10
Discharge density
During high frequency stimulation
B
artifact
2 sec
C
20 ms
Frequency of intervals
125
100
75
50
25
0
0 1 2 3 4 5 6 7 8 9 10
Discharge density

Stimulation HF homolatérale

A

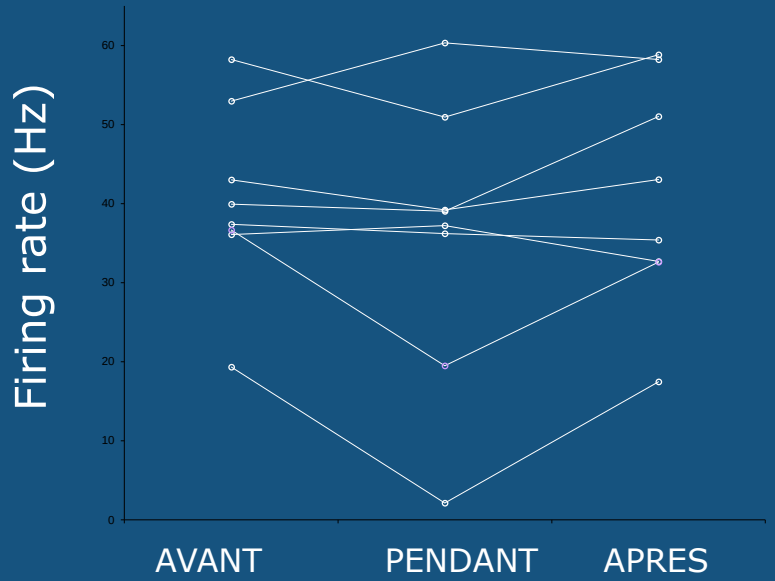


