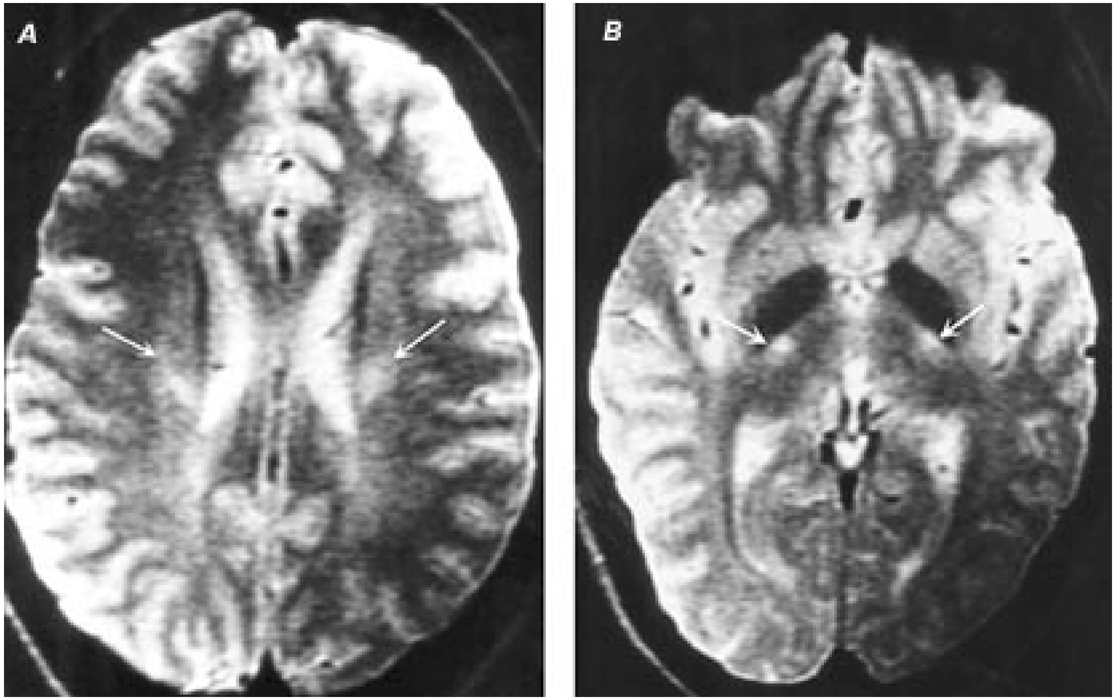
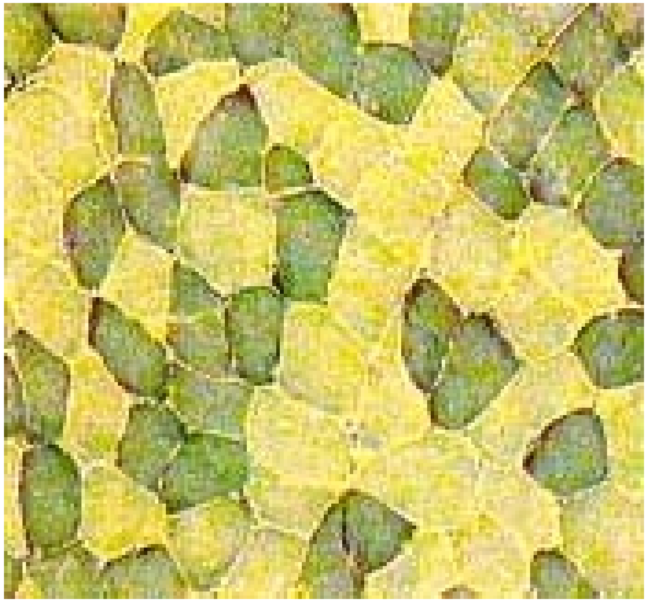
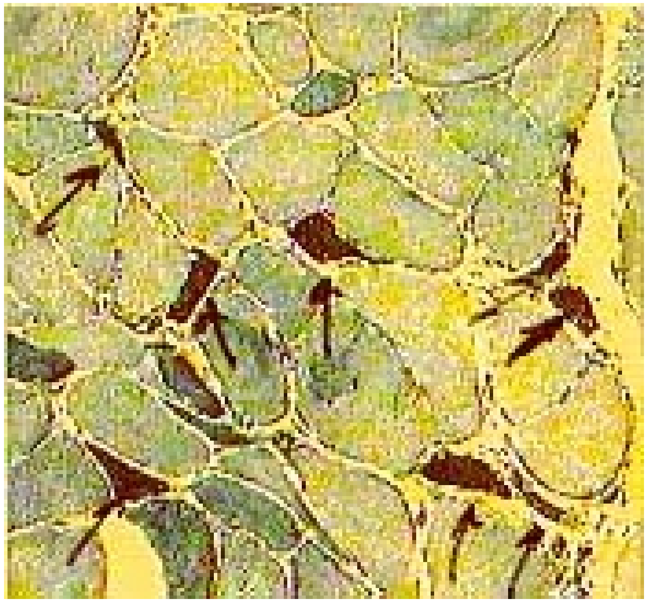
A. Axial T2-weighted MRI scan through the lateral ventricles of the brain reveals abnormal high signal intensity within the corticospinal tracts (arrows). B. Axial T2-weighted image through the level of the internal capsules reveals abnormal foci of high singal intensity in the posterior limbs of the internal capsule (arrows). This MRI feature represents an increase in water content in myelin tracts undergoing Wallerian degeneration secondary to cortical neuronal loss. This finding is commonly present in ALS, but can also be seen in AIDS-related encephalopathy, infarction, or other disease processes that produce neuronal loss in a symmetric fashion.



ALS

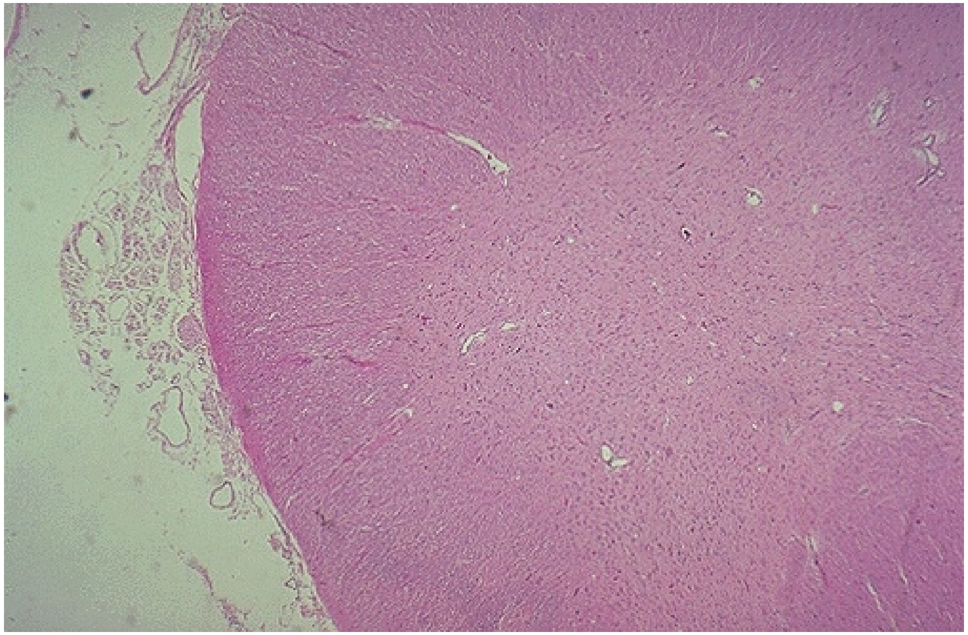


Normal muscle biopsy

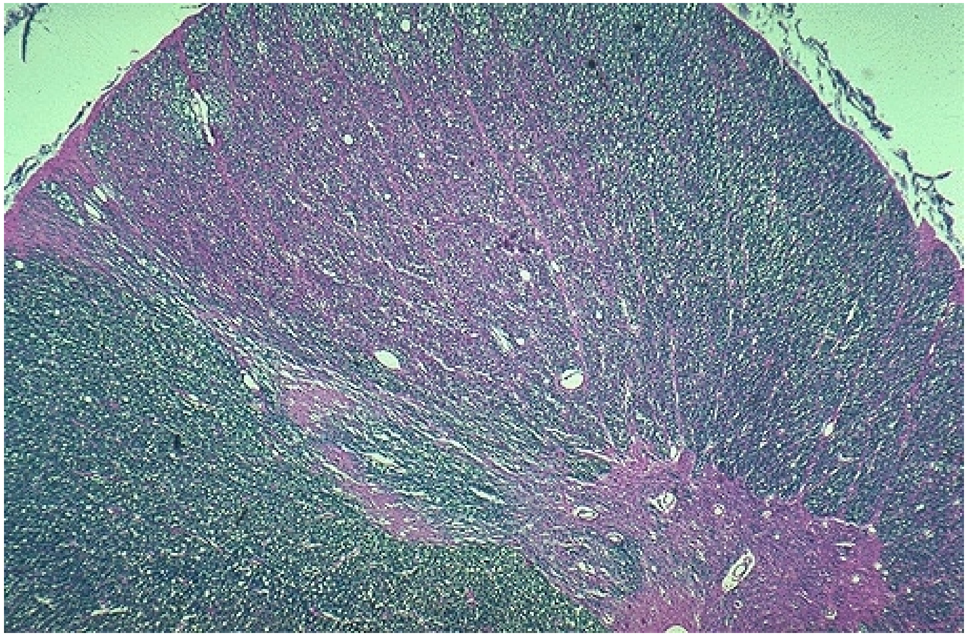


ALS muscle biopsy

Where are the anterior horn cells in this section of spinal cord? They are absent in a patient with amyotrophic lateral sclerosis (ALS).

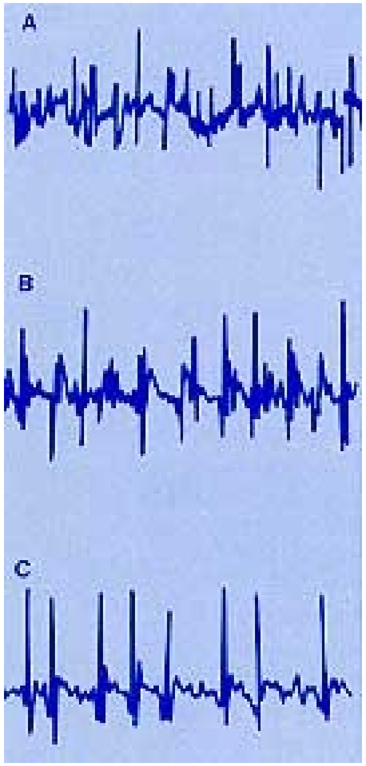


This Luxol-fast-blue stain of spinal cord in a patient with ALS demonstrates lateral column degeneration with gliosis--the "sclerosis" of ALS.



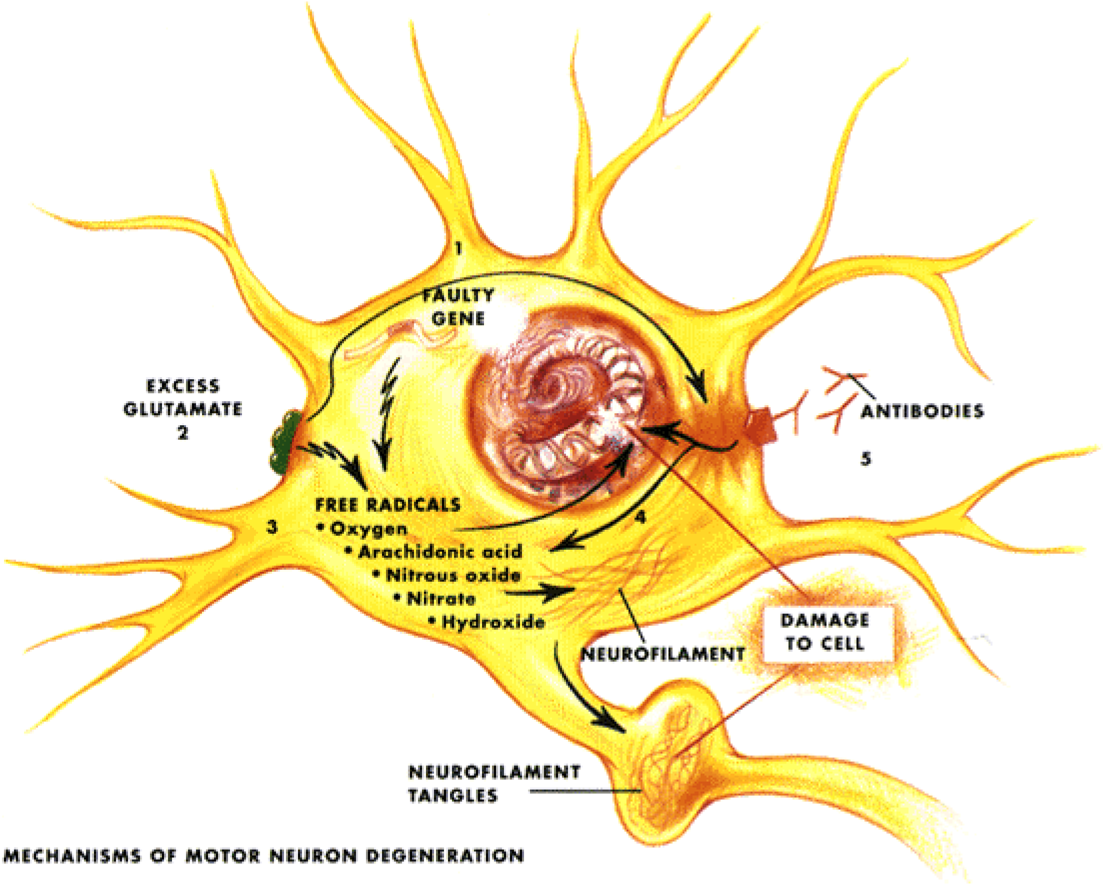
Amyotrophic lateral sclerosis (ALS) is uncommon. It begins in middle age and proceeds to death in several years. There is loss of anterior horn cells, so that patients present with progressive weakness that proceeds to paralysis from neurogenic muscular atrophy. Because of the loss of anterior horn cells, the anterior (ventral) spinal motor nerve roots demonstrate atrophy, as seen here in comparison with a normal spinal cord.

