Parkinson disease
: pathogenesis and treatments

분당서울대학교병원
신경과 김종민

Contents

- Understanding of Parkinson disease
- History of Parkinson disease
- Treatments of Parkinson disease

3 axes of PD

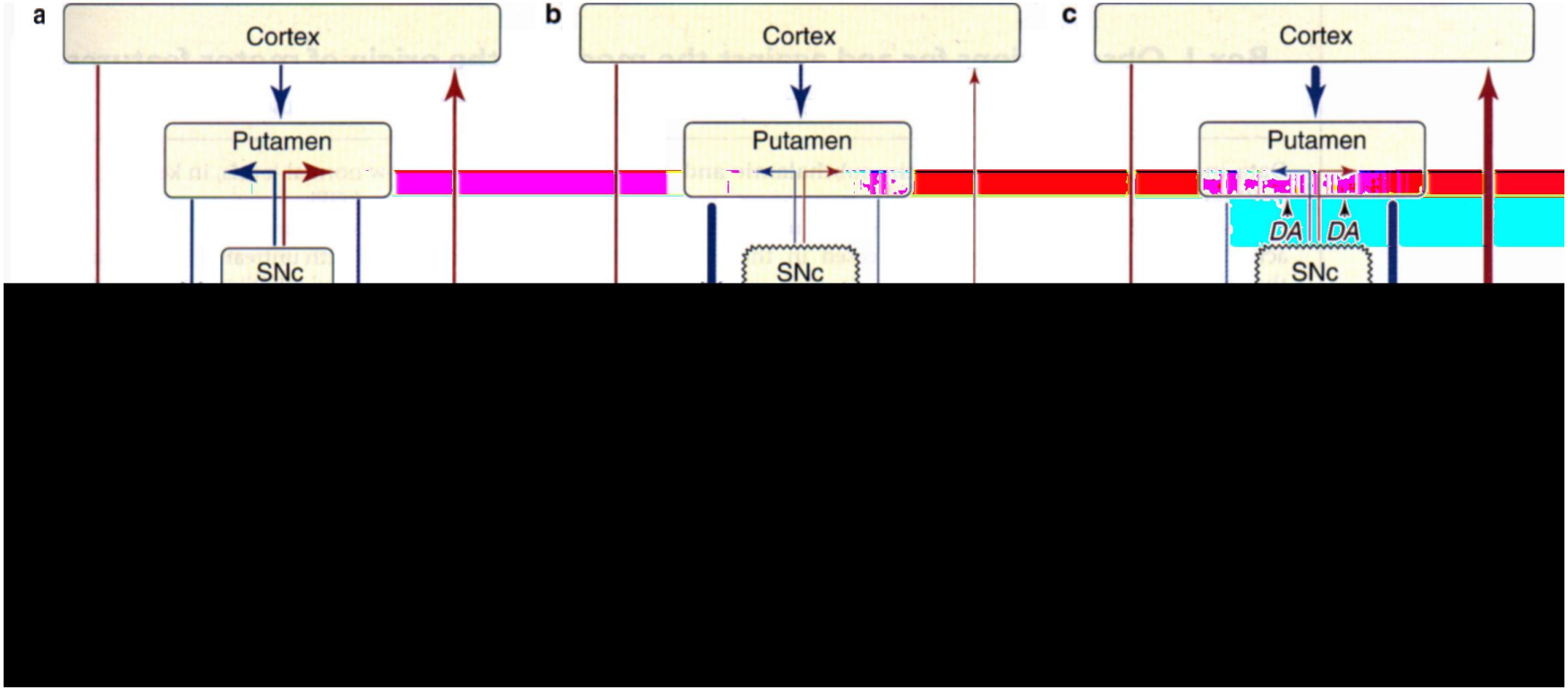
- Basic clinical manifestations
- Simple physiology of abnormal pathways
- Complex molecular pathogenesis

Basic clinical manifestations

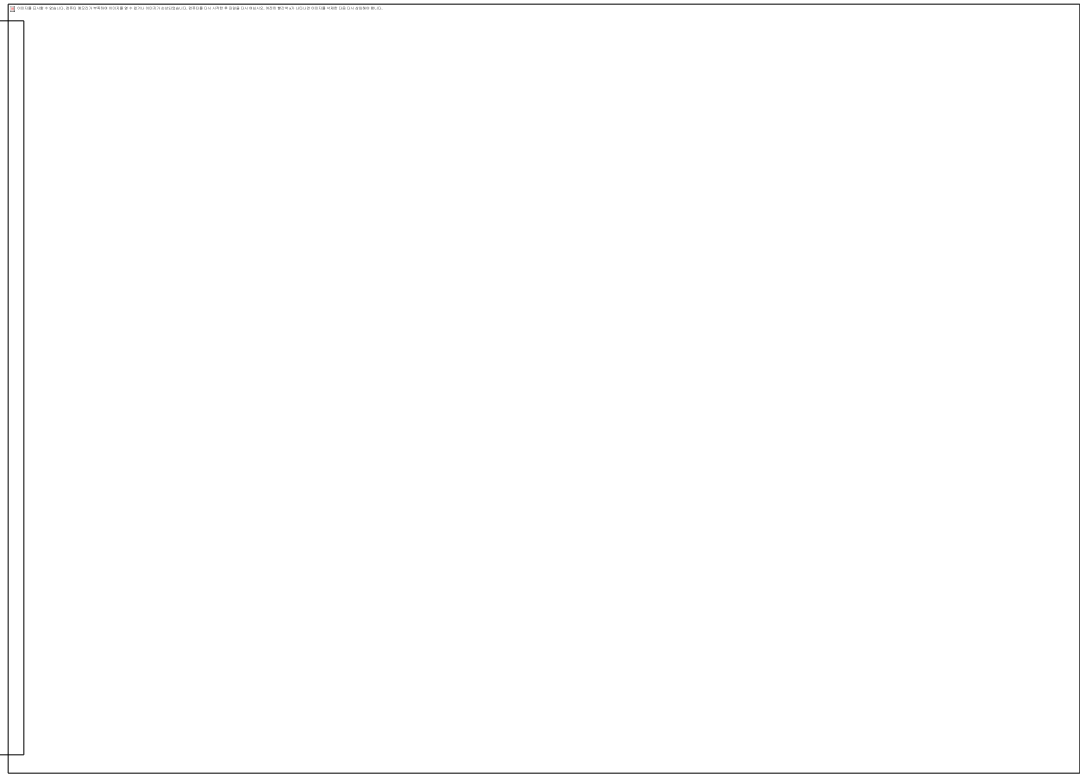
Parkinson disease (PD)

- Bradykinesia
- Rigidity
- Tremor
- Postural imbalance / gait disturbance
- Freezing
- Dyskinesia
- Chorea / Dystonia

Simple physiology of abnormal pathways



Cortico-basal ganglia network.

