

# Serendipity in Neurology (It's Not All Science)

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**Departments of Neurology and Pharmacology**

**Wayne State University School of Medicine**

# Goals of this talk

- To serve as a “whistle blower” against the myth that the clinical practice of neurology (specifically, my sub-specialty of movement disorders) has made progress solely from its scientific underpinnings
- To illustrate how serendipitous observations have enriched modern neurological practice

# Sastry Foundation Parkinson Disease Research Program



# What keeps me busy in the Department of Neurology, WSU School of Medicine

- **Clinical sub-specialty of movement disorders, a collection of conditions ranging from Parkinson disease, other tremor conditions, gait and balance disorders, Tourette syndrome, neurodegenerative diseases, genetic neurological problems, and much more**
- **Clinical research into symptomatic control of movement disorders and to slow down disease progression**
- **An adjunct appointment in the Department of Pharmacology (with Professor Sokol Todi and Assistant Professor Wei-Ling Tsou), studying mechanisms of Parkinson disease as can be modeled in the fruit fly**
- **Collaborative with Professor Mark Haacke and Associate Professor Yongsheng Chen on developing new uses for magnetic resonance imaging (MRI) in neurological disorders**

# *Serendipity*

**Definition (Merriam-Webster dictionary):**

**“The gift of finding valuable or agreeable things  
not looked for”**







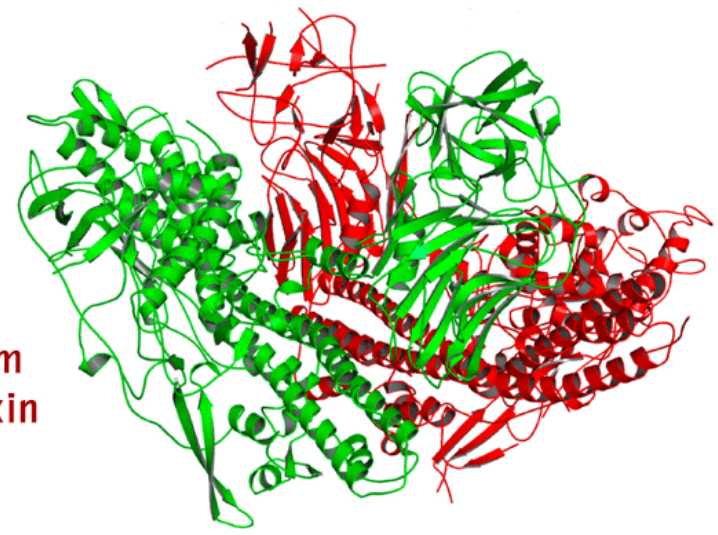




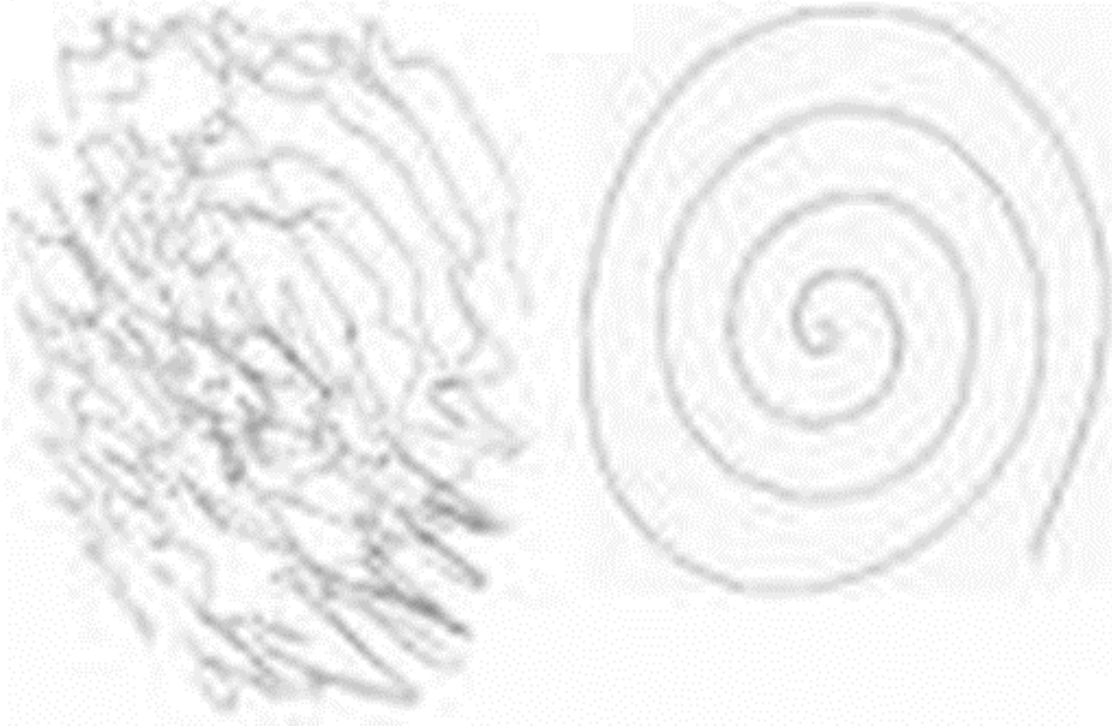




Botulinum Neurotoxin



# Essential (familial) tremor

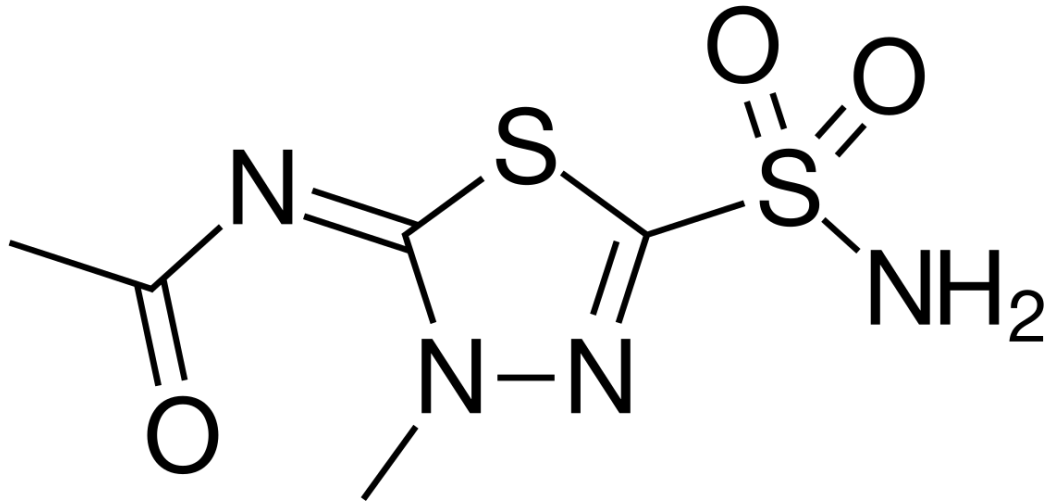


# The first successful pharmacological approach to treating tremors

In more than half of hereditary tremor subjects, intensity of shaking is greatly reduced after ingesting small quantities of ethanol