ALS



Normal myogram ALS myogram

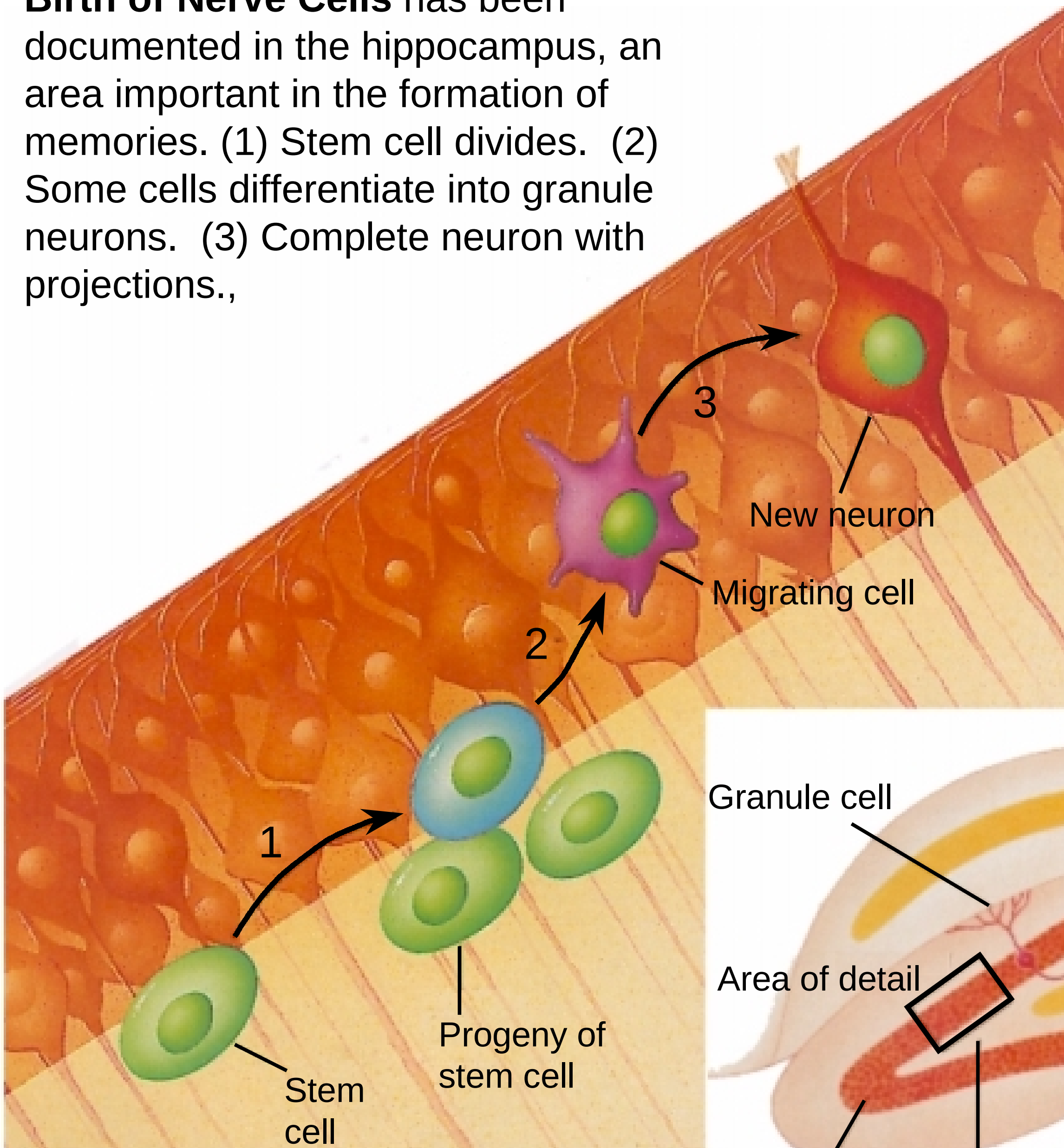
ALS

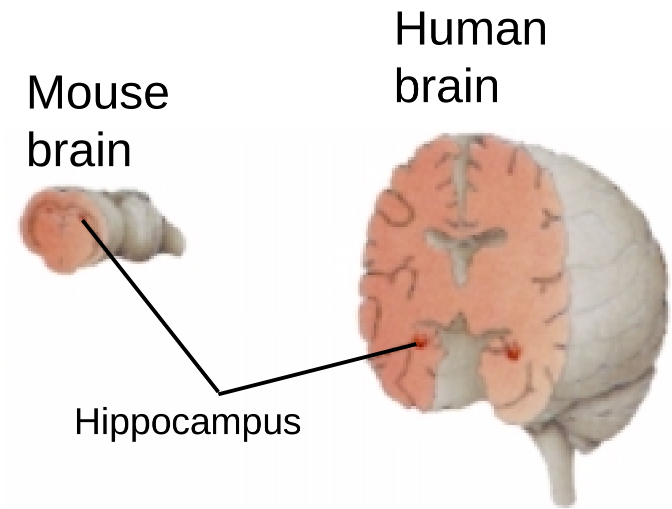


MECHANISMS OF MOTOR NEURON DEGENERATION

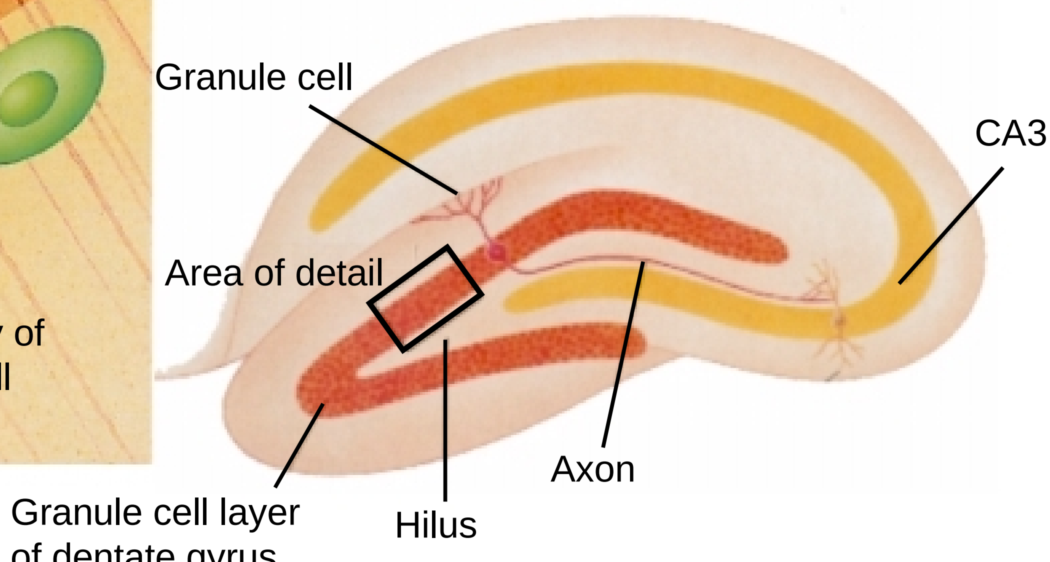
ALS

Birth of Nerve Cells has been documented in the hippocampus, an area important in the formation of memories. (1) Stem cell divides. (2) Some cells differentiate into granule neurons. (3) Complete neuron with projections.,



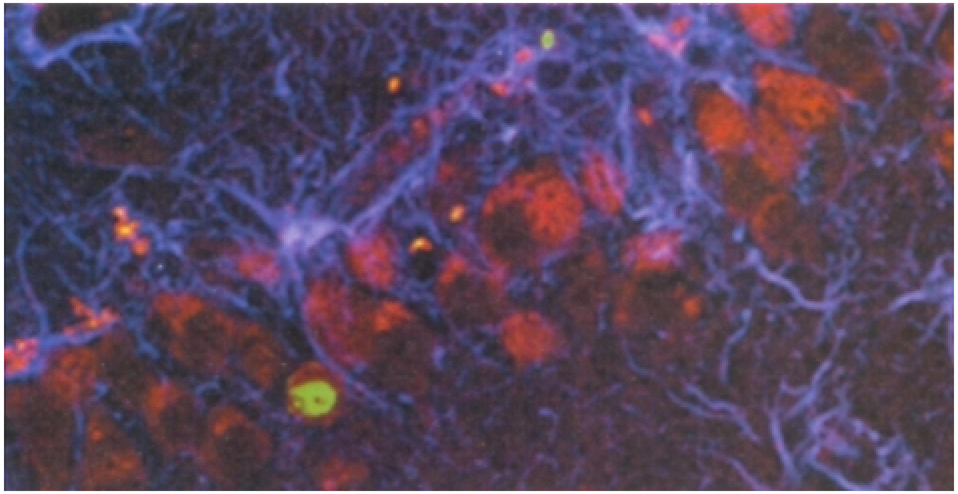


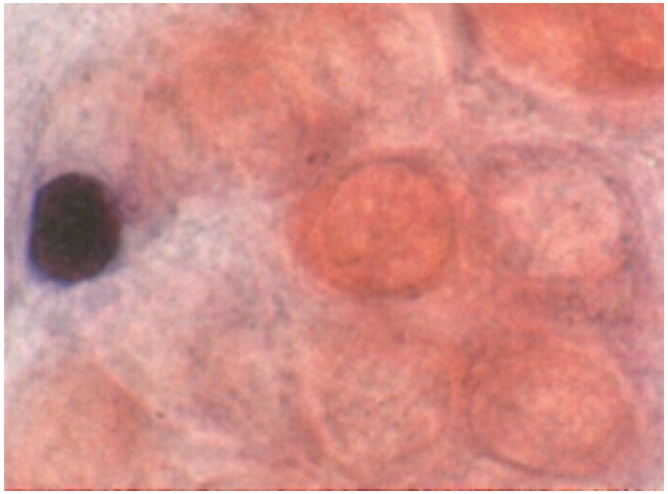
Hippocampus



Neural Regeneration

Proof of Neuron Formation

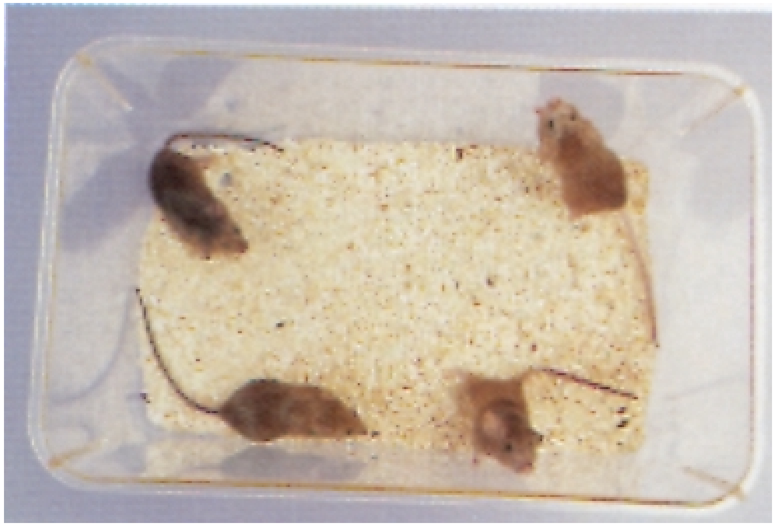


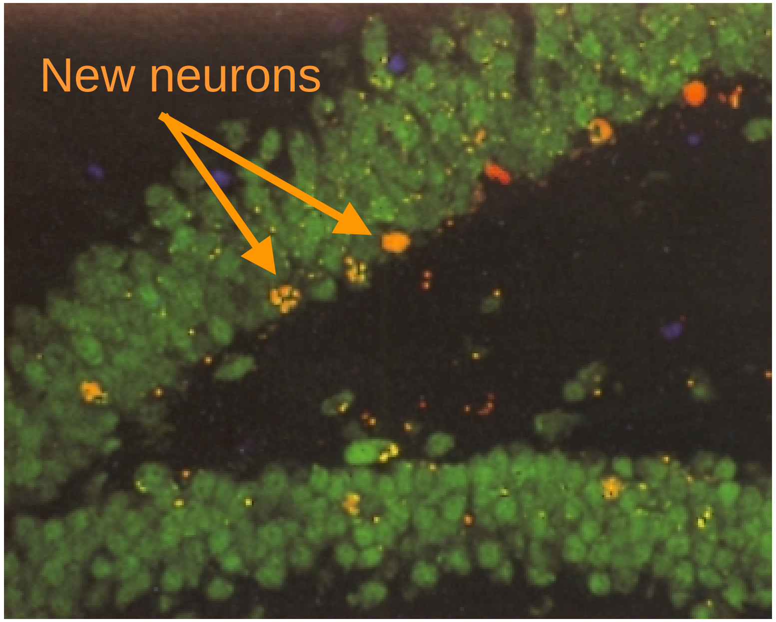


Micrographs of hippocampal tissue from adults who died of cancer. Neurons in the left picture marked by the green fluorescent substance and in the right picture marked by the dark substance contain BrdU (bromodeoxyuridine) in the chromosomes in their nuclei. BrdU was used in the patients to assess tumor growth and is incorporated in new DNA formed prior to mitosis.

