New DBS targets for Parkinson,s Disease

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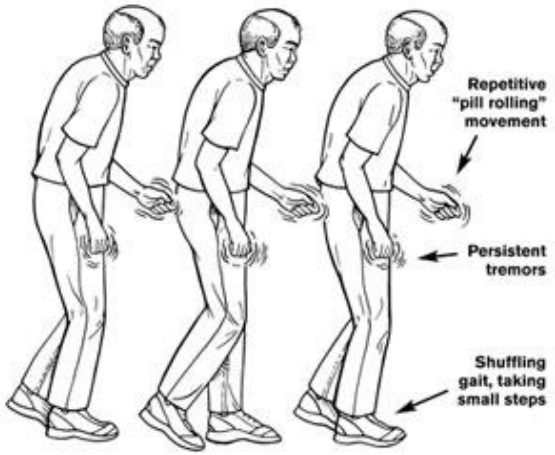
Parkinson's Disease; Paralysis Agitans

Progressive disease of central nervous system

Symptoms can be halted but not cured

Symptoms

- Bradykinesia
- Rigidity



mid-20’s to 70’s

t start with slow progression over

Cause of PD

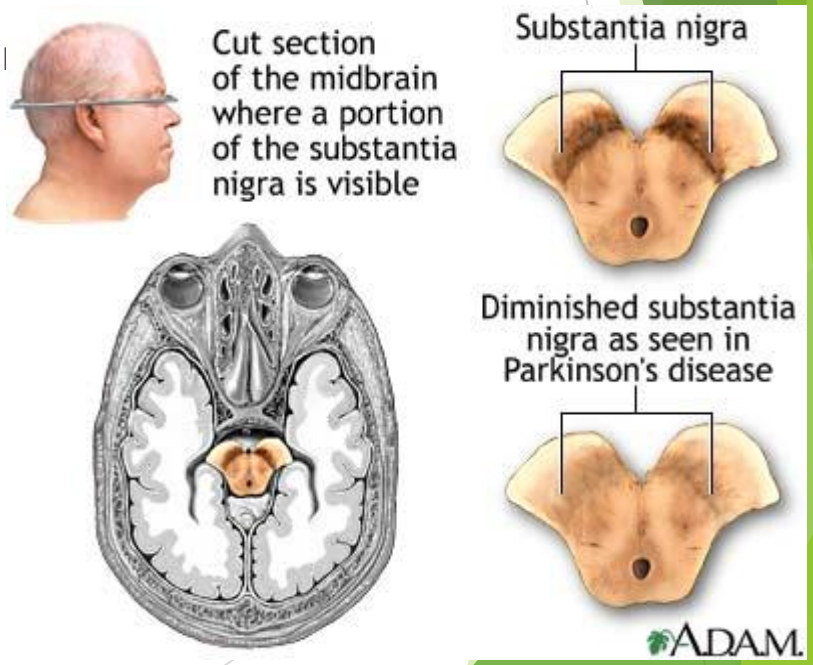
Degeneration of neurons in Substantia Nigra