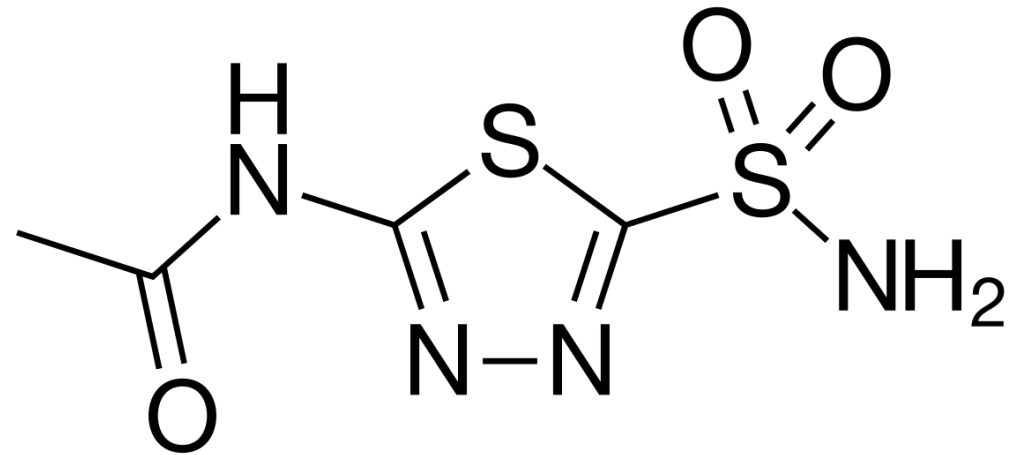


## A change of one carbon atom confers anti-tremor effect



**methazolamide**

anti-tremor effect

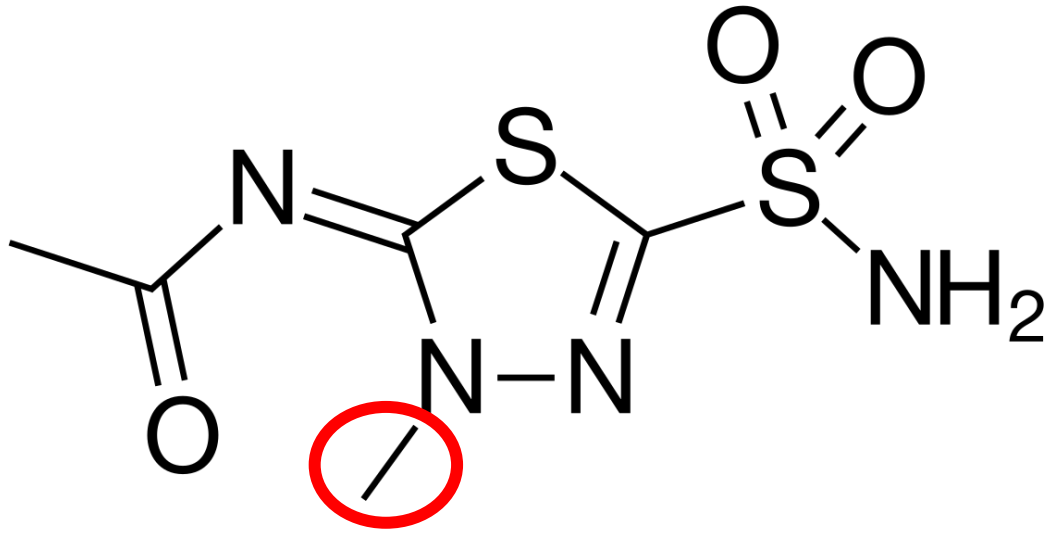


**acetazolamide**

no anti-tremor effect

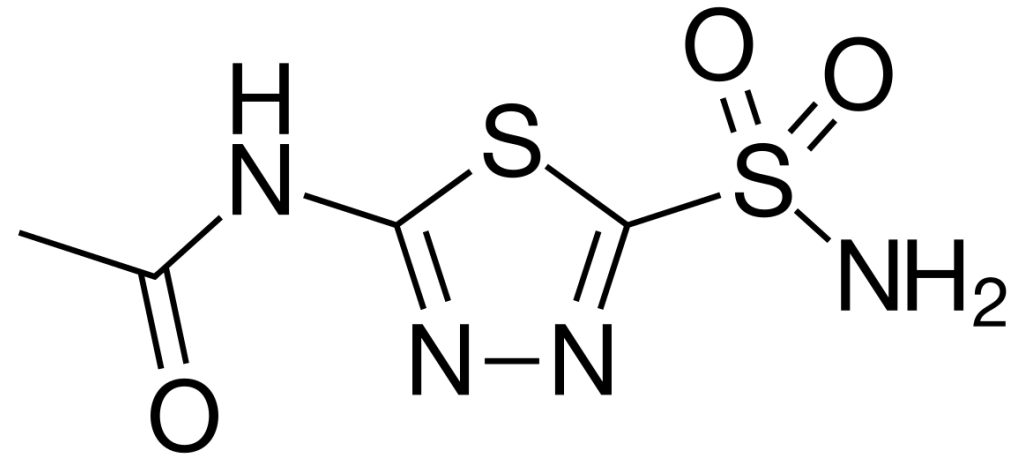


## A change of one carbon atom confers anti-tremor effect



**methazolamide**

anti-tremor effect



**acetazolamide**

no anti-tremor effect

# James Parkinson, MD (1817)

AN  
ESSAY  
ON THE  
SHAKING PALSY.

BY  
*JAMES PARKINSON,*  
MEMBER OF THE ROYAL COLLEGE OF SURGEONS.

LONDON:  
PRINTED BY WHITTINGHAM AND ROWLAND,  
*Garrett Street.*  
FOR SHERWOOD, NEELY, AND JONES,  
PATERNOSTER ROW.  
1817.

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## James Parkinson, MD (1817)

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...The first symptoms perceived are, a slight sense of weakness, with a proneness to trembling in some particular part...

## James Parkinson, MD (1817)

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...The tremulous motion of the limbs occur during sleep, and augment until they awaken the patient, and frequently with much agitation and alarm...

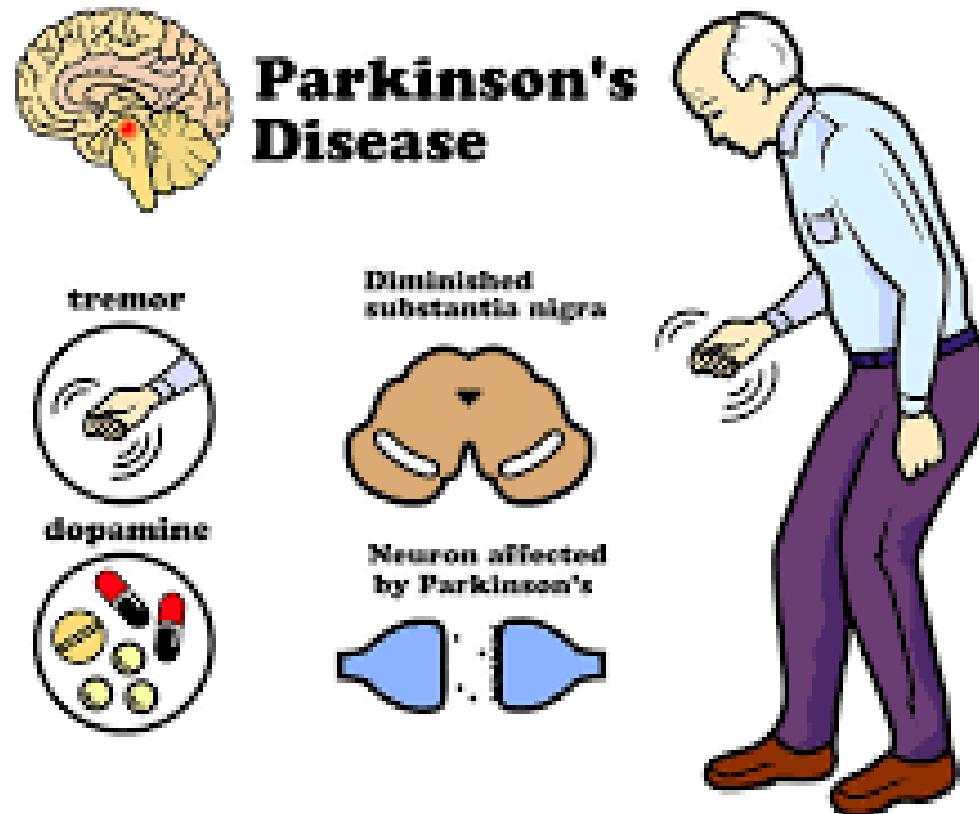
## James Parkinson, MD (1817)

AN ESSAY ON THE SHAKING PALSY.  BY <i>JAMES PARKINSON,</i> MEMBER OF THE ROYAL COLLEGE OF SURGEONS.  LONDON: PRINTED BY WHITTINGHAM AND ROWLAND, <i>Garrett Street.</i> FOR SHERWOOD, NEELY, AND JONES, PATERNOSTER ROW. 1817.	<b>CONTENTS.</b>  CHAP. I. DEFINITION—HISTORY—ILLUSTRATIVE CASES..... 1  CHAP. II. PATHOGNOMONIC SYMPTOMS EXAMINED—TREMOR COACTUS—SCELOTYRBE FESTINANS..... 19  CHAP. III. SHAKING PALSY DISTINGUISHED FROM OTHER DIS- EASES WITH WHICH IT MAY BE CONFOUNDED..... 27  CHAP. IV. PROXIMATE CAUSE—REMOTE CAUSES—ILLUSTRATIVE CASES..... 33  CHAP. V. CONSIDERATIONS RESPECTING THE MEANS OF CURE. 56
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...As the disease proceeds, the hand fails to answer with exactness to the dictates of the will...

# Parkinson disease

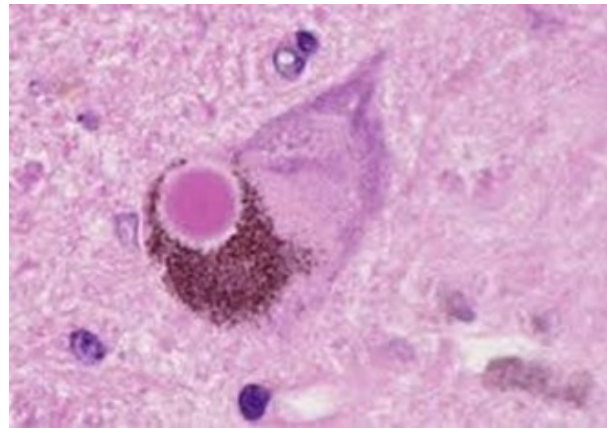
A collection of characteristic clinical features comprising a syndrome and associated with distinctive pathology



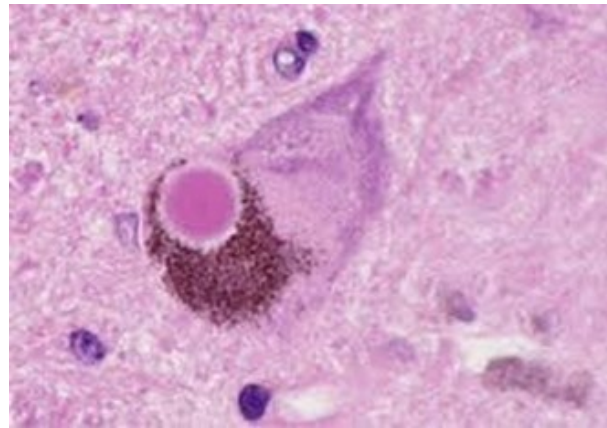
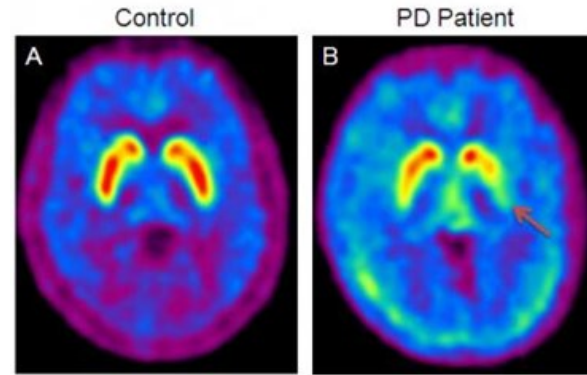
# The many identities of Parkinson disease