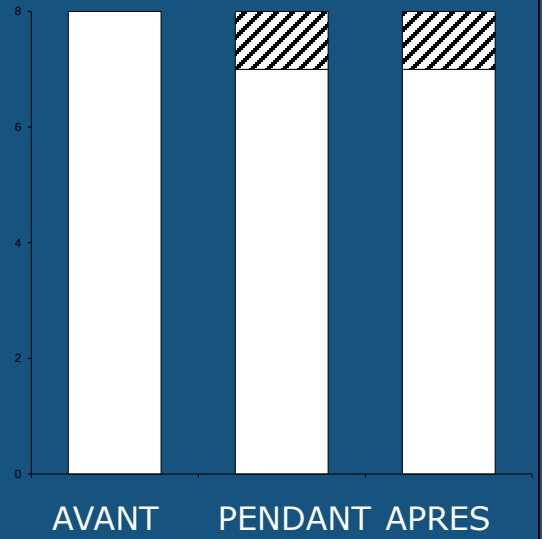


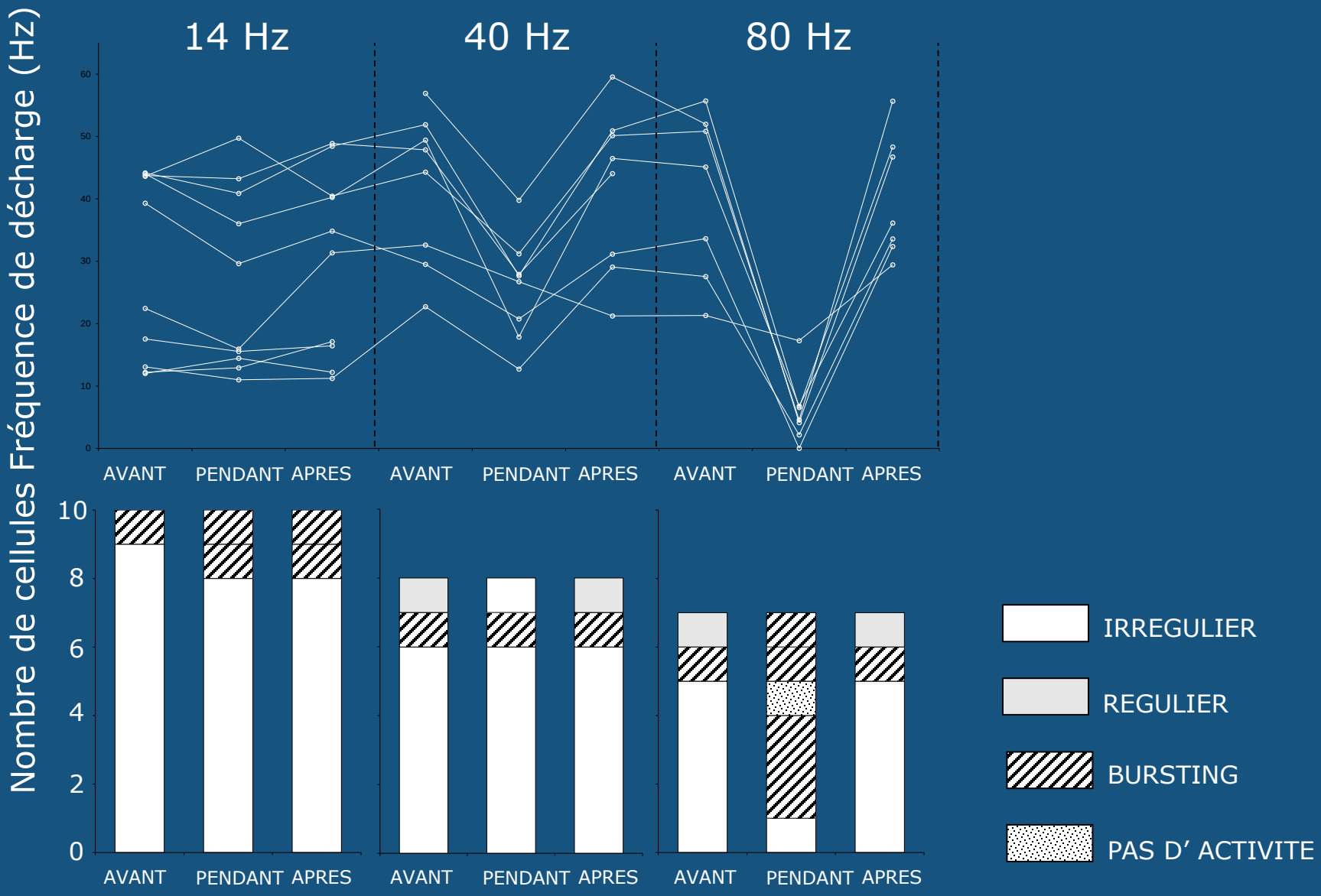


Procedure 'Placebo'

B






Nombre de cellules Fréquence de décharge (Hz)
14 Hz
40 Hz
80 Hz
AVANT
PENDANT
APRES
IRREGULIER
REGULIER
BURSTING
PAS D' ACTIVITE