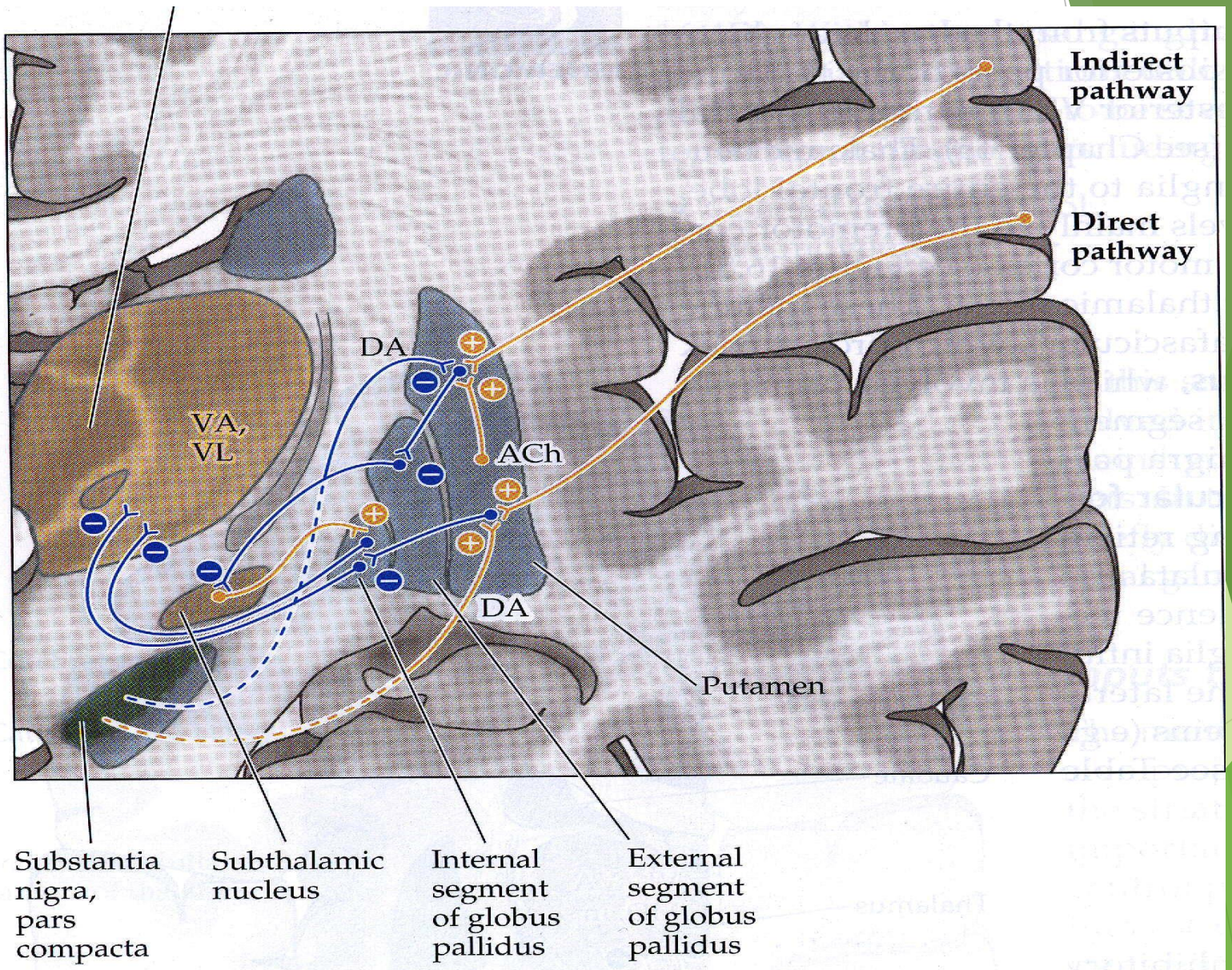
Loss of dopamine projection pathways in CNS