# The many identities of Parkinson disease

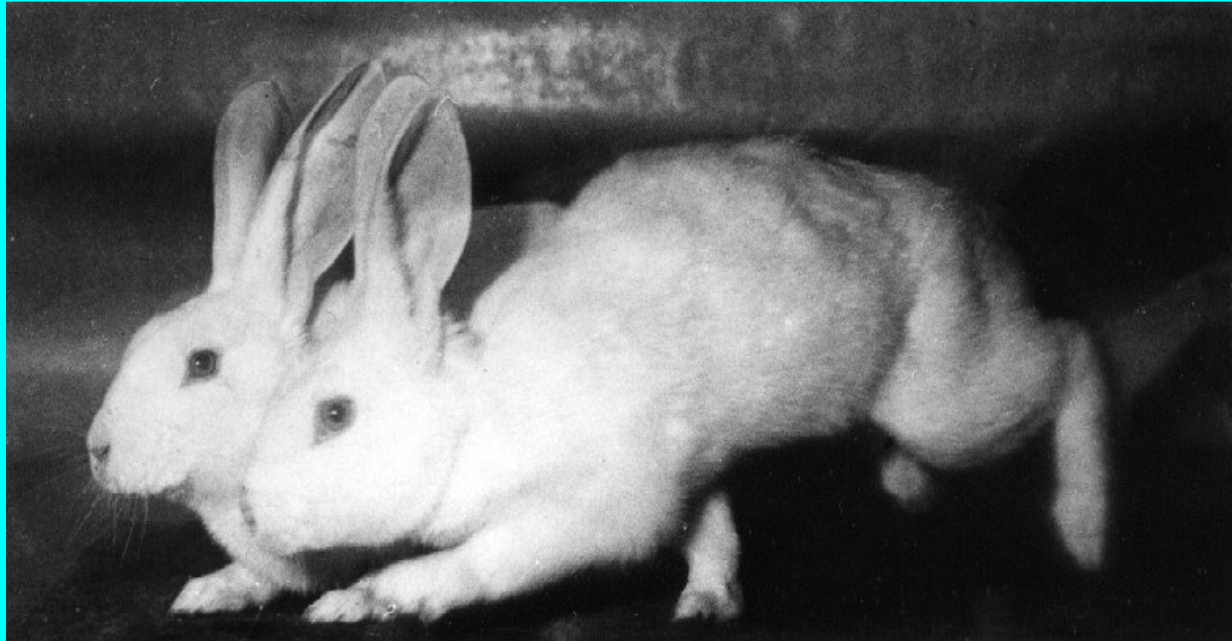


# The many identities of Parkinson disease

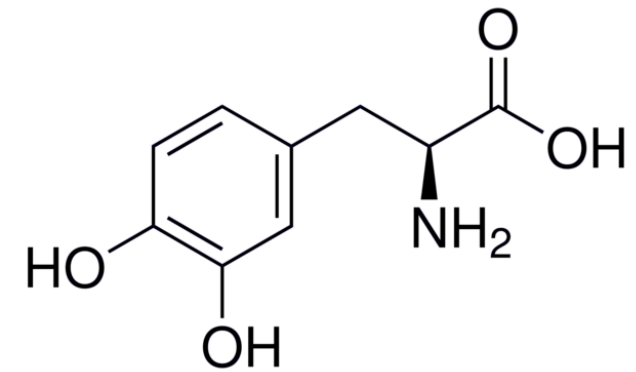
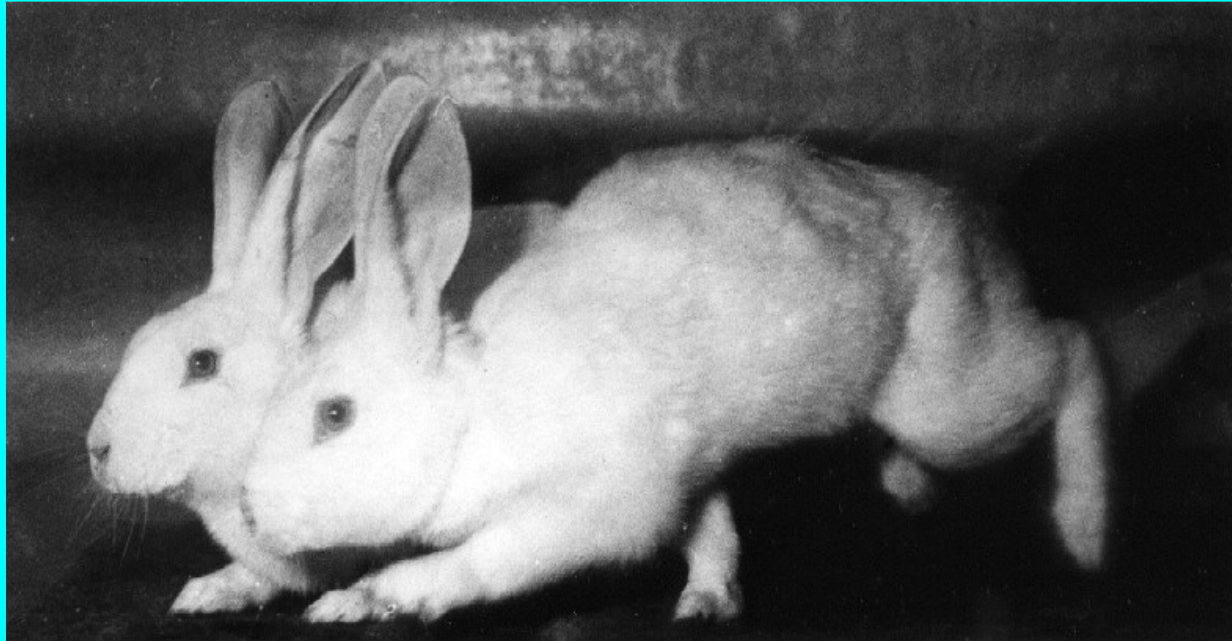




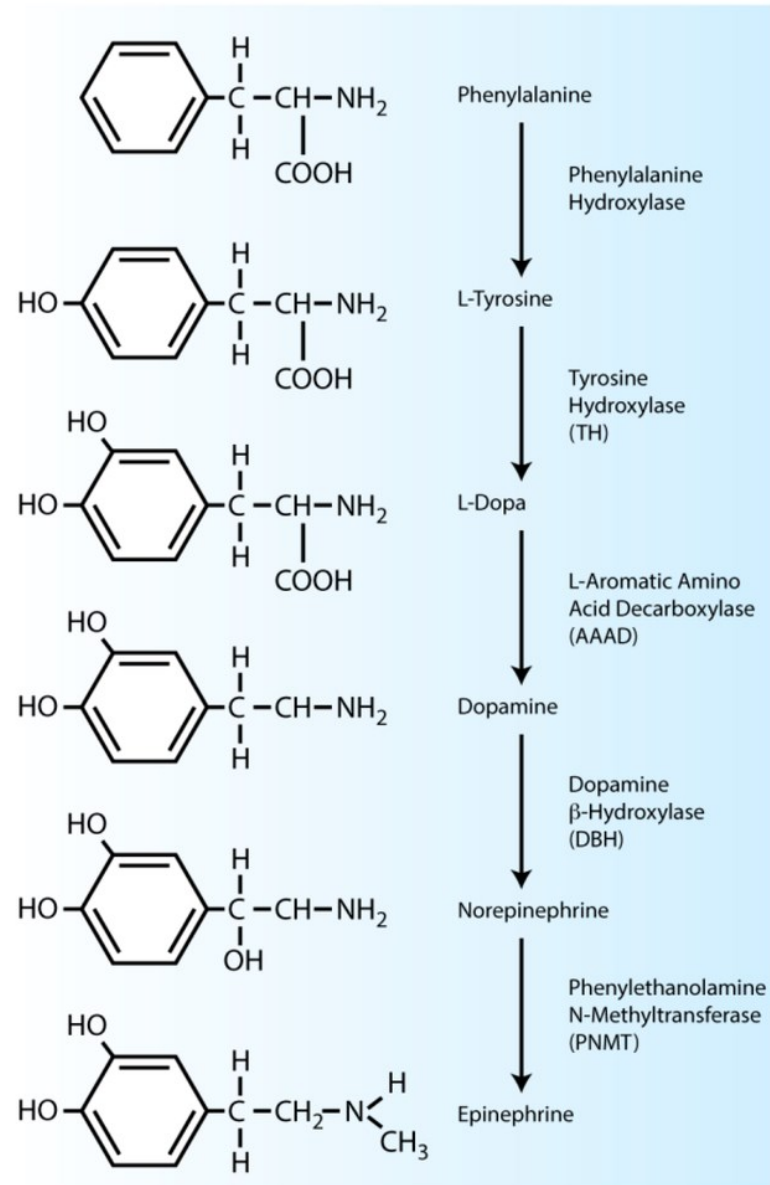
# Levodopa reversing reserpine-induced immobility (Arvid Carlsson, 1957)



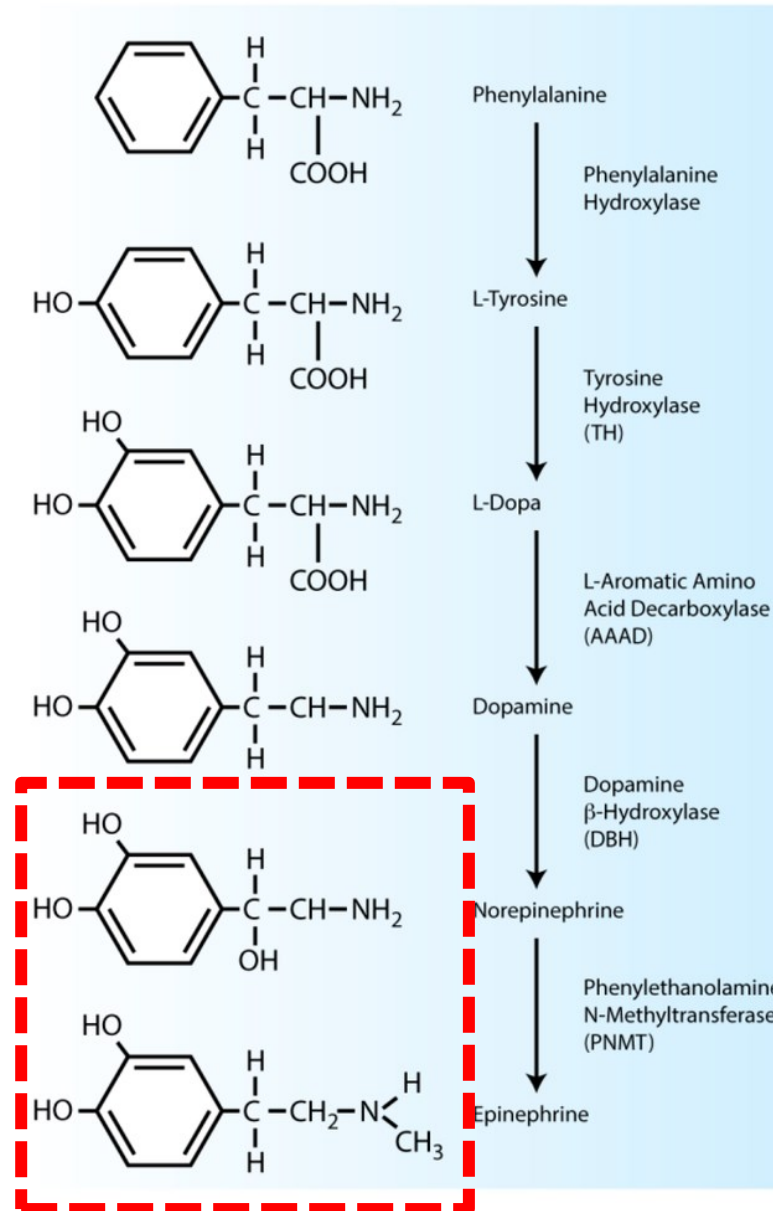
# Levodopa reversing reserpine-induced immobility (Arvid Carlsson, 1957)