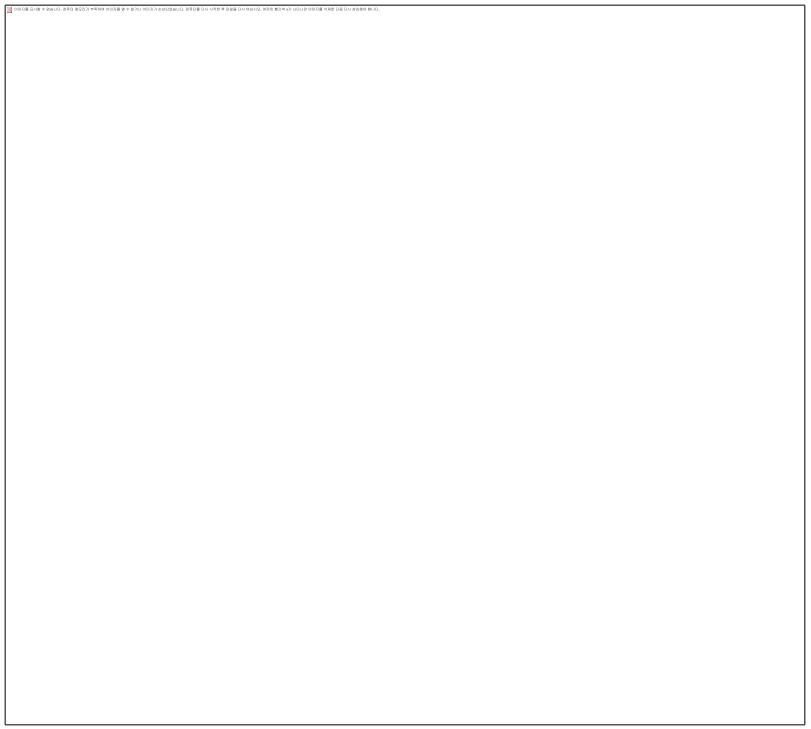


The box and arrow network of the different pathways of the basal ganglia.

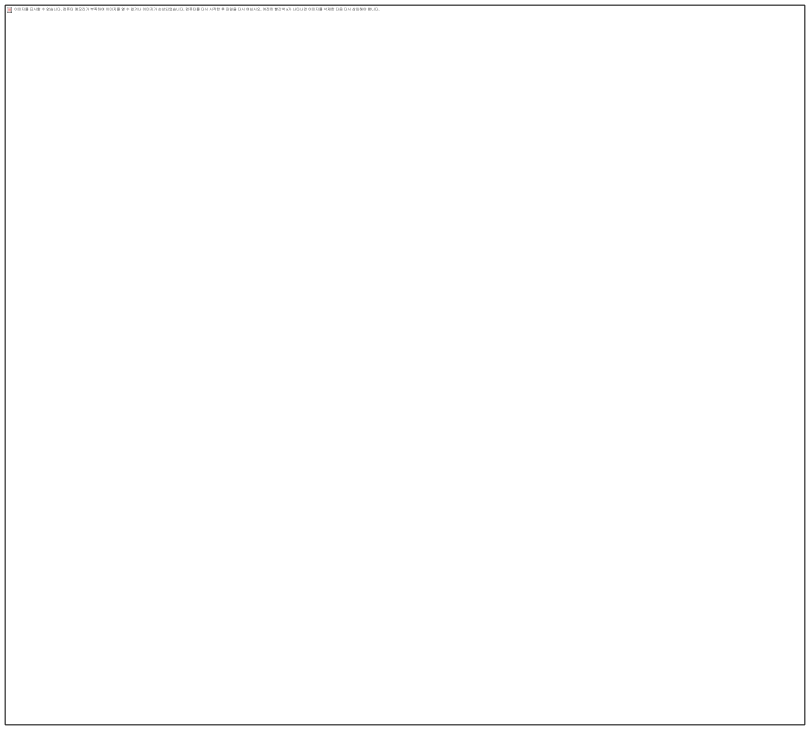
(a) The early Albin–DeLong network. (b) The up-to-date network.

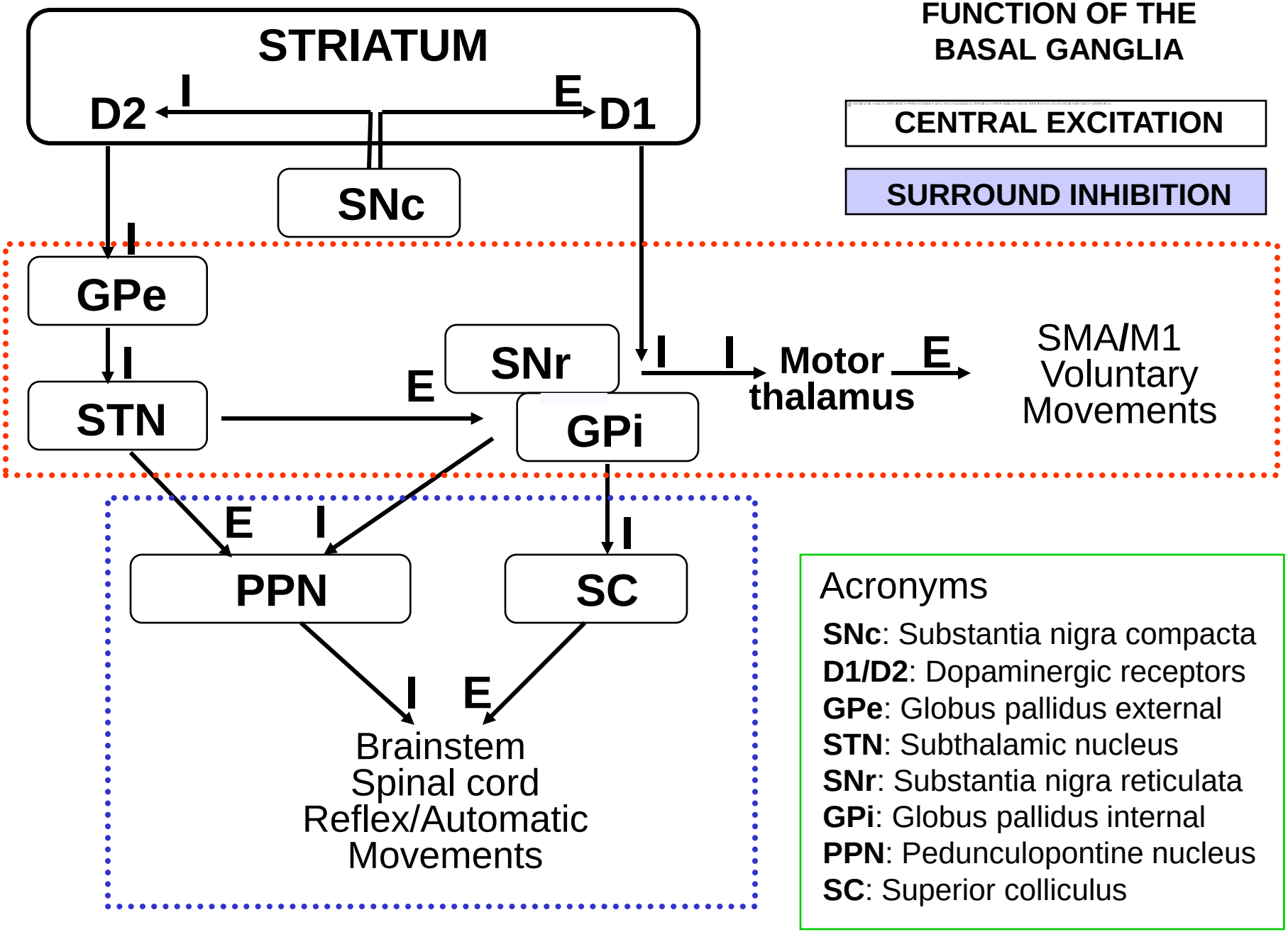
Glutamatergic synapses are denoted by arrows, GABAergic synapses by circles and dopaminergic synapses by squares.