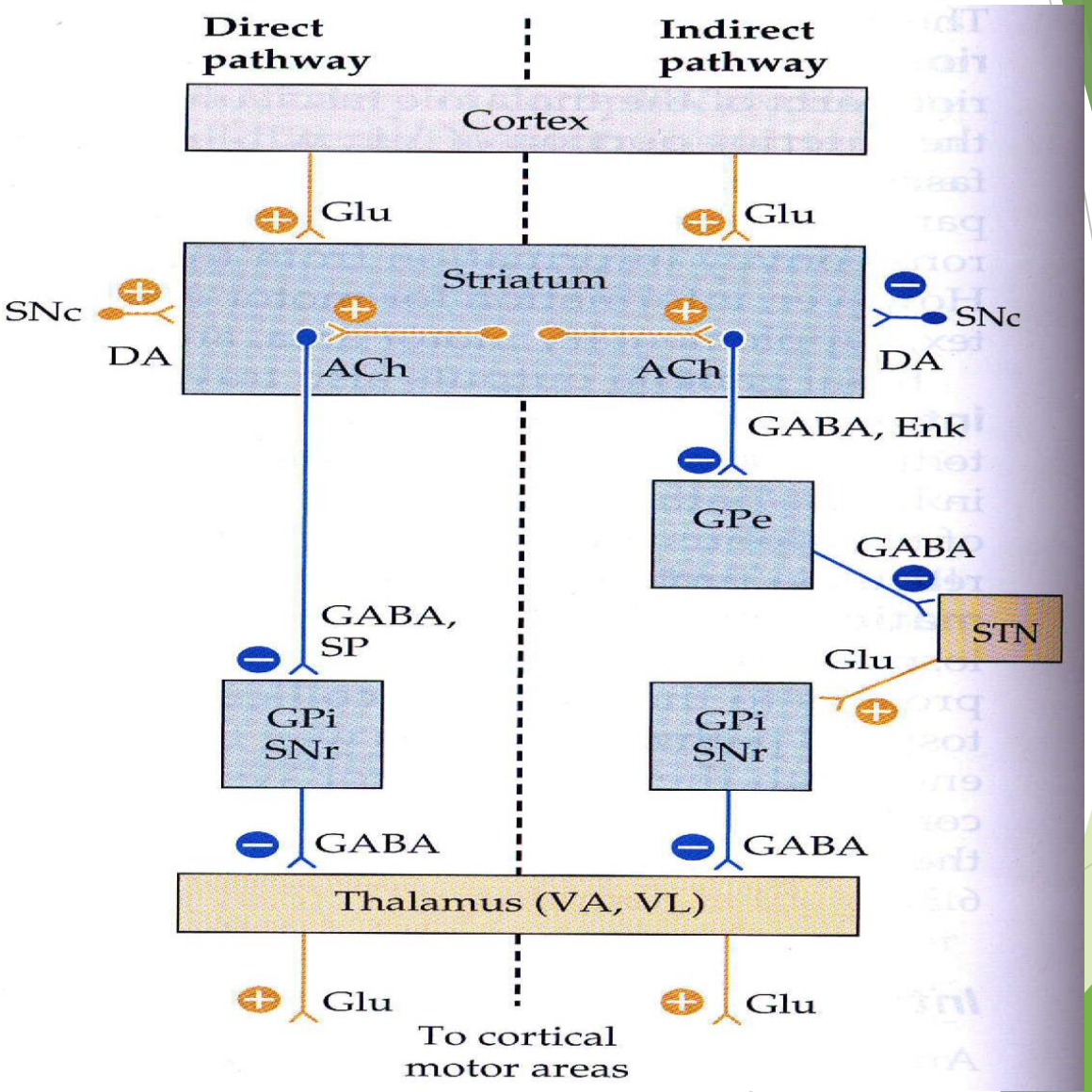
Deregulation of motor control pathways

As disease progresses develop other sympto

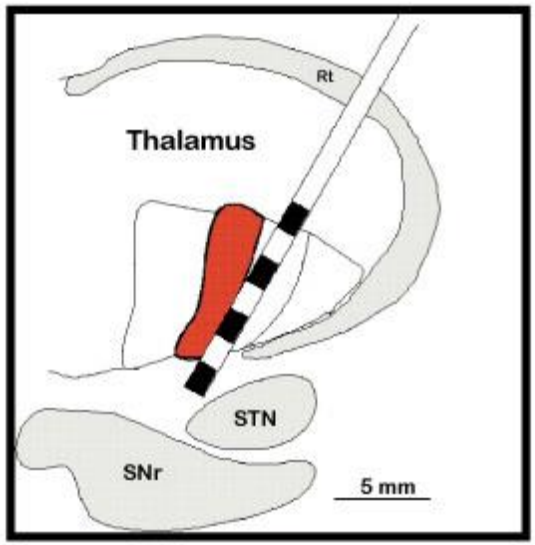
- Swallowing difficulties
- Gait instability
- Cognitive deterioration
- Incontinence
- Sleep disturbances



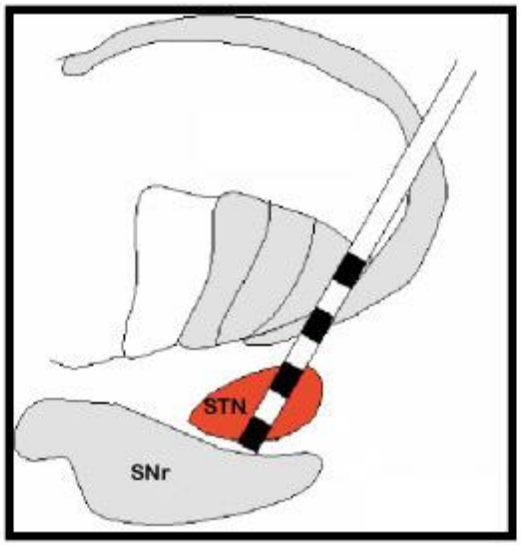

Indirect pathway
Direct pathway
DA
VA, VL
ACh
DA
Putamen
Substantia nigra, pars compacta
Subthalamic nucleus
Internal segment of globus pallidus
External segment of globus pallidus


Direct pathway
Indirect pathway
Cortex
Glu
Glu
Striatum
SNc
DA
ACh
ACh
SNc
DA
GABA, Enk
GPe
GABA
STN
Glu
GABA, SP
GPi SNr
GPi SNr
GABA
GABA
Thalamus (VA, VL)
Glu
Glu
To cortical motor areas