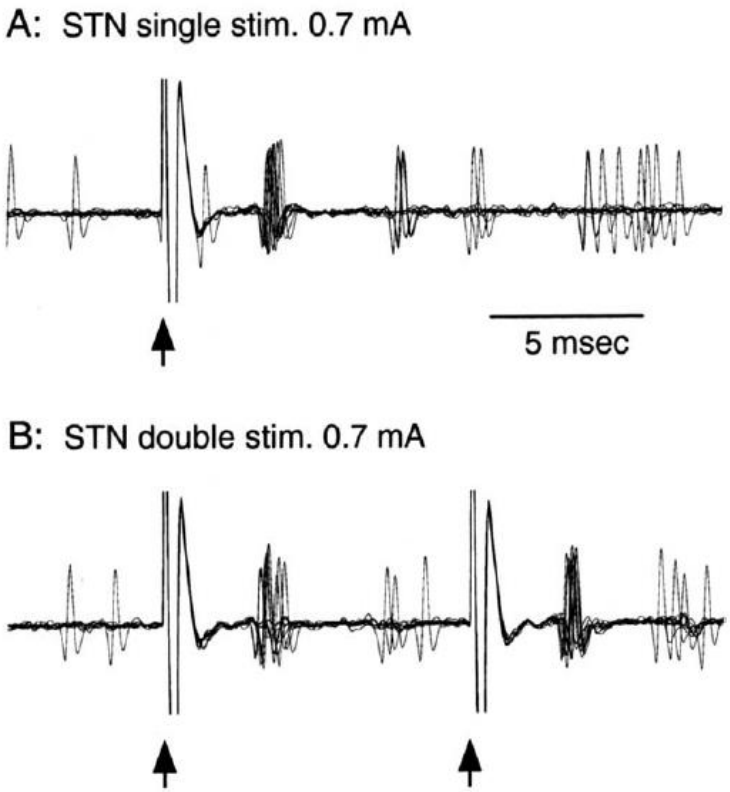
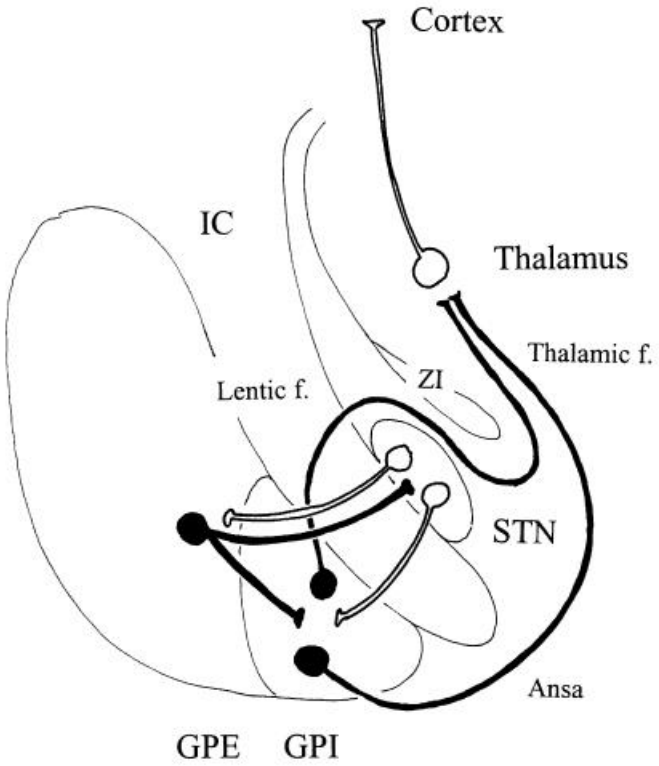


Figure 1. *A*, *B*, Responses of a GPe neuron to single stimulation (stim.; *A*) and double stimulation (stim.; *B*) of the STN. Ten overlapped traces show that single or double stimulation of the STN (marked by arrows) induced highly synchronized spiking ~3.5 ms after each stimulus. The second spikes following the initial short-latency spikes were also synchronized. Stimulus arti-

STN stim → GPe recordings



Kita H, Tachibana Y, Nambu A, Chiken S.

Balance of monosynaptic excitatory and disynaptic inhibitory response of the globus pallidus induced after stimulation of the subthalamic nucleus in the monkey. *J. Neurosci.* 2005; 21:8611-8619.