- Input
- Output



- Direct pathway
- Indirect pathway

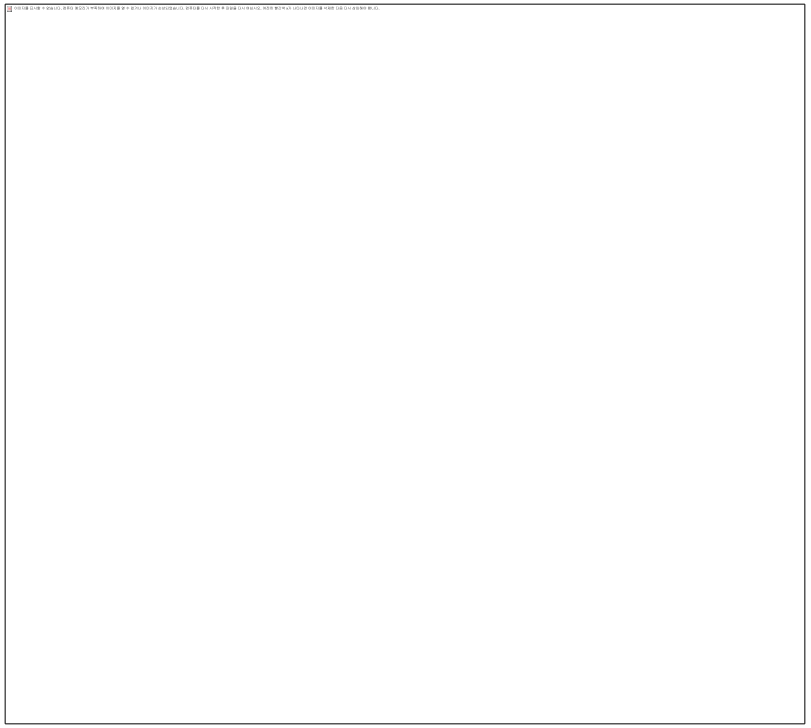


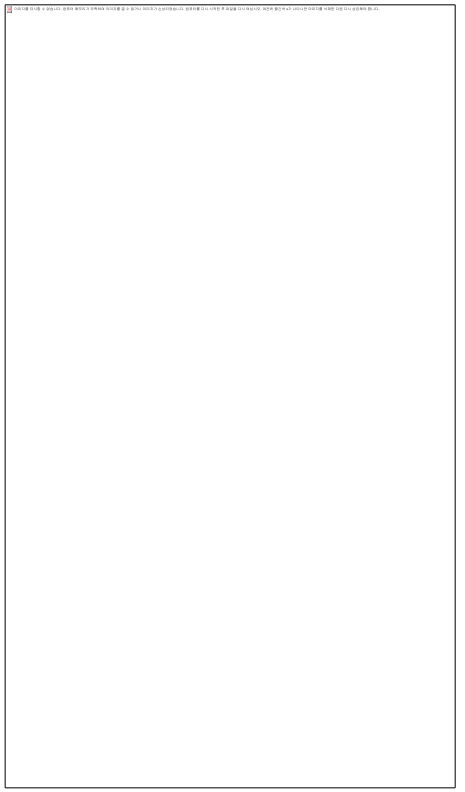

FUNCTION OF THE BASAL GANGLIA
CENTRAL EXCITATION
SURROUND INHIBITION
STRIATUM
D2
I
E
D1
SNc
GPe
I
STN
I
E
SNr
GPi
I
I
Motor thalamus
E
SMA/M1 Voluntary Movements
E
I
PPN
I
SC
I
E
Brainstem Spinal cord Reflex/Automatic Movements
Acronyms
SNc: Substantia nigra compacta
D1/D2: Dopaminergic receptors
GPe: Globus pallidus external
STN: Subthalamic nucleus
SNr: Substantia nigra reticulata
GPi: Globus pallidus internal
PPN: Pedunculopontine nucleus
SC: Superior colliculus

bradykinesia

성충자

F/58 10089992
IPD





rigidity

Abnormal neuronal activity in cortex/BG – spinal cord

(1) Spinal mechanism (increased α-motoneuron excitability)

- Ia afferent (dorsal root sectioning : rigidity, abolished)
- Ib interneuron (inhibition $\uparrow$ of Ib : disinhibition of α-motoneuron)
- mediated via pontine nucleus gigantocellularis and dorsal *reticulospinal tract*

(2) Abnormal hyperactive *long latency reflex relaying in the brain*

- stiffness interrupted at a 5-8 Hz frequency : cogwheel phenomenon
- degree of rigidity : relatively independent of stretch velocity
- reinforced by contralateral movement (voluntary > passive), stress, and anxiety