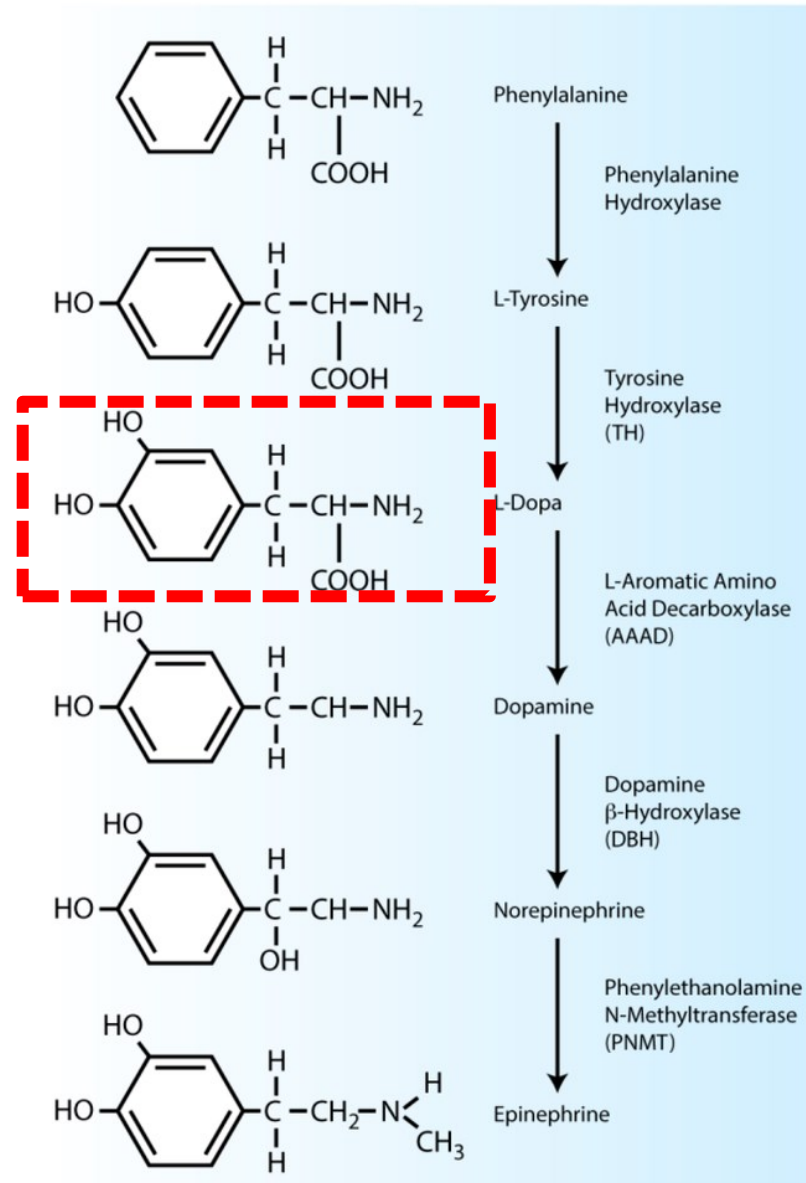
### Pathway of catecholamine biosynthesis

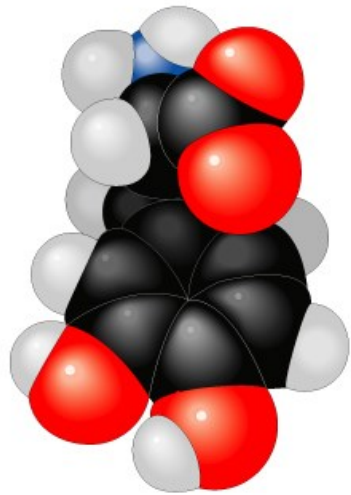


### Pathway of catecholamine biosynthesis



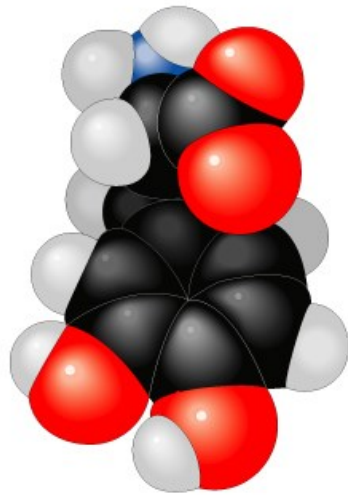
### Pathway of catecholamine biosynthesis



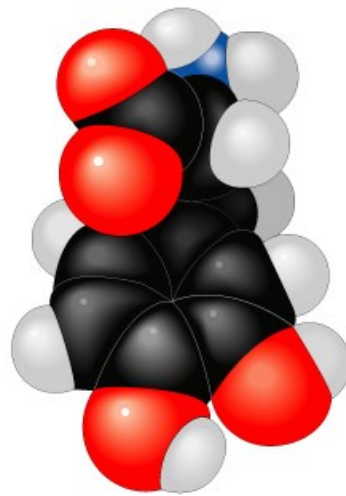


L-DOPA  
**3,4-dihydroxyphenylalanine**



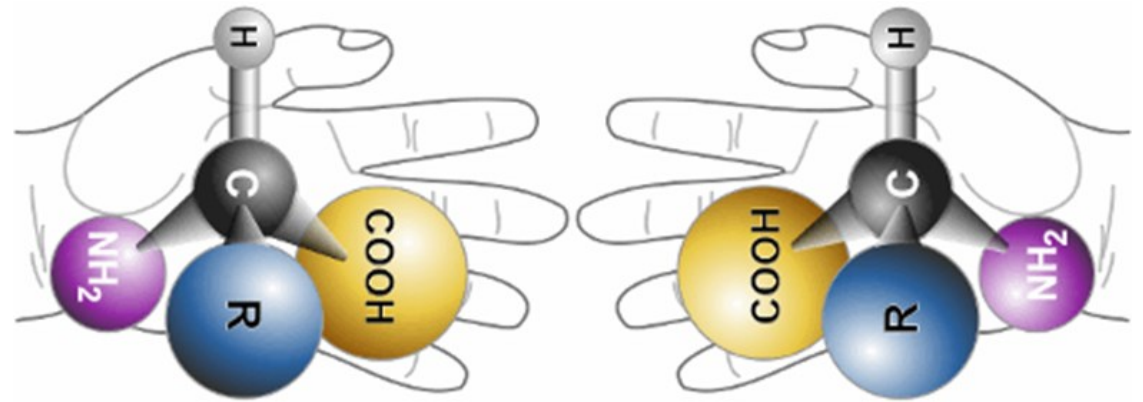


L-DOPA

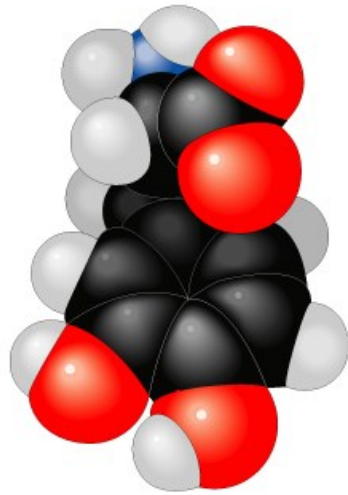


D-DOPA

**3,4-dihydroxyphenylalanine**







L-DOPA  
**3,4-dihydroxy-L-phenylalanine**

Cortex

**Striatum**

caudate

putamen

**Globus pallidus**

externa (GPe)

interna (GPI)

**Thalamus**

thalamic nuclei

ventrolateral nucleus


Subthalamic nucleus


Superior colliculus


**Substantia nigra**


pars reticulata (SNpr)


pars compacta (SNpc)


 Direct – D1-mediated

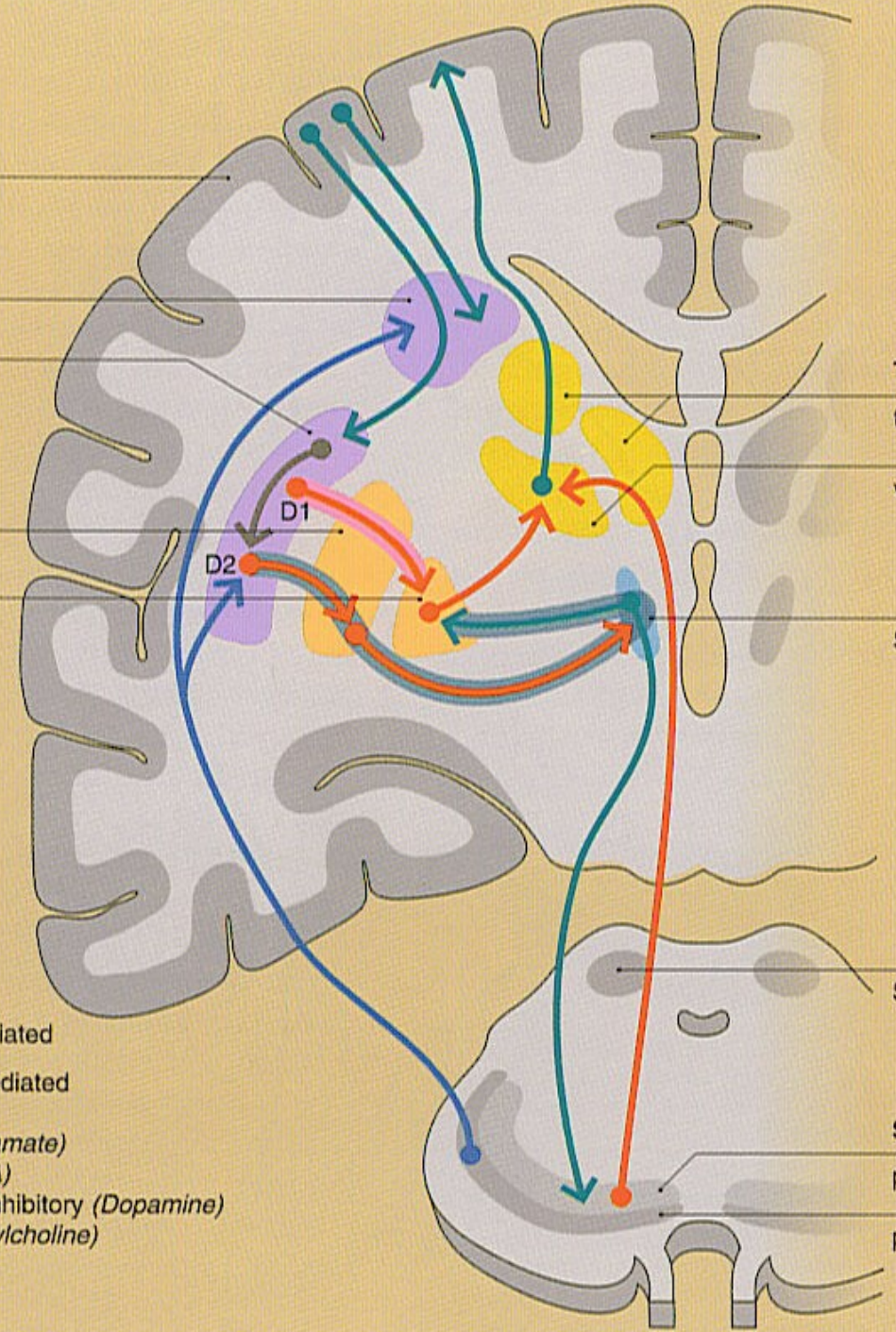
 Indirect – D2-mediated

 Excitatory (*Glutamate*)