STN - BHFS → GPi recordings : strong inhibition

Inhibition during BHFS →

Inhibition suppressed by GABA blocker →

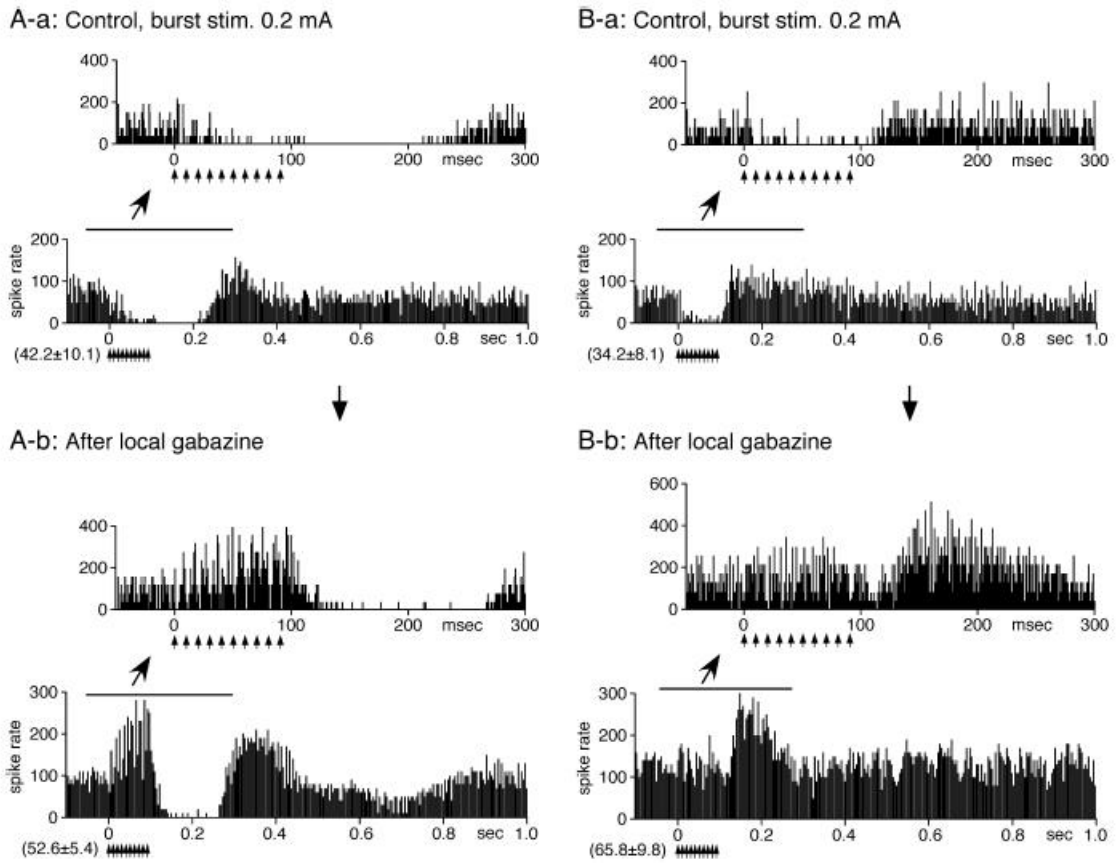


Figure 6. STN-BHFS evoked a long inhibition in a majority of GPi neurons. Recordings in *A* and *B* are from two different neurons.

Kita H, Tachibana Y, Nambu A, Chiken S.

Balance of monosynaptic excitatory and disynaptic inhibitory response of the globus pallidus induced after stimulation of the subthalamic nucleus in the monkey. *J. Neurosci.* 2005; 21:8611-8619.

