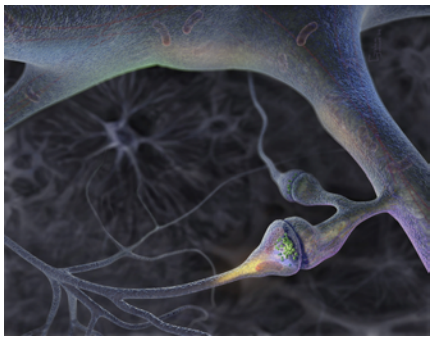
EPFL

Parkinson's Disease

Basal ganglia: function and pathology

Bernard Schneider
October 2024



EPFL

Lecture plan

1. Basal ganglia circuitry

2. Nigrostriatal degeneration and symptomatic treatments
   - Motor symptoms → dopamine replacement
   - Deep brain stimulation

3. Neuronal degeneration / Lewy body pathology
   - Selective vulnerability of neuronal subtypes
   - Spreading of the α-synuclein pathology

4. PD etiology: organelle quality control
   - Recessive forms: parkin, PINK1 and mitochondrial turnover

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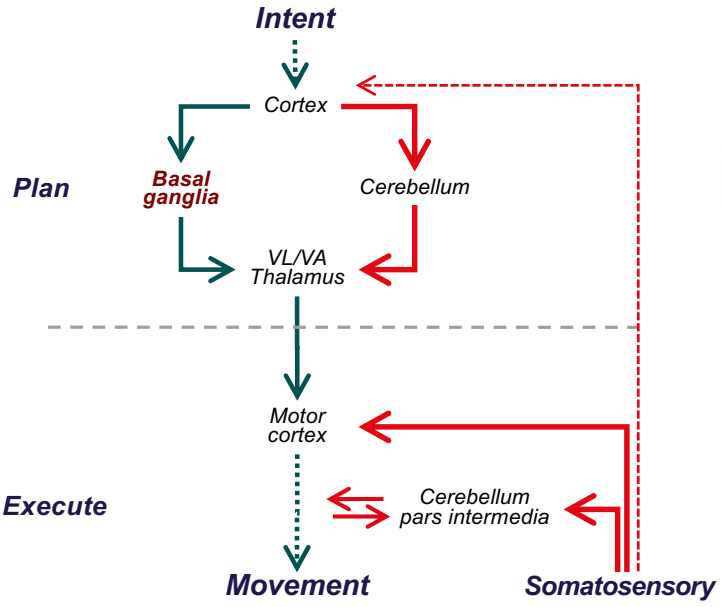
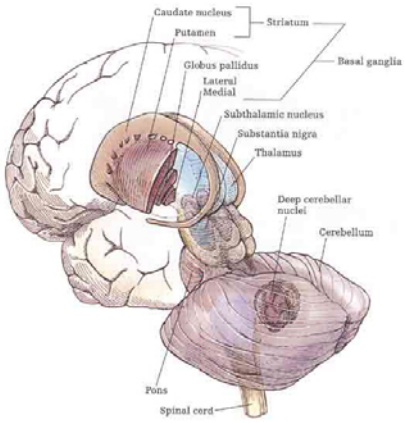
Basal ganglia: movement control





Basal ganglia: structure

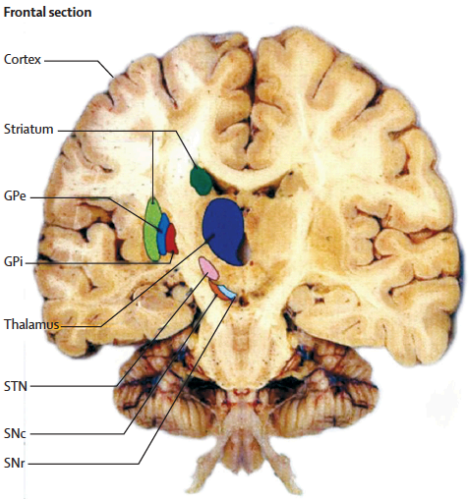
Basal ganglia:

