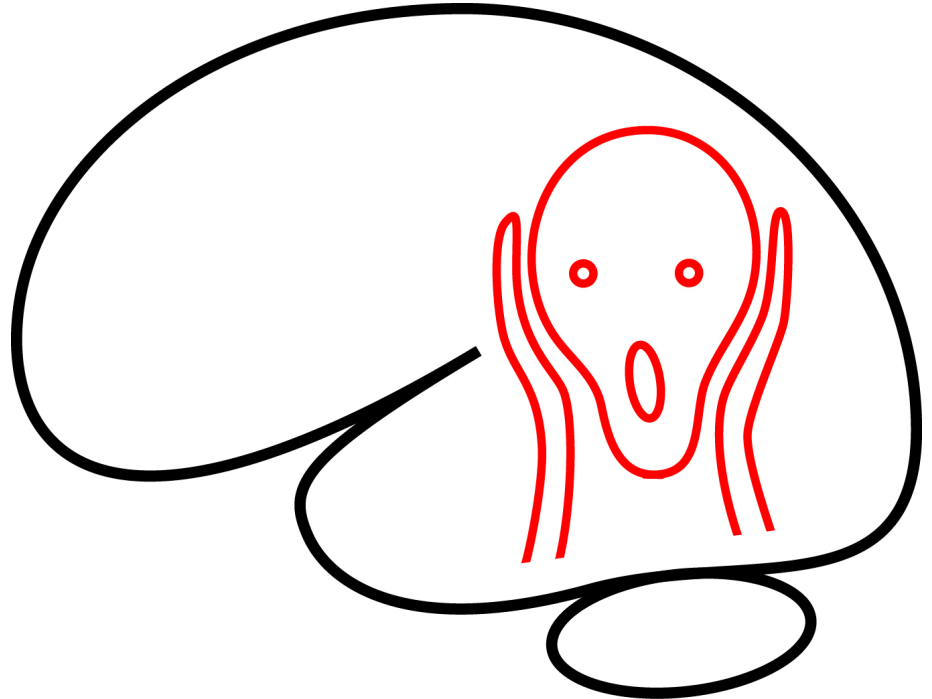


7.4 Brain dysfunction

Cellular Mechanisms of Brain Function

Prof. Carl Petersen



Brain dysfunction

Prevalence of brain disorders

Gustavsson *et al.* Cost of disorders of the brain in Europe 2010.
European Neuropsychopharmacology 21: 718–779 (2011).

Gustavsson *et al.* (2011) investigated the overall burden of brain disorders in 2010 across 30 European countries with a total population of ~500 million people.

Total financial burden : ~ **€ 800 billion** = ~ **\$ 1 trillion**

Number of affected people: > **150 million people**

Prevalence of brain disorders in Europe 2010

		€ billion	People million
1	Mood disorders	113	33
2	Dementia	105	6
3	Psychotic disorders	94	5
4	Anxiety disorders	74	69
5	Addiction	66	16
6	Stroke	64	8
7	Headache	44	153
8	Mental retardation	43	4
9	Sleep disorders	35	45
10	Traumatic brain injury	33	4

		€ billion	People million
11	Personality disorders	27	4
12	Child/adolescent disorders	21	6
13	Somatoform disorder	21	20
14	Multiple sclerosis	15	0.5
15	Parkinson's disease	14	1
16	Epilepsy	14	3
17	Neuromuscular disorders	8	0.3
18	Brain tumor	5	0.2
19	Eating disorders	1	2

Gustavsson *et al.* (2011)

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Gustavsson *et al.* (2011)

Parkinson's disease – Symptoms

Dr. James Parkinson (1817) *An Essay on the Shaking Palsy*.
published by Whittingham and Rowland, London.

Age-related, slow, progressive neurodegenerative disorder.

Early symptoms of Parkinson's disease:
slowness of movements, difficulty in walking, shaking, rigidity

Later other symptoms also become important:
dementia, depression

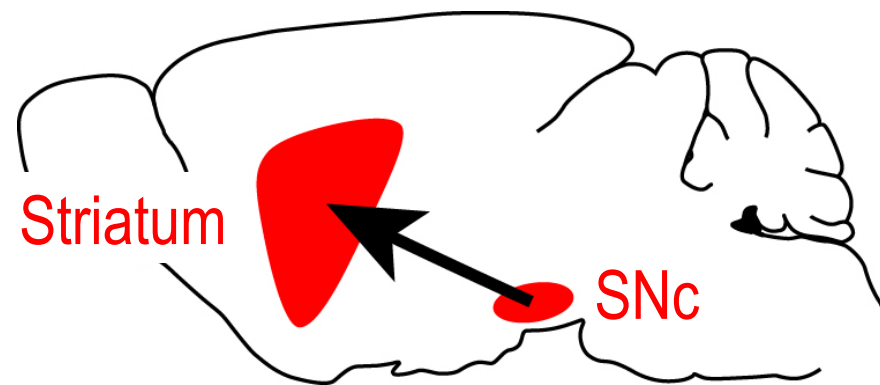
Parkinson's disease – Loss of dopamine neurons

Symptoms of Parkinson's disease are caused by the degeneration of dopaminergic neurons in the *substantia nigra pars compacta* (SNc). The degenerating neurons have cytoplasmic, protein-rich inclusions, termed Lewy bodies, which contain α -synuclein.