STN stimulation → GPi recordings

Suppressed GPi inhibition by GPe blockade with GLU & GABA blockers →

Suppressed GPi excitation after GPi application of GLU & GABA blockers →

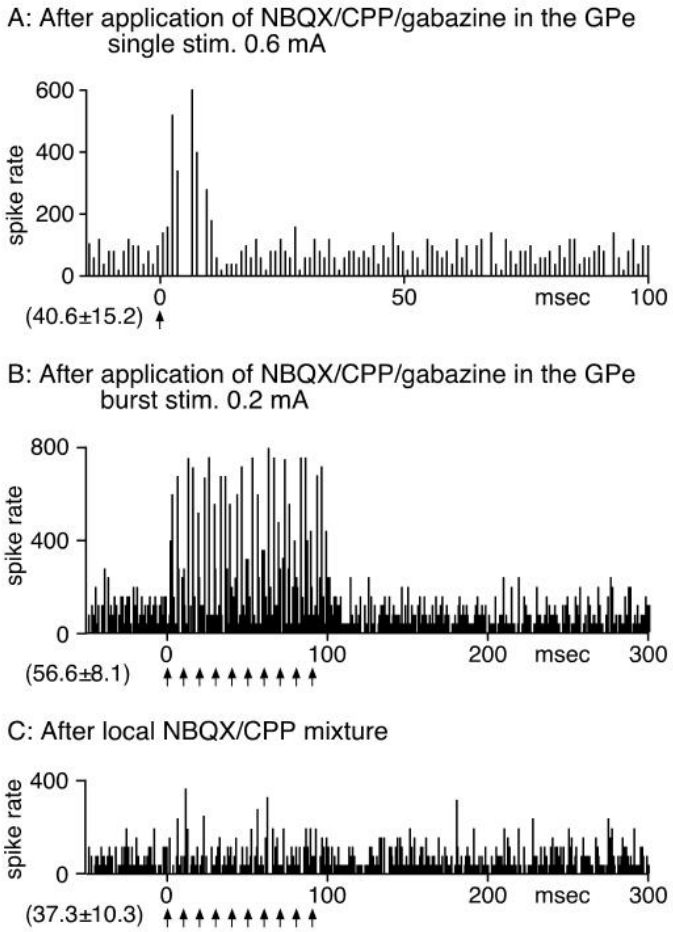
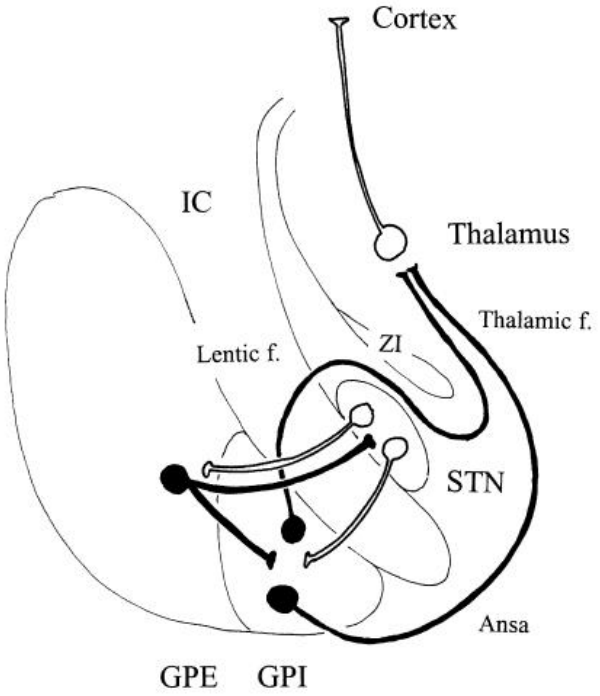


Figure 7. The blockade of the GPe suppressed the inhibition of GPi neurons evoked by STN stimulation. Before GPi recording, a mixture of NBQX, CPP, and gabazine (0.5 mM each; 0.6 μl)



Kita H, Tachibana Y, Nambu A, Chiken S.

Balance of monosynaptic excitatory and disynaptic inhibitory response of the globus pallidus induced after stimulation of the subthalamic nucleus in the monkey. *J. Neurosci.* 2005; 21:8611-8619.