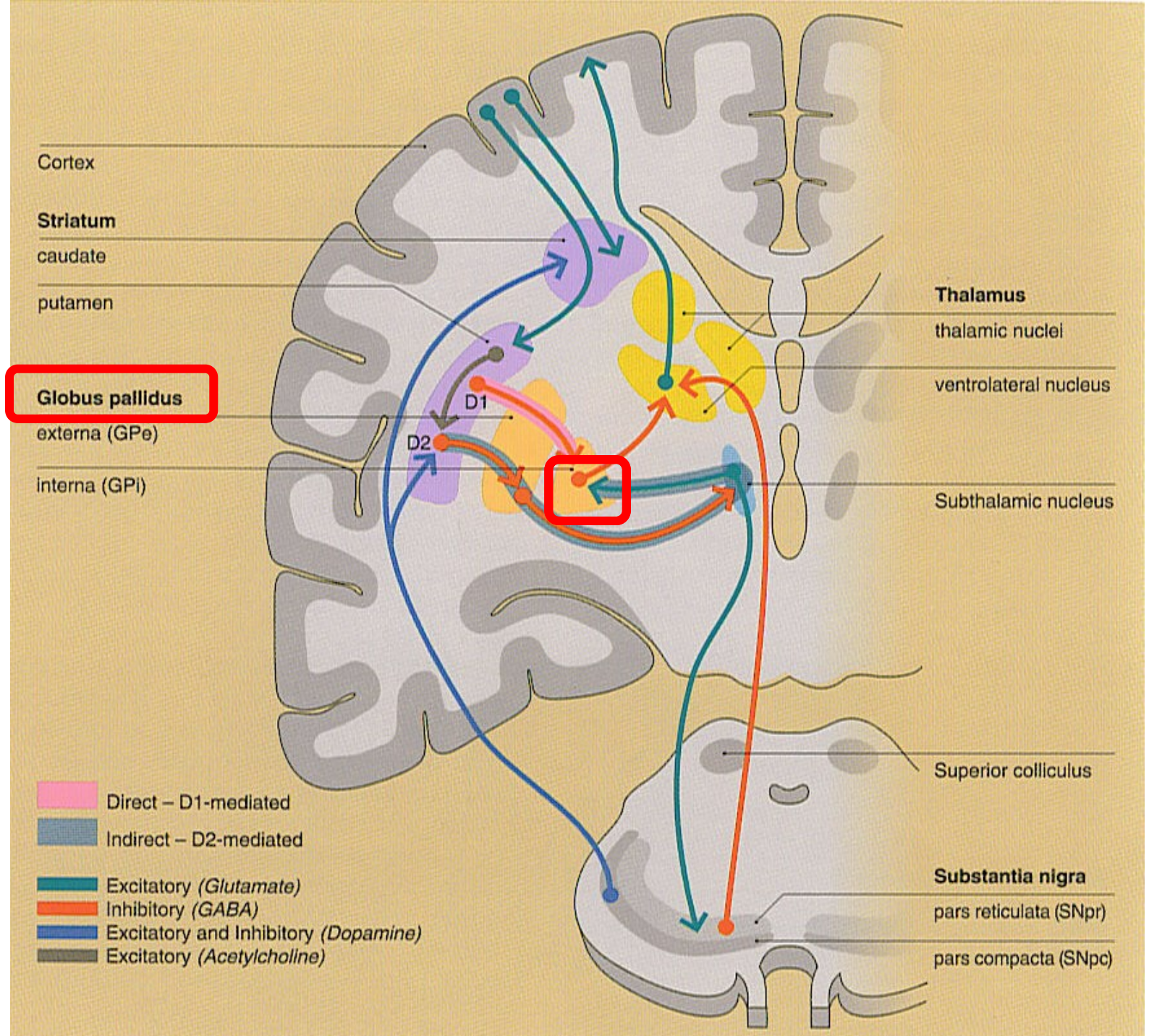
 Inhibitory (*GABA*)

 Excitatory and Inhibitory (*Dopamine*)

 Excitatory (*Acetylcholine*)









Cortex

**Striatum**

caudate

putamen

**Globus pallidus**

externa (GPe)

interna (GPI)

Direct – D1-mediated

Indirect – D2-mediated

Excitatory (*Glutamate*)

Inhibitory (*GABA*)

Excitatory and Inhibitory (*Dopamine*)

Excitatory (*Acetylcholine*)

**Thalamus**

thalamic nuclei

ventrolateral nucleus

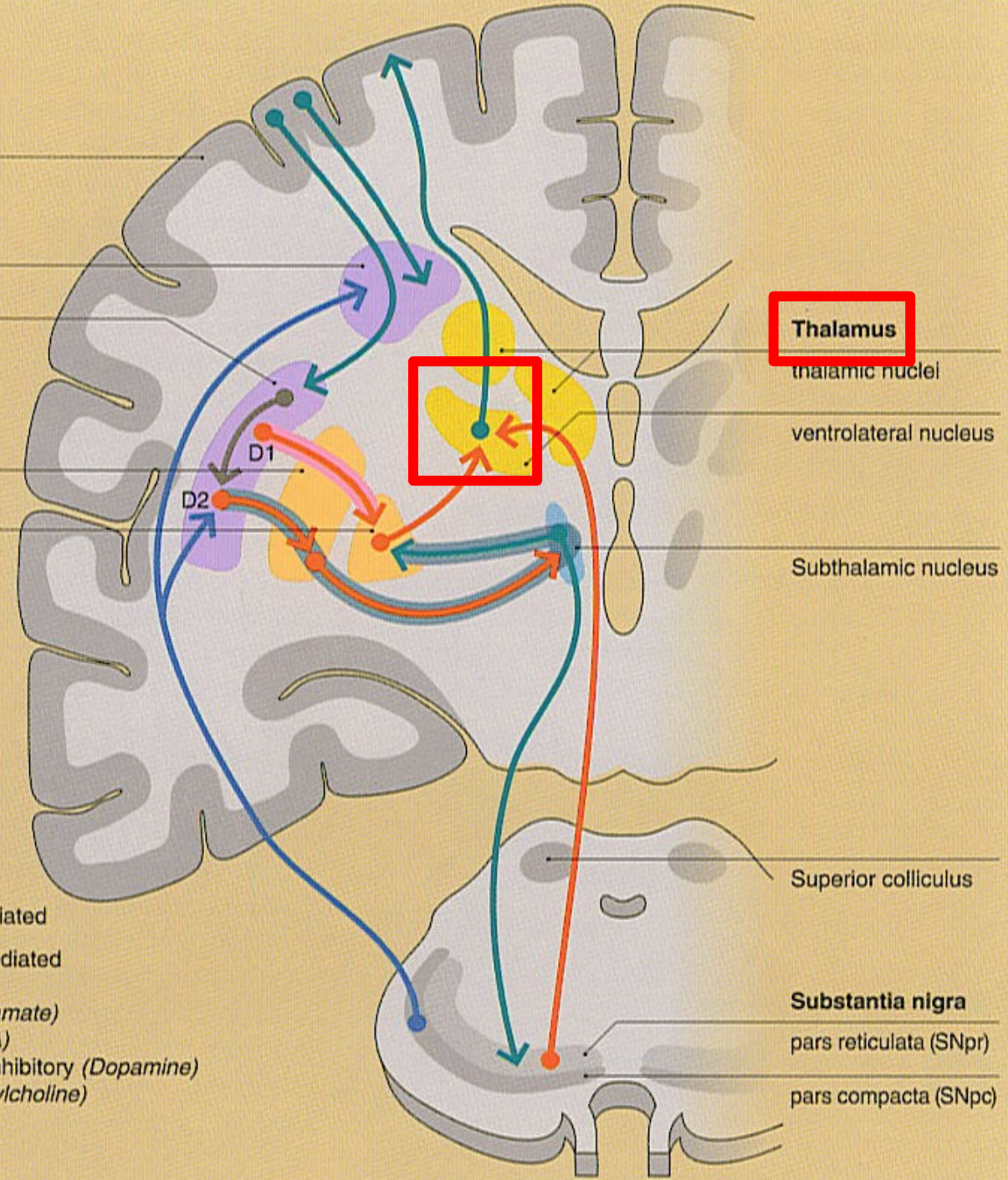
Subthalamic nucleus

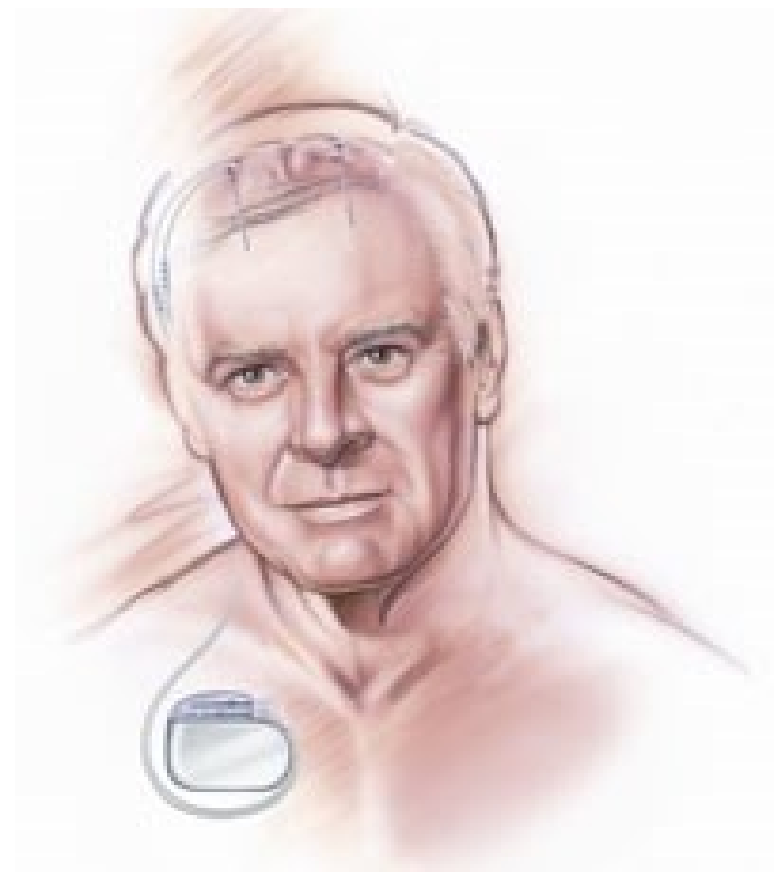
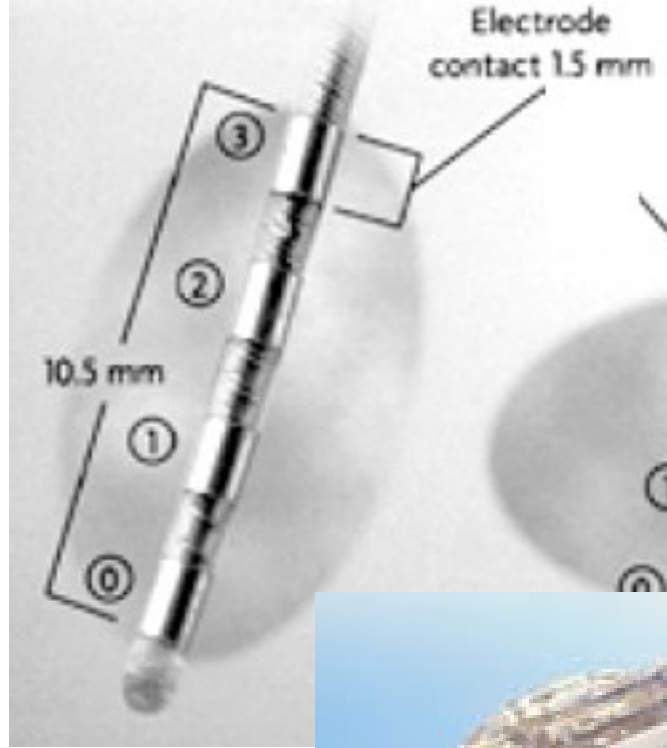
Superior colliculus