Clinical motor symptoms:

60% SNc cells lost

80% loss of striatal dopamine



Parkinson's disease – Environmental influences

Probably anything that causes degeneration of SNc dopaminergic neurons, will give rise to symptoms similar to Parkinson's disease.

Illicit use of intravenous drugs contaminated with methyl-phenyl-tetrahydropyridine (MPTP) has induced a Parkinson's disease-like syndrome in a number of people. MPTP crosses the blood-brain barrier, and in the brain is metabolised to the cation 1-methyl-4-phenylpyridinium (MPP⁺), which induces mitochondrial toxicity. In animal models, administration of MPTP causes Parkinson's like symptoms and a loss of dopaminergic neurons.

Parkinson's disease – Genetic influences

Genome wide association studies reveal susceptibility loci for Parkinson's disease, e.g.

α -synuclein – many different mutations with varying strength of influence upon the chance of getting Parkinson's disease

A53T mutation is dominant

REP1 dinucleotide repeat expansion has smaller effect

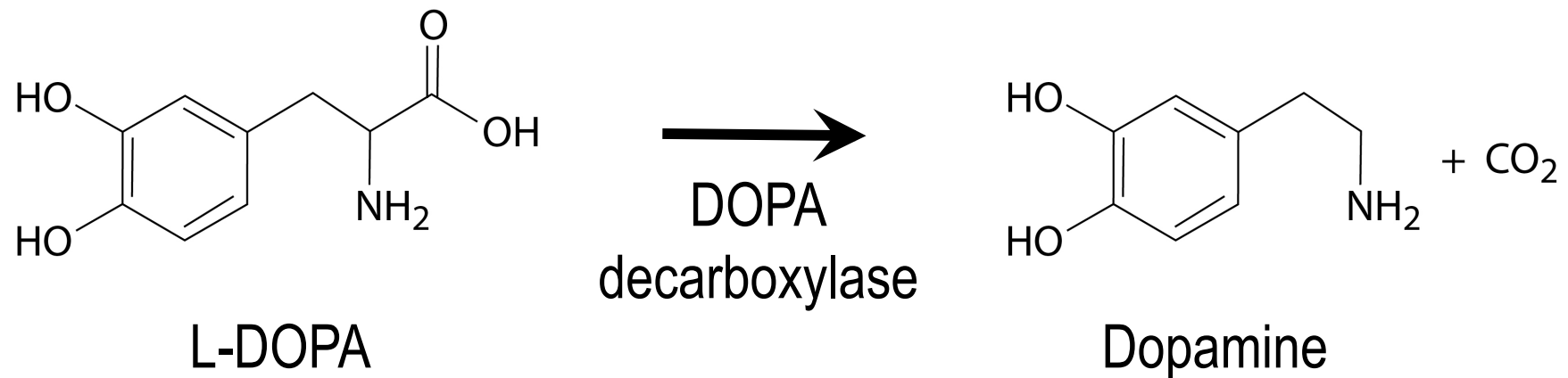
LRRK2 (Leucine-Rich Repeat Kinase 2)

many variants R1441C/G/H, I2020T, Y1699C, G2019S

aberrantly increased kinase activity?