Authors conclusion

STN HFS might inhibit the majority of the neurons in the GPi

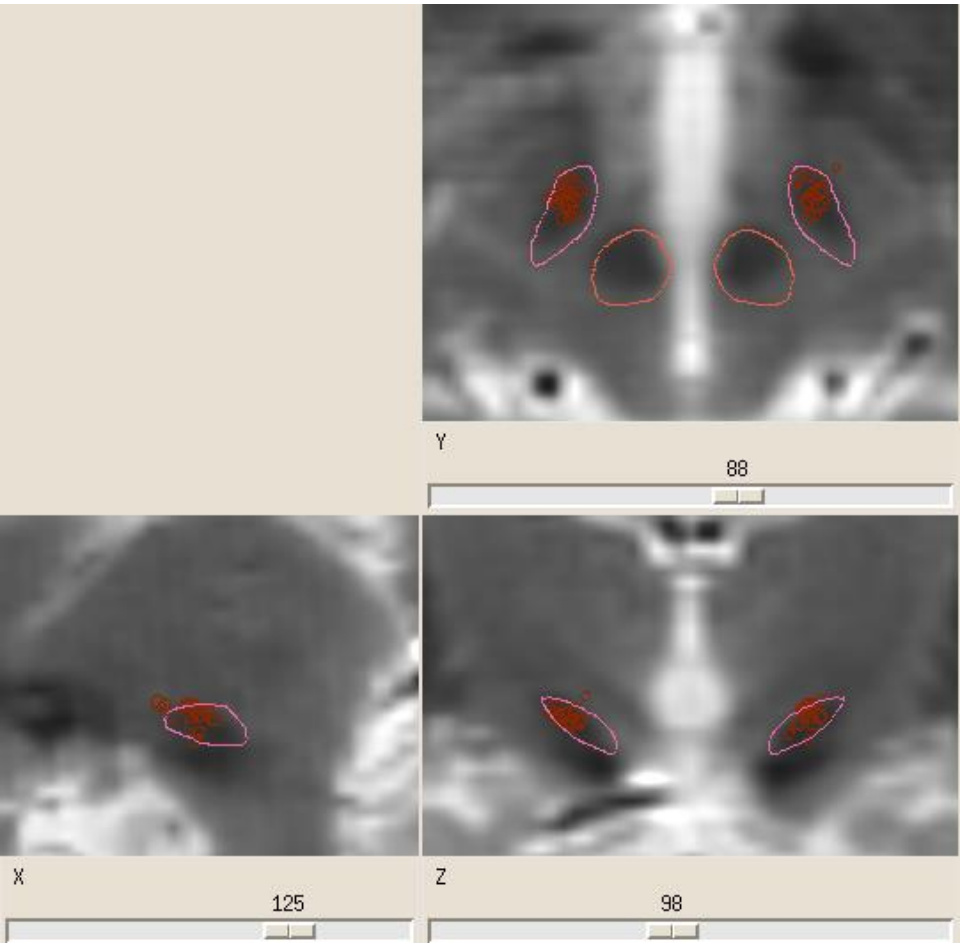
due to the fact that STN-GPe-GPi inhibitory response dominates over the STN-GPi excitatory response in GPi

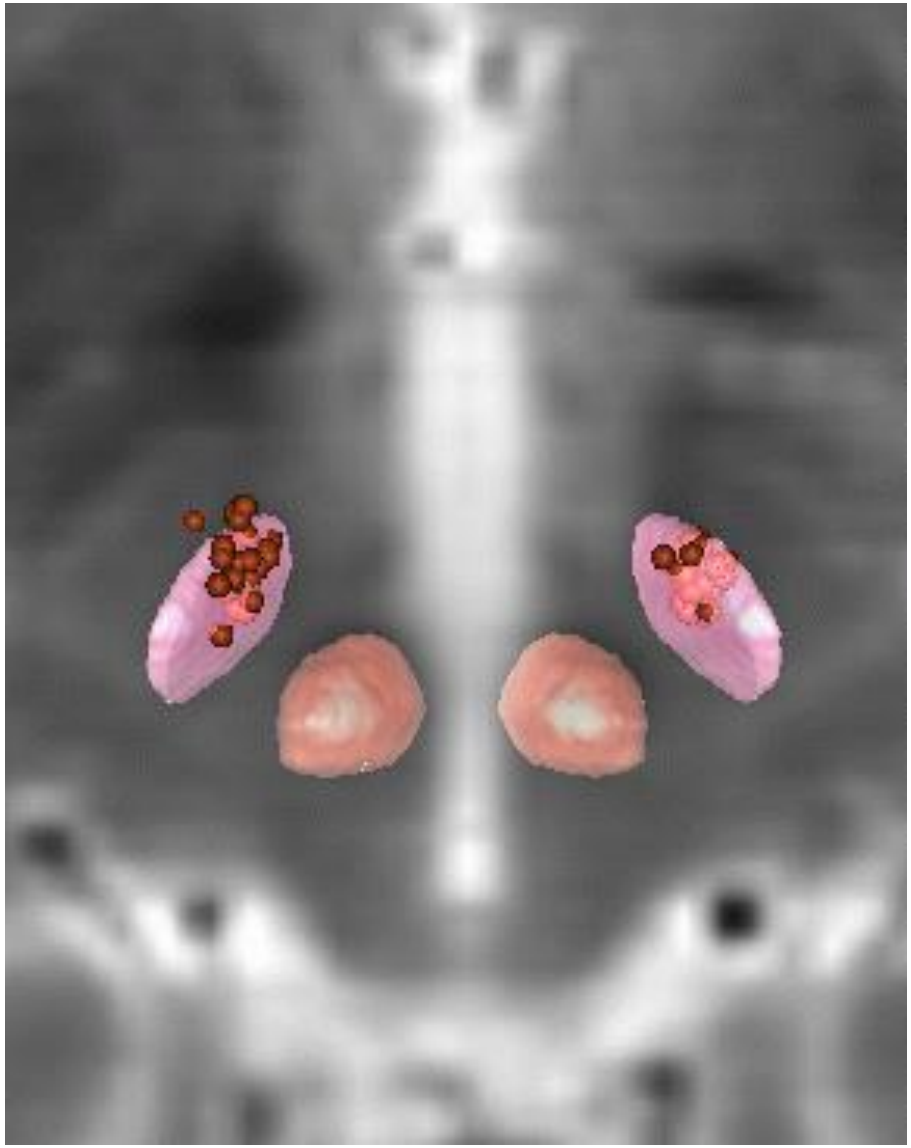
(however) « there may be also a disruption by HFS of the abnormal discharge patterns in the GPi »