Tremor in PD

1. mechanical-reflex : smaller

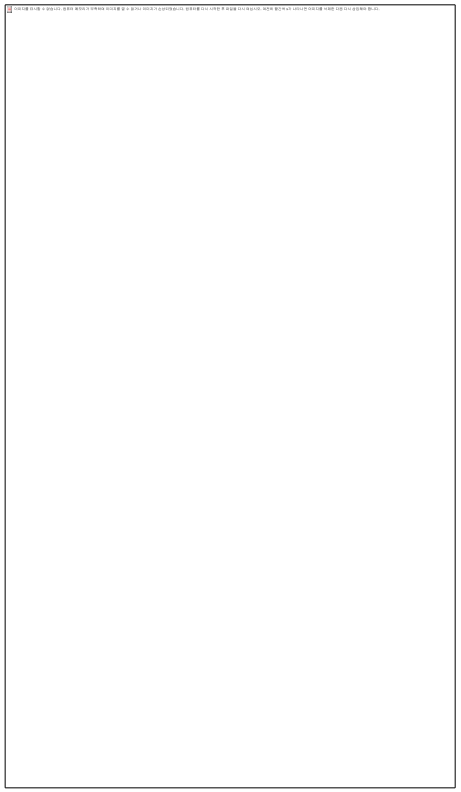
2. **central-neurogenic : larger**
- frequency : not $f=(K/I)^{1/2}$
- originate from ***an oscillating neuronal network within the central nervous syst***em

3. feedforward loop : from cerebellum
- 3 movement patterns : reflex, tonic, ballistic
- alteration in the control of one of these three patterns

4. long latency reflex (long-loop reflex)
- transcortical loop, intention, 25-100 msec
- descending control of segmental circuitry :

in GPi, STN, Thalamus

Tremor cells



Overactivity of GPi/SNr

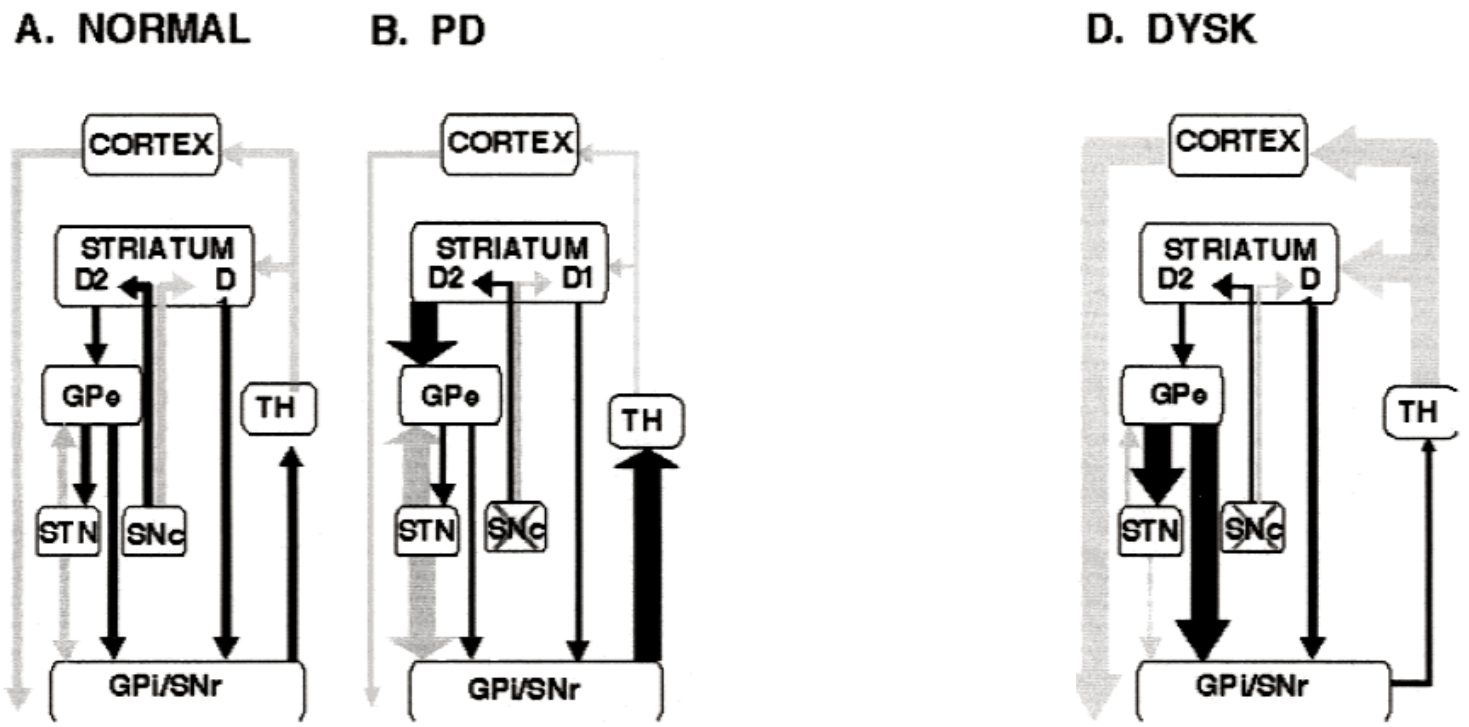
→ inhibitory input to thalamus

→ ***hyperpolarization*** of thalamic cells

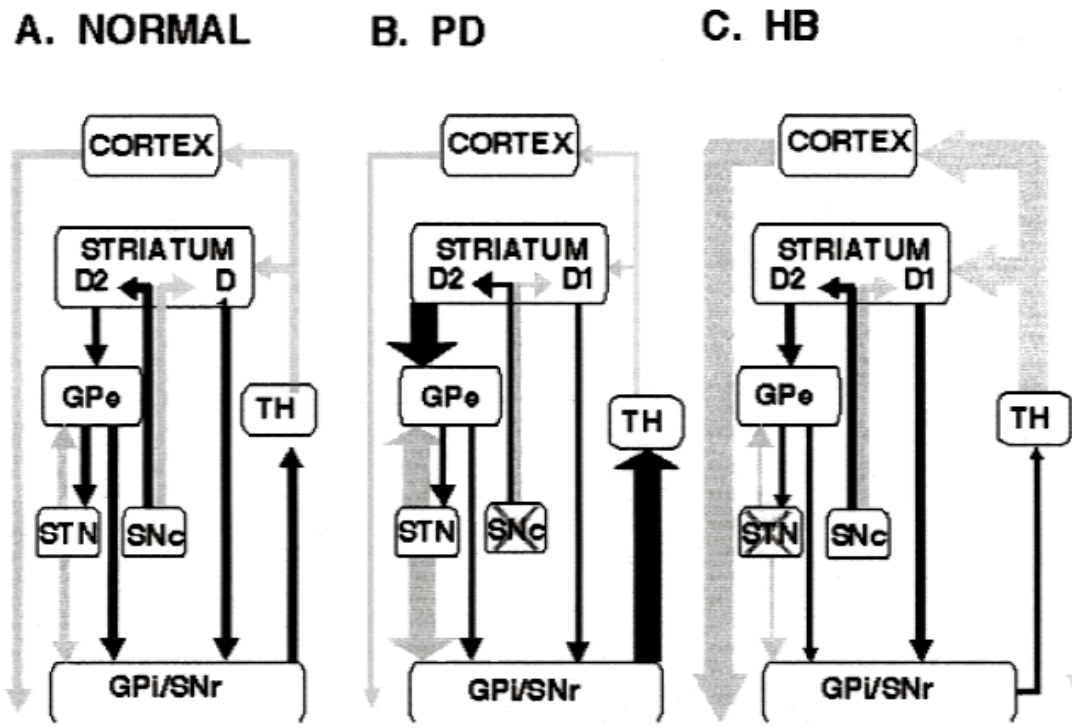
→ bursting oscillation of thalamic tremor cells