**Substantia nigra**

pars reticulata (SNpr)

pars compacta (SNpc)



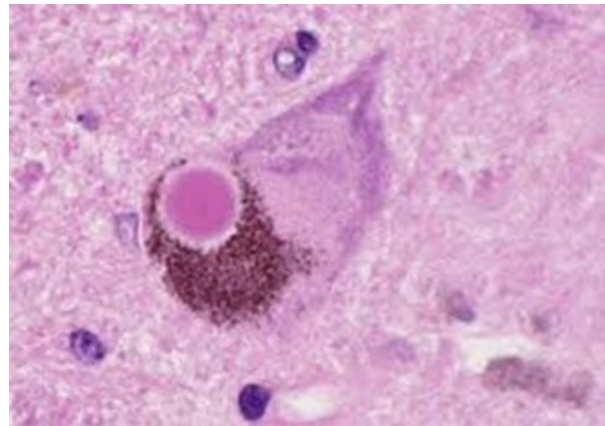
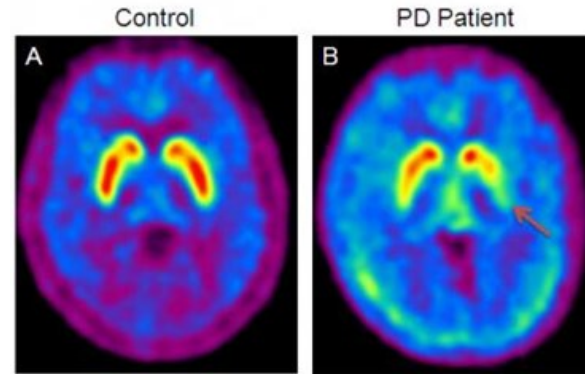


## Deep brain stimulation





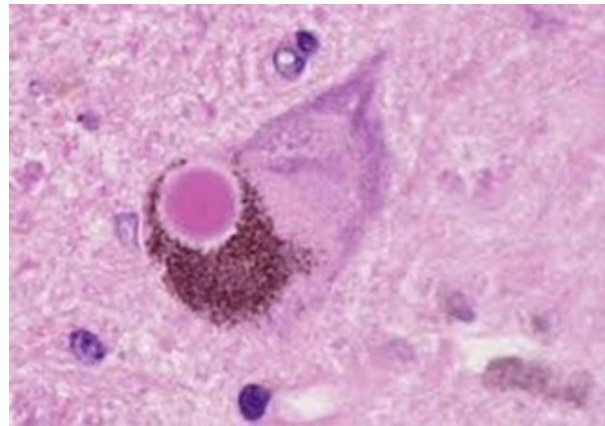
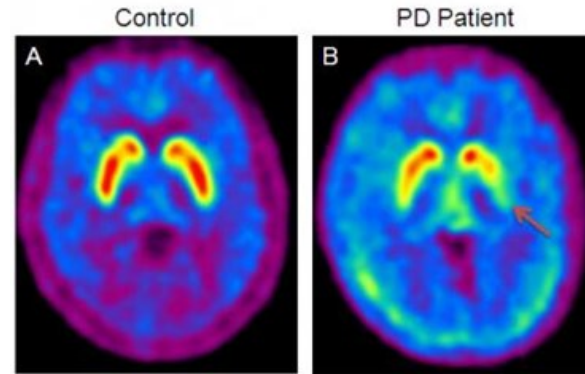
# The many identities of Parkinson disease



**Contursi Terme (Campania region  
of south-western Italy)**



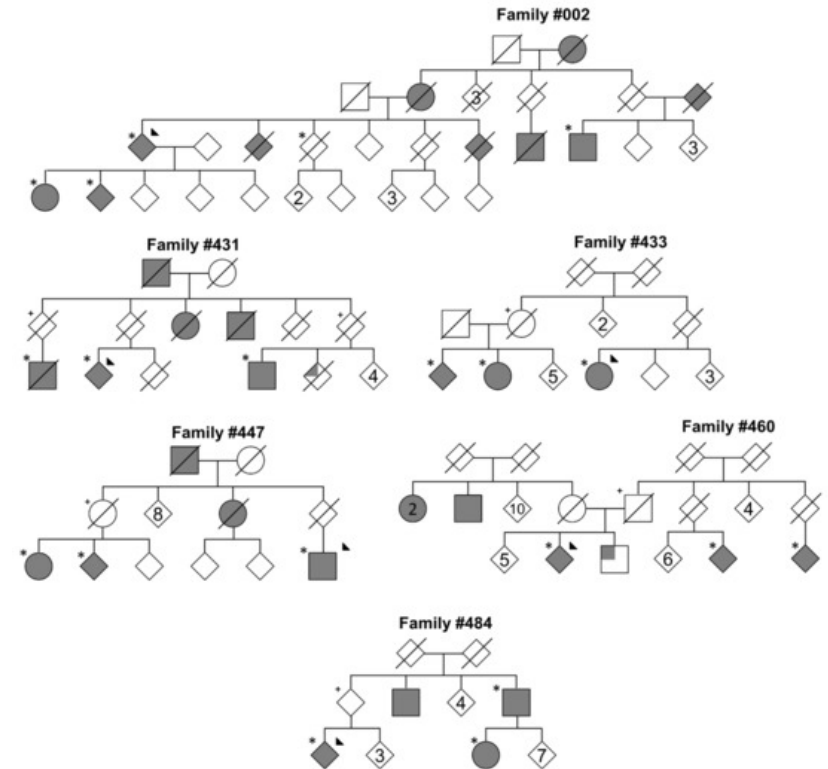
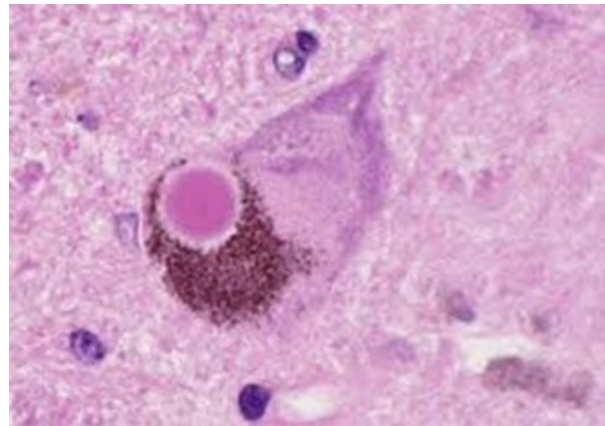
# The many identities of Parkinson disease



**Contursi Terme (Campania region  
of south-western Italy)**

# The many identities of Parkinson disease

Sixty individuals among five generations of families living in Contursi were determined to have Parkinson disease

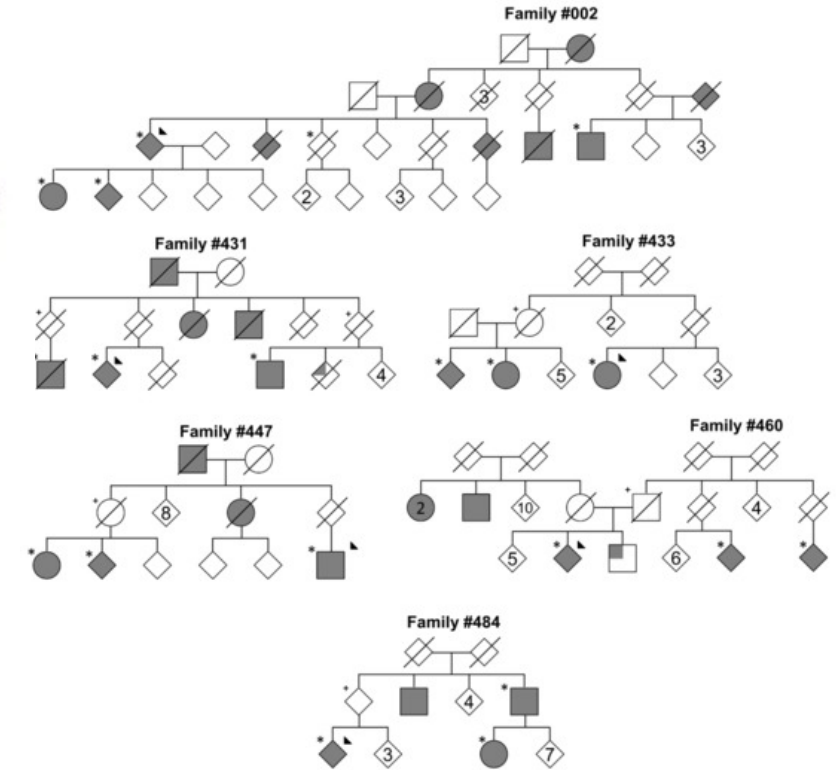
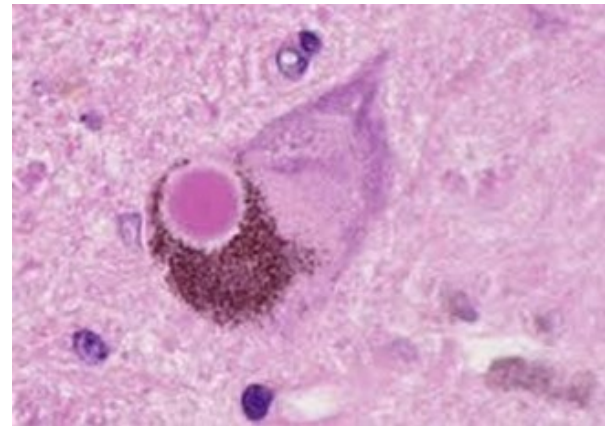