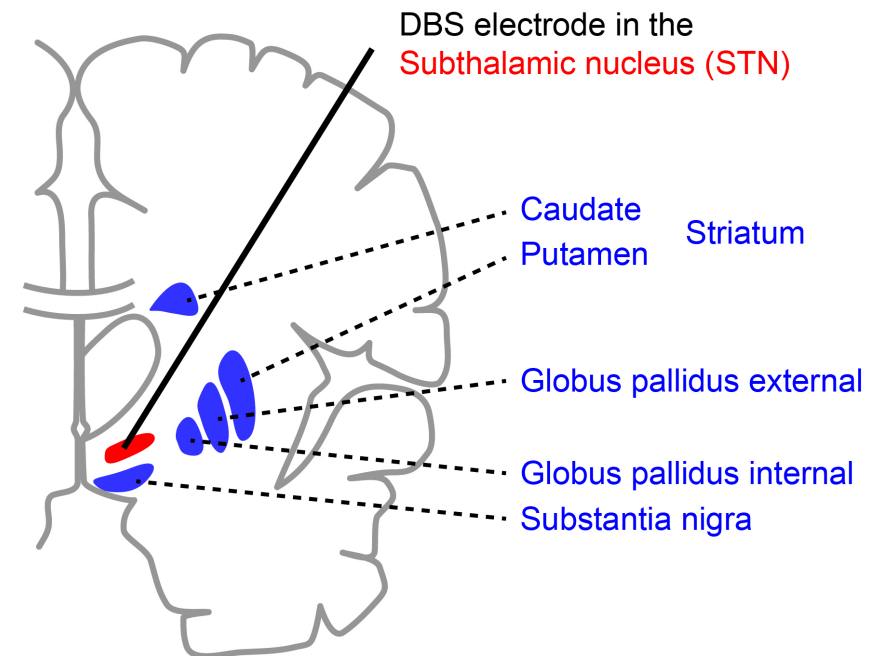
Parkinson's disease – L-DOPA treatments

L-DOPA is a precursor for the synthesis of dopamine. L-DOPA crosses the blood-brain barrier and increases brain dopamine thus alleviating symptoms of Parkinson's disease. However, high doses and long-term use are associated with serious side-effects.



Parkinson's disease – Brain stimulation treatment

When drug treatments fail, then some symptoms of Parkinson's disease can be alleviated by '*Deep Brain Stimulation*' (DBS). DBS consists of bilateral implantation of electrical stimulation electrodes in the **subthalamic nucleus (STN)**. High frequency electrical stimuli are then continuously applied to the **STN**, and provide immediate relief of symptoms.



Parkinson's disease – Brain stimulation treatment



You can learn more about '*Deep Brain Stimulation*' from many remarkable YouTube videos, e.g.

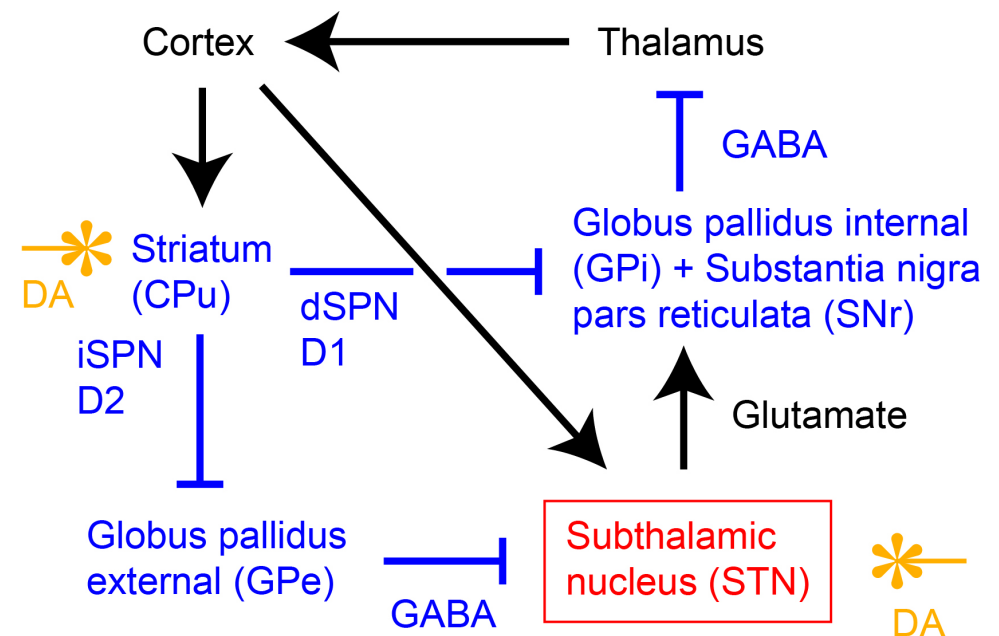
Prof. Hagai Bergman, Hebrew University of Jerusalem
http://www.youtube.com/watch?v=mMRX_Noco7g

Patient Andrew Johnson, Auckland
<http://www.youtube.com/watch?v=uBh2LxTW0s0>

Parkinson's disease – Mechanisms of DBS

Several different mechanisms have been proposed to account for how DBS of the **subthalamic nucleus (STN)** alleviates some of the symptoms of Parkinson's disease.

Further research is needed.



Brain dysfunction

- The brain is a delicate biological organ with many disorders.
- Neuroscientists are developing therapies for brain disorders.
- For example, Parkinson's disease is associated with loss of dopaminergic neurons, and the symptoms can be treated by drugs and deep brain stimulation.