→ central tremor

dyskinesia

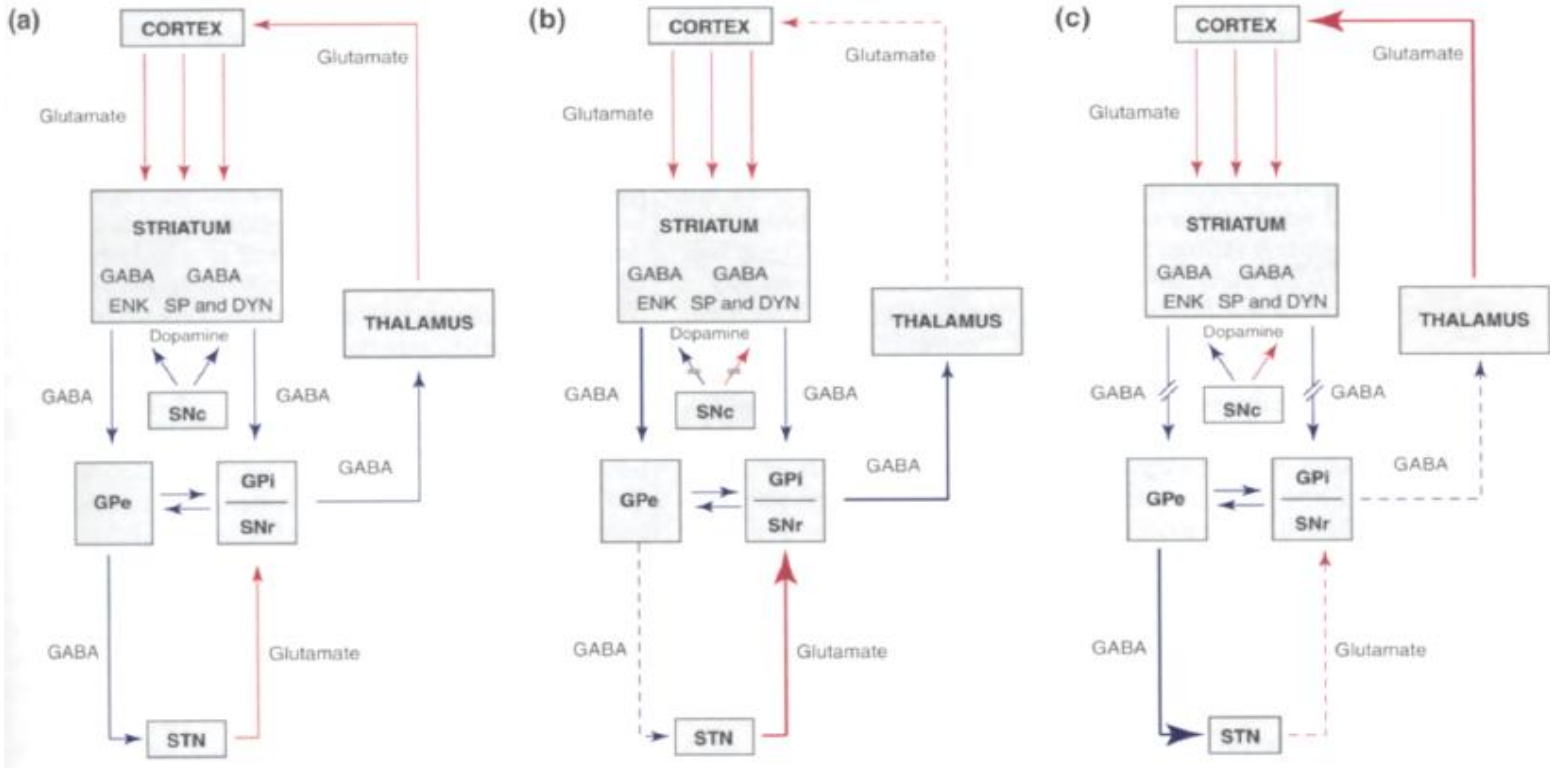

A. NORMAL
B. PD
D. DYSK
CORTEX
STRIATUM
D2
D
D1
GPe
TH
STN
SNc
GPi/SNr

hemiballism

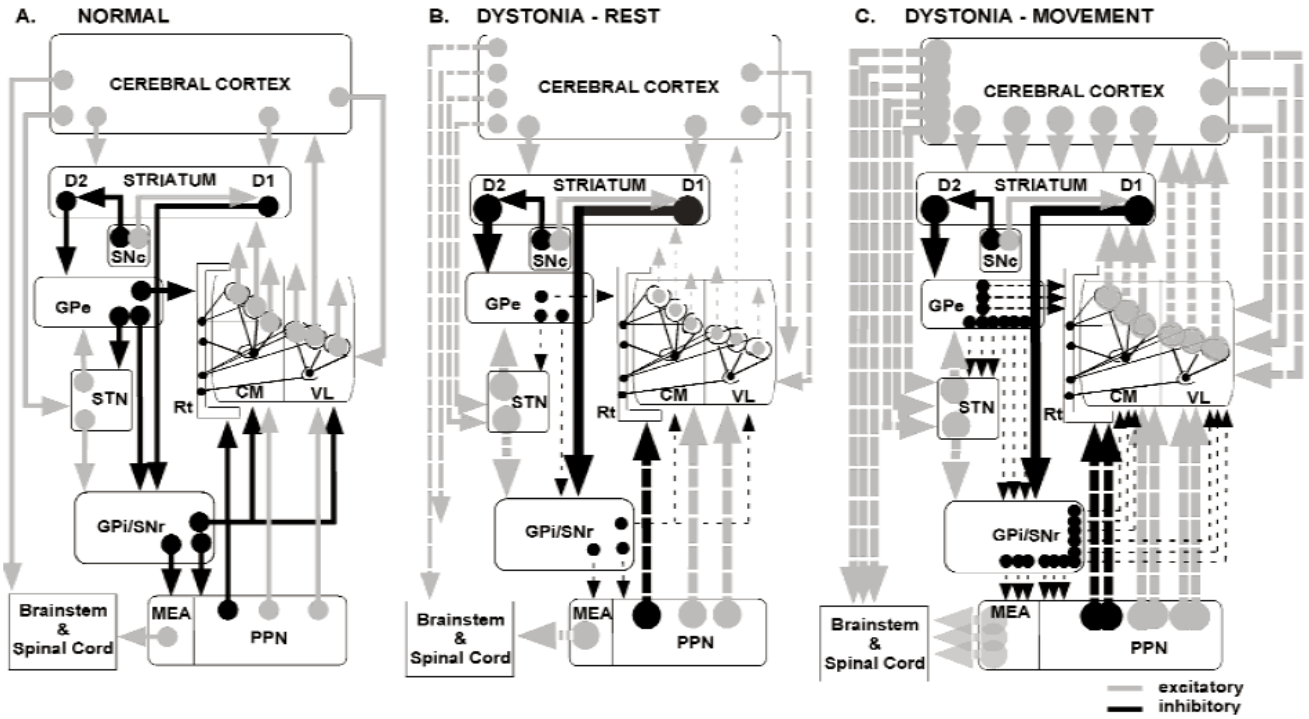


chorea

Huntington chorea



dystonia


A. NORMAL
CEREBRAL CORTEX
D2
STRIATUM
D1
SNc
GPe
STN
Rt
CM
VL
GPi/SNr
Brainstem & Spinal Cord
MEA
PPN
B. DYSTONIA - REST
CEREBRAL CORTEX
D2
STRIATUM
D1
SNc
GPe
STN
Rt
CM
VL
GPi/SNr
Brainstem & Spinal Cord
MEA
PPN
C. DYSTONIA - MOVEMENT
CEREBRAL CORTEX
D2
STRIATUM
D1
SNc
GPe
STN
Rt
CM
VL
GPi/SNr
Brainstem & Spinal Cord
MEA
PPN
excitatory
inhibitory