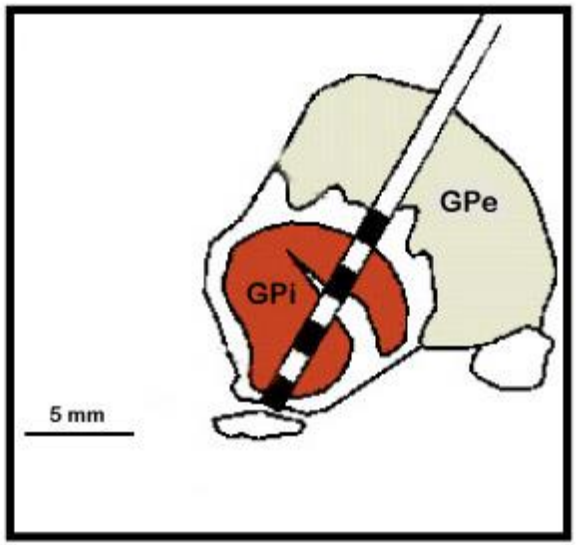
Target Sites for Activa Therapy



Vim Thalamus:
Essential Tremor



Subthalamic Nucleus:
Parkinson's disease
and Dystonia



Globus Pallidus:
Parkinson's disease
and Dystonia

Thalamus

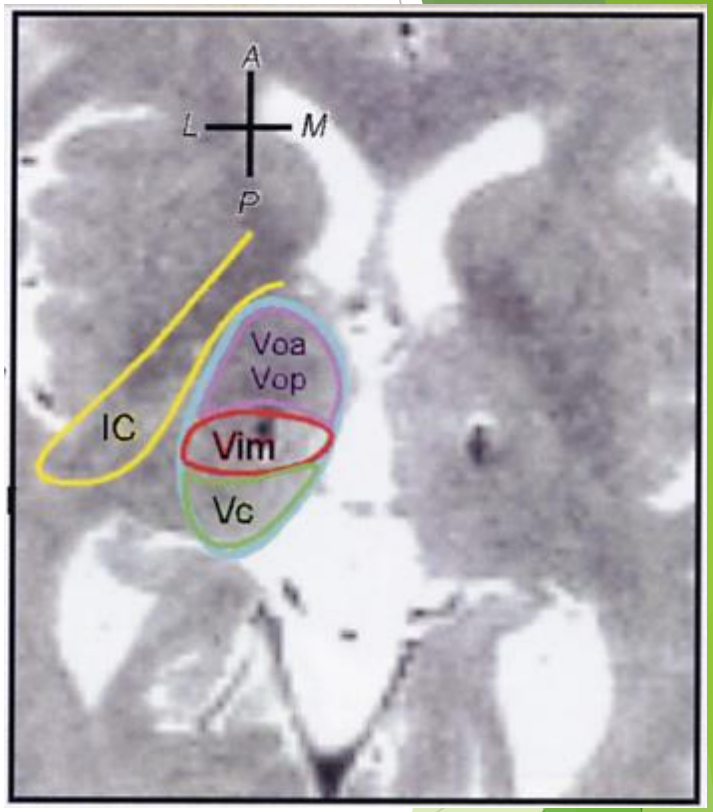
- Anterior division: Anterior nucleus
- Medial division: dorsomedial nucleus
- Lateral division: ventral tier: VPL, VPM, VIM

  MGB, LGB

  Dorsal tier: Pulvinar
- Intralaminar nuclei: CM, PF
- Reticular nucleus

Regional VIM Anatomy

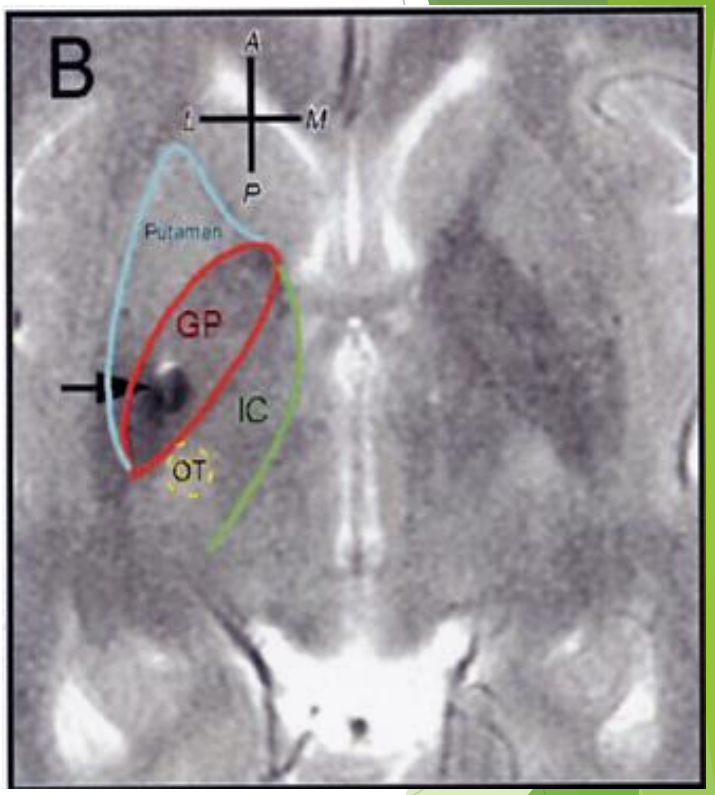
- Internal Capsule – ventral and lateral
  - Stimulation can cause tonic contracture
- Ventral Caudal (Vc) thalamus (sensory relay) – posterior
  - Stimulation can cause intolerable paresthesia
- Ventral Oralis Posterior (Vop) thalamus – anterior
  - Stimulation may cause no effect on tremor