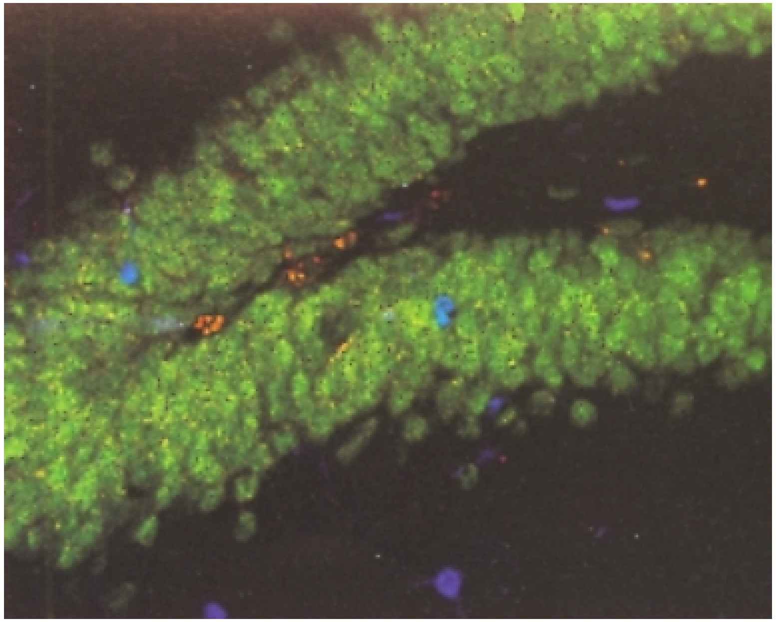
Exercise

No Exercise

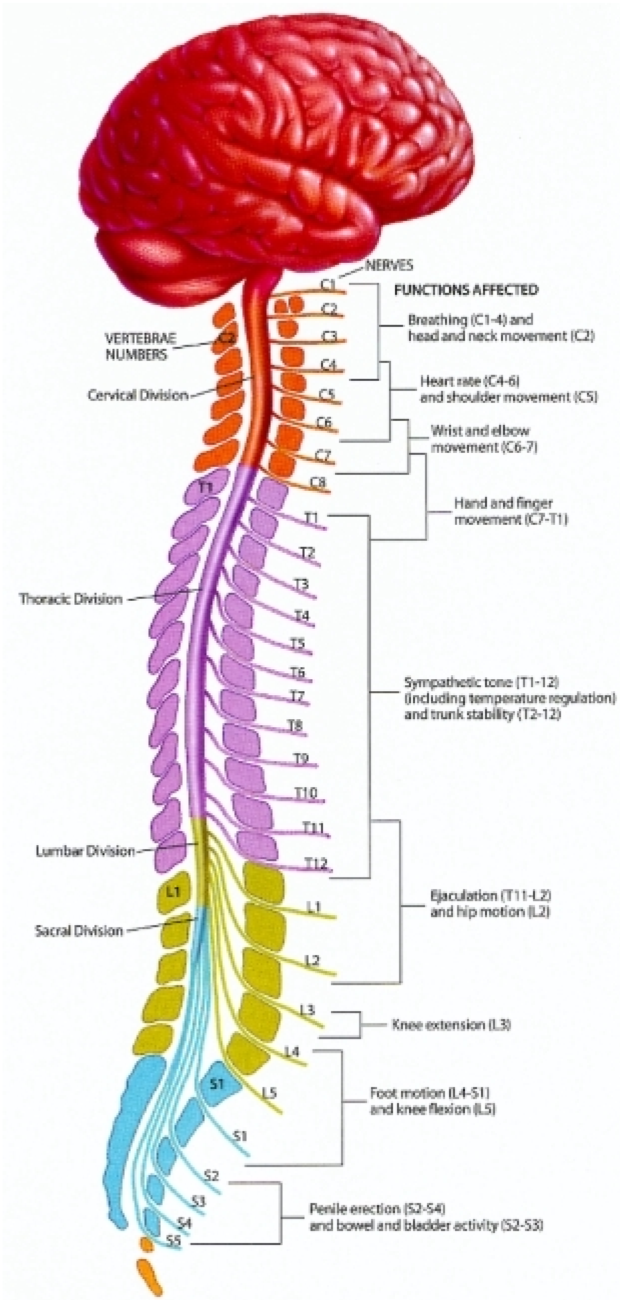


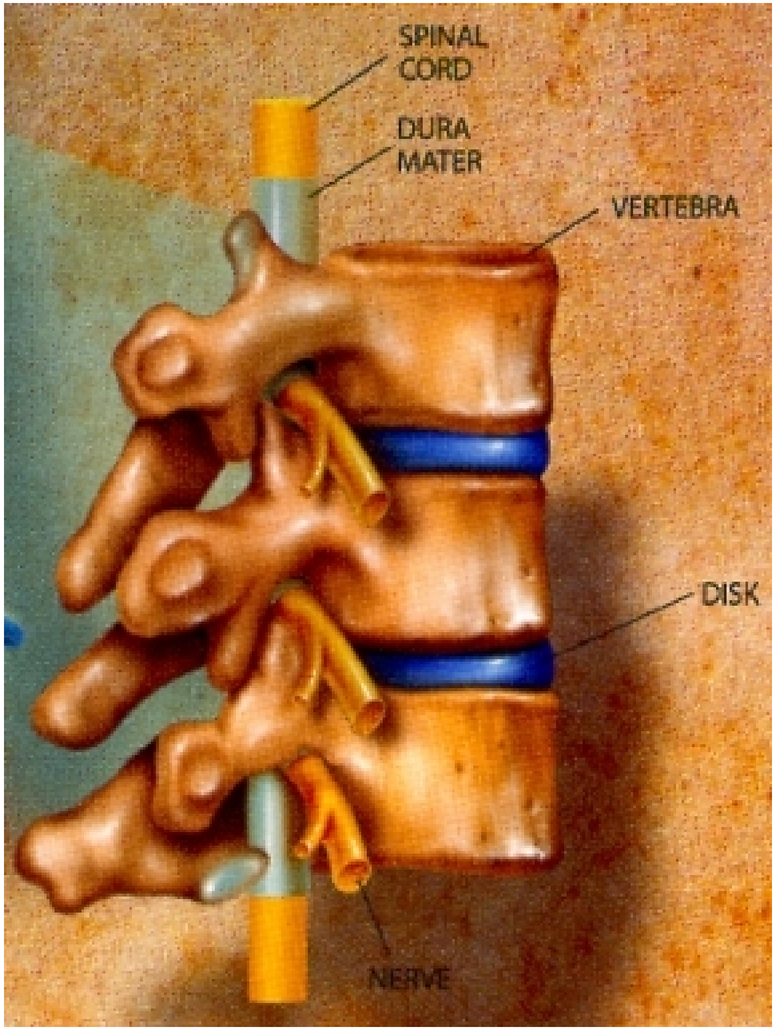


Hippocampus with many new neurons



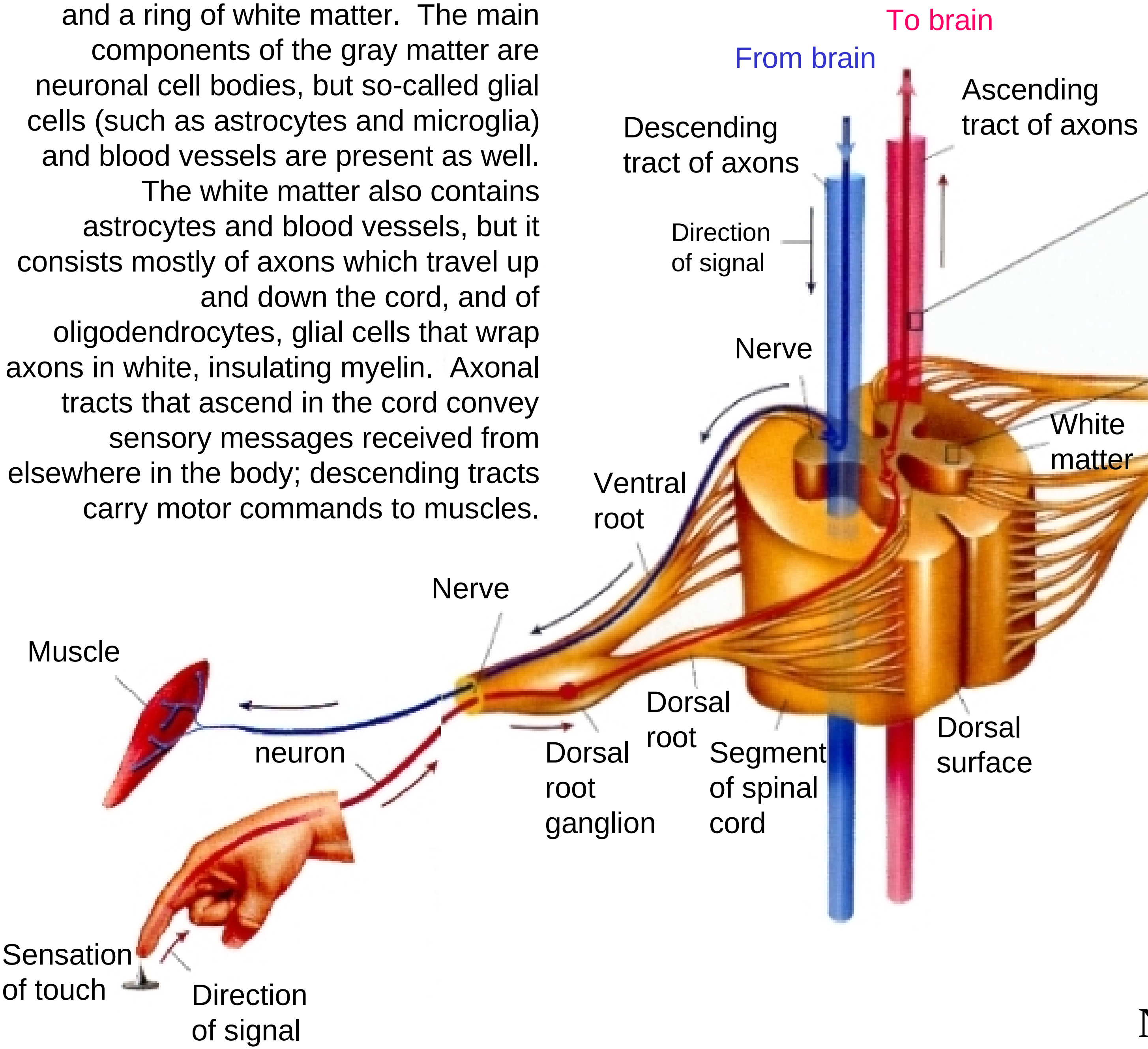
Hippocampus with few new neurons

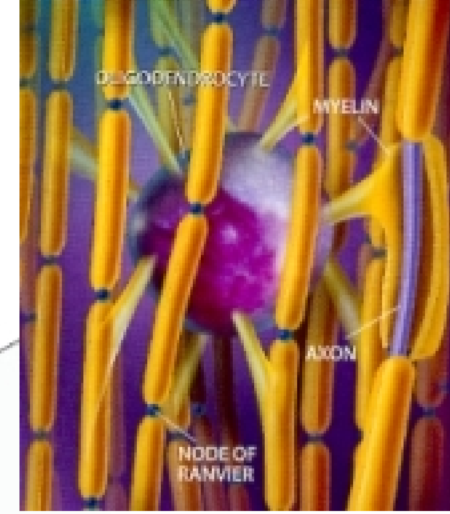




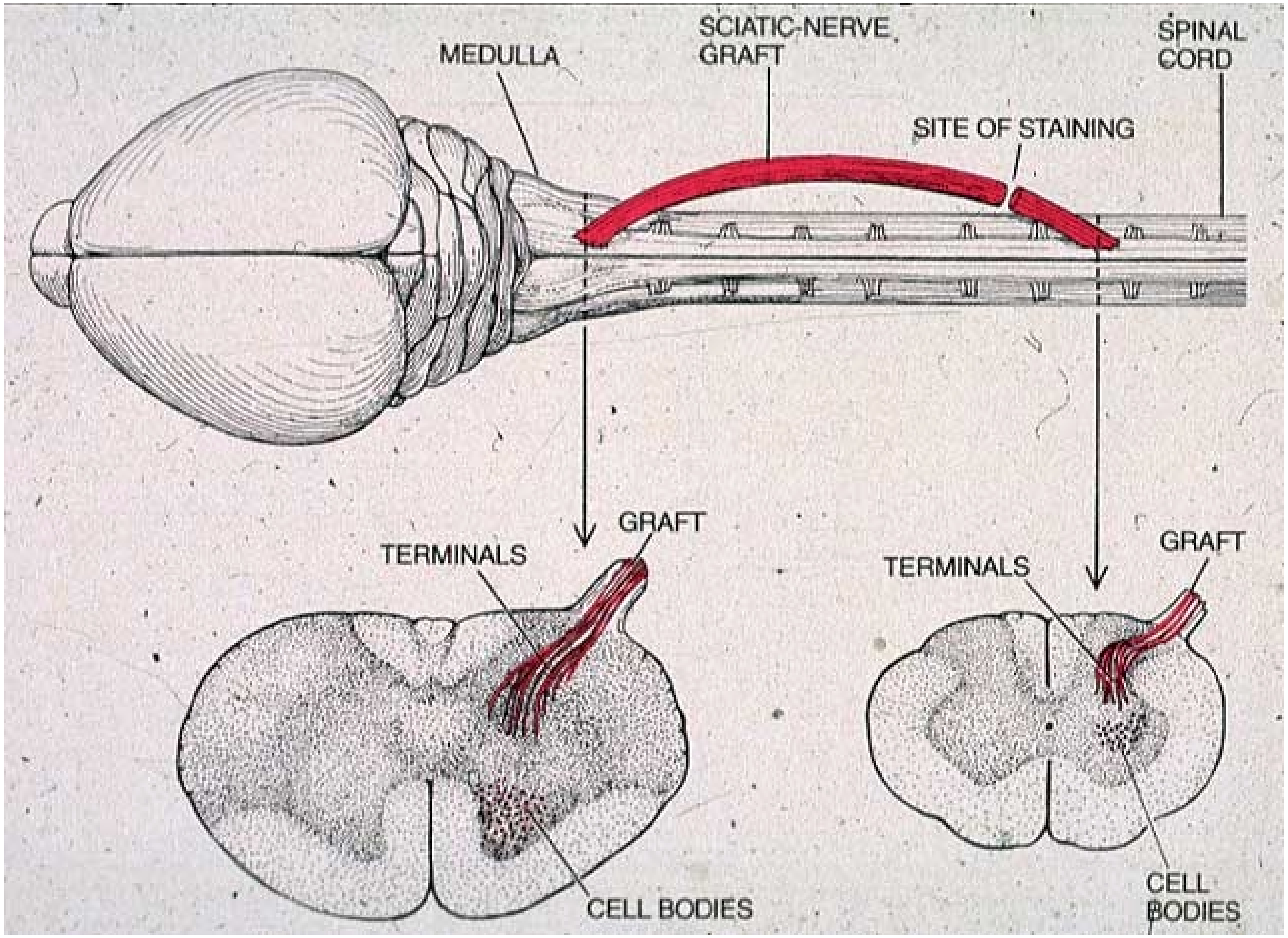
Neural Regeneration

Segment of spinal cord reveals the butterfly-shaped gray matter at the core and a ring of white matter. The main components of the gray matter are neuronal cell bodies, but so-called glial cells (such as astrocytes and microglia) and blood vessels are present as well. The white matter also contains astrocytes and blood vessels, but it consists mostly of axons which travel up and down the cord, and of oligodendrocytes, glial cells that wrap axons in white, insulating myelin. Axonal tracts that ascend in the cord convey sensory messages received from elsewhere in the body; descending tracts carry motor commands to muscles.