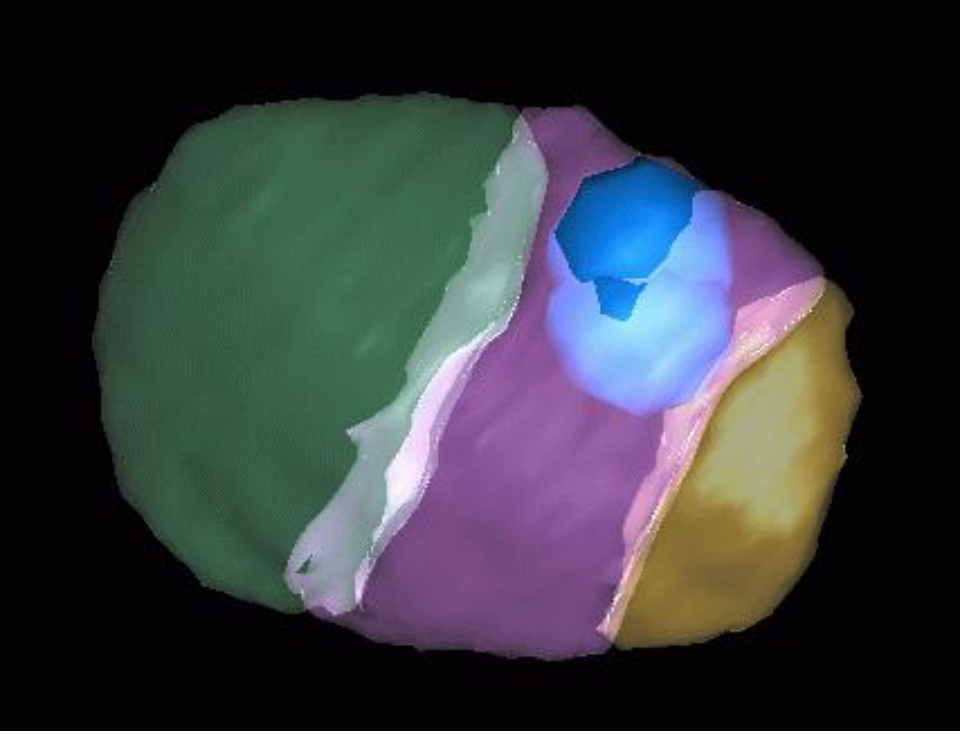
Hashimoto T, Elder CM, Okun MS, Patrick SK, Vitek JL. Stimulation of the subthalamic nucleus changes the firing pattern of pallidal neurons. *J Neurosci*. 2003 Mar 1;23(5):1916-23