Vo = ventral oral (pallidal relay)
Vim = ventral intermediate (cerebellar relay)
Vc = ventral caudal (principle somatosensory nucleus)
IC = internal capsule

Regional GPi Anatomy

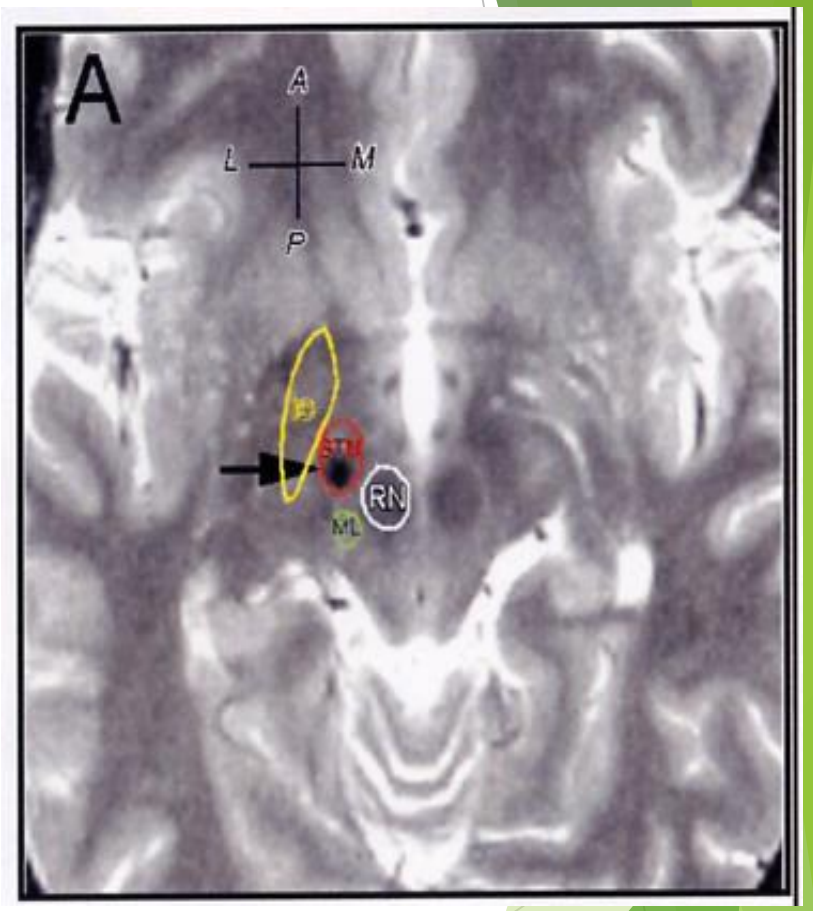
- Internal Capsule - posterior
  - Stimulation can cause tonic contracture
- Optic Tract – ventral
  - Stimulation can cause visual disturbances



GP = globus pallidus
IC = internal capsule
OT = optic tract

Regional STN Anatomy

- Target is the dorsal-lateral portion of STN
  - Medial lemniscus – posterior
    - Stimulation can cause intolerable paresthesia
  - Internal Capsule – anterior, lateral and ventral
    - Stimulation can cause tonic contracture
  - CN III – medial caudal
    - Stimulation can cause diplopia
  - Hypothalamus – medial rostral
    - Stimulation can cause autonomic symptoms
  - Ventral Medial STN
    - Stimulation can cause mood changes