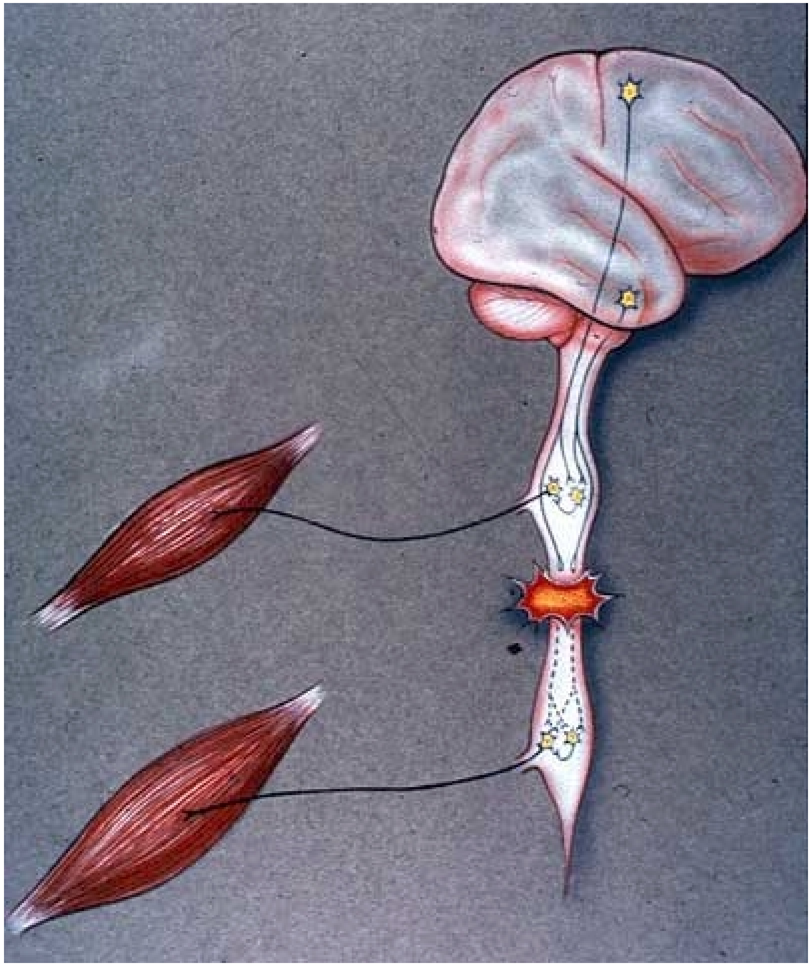


Neural Regeneration



Neural Regeneration

Neural Regeneration



Neural Regeneration

Targets for Therapy in Spinal Cord Injury

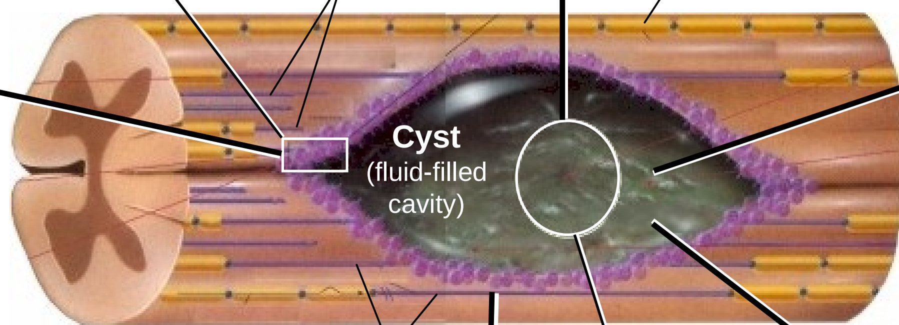
Glial scar

Prevent Expansion of Initial Damage

- Deliver agents that block excitotoxic injury to surving cells
- Administer compounds that prevent cell suicide of that bolster defenses of stressed cells

Promote Axon Regeneration

- Deliver agents to overcome natural inhibitors of regeneration and induce axonal growth
- Administer compounds that direct axons to their proper targets



Create Bridges

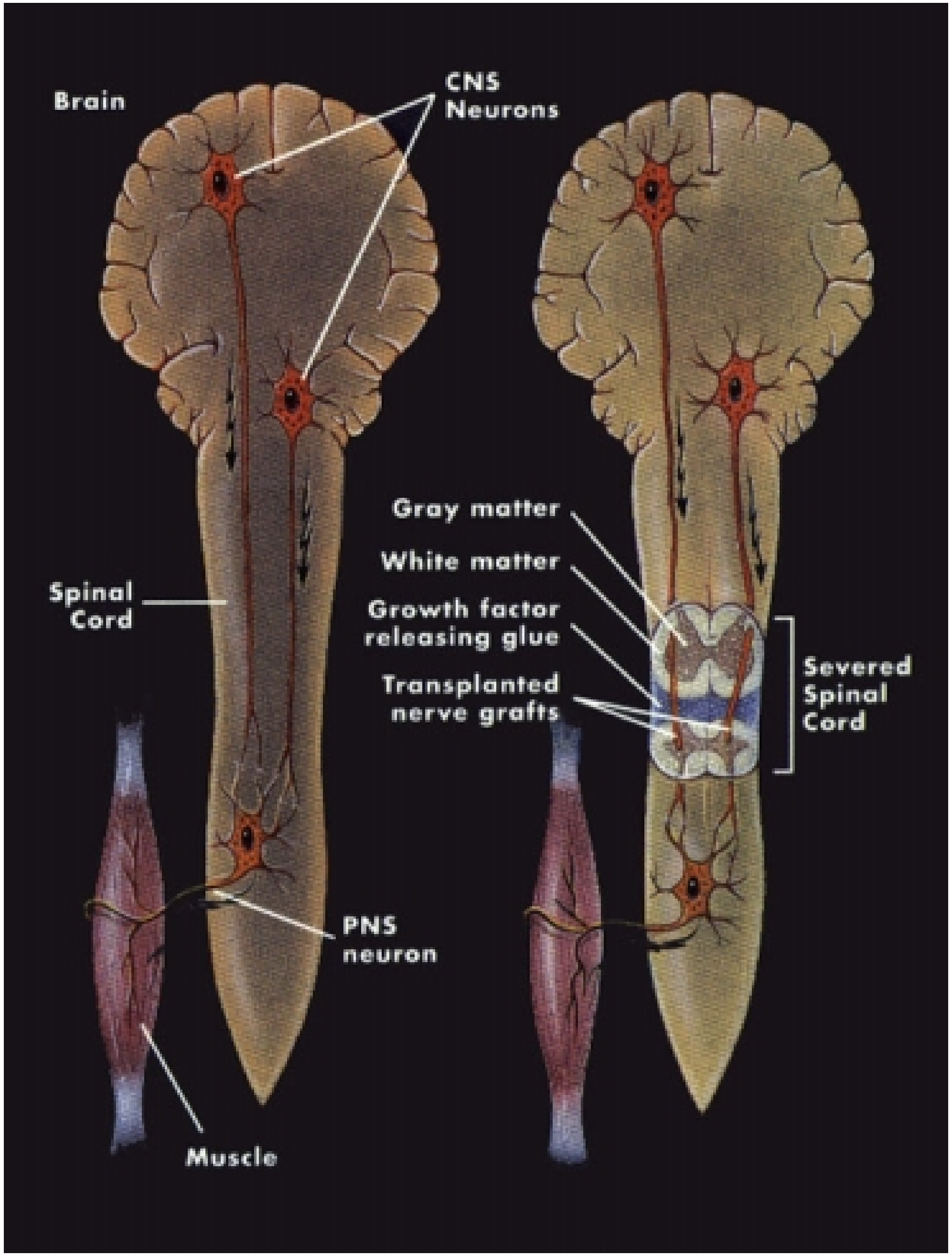
- Implant (into cyst) tissue that can serve as a scaffolding for axons and encourage them to grow