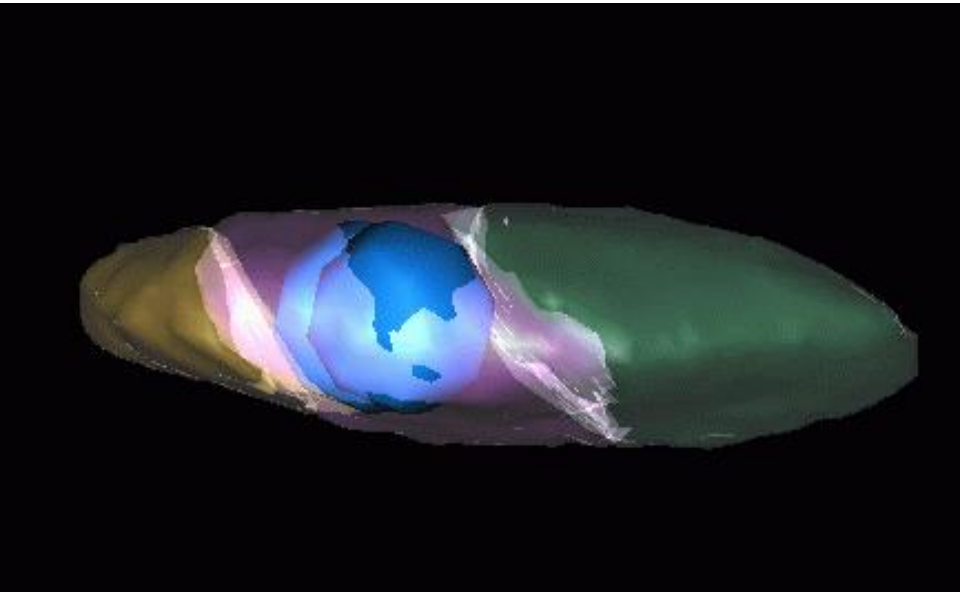
Kita H, Tachibana Y, Nambu A, Chiken S.

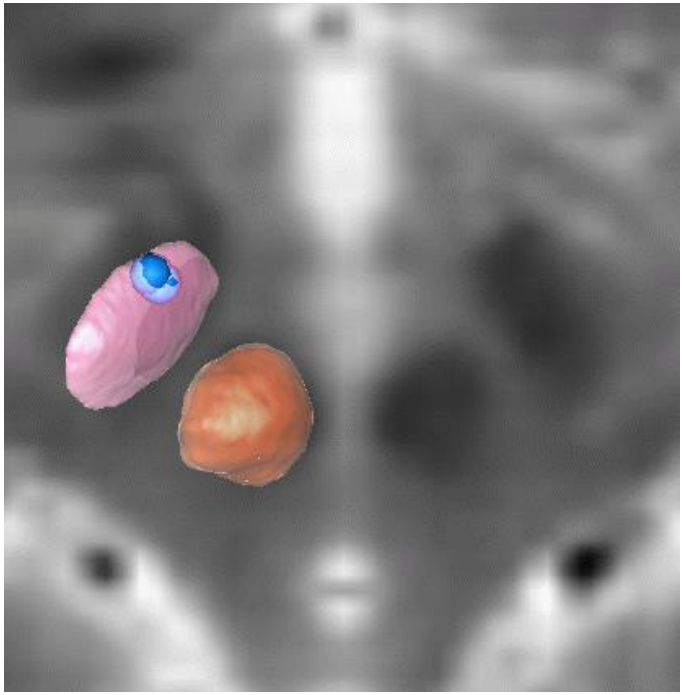
Balance of monosynaptic excitatory and disynaptic inhibitory response of the globus pallidus induced after stimulation of the subthalamic nucleus in the monkey. *J. Neurosci.* 2005; 21:8611-8619.


Y
88
X
125
Z
98









谢谢您！