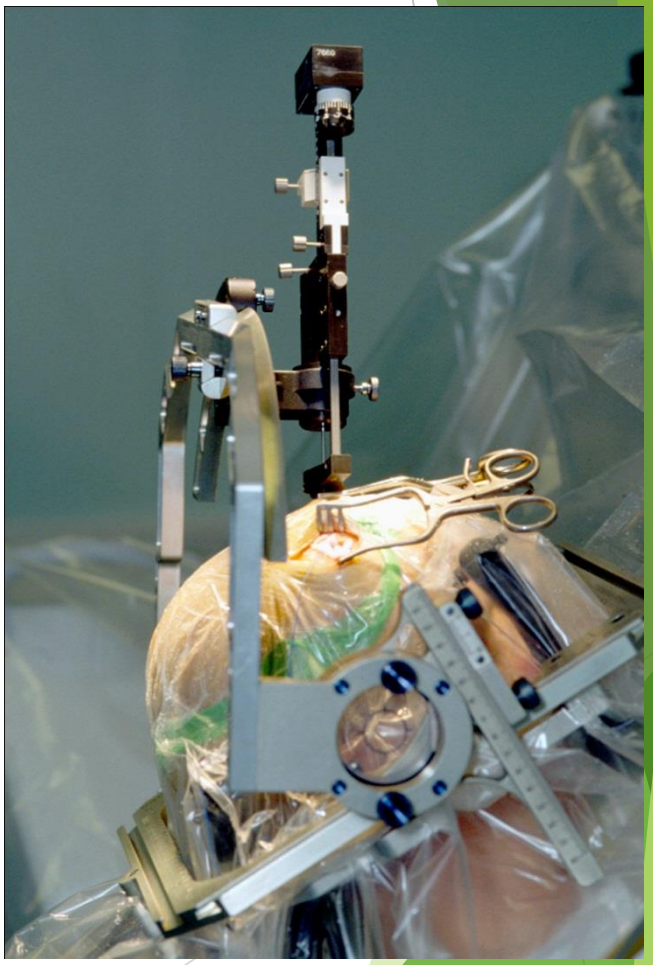
IC = internal capsule

STN = subthalamic nucleus

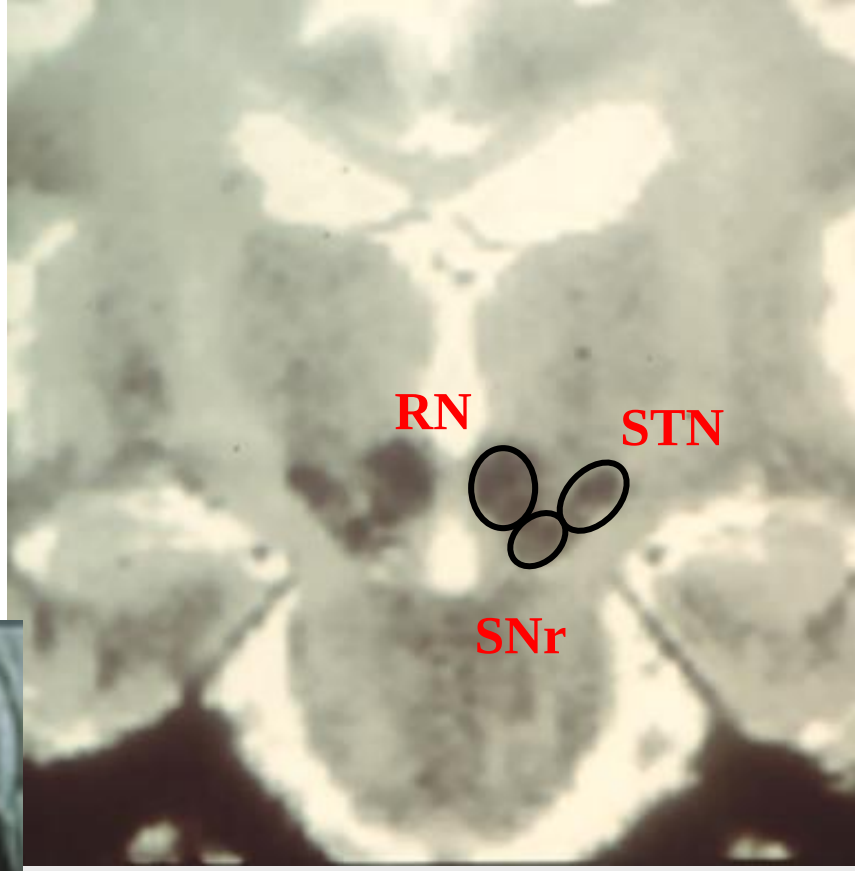
ML = medial lemniscus

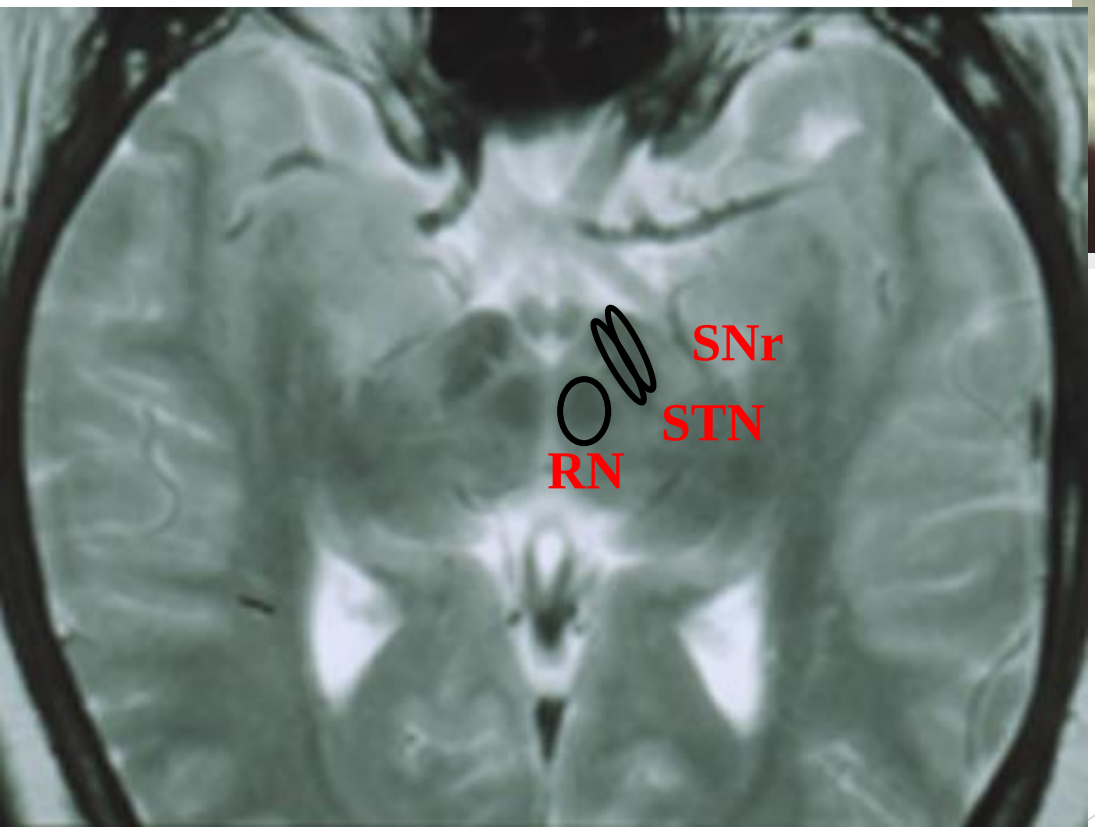
RN = red nucleus

Implantation and Testing



Direct targeting





Targets: current limitations

- PD: Poor effect or worsening of:

  Gait

  Speech

  Swallowing

  Cognition

The Future

- “New” targets
- “New” techniques
- “New” indications

New Targets

- PPN: Good effect on gait