Complex molecular pathogenesis

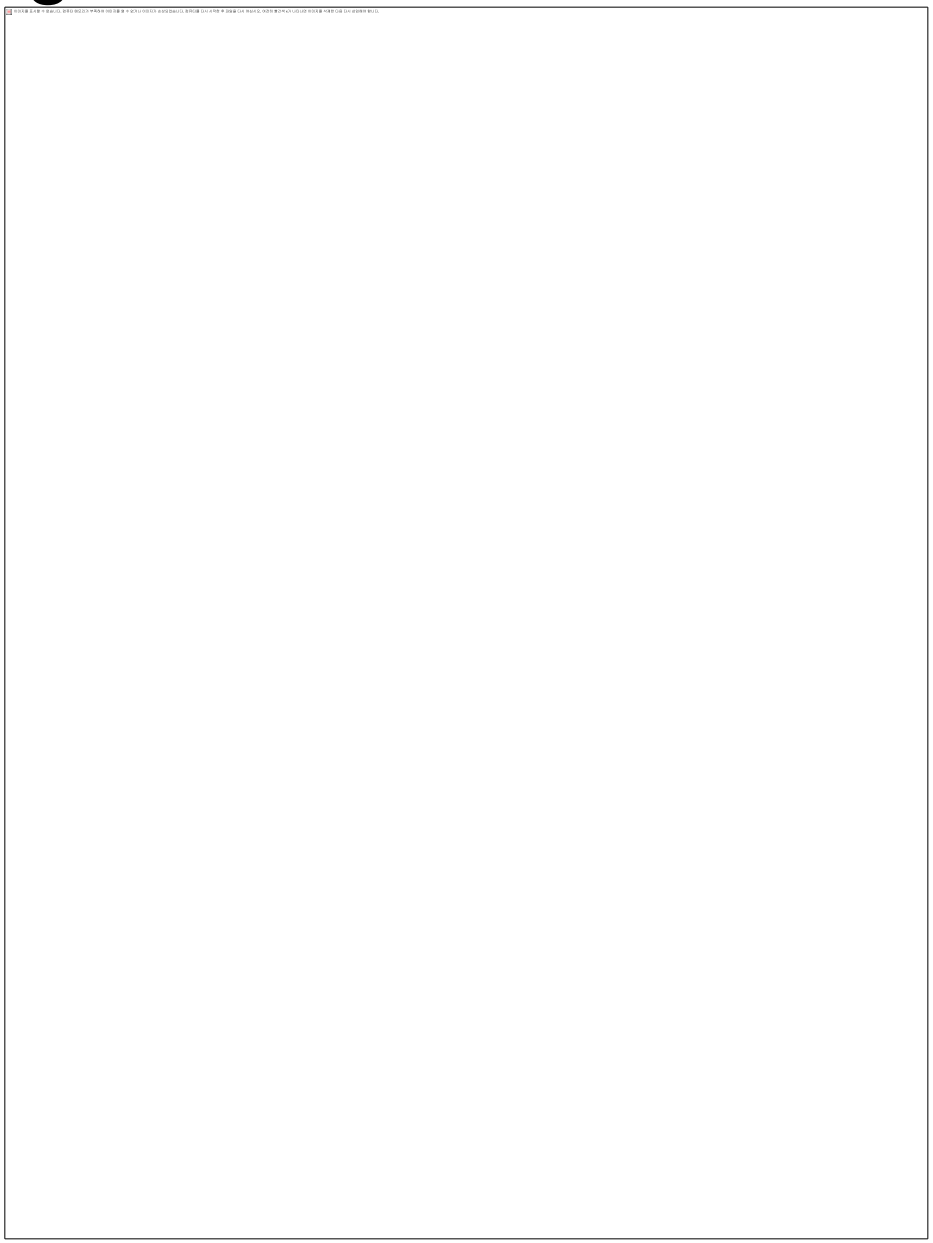
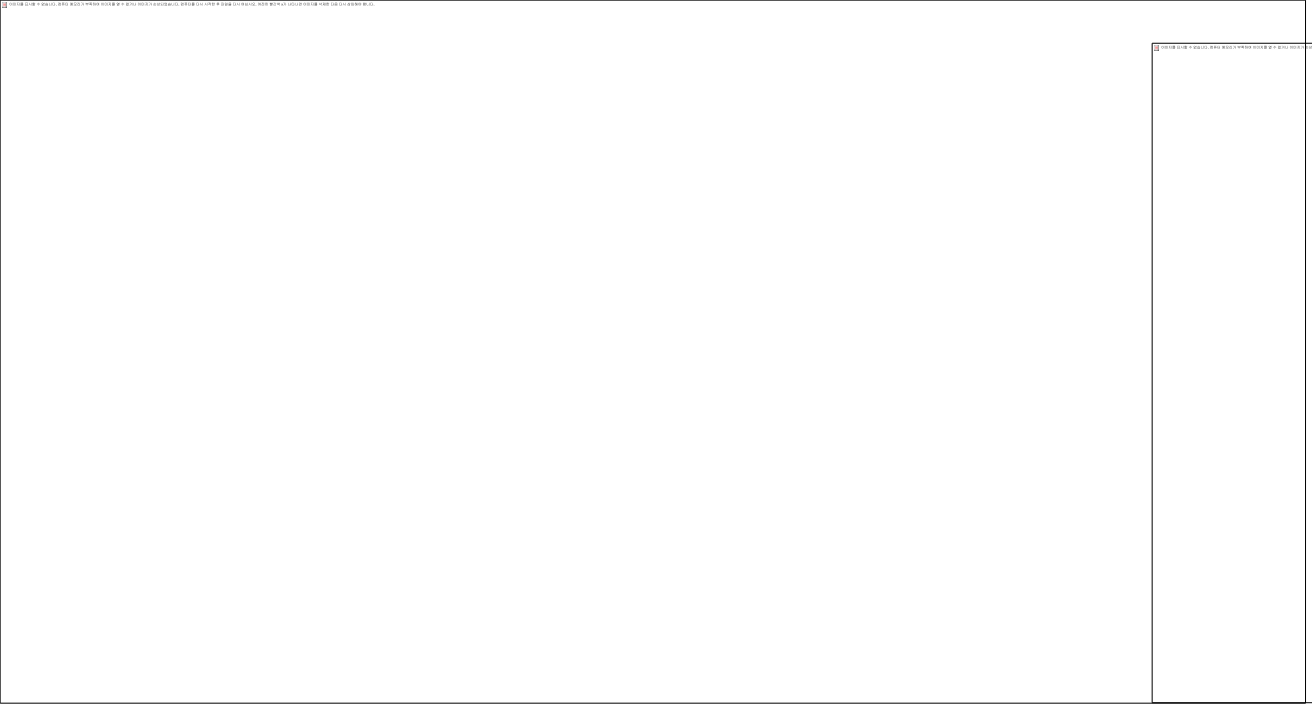