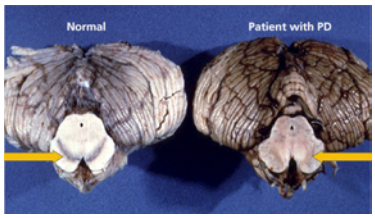
striatum *caudate*
putamen

globus pallidus *interna*
externa

subthalamic nucleus

substantia nigra *pars compacta*
pars reticulata

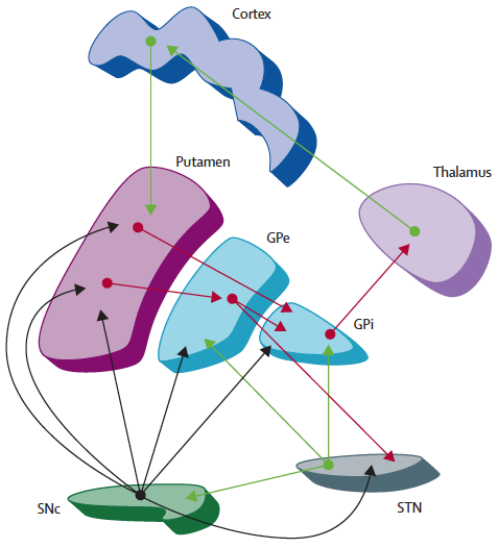




Stoessl AJ, Lancet 2014
Obeso JA, Lancet 2014

Basal ganglia: circuits / neurotransmitters

Motor circuit: associated neurotransmitters



Glutamate

GABA

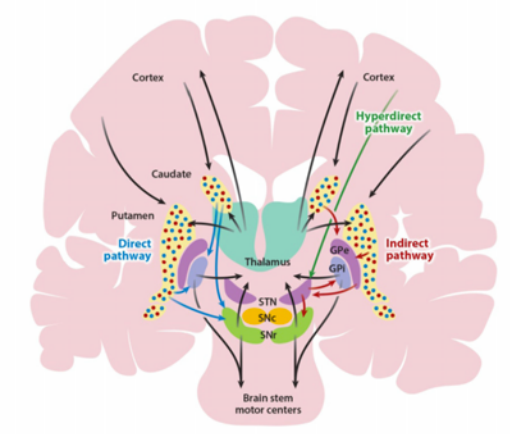
Dopamine

GP: globus pallidus
STN: subthalamic nucleus
SN: substantia nigra

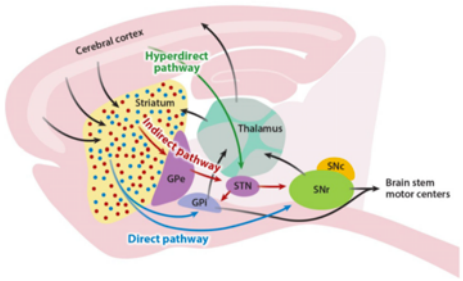
Stoessl AJ, Lancet 2014

Basal ganglia: circuit for motor control

Human brain



Rodent brain



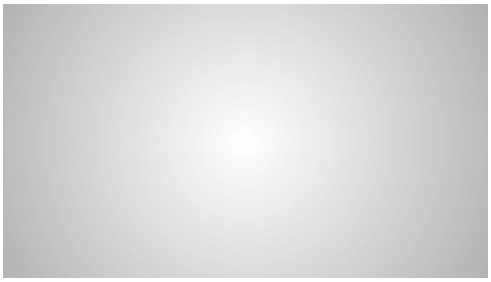
- **Input nuclei of the Basal Ganglia:**
  striatum
  STN
- **Output nuclei of the Basal Ganglia**:
  SNr
  GPi

- Nelson AB & Kreitzer AC, Ann Rev Neurosci 2014

Basal ganglia: movement disorders

Tremor/bradykinesia: Parkinson's disease

Dyskinesia/hyperkinesia:
Huntington's disease/chorea



Dystonia:
abnormal sustained muscle contraction
co-activation of normally antagonistic muscle groups

Lecture plan

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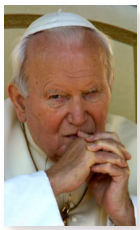
Parkinson's disease

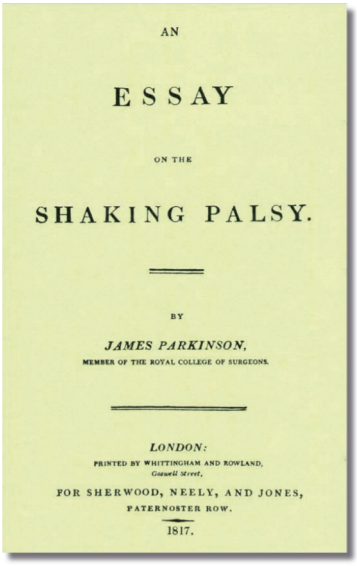
Epidemiology

- 1-2% of the population over the age of 65 years (4-5% by the age of 85)
- Average age of onset typically between 58-65 years
- Found world-wide, more common in industrialized countries
- Symptom severity increases over time
- Men ≥ women

Parkinson's disease

First clinical description


AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON,

MEMBER OF THE ROYAL COLLEGE OF SURGEONS.

LONDON:

PRINTED BY WHITTINGHAM AND ROWLAND,

Goswell Street,

FOR SHERWOOD, NEELY, AND JONES,

PATERNOSTER ROW.

1817.

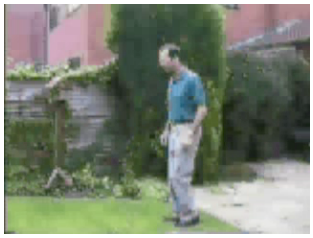
James Parkinson, 1817

" *...involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace, the senses and the intellects uninjured*."

- rhythmic tremor at rest
- rigidity
- bradykinesia / akinesia

Parkinson's disease: symptoms

Shuffling



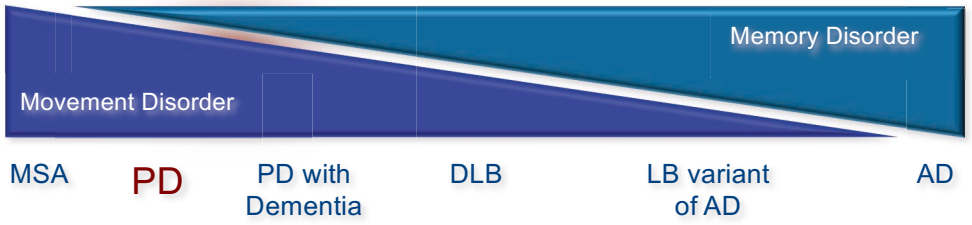
Postural instability

Tremor at rest

Initiation of movement

Parkinsonism: a syndrome

Parkinsonism: a syndrome not clearly delineated

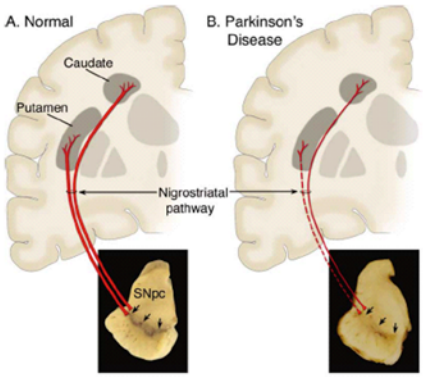


MSA	Multiple System Atrophy
PD	Parkinson's disease
DLB	Dementia with Lewy bodies
AD	Alzheimer's disease

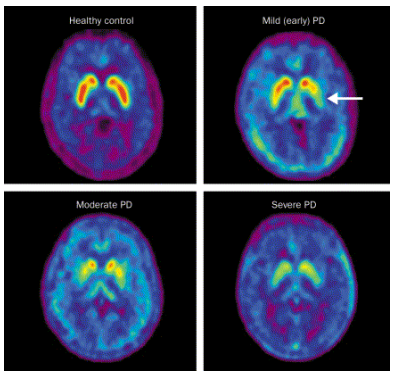
- *Modified from Arch Neurol 2001; 58:186*

Parkinson's disease: pathology

Loss of pigmented neurons residing in the *Substantia Nigra pars compacta* and innervating the striatum