Compensate for Demyelination

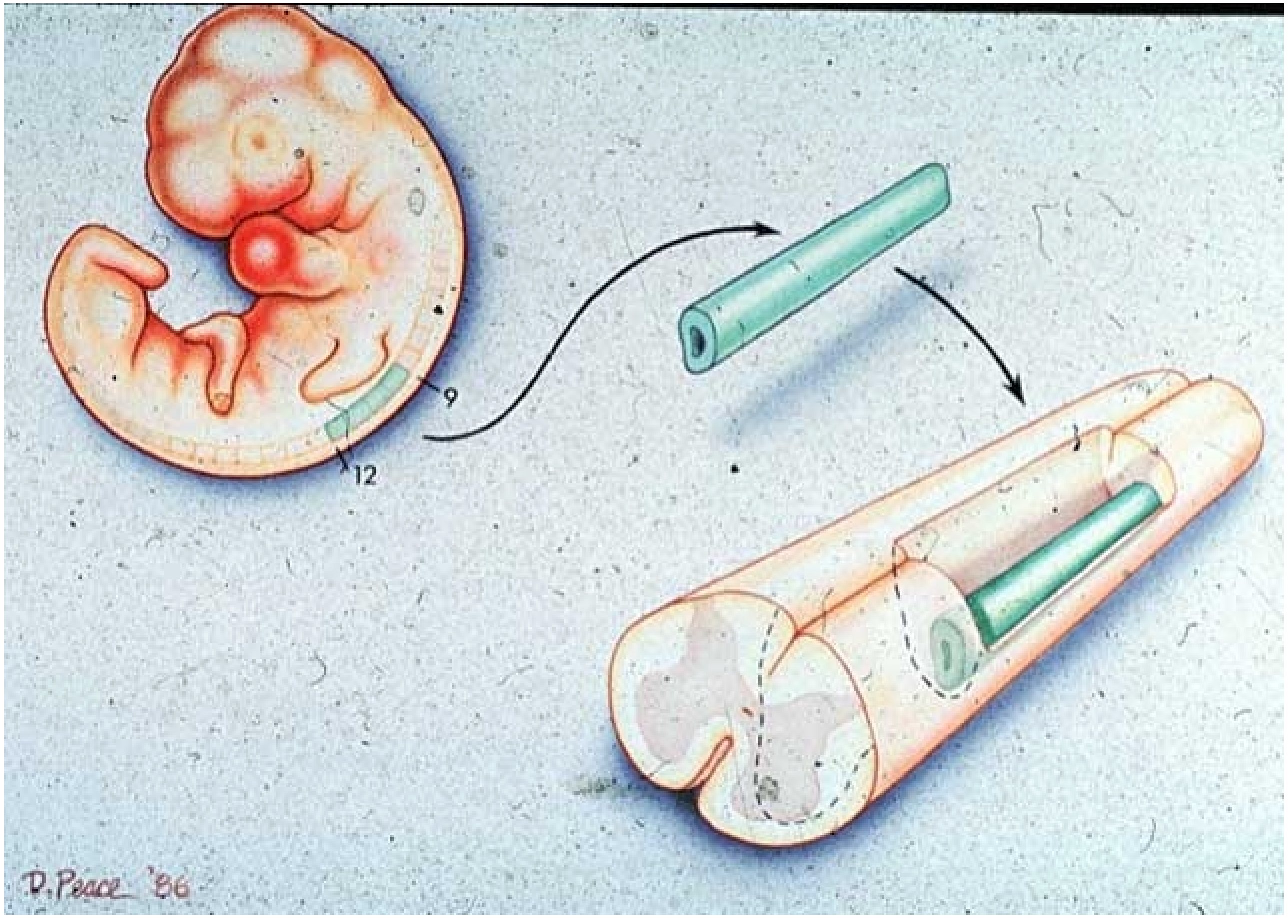
- Supply chemicals that prevent dissipation of impulses at demyelinated areas
- Provide agents to encourage oligodendrocytes to remyelinate axons
- Replenish lost oligodendrocytes

Replace Dead Cells

- Implant cells able to produce all the lost cell types
- Deliver substances that can induce undifferenttiated cells already in the cord to replace dead cells