- ZI: Good effect on tremor: MS
- Imaging techniques essential in identifying (eg fMRI) and localising (eg high field magnets) new targets

New Targets

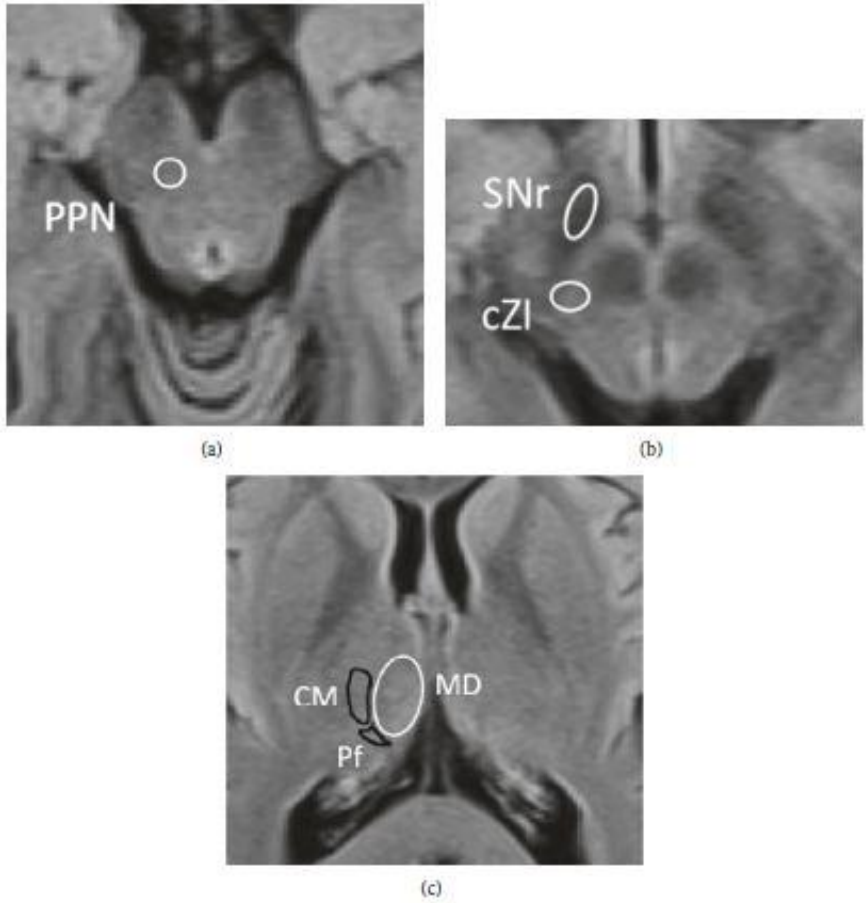


FIGURE 1: Axial MRI imaging at the level of the midbrain and thalamus, demonstrating the anatomical locations of DBS targets described in the review. CMPf, centromedian-parafascicular nuclear complex; cZI, caudal zona incerta; PPN, pedunculopontine nucleus; SNr, substantia nigra pars reticulata.