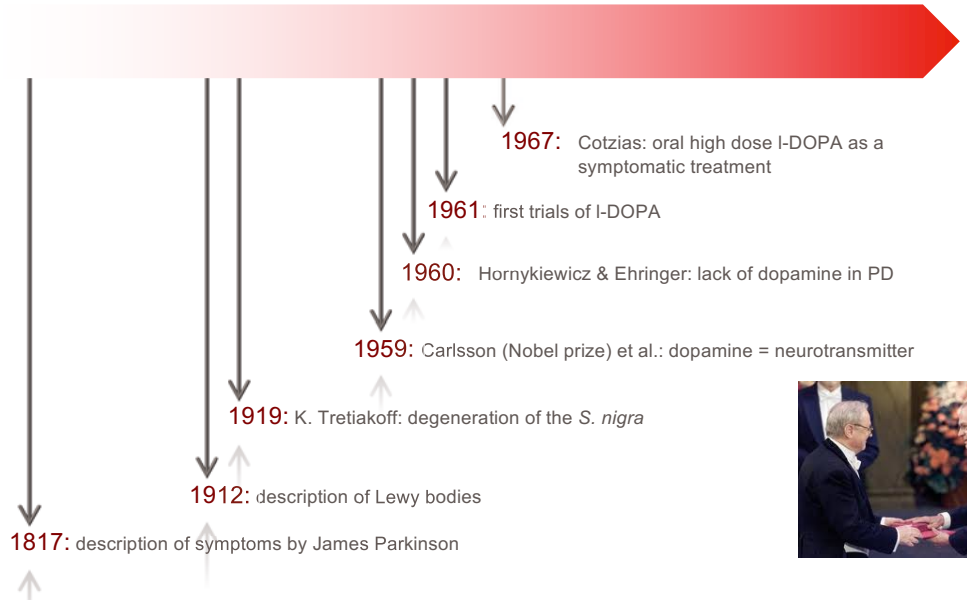
18-fluorodopa PET scan



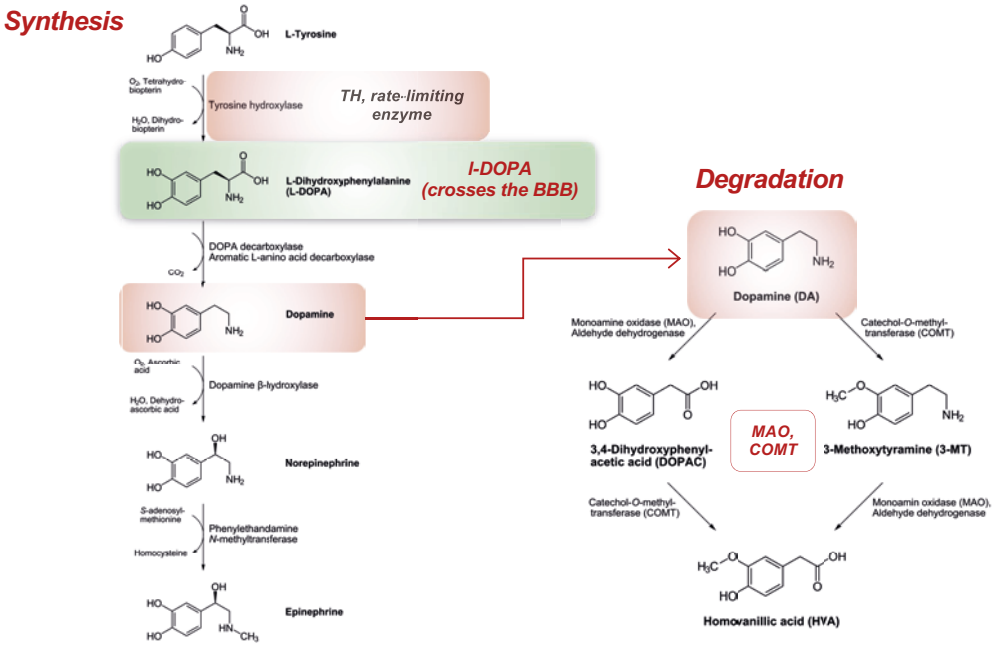
- Late 50s: dopamine is present in the mammalian brain, mainly in the striatum
- 1960: Ehringer & Hornykiewicz discover the decrease in striatal dopamine content
- <50% striatal dopamine loss ⇒ no symptoms
- **>70% striatal dopamine loss ⇒ Parkinsonian symptoms**
- At death, >90% loss of dopamine

Parkinson's disease: loss of dopamine

Dopamine in Parkinson's disease: a few milestones…



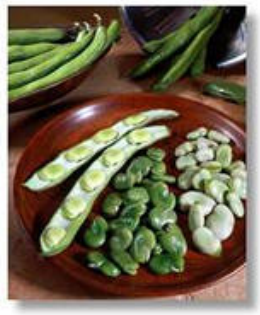
Dopamine biosynthesis (catecholamines)

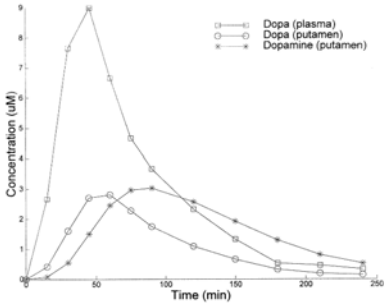


L-DOPA: a therapeutic precursor for dopamine biosynthesis

L-DOPA (levodopa)

- L-DOPA: first synthesis in 1911 (Casimir Funk)
- L-DOPA has poor pharmacodynamic properties:
  - blood half-life of approx. 1hr
  - absorbed in the upper small intestine
  - metabolized to dopamine in the periphery
  - metabolized rapidly in the CNS





Parkinson's disease - Question 1

1913: Marcus Guggenheim (Hoffmann-la Roche) isolated the L-DOPA enantiomer from Vicia faba. He ingested the compound and immediately started vomiting as L-DOPA was converted to dopamine, which induces nausea via the medulla oblongata, a CNS region accessible to peripheral dopamine. L-DOPA is now an effective drug for PD, why?