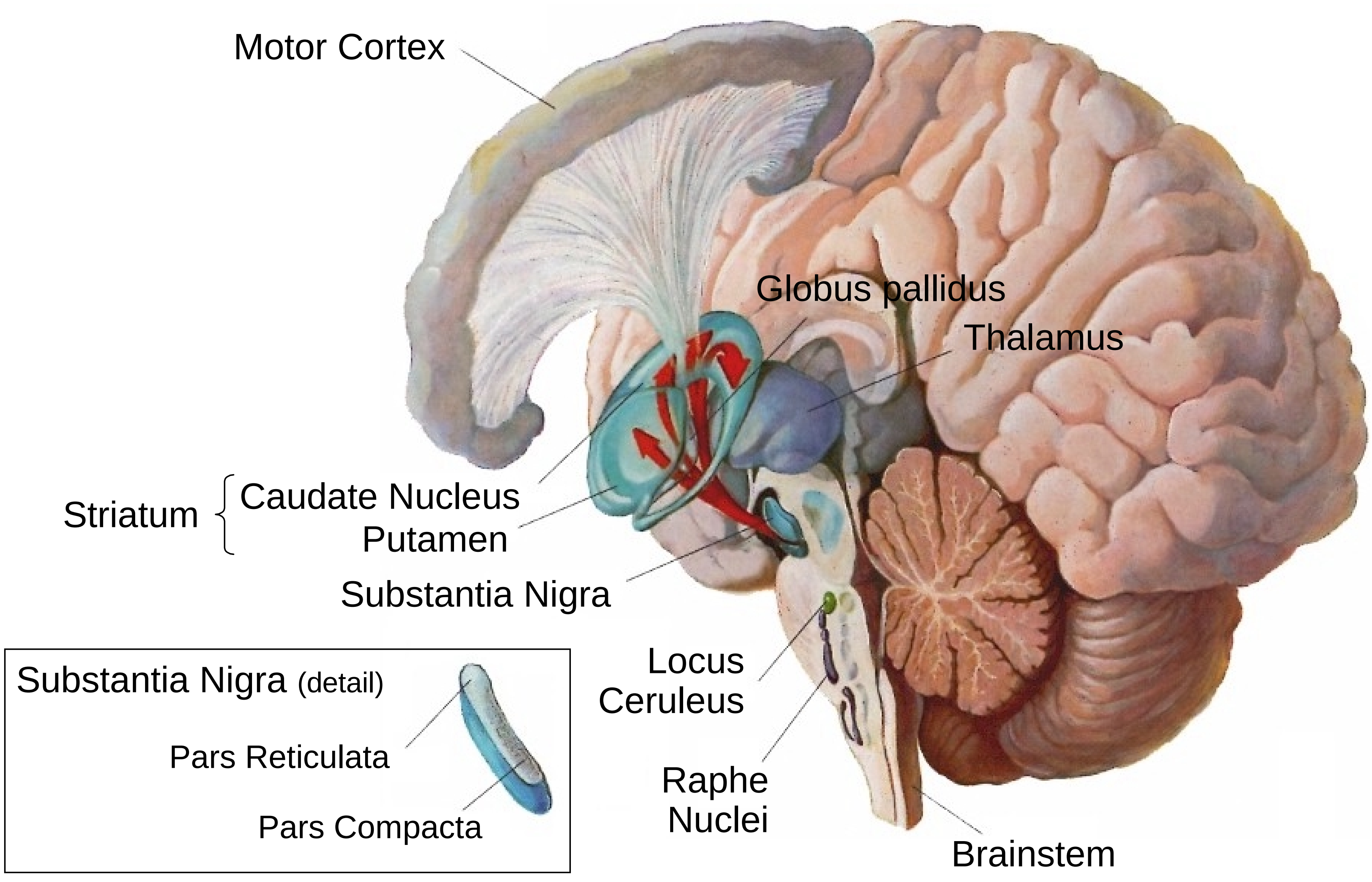


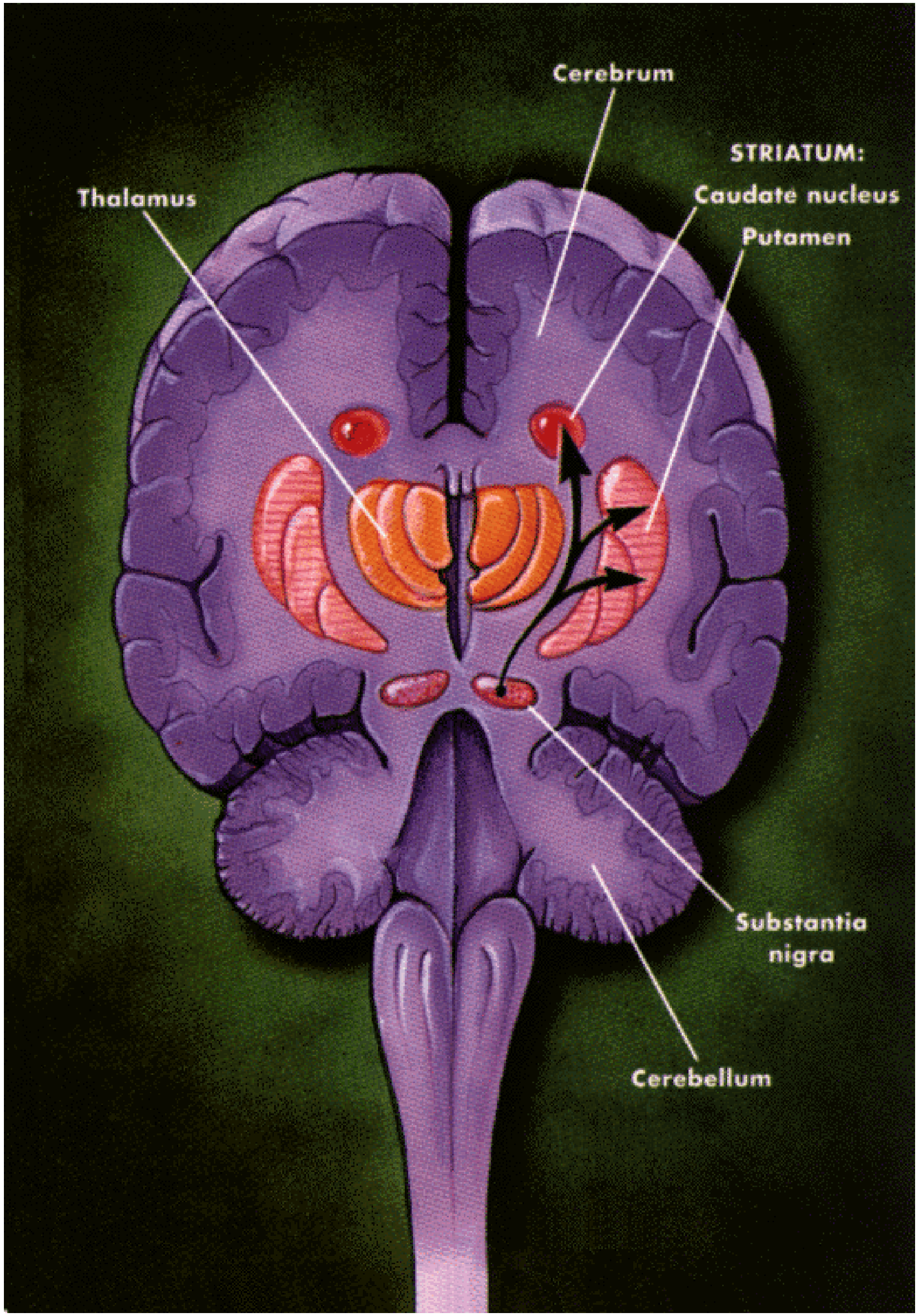
Neural Regeneration



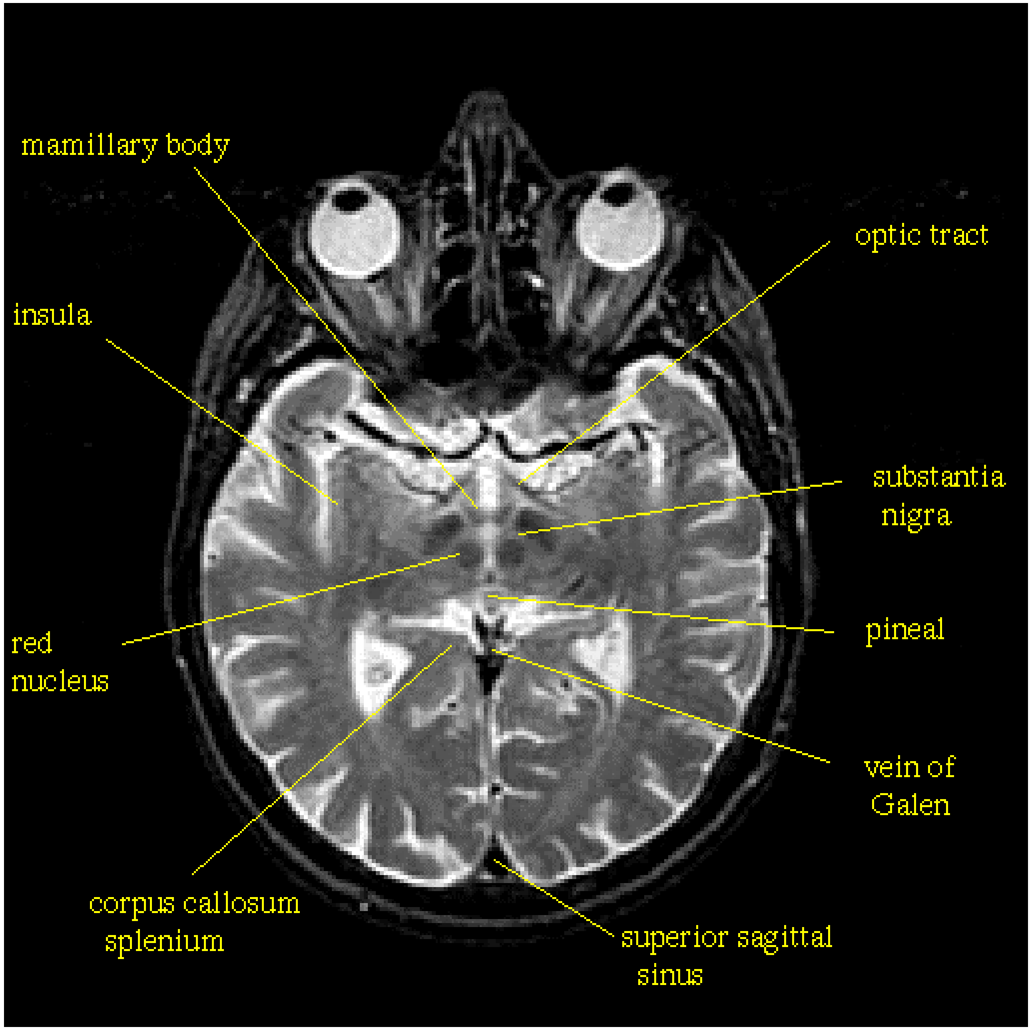
Neural Regeneration

Brain Regions Affected by Parkinson's Disease

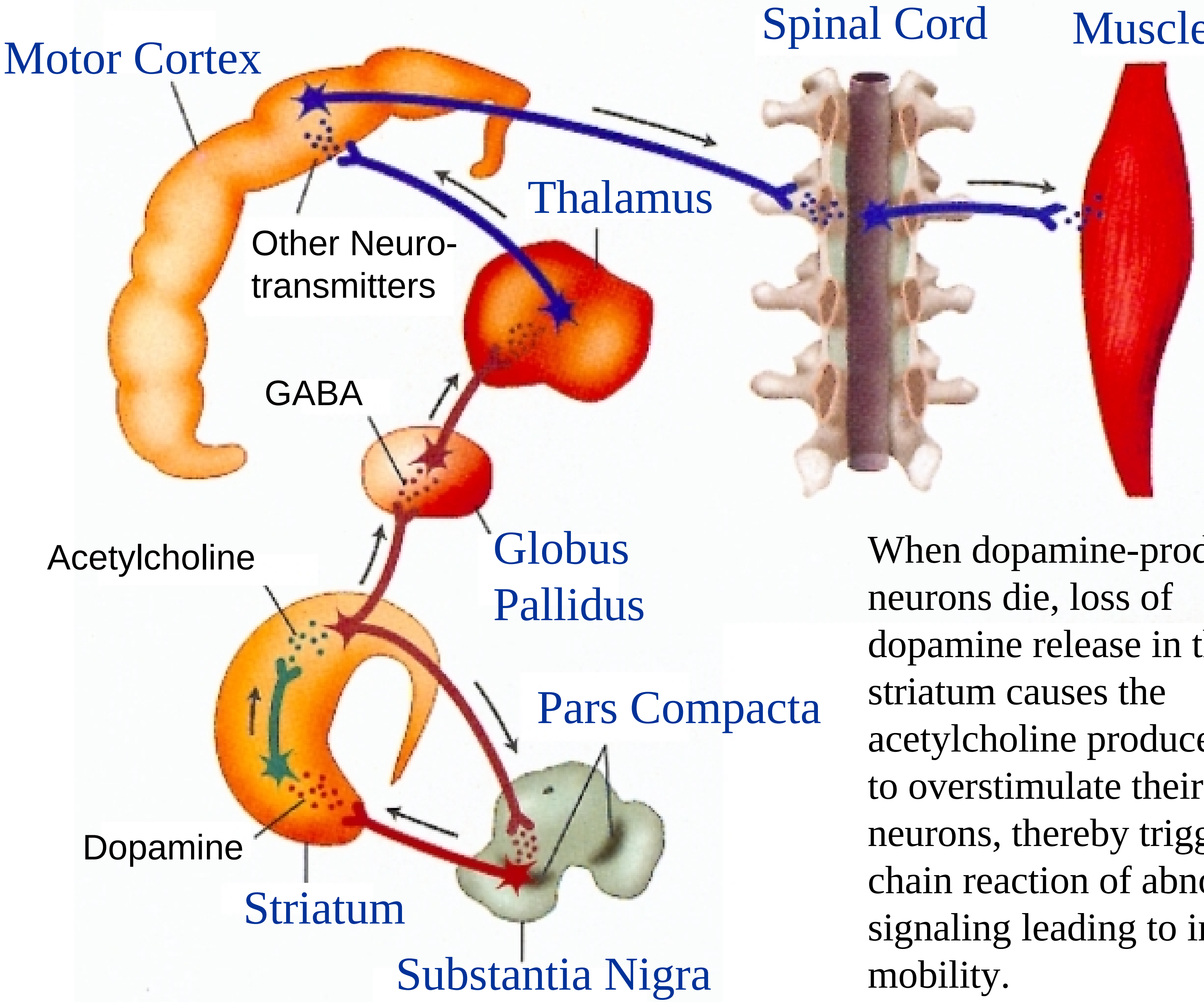




Parkinson’s disease



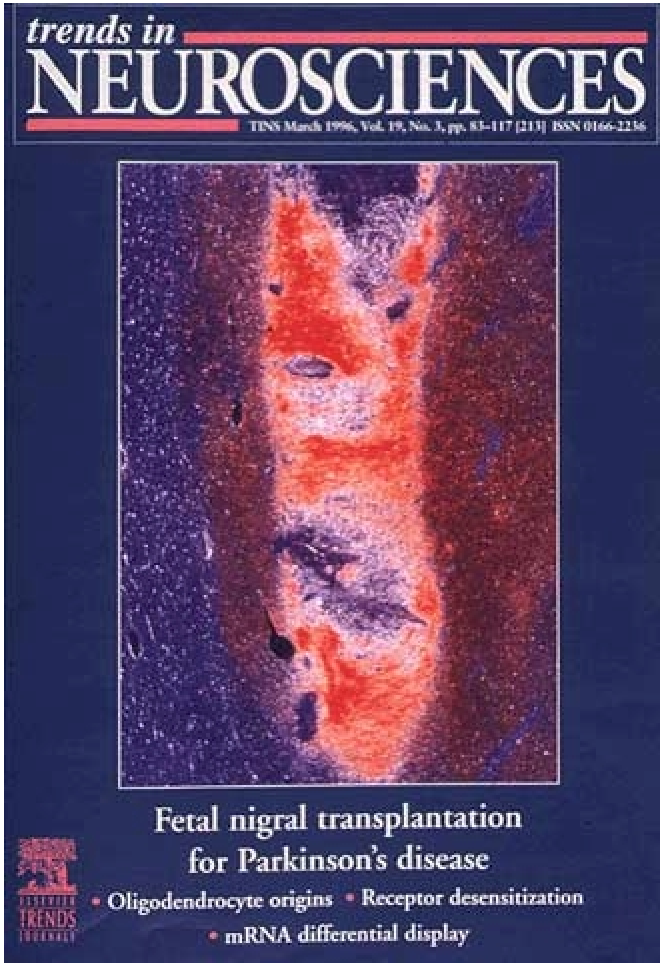
Parkinson’s disease

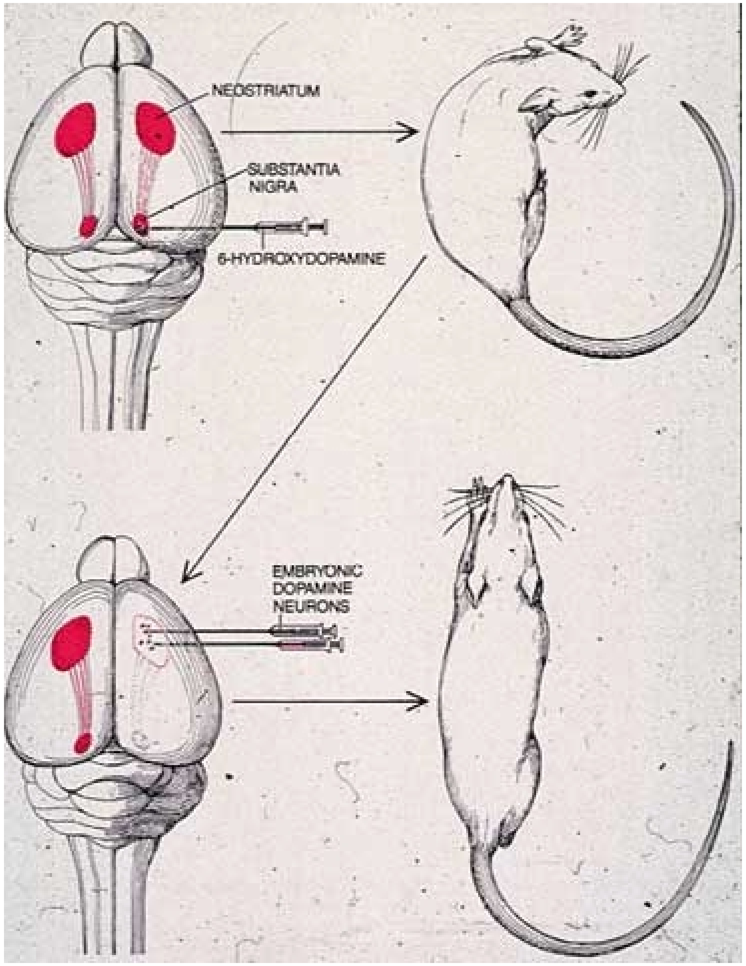


When dopamine-producing neurons die, loss of dopamine release in the striatum causes the acetylcholine producers there to overstimulate their target neurons, thereby triggering a chain reaction of abnormal signaling leading to impaired mobility.

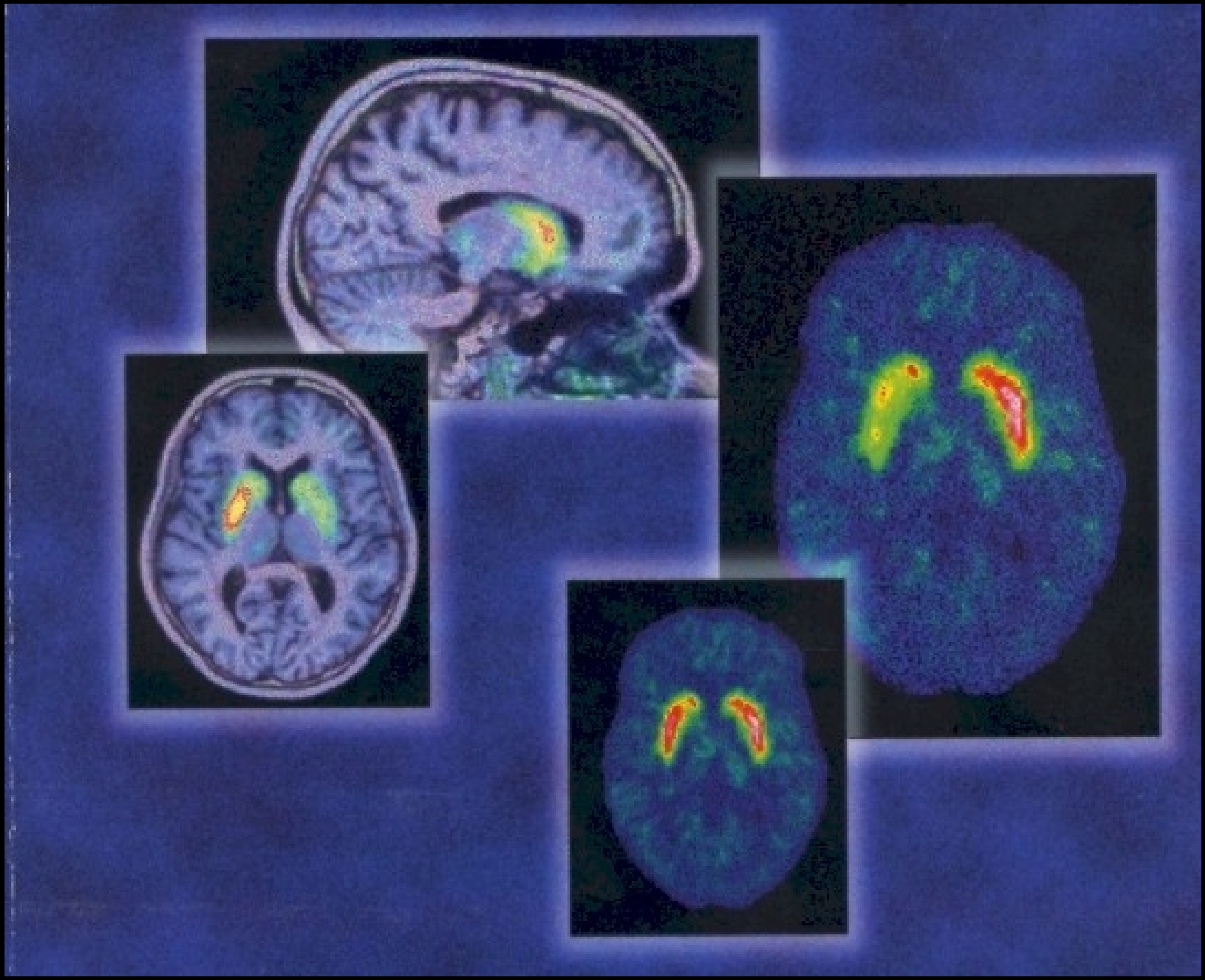
Parkinson's disease

So-called frozen addicts posed together in 1991, after having received treatment. Nine years earlier all suddenly became immobile, as if they had instantly acquired Parkinson's disease, after taking heroin containing an impurity, MPTP. Studies of how MPTP led to the freezing has generated many insights into the biochemical reactions that could contribute to a more classical presentation of the disease,