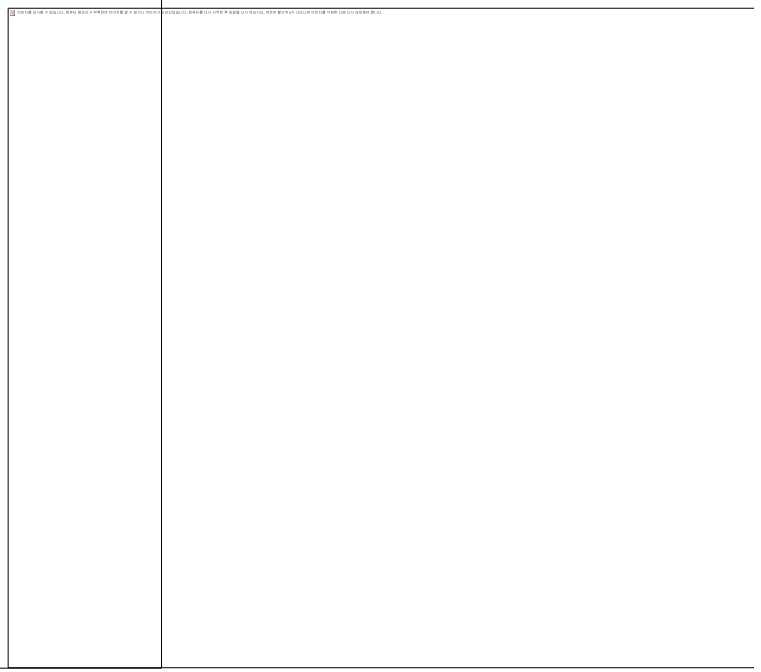
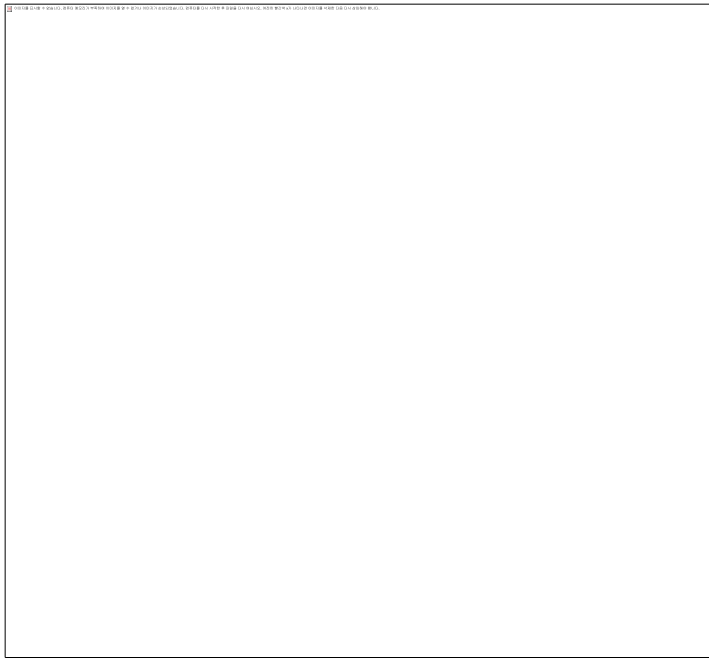
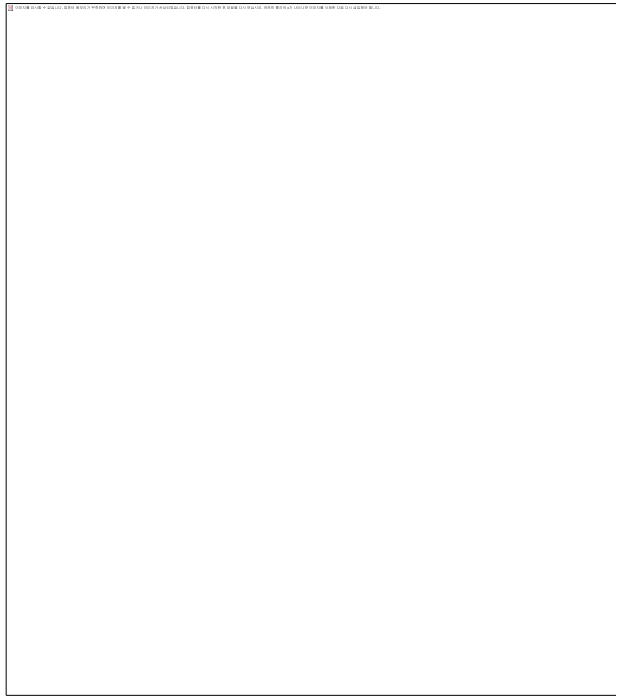