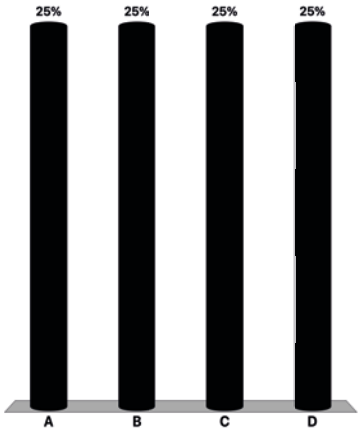
(1 correct answer)

A. L-DOPA is injected in the brain

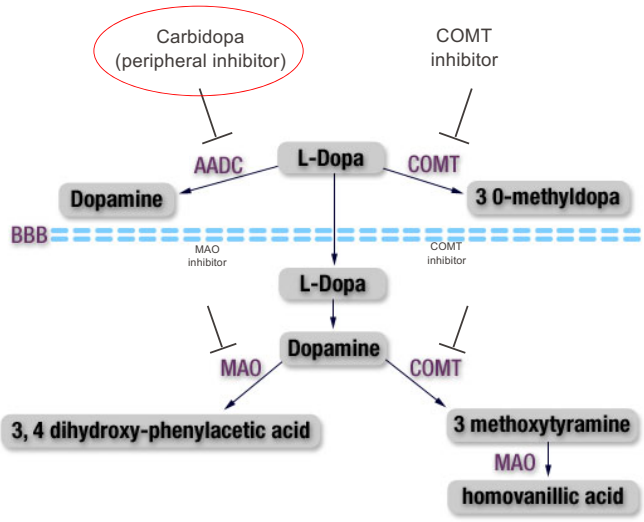
B. A compound is co-administered to block L-DOPA to dopamine conversion in the periphery

C. A modified form of L-DOPA is used that accumulates only in the brain

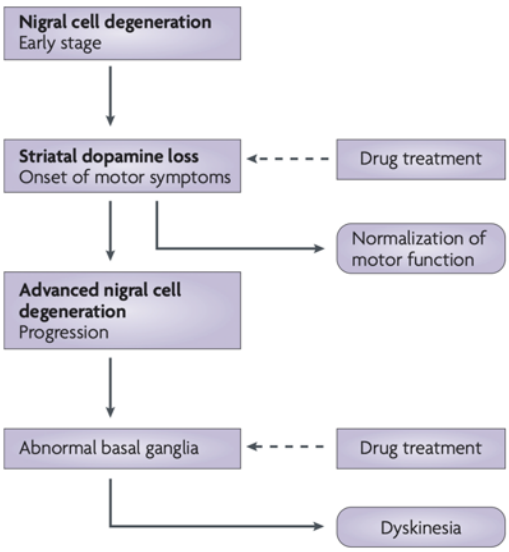
D. The dose of L-DOPA was adapted to prevent this side effect



L-DOPA

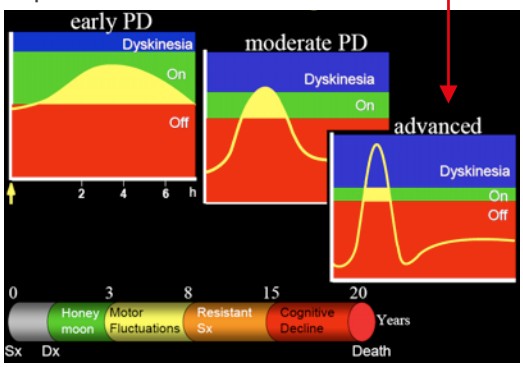


L-DOPA treatment: dyskinesia as a severe side-effect



- *No more buffering capacity in presynaptic vesicles*
- *Reflects blood pharmacodynamics*

Dopamine levels



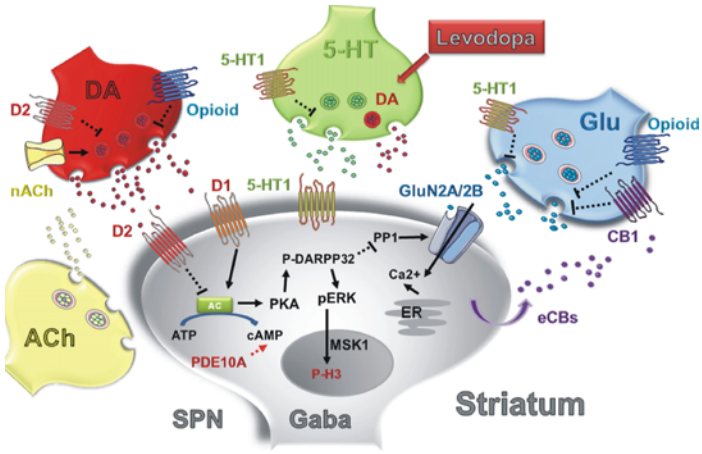
Sx: symptoms; Dx: diagnosis

Dyskinesia: involuntary movements as a side effect of l-DOPA
Dyskinesia likely due to pulsatile l-DOPA exposure

- *doi:10.1038/nrn2471*

L-DOPA treatment: dyskinesia as a severe side-effect

Example of dyskinesia mechanism: faulty dopamine neurotransmission



L-dopa ⇒ dopamine (DA) ⇒ serotonergic neurons
DA is then released non-physiological, unregulated manner in the extrasynaptic cleft ⇒ "false transmitter" causing abnormal and pulsatile activation of striatal DA receptors.

- *https://doi.org/10.1002/ana.25364*

Parkinson's disease - Question 2

L-DOPA treatment is poorly effective in late-stage PD patients because… (indicate all correct answers)

A. L-DOPA does not cross the BBB

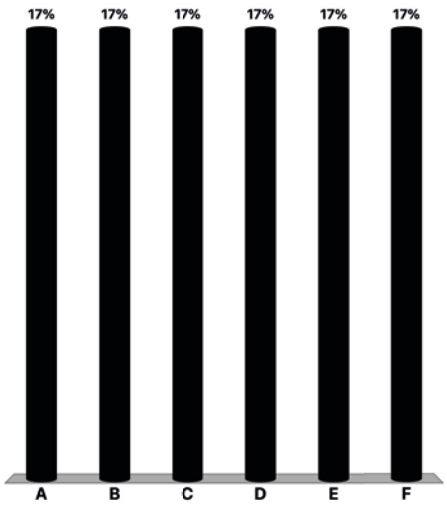
B. Dopamine can no more be synthesized from L-DOPA