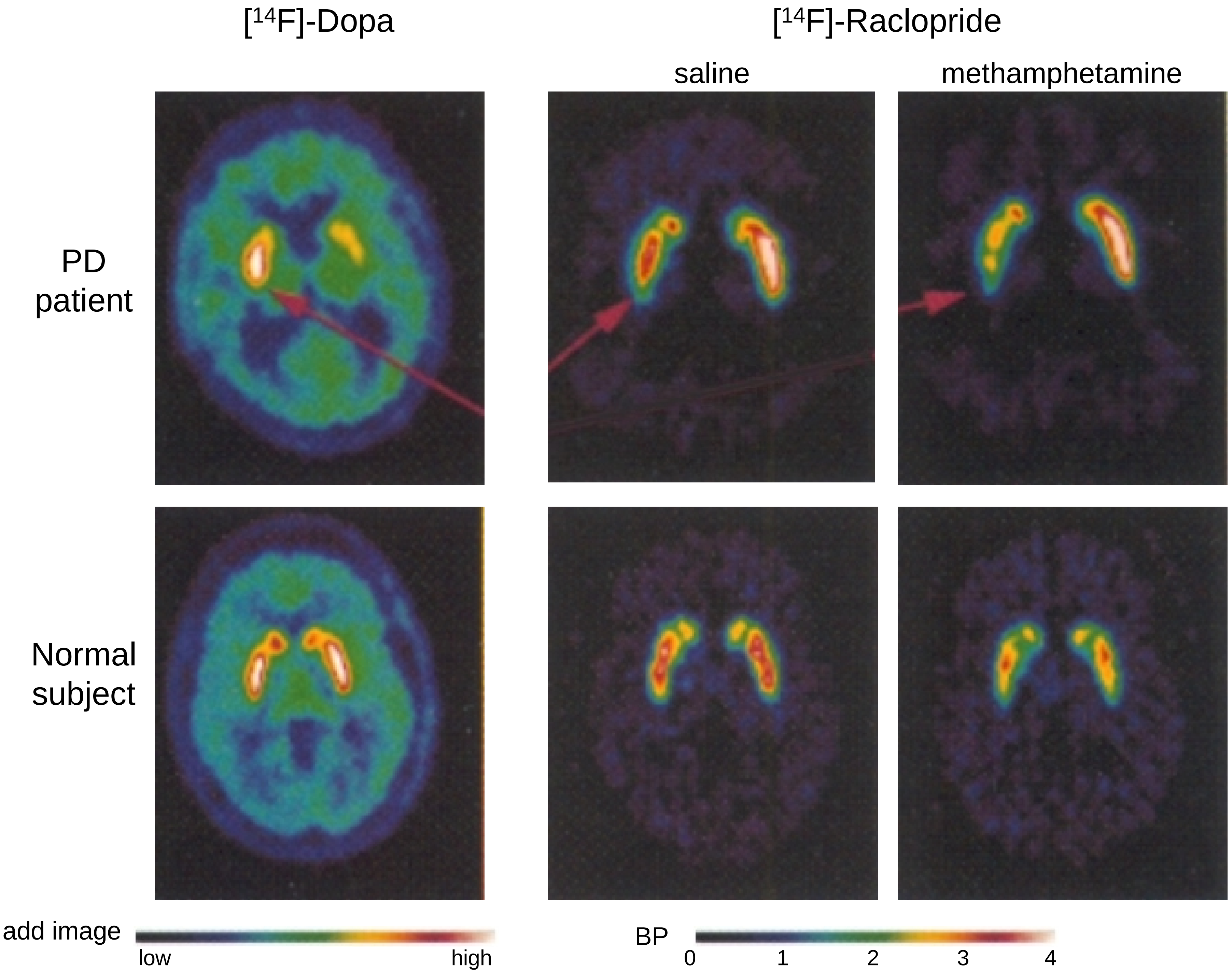


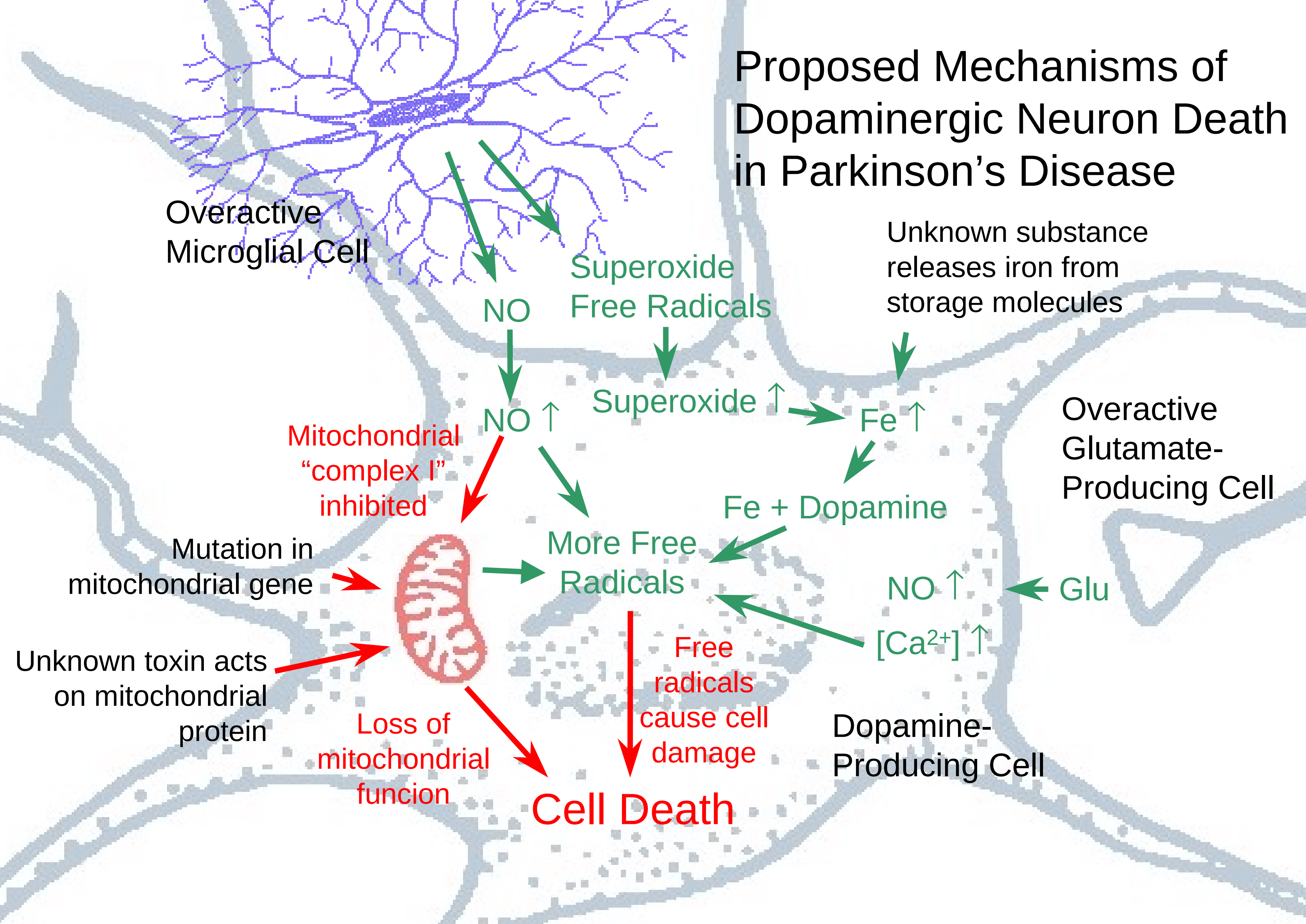


Parkinson's disease



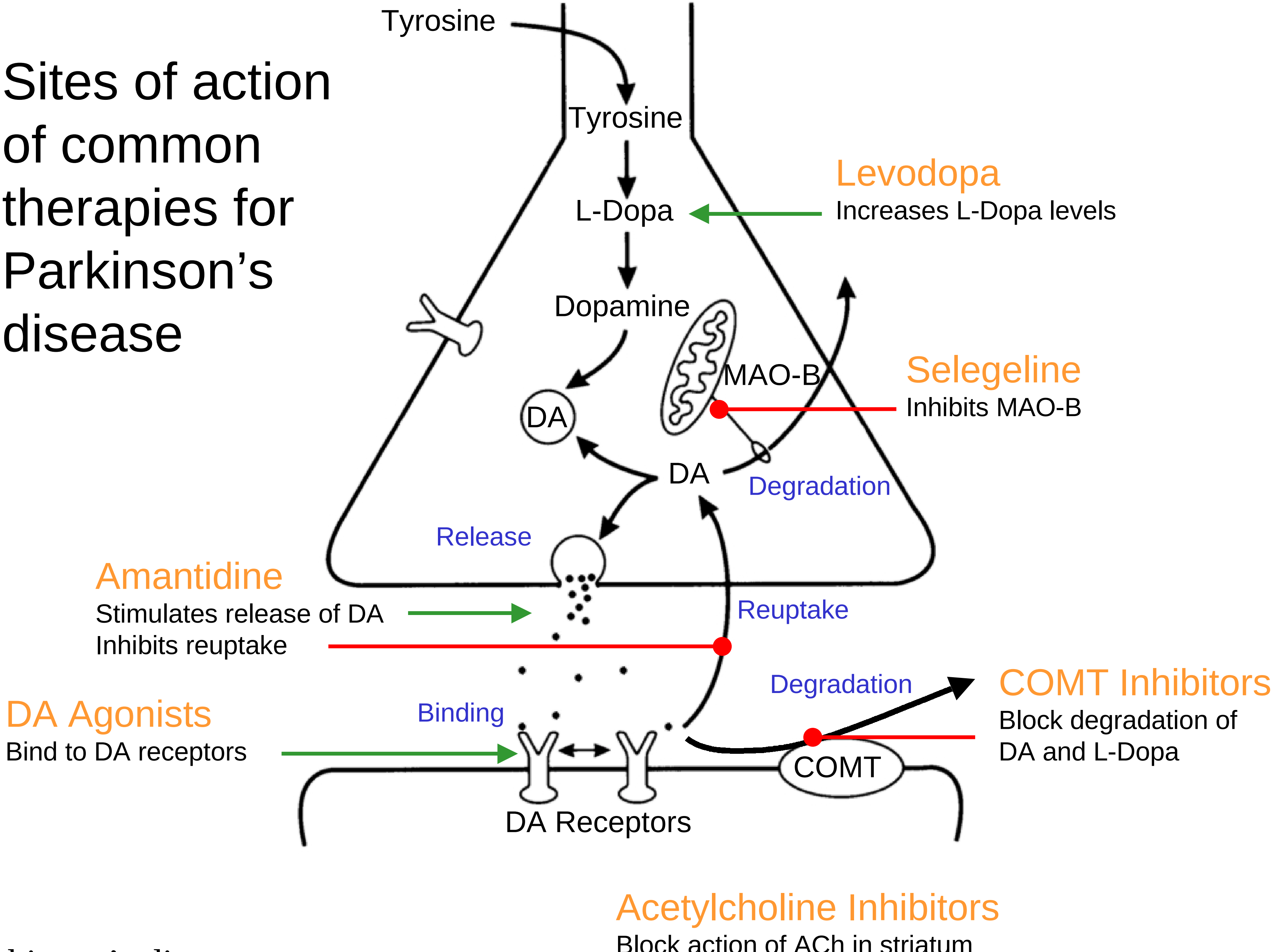
Functional imaging of dopamine release in a Parkinson’s patient ten years after dopaminergic mesencephalic neurons were transplanted into the striatum. Transplanted neurons were shown to release synaptically active dopamine in response to amphetamine stimulation.