Family trees showing a dominant pattern of inheritance

# The many identities of Parkinson disease



Alpha-synuclein



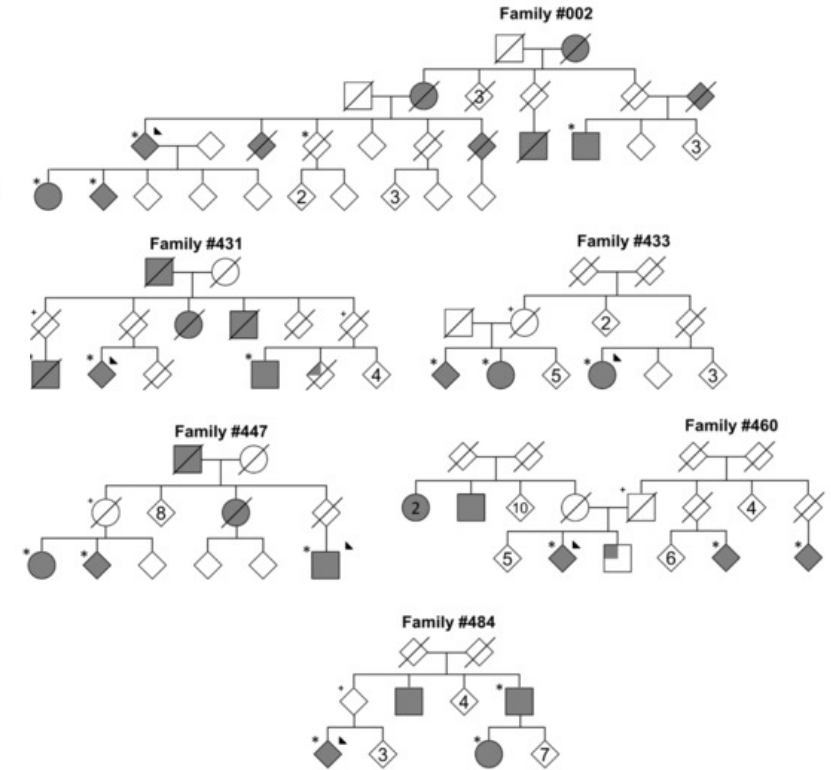
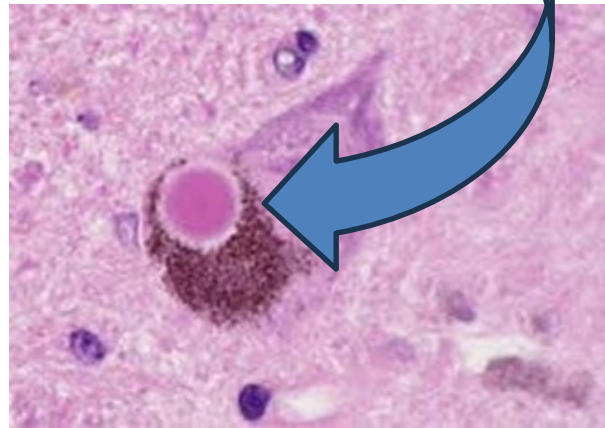
Family trees showing a dominant pattern of inheritance



# The many identities of Parkinson disease



Alpha-synuclein

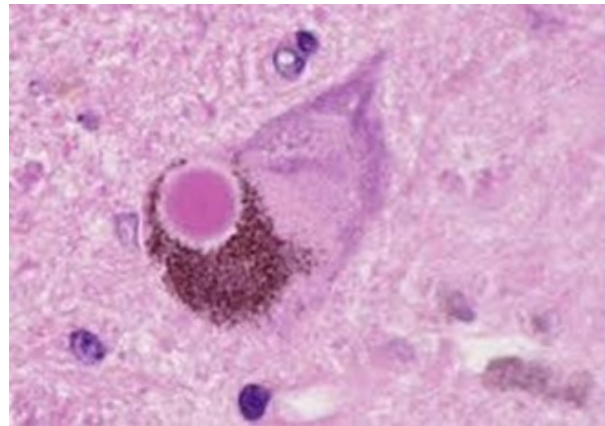


Family trees showing a dominant pattern of inheritance

# The many identities of Parkinson disease

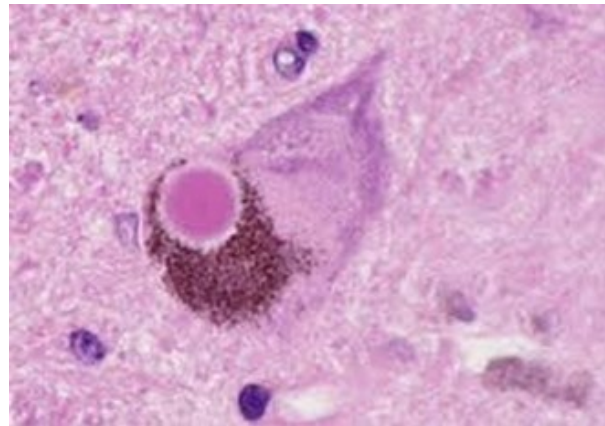
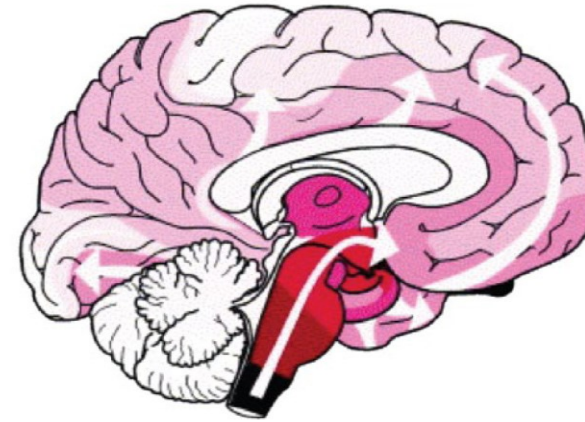


**Impaired sense of smell**



**Acting out dreams**

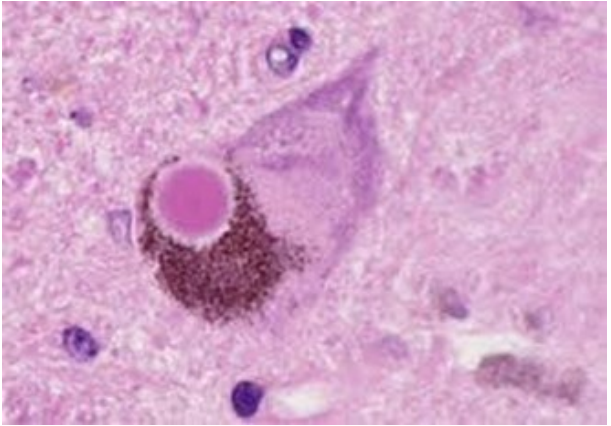
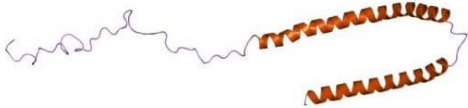
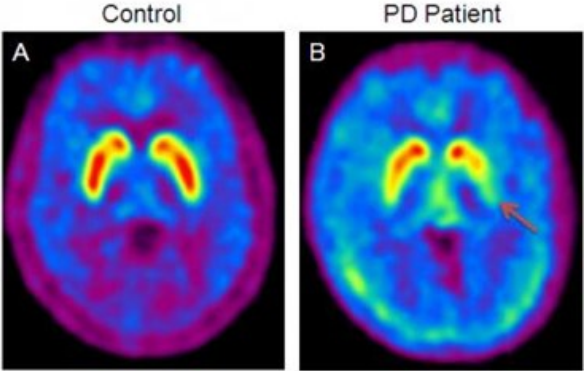
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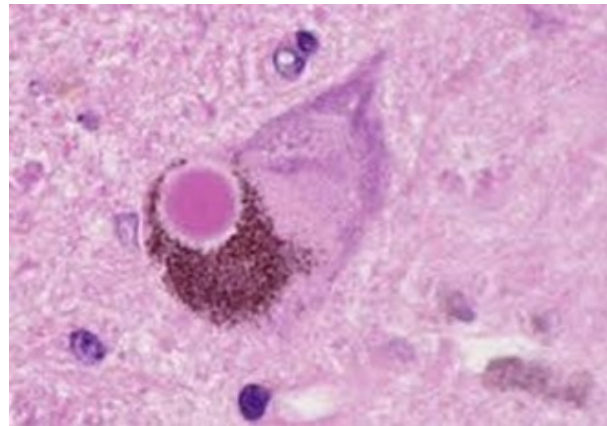
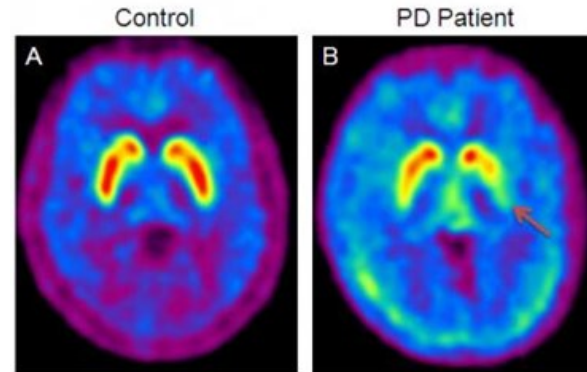
**Brain regions affected in very early Parkinson disease causing sleep disturbance and impaired sense of smell**