C. There is not enough presynaptic vesicles to store dopamine in the striatum

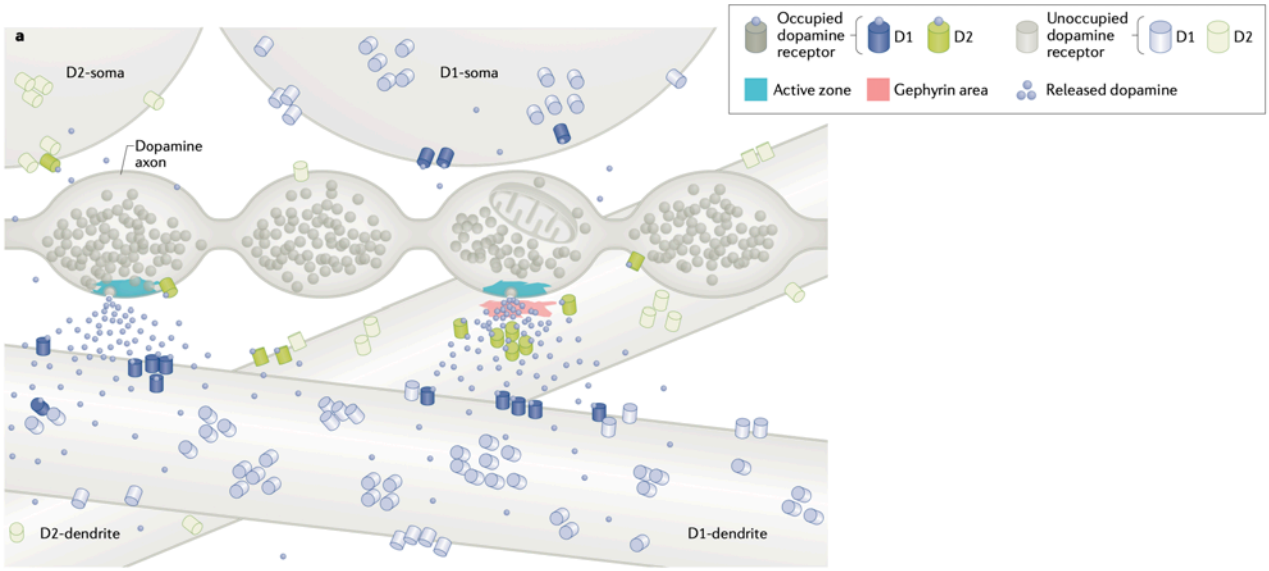
D. There is not enough dopamine transporter to recapture dopamine

E. Striatal neurons have degenerated

F. Other symptoms appear that do not respond to L-DOPA



Parkinson's disease: dopamine signaling in the striatum



- https://doi.org/10.1038/ s41583-021-00455-7

Parkinson's disease: dopamine signaling in the striatum

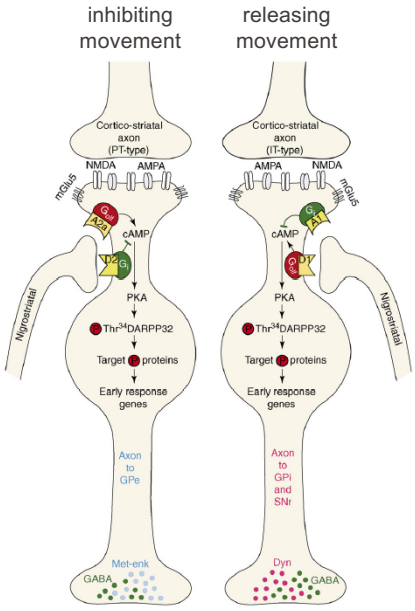
Medium-sized spiny neurons

~ 95% of all neurons in the striatum

push-pull system to release or inhibit movement

« **Direct pathway** » MSNs
D1 receptor ➔ activation

« **Indirect pathway** » MSNs
D2 receptor ➔ inhibition

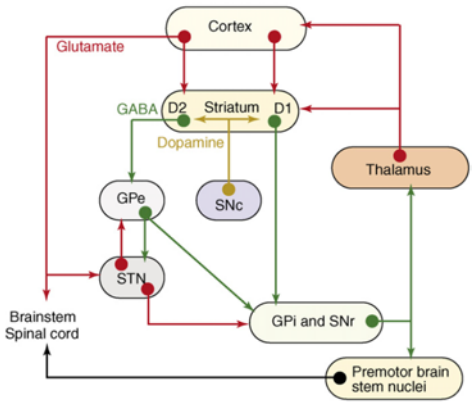


- Cenci MA, TINS 30(5), 2007

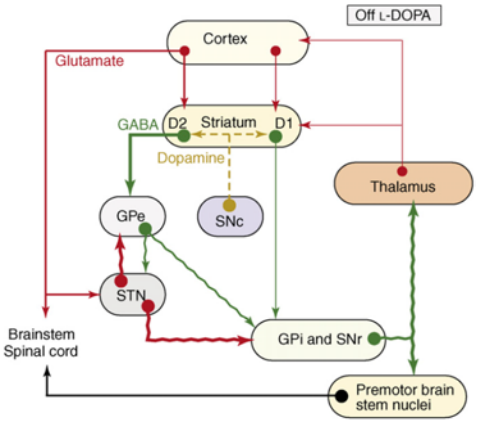
Parkinson's disease: role of dopamine in the basal ganglia

How does PD affect the basal ganglia circuitry ?

Normal basal ganglia



Parkinsonism

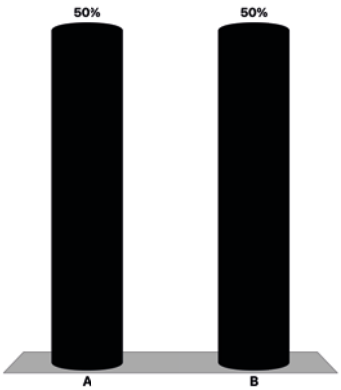


Parkinson's disease - Question 3

In multiple system atrophy (MSA), there is degeneration of dopaminergic neurons in the substantia nigra which is similar to PD. However, the disease also affects multiple brain regions including medium spiny neurons in the striatum.