Fig. 4. Progression of PD-related intraneuronal pathology. The pathological process targets specific subcortical and cortical induction sites (a–i). (a and e) Lesions initially occur in the dorsal IX/X motor nucleus and frequently (a and d) in the anterior olfactory nucleus as well. Thereafter, less susceptible brain structures gradually become involved (see white arrows). The pathology in the anterior olfactory nucleus expands less readily into related areas than that evolving in the brain stem. The brain stem pathology takes an upward course (see white arrows). (a–d, g–h) Cortical involvement follows, commencing with the anteromedial temporal mesocortex (tr and er in g and h). From there, the neocortex succumbs, beginning with high order sensory association and prefrontal areas. First order sensory association/premotor areas and, thereafter, primary sensory and motor fields follow suit. In (a–h), the gradual decrease in shading intensity is intended to represent the topographical expansion of the lesions during the course of the disease. Simplified diagram (i) showing the topographic expansion of the lesions (from left to right: dm to fc) and, simultaneously, the growing severity on the part of the overall pathology (from top to bottom: stages 1–6). With the addition of further predilection sites, the pathology in the previously involved regions increases. List of abbreviations: ab, accessory basal nucleus of the amygdala; ac, accessory cortical nucleus of the amygdala; ai, agranular and dysgranular insular cortex; ba, basal nucleus of the amygdala; bn, basal nucleus of Meynert; ca, caudate nucleus; CA1, first sector of the Ammon's horn; CA2, second sector of the Ammon's horn; *cc*, corpus callosum; ce, central nucleus of the amygdala; cl, claustrum; cm, centromedian nucleus of the thalamus; co, coeruleus–subcoeruleus complex; cr, nucleus raphes centralis; db, interstitial nucleus of the diagonal band; dm, dorsal motor nucleus of the glossopharyngeal and vagal nerves; do, dorsomedial nucleus of the hypothalamus; dr, nucleus raphes dorsalis; dv, dorsal nuclear complex of the glossopharyngeal and vagal nerves containing melanized projection neurons; en, entorhinal region; er, ectorhinal region (mesocortex); *fo*, fornix; fc, first order sensory association areas, premotor areas, as well as primary sensory and motor fields; gi, granular insular cortex; gr, granular nucleus of the amygdala; hc, high order sensory association areas and prefrontal fields; hn, motor nucleus of the hypoglossal nerve; in, infundibular nucleus of the hypothalamus; iz, intermediate reticular zone; la, lateral nucleus of the amygdala; ld, laterodorsal nucleus of the thalamus; lg, lateral geniculate body of the thalamus; lt, lateral nuclei of the thalamus; me, medial nucleus of the amygdala; *ml*, medial lemniscus; *mf*, medial longitudinal fascicle; mc, anteromedial temporal mesocortex; *ot*, optic tract; pa, paraventricular nucleus of the thalamus; pe, pallidum, external segment; pf, parafascicular nucleus of thalamus; pi, pallidum, internal segment; pn, parabrachial pigmented nucleus; po, pontine nuclei; pu, putamen; pv, paraventricular nucleus of the hypothalamus; re, reticular nucleus of the thalamus; ru, red nucleus; ro, nucleus raphes obscurus; sb, subiculum; sc, superior cerebellar peduncle; sn, substantia nigra; so, supraoptic nucleus; sp, subparafascicular nucleus; *st*, solitary tract; tl, lateral tuberal nucleus of the hypothalamus; tm, tuberomamillary nucleus of the hypothalamus; tr, transentorhinal region (mesocortex); vm, ventromedial nucleus of the hypothalamus; zi, zona incerta.









Now…

- Marsden and DeLong : “automatic execution of learned motor plans”
- Albin-DeLong model of basal ganglia

  - qualitative information flow (box-and-arrow) model of microcircuitry

  (1989 – 1990, *Trends in neurosciences*)
- Role of basal ganglia

  Action selection model (Mink, 1996)

  Dimensionality reduction model (Bar-Gad, 2000)

Era of levodopa

- Babinski :
  motor fluctuation (1920)

- Hoehn and Yahr : clinical progression (1969)
- Ehringer, Hornykiewicz : loss of dopamine (1961)
- In 1962, Barbeau : oral levodopa
  Birkmayer, Hornykiewicz : IV levodopa

→ *Numerous dopamine agonists, DBS …*

Principles of Treatments

- Functionally independent as long as possible
- Encouraged to remain active and mobile
- Therapy : individualized
- Protective therapies, priority
- Do not hurry, hold off

Potential neuroprotective agents in PD

- Antioxidant & Bioenergetics

coenzyme Q10

creatine

vitamin C

vitamin E

- NMDA antagonist

amantadine

remacemide

- Anti-inflammatory

minocycline

- Anti-apoptotic & trophic factors

selegiline

rasagiline

GDNF

BDNF

- Dopamine agonists

Early PD, mild symptoms

- Neuroprotection
- Dopamine agonists

Dopamine agonists – receptor affinity & dosage

			T1/2
• Bromocriptine	D2 ago D1 ant	(10)	6
• Pergolide	D2 = D3 > D1	(1)	24
• Pramipexole	D3 > D2 > D4	(1)	12
• Ropinirole	D3 > D2 > D4	(4)	6

Early PD, moderate symptoms

- < 50

dopamine agonists, anticholinergics, amatadine

- > 50

levodopa

Advanced PD with non-motor symptoms

- Motor fluctuation & Dyskinesia
- Autonomic dysfunction
- Sleep disturbances
- Depressive mood
- Dementia

Fluctuation & Dyskinesia

- Prolongation of levodopa on-time
- Dopamine agonists
- Amantadine
- Surgery : deep brain stimulation

Autonomic dysfunction

- Orthostatism : fludrocortisone, midodrine
- Urogenic bladder : anticholinergic
- Impotence : sildenafil
- Constipation : exercise, fiber diet

Sleep disturbances

- Insomnia & day-time sleepiness
- RLS : dopaminergic drugs
- RBD : clonazepam

Depressive mood

- 50% of PD
- NE, 5-HT dysfunction
- SSRI, first-line treatment
- bupropion, mirtazapine, venlafaxine, TCA

Dementia

- 40-50% of PD
- DLB vs PDD
- incidental Lewy body disease
- Braak's staging
- AChE inhibitors