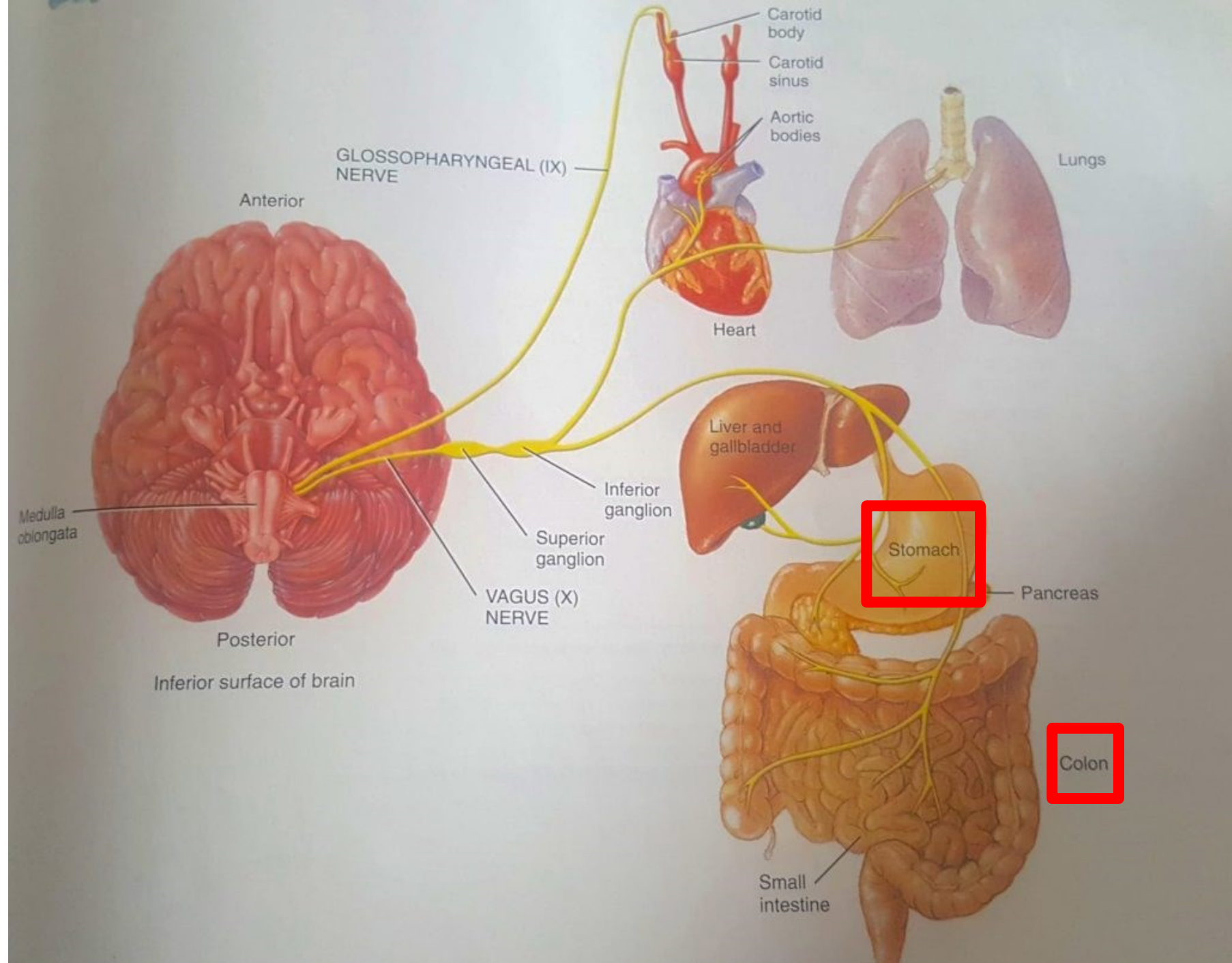


# The many identities of Parkinson disease

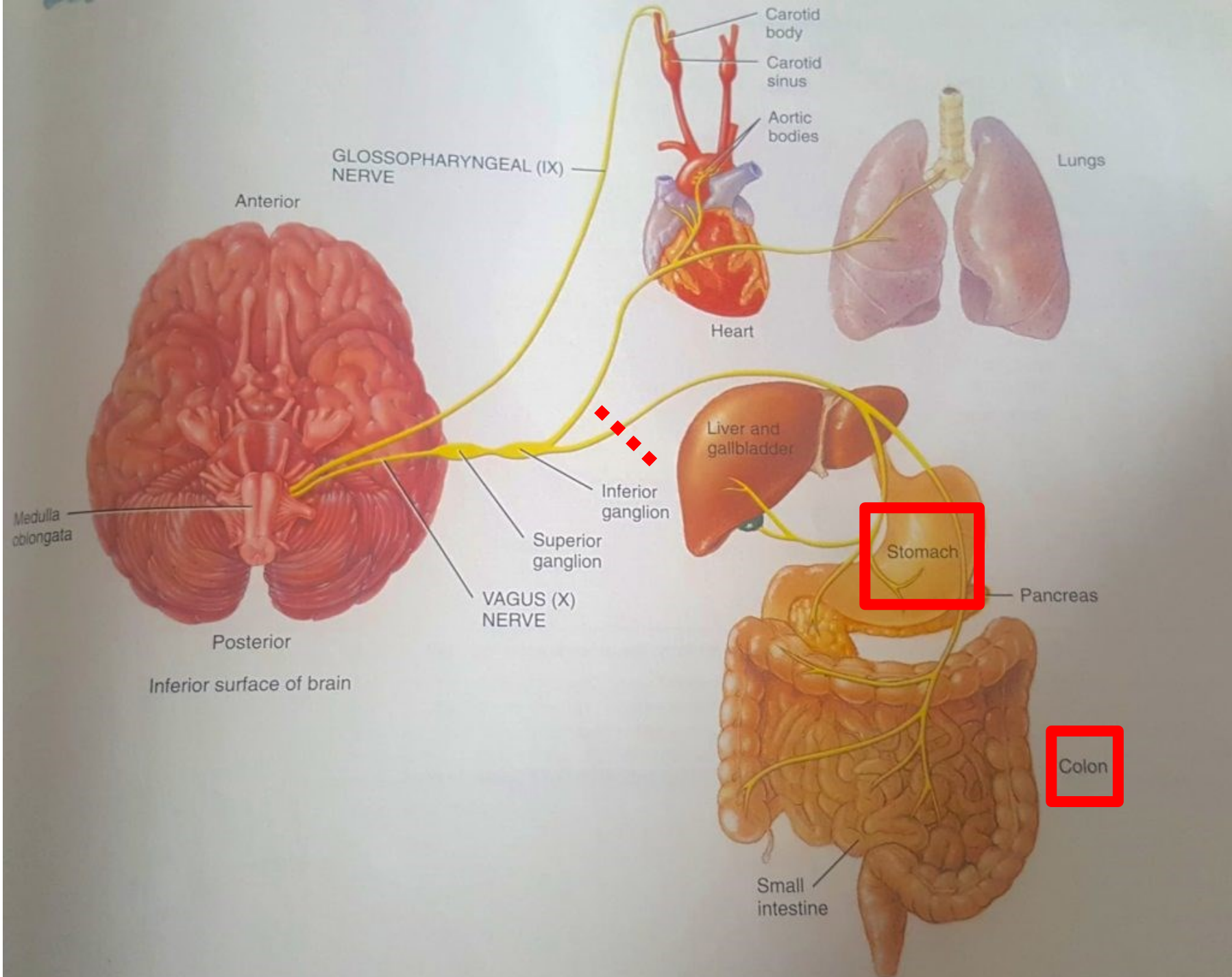


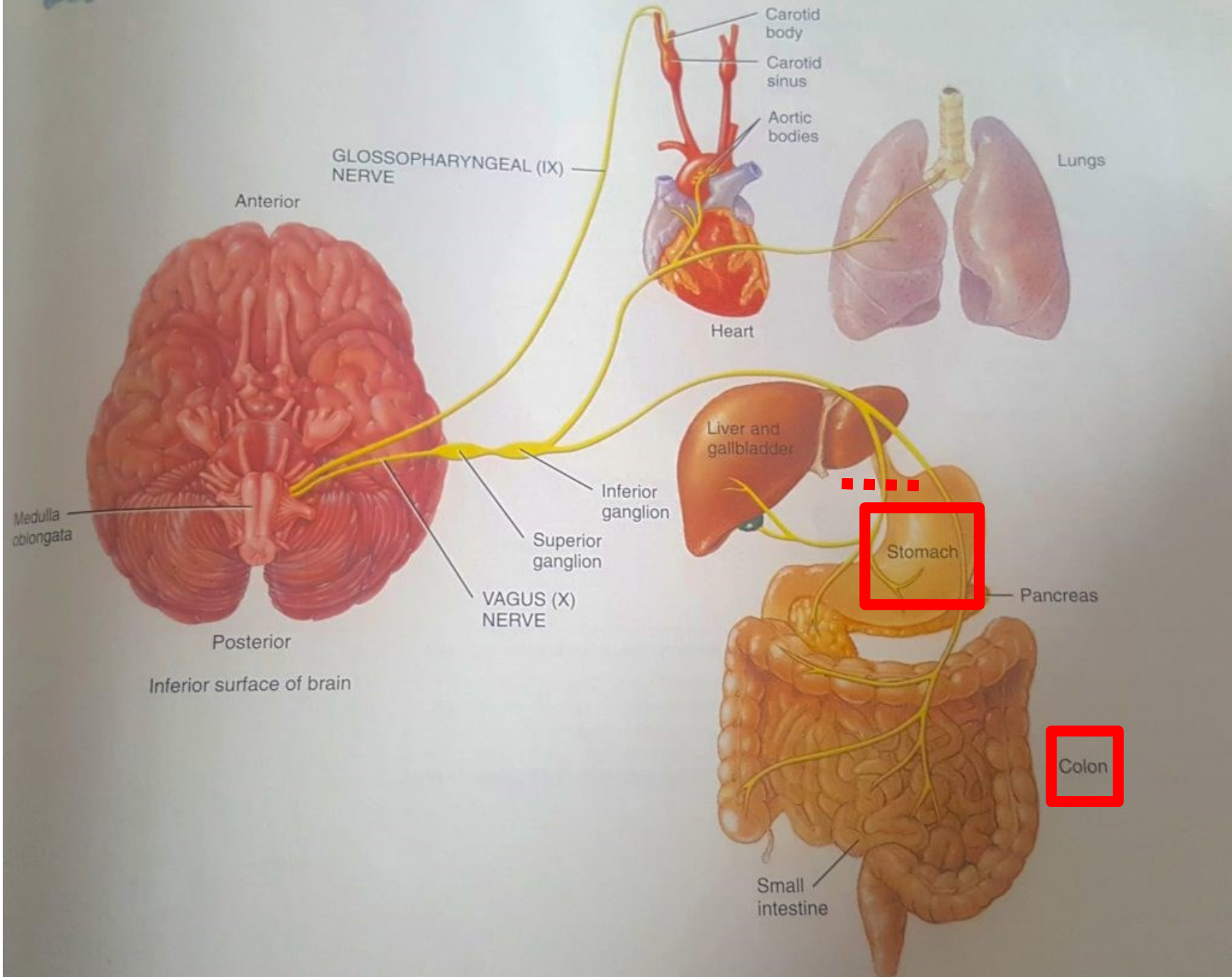
# The many identities of Parkinson disease













“ In the fields of  
observation chance  
favors only the  
prepared mind. ”

~ *Louis Pasteur*