MSA patients have Parkinsonian symptoms that respond well to levoDOPA treatment:

A. Vrai
B. Faux

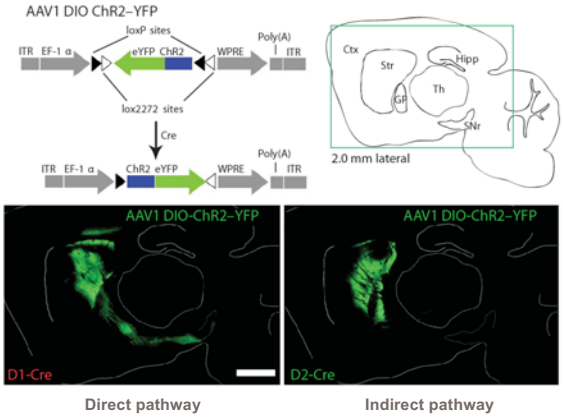


Regulation of parkinsonian motor behaviours by optogenetic control of basal ganglia circuitry

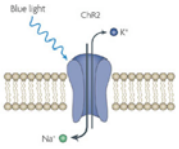
nature 2010

Alexxai V. Kravitz[1], Benjamin S. Freeze[1,4,5], Philip R. L. Parker[1,3], Kenneth Kay[1,5], Myo T. Thwin[1], Karl Deisseroth[6] & Anatol C. Kreitzer[1,2,3,4,5]

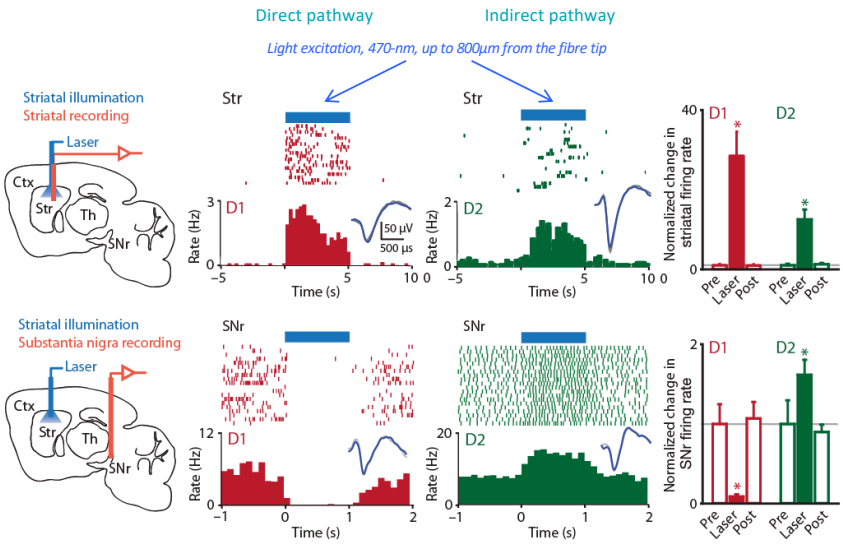
Optogenetics: *modulation of electrical activity by expression of light-activated regulators of transmembrane conductance*



Basal ganglia: role of the striatum in motor control



Optogenetic control of D1 and D2 medium spiny neurons has opposite effects on the output in the *substantia nigra pars reticulata*



Parkinson's disease: question 4

What is the behavioral effect of **light stimulation** in the striatum of D2R-Cre mice injected with AAV-DIO-ChR2 ?

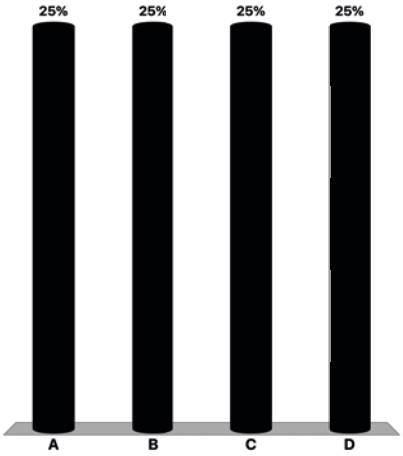
(1 correct answer)

A. No change in animal motor behavior

B. Constant hyperactivity

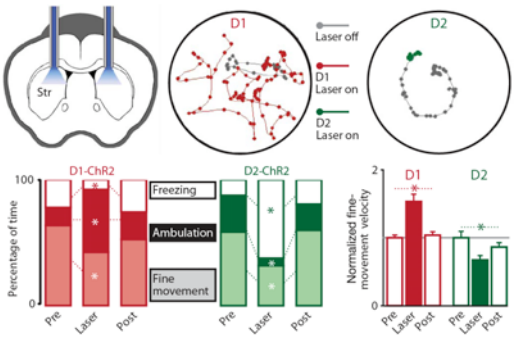
C. Transient hyperactivity

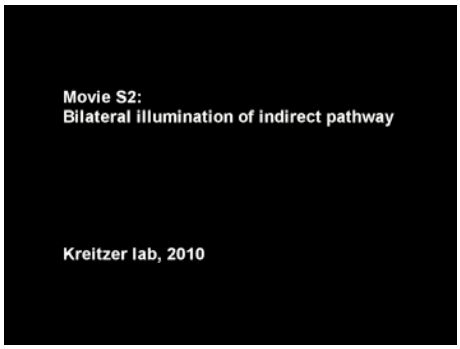
D. Mouse freezing during exposure to light



Basal ganglia: role of the striatum in motor control

- Activation of D1 striatal neurons increases spontaneous motor activity
- Activation of D2 striatal neurons reduces spontaneous motor activity





Light-activation of the « indirect » D2 pathway leads to mouse freezing

Parkinson's disease: question 5

A toxin is injected in the striatum to induce the selective degeneration of nigrostriatal neurons. The experiment is performed in D1R-Cre mice previously injected with AAV-DIO-ChR2.

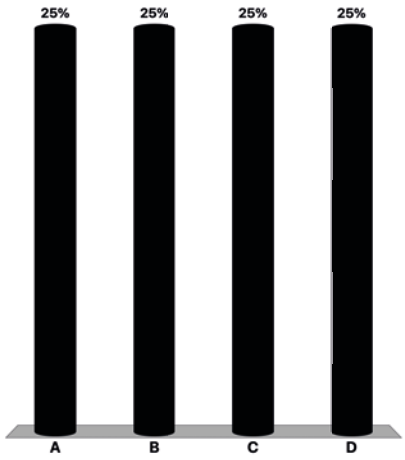
What is the behavioral effect of light stimulation ? (1 correct answer)