New Techniques

- Motor cortex stimulation
- GDNF(Glial cell line- derived neurotrophic factor)
- “stem cells”

New DBS Targets for Parkinson's Disease

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کنگره سالانه انجمن جراحان اعصاب ایران

15-20 اردیبهشت 1397

- Parkinson’s Disease (PD) is a Progressive Neurodegeneratives condition characterized by bradykinesia , tremor , rigidity and postural instability (PI) , in addition to numerous non motor manifestations.
- Well – established DBS targets include the subthalamk nucleus (STN) , the globus pallidus pars interna (GPi) and ventral intermediate nucleus (VIM) of the thalamus.

- Management of axial signs (postural instability , freezing of gait (FOG) , axial domains of speech and swallowing , non motor symptoms (NMS)such as cognitive decline in Parkinson’s disease is unsatisfactory with the current medical treatment those have a significant impact on prognosis and quality of life.
- STN stimulation is less effective on axial signs.
- Allernative treatment for axial signs and NMS(congitive decline)are urgently needed.

New DBS targets for refractory motor symptoms

1- Refractory tremor:

a) Caudal Zona Incerta (cZI)
b) Centromedian and parafascicular nuclei.

2- Refractory axial motor symptoms - Gait and Balance.

a) Pedunclopontine nucleus (PPN)
b) Combined PPN and ZI
c) Substantia Nigra Pars Reticulata
d) Motor cortex (extradural motor cortex stimulation) (EMCS)
e) Centromedian and parafascicular Nuclei

3- Refractory Axial symptoms – speech and swallowing

- cZI
- STN
- EMCS

Nonmotor Symptoms of PD

- PPN – DBS is capable of modulating the NMS of PD , including cognition , sleep and attention . Executive function and working memory and improving delayed recall and verbal fluency.
- STN and nucleus basalis of Meynert (NBM) stimulation in PD dementia (PDD) : significant improvement in memory and cognition
- Fornix hypothalamus stimulation.

- A multi- target approach has been considered to improve dopaminergic and non- dopaminergic symptoms.

Allernative paradigm of stimulation of traditional targets , as closed- loop stimulations might increase benefit of stimulation.

- Stimulation is real- time adjusted to the ongoing neural activity , such as oscillatory activity.
- A closed- loop system allows automatically changing the output based on the difference between the feedback signals to the input signals.

- A Wireless Instantaneous Neurochemical Concentration Sensor (WINCS), a device allowing near- real time detection of neurochemical changes , has been recently developed.
- WINCS could integrate a closed – loop DBS system as electrochemical feedback , which would allow a better adaptation of stimulation parameters.

Centromedian and para fascicular nuclei (CMPf)

- CMPf nuclei are the two main constituents of the intralaminar nucleus of the thalamus and have several connections within the basal ganglia , with projections to the STN , substantia nigra (SN) , and GPi.
- It has been postulated the CMPf-DBS affects other thalamic components [VOA and VIM] whose role in termor control has been well established.

Pedunculopontine Nucleus (PPN)

- The mesen cephelic locomotor region (MLR) appears critical for normal gait function.
- The PPN is a key component of the MLR.
- Widespread projections involving the PPN include direct glutamatergic inputs from the motor cortex and GABAergic inputs from SNr, Gpi , STN and deep nuclei of the cerebellum.
- The PPN appears to play a key role in the initiation , acceleration , and termination of locomotion through connections to the basal ganglia and higher cortical regions.

Multi –Target- Approach

- A multi- target approach has been considered to improve dopaminergic and non- dopaminergic symptoms.
- The stimulation of combined targets might allow a modulation of the basal ganglia loop due to the reciprocal strong interconection among these structures , as the case for PPN and STN.
- Other Stiudies have focused on the combination of bilateral PPN and cZI stimulations.
- Combined STN- SNr stimulation has also been proposed in order to better manage axial signs.
- Combination of CMPf- and GPi DBS reduces UPDRSIII score by 49.9%.

Caudal Zona Incerta

- The ZI is a small heterogeneous cellular nucleus that likes within the anatomical location termed the posterior subthalamic area (PSA).
- ZI plays a role in visceral , function , arousal , attention and posture and locomotion , with the cZI mediating the latter.
- The cZI has widespread afferent and efferent projections amongst the cerebral cortex , diencephalon , brainstem , cerebellum and spinal cord, the majority of which are GABAergic.
- The CZI may act as an integrator within and between the basal ganglia – thalamocortical loop and the cerebello thalamo cortical loop assisting in the synchronization of oscillatory neuronal firing in both of these pathways.