A. Constant hyperactivity

B. Rescue of parkinsonian bradykinesia observed in these mice

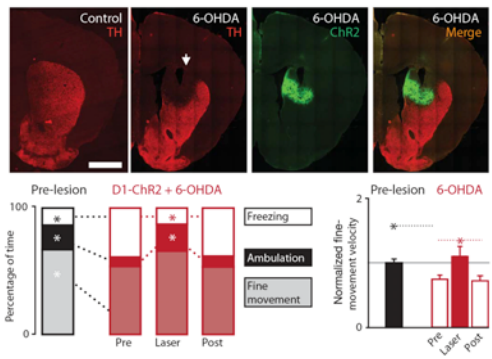
C. No change in motor activity

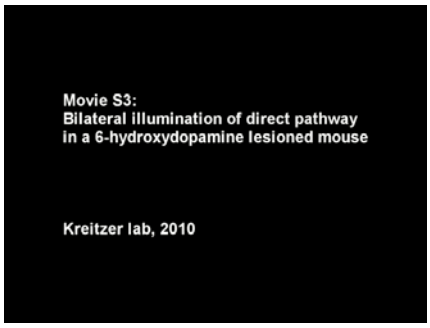
D. Development of parkinsonian symptoms



Basal ganglia: role of the striatum in motor control

- Activation of D1 striatal neurons increases spontaneous motor activity can correct reduced motor activity due to 6-OHDA-induced lesions of the nigrostriatal system



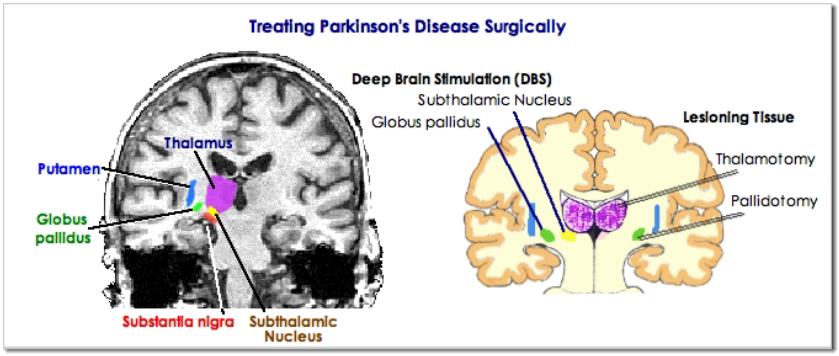


Light-activation of the « direct » D1 pathway restores mouse motor activity

Basal ganglia: symptomatic treatments

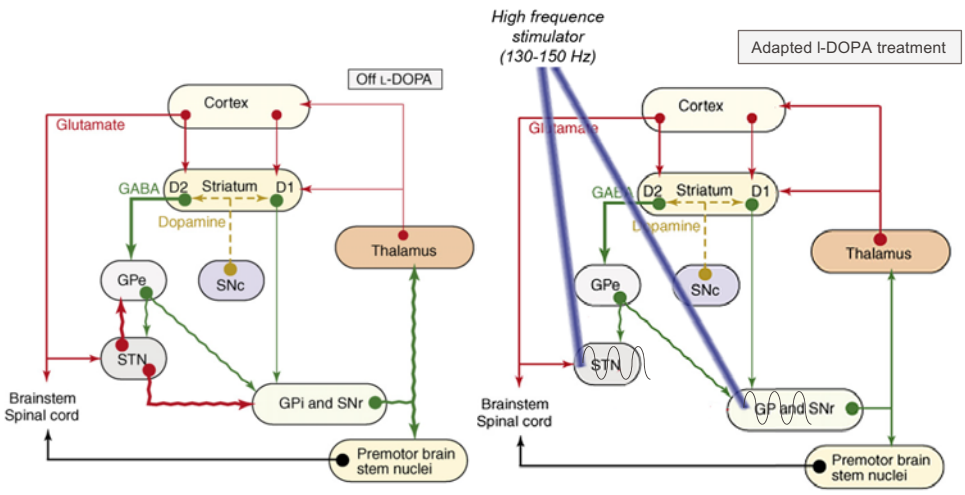
Functional interventions on the circuitry of the basal ganglia

- Surgical ablation: pallidotomy, thalamotomy (for tremor only)
- **Functional interference: Deep brain electrical stimulation (DBS)**
- Subthalamic or striatal gene therapy:
  glutamic acid decarboxylase / AADC / combined enzymes for dopamine synthesis



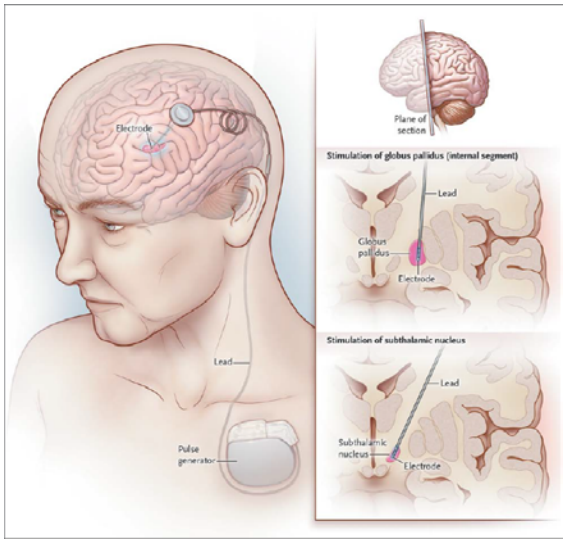
Basal ganglia: deep brain stimulation

Parkinsonism | Deep Brain Stimulation



Basal ganglia: symptomatic treatments

Deep Brain Stimulation



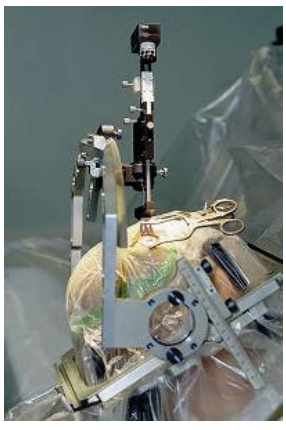
- Developed by Alim-Louis Benabid in 1980s (Grenoble)
- Discovery of DBS efficacy was made when performing thalamotomy using thermocouple electrodes
- Various stimulation frequencies were tested with the electrode to verify placement
- High frequencies (>100 Hz) were found to alleviate tremor

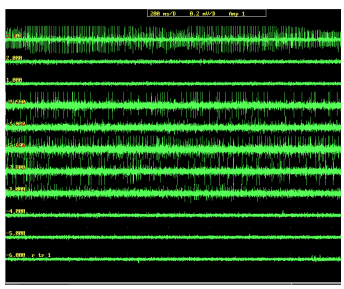
Okun MS et al., N Engl J Med 367;16 2012

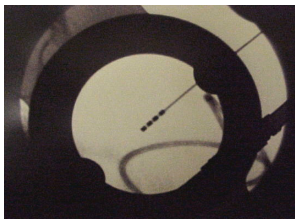
Basal ganglia: deep brain stimulation

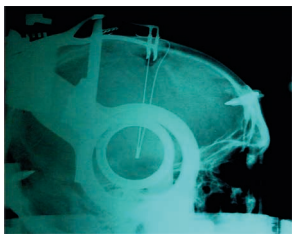
Stereotaxic implantation of the electrodes

- Adjustable, reversible
- High frequency, pulsatile electrical stimulation
- Placement: by MRI or CT
  physiologically by coordinated firing and tremor monitoring





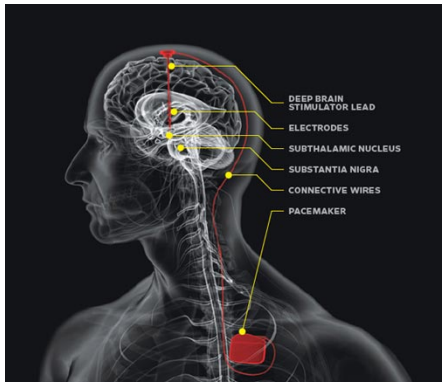




Basal ganglia: deep brain stimulation

Deep Brain Stimulation: clinical benefits

- Improvement in “OFF” state, some improvement in “ON” state
- Reduction in l-DOPA
- With disease progression, worsening of motor function is not prevented
- No demonstration of a disease-modifying effect



- **FDA approval:**

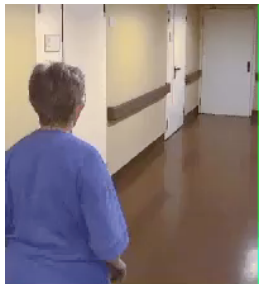
  for essential tremor in 1997

  for Parkinson’s disease in 2002

  for dystonia in 2003
- **>100,000 patients** treated worldwide

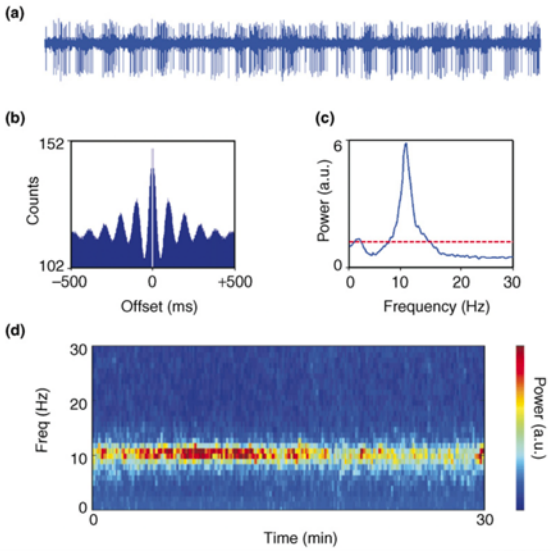
Basal ganglia: deep brain stimulation

Deep Brain Stimulation (DBS)



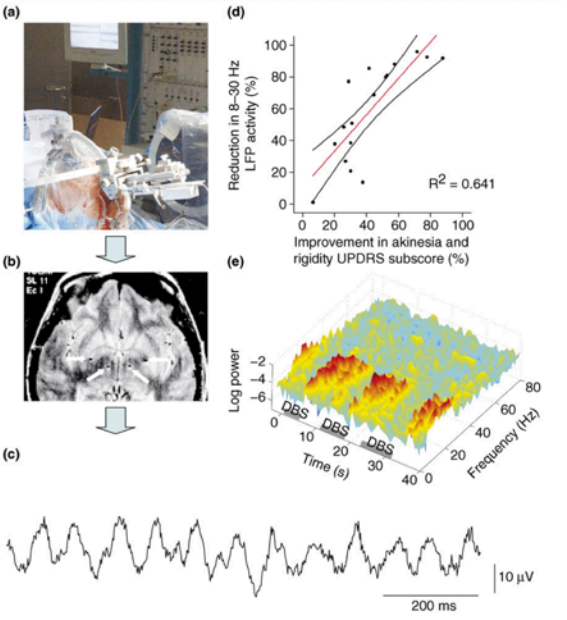
DBS relieves pathological synchrony in the basal ganglia

Globus pallidus recording in a Parkinsonian monkey (following MPTP intoxication) ➔ 10 Hz oscillations

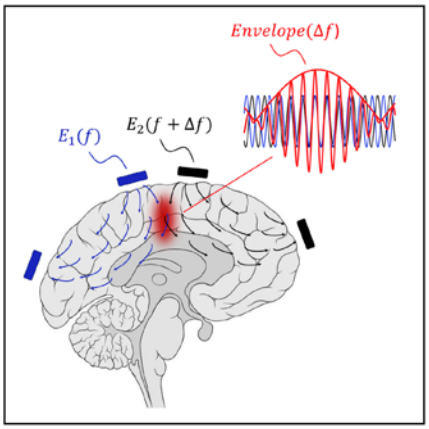


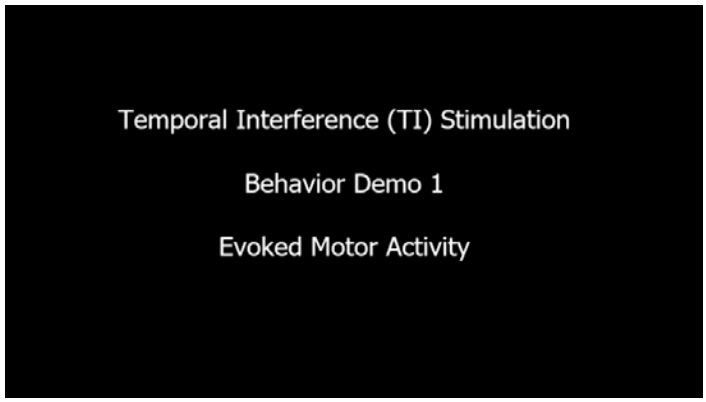
- *Hammond C et al, 2007 TRENDS in Neurosciences Vol.30 No.7*

DBS blocks 15 Hz oscillations in PD patient



Non-invasive deep brain stimulation: temporal interference stimulation





- Cell — Article
  Noninvasive Deep Brain Stimulation via Temporally Interfering Electric Fields
  Authors
  Nir Grossman, David Bono, Nina Dedic, ..., Li-Huei Tsai, Alvaro Pascual-Leone, Edward S. Boyden