[14F]-Dopa
[14F]-Raclopride
saline
methamphetamine
PD patient
Normal subject
add image
low
high
BP
0
1
2
3
4



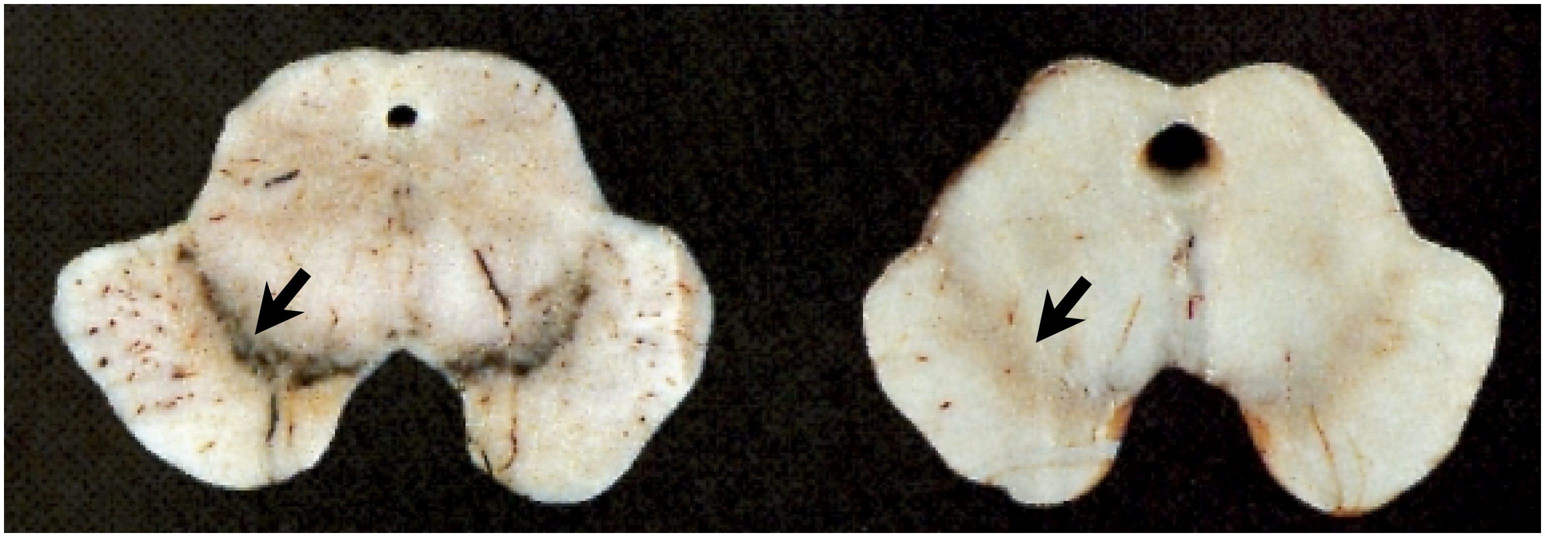
Parkinson's disease

Sites of action of common therapies for Parkinson's disease

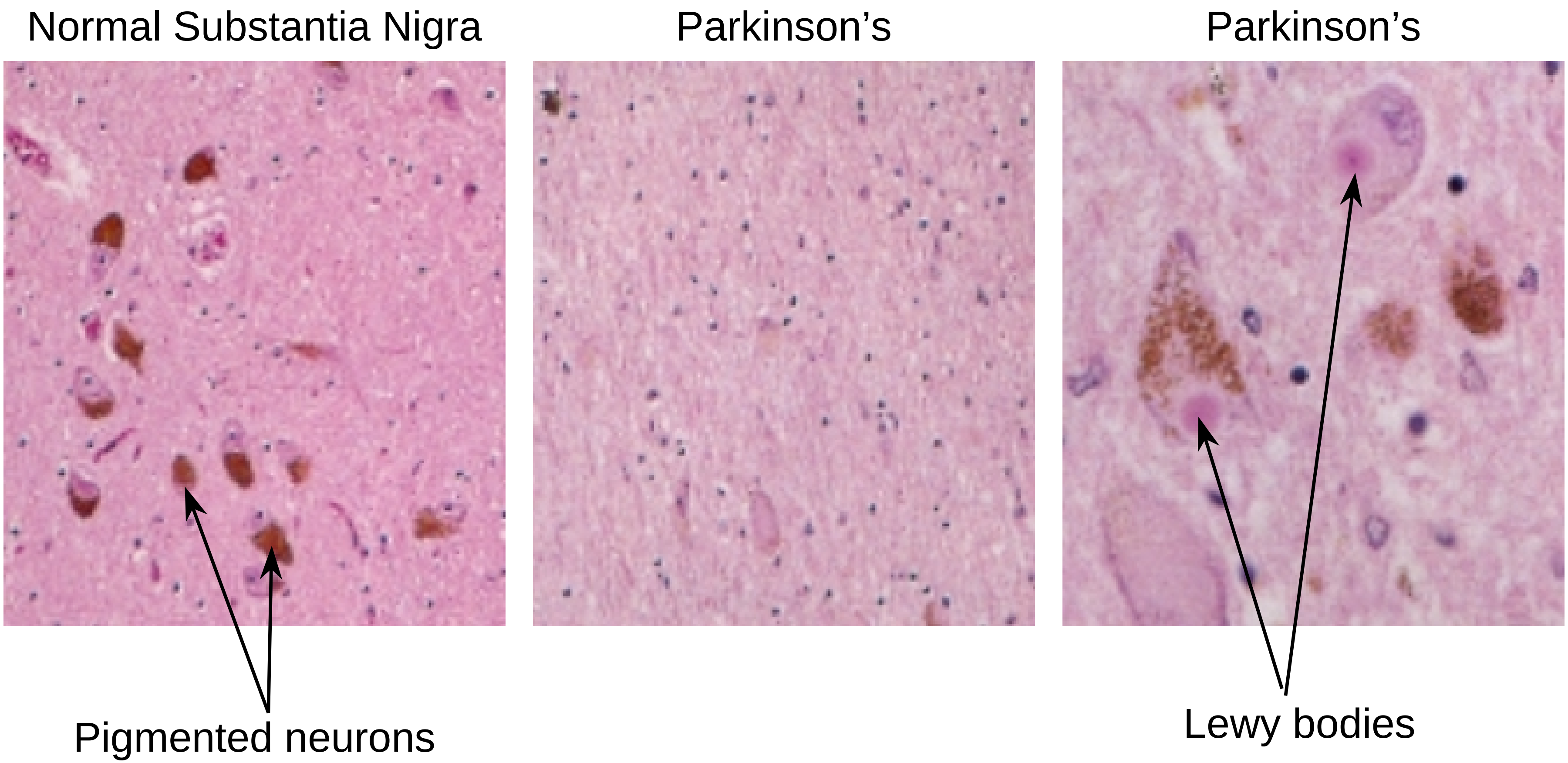


Parkinson’s disease

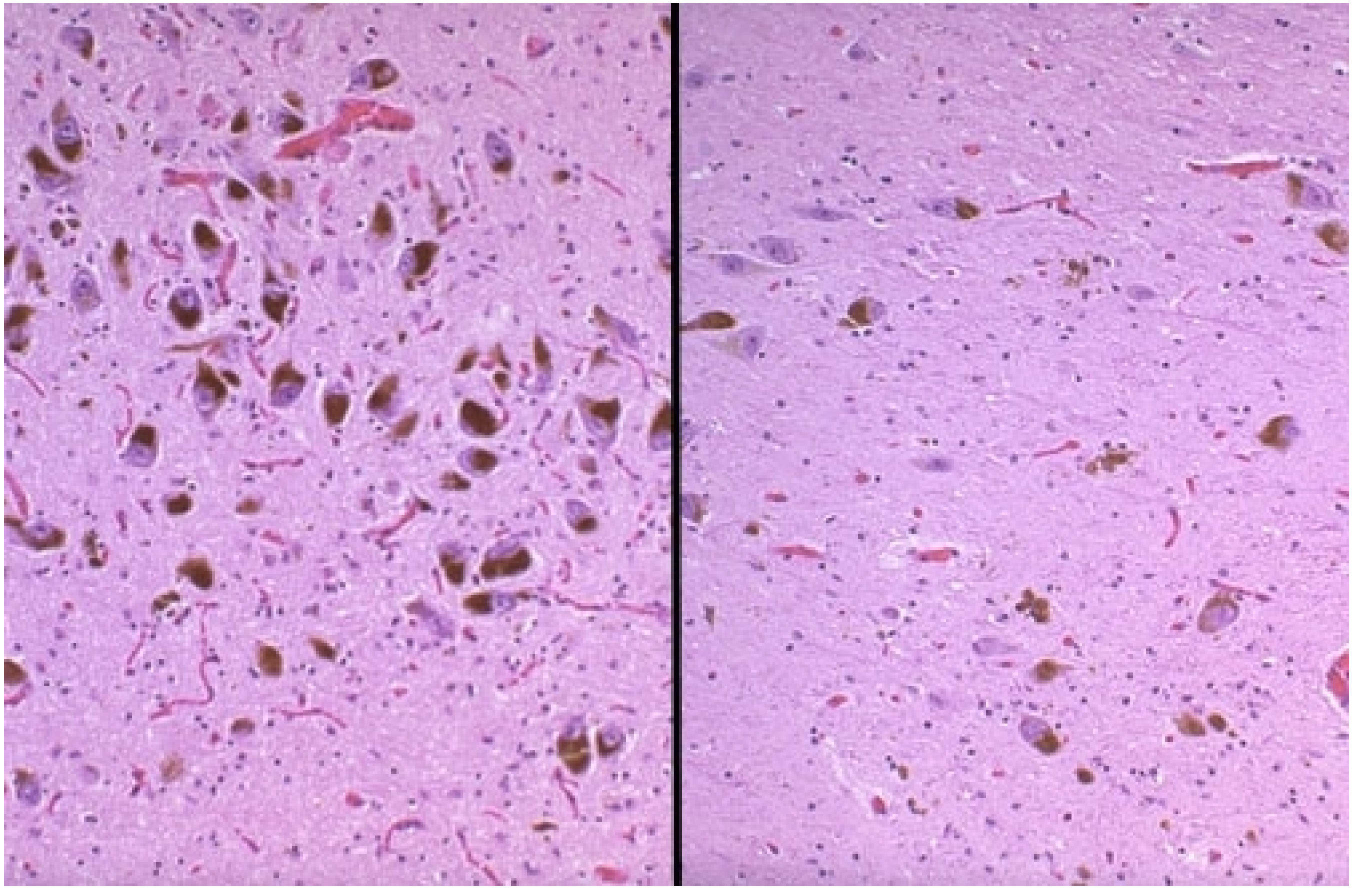
Normal Parkinson’s



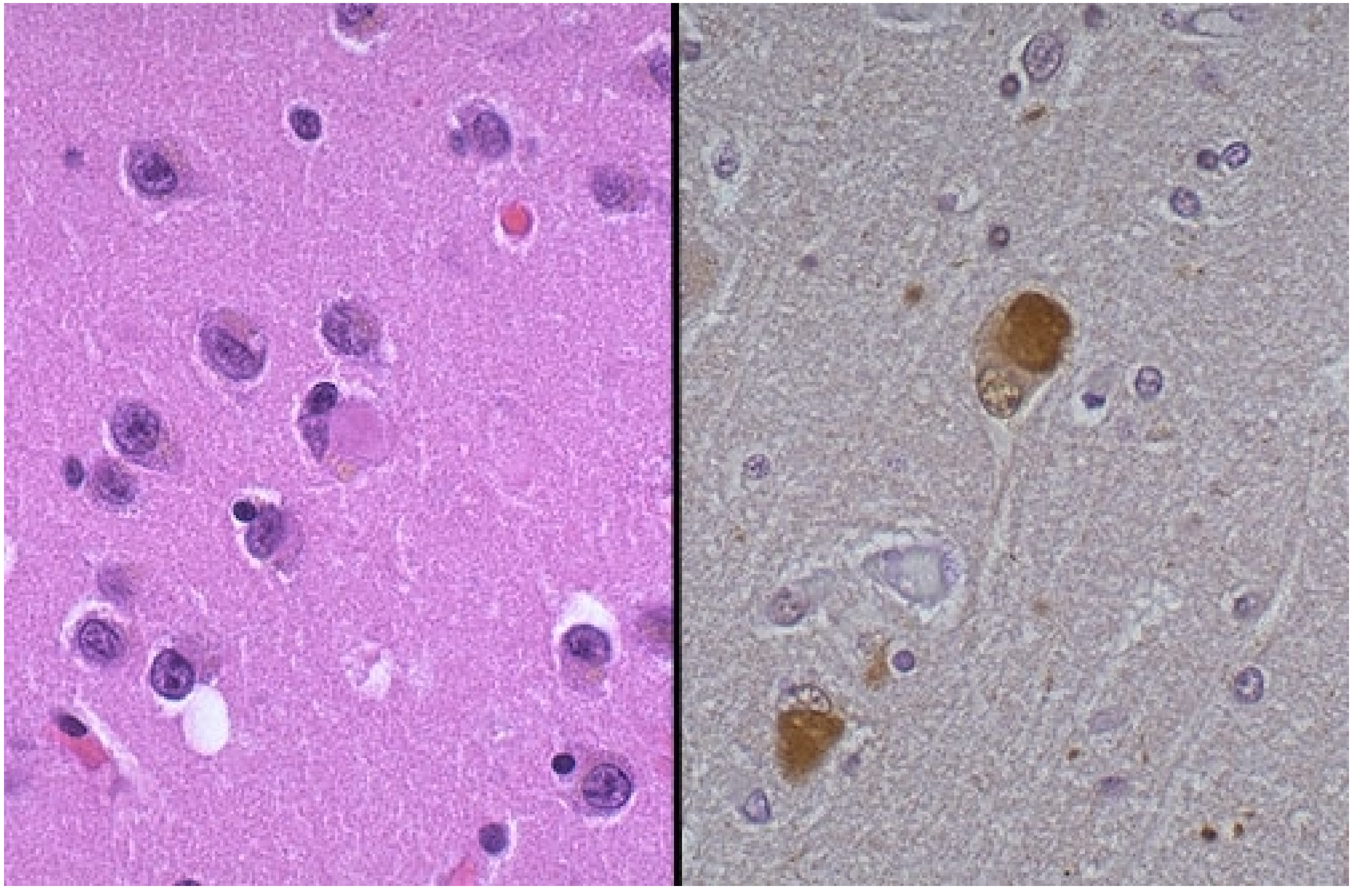
The pars compacta region of the substantia nigra in the normal brain appears dark because dopamine-producing neurons are highly pigmented; as neurons die from Parkinson’s disease, the color fades.



Parkinson's disease



At the left, normal numbers of neurons in the subtantia nigra are pigmented. At the right, there is loss of neurons and loss of pigmentation with Parkinson's disease.



At the left, an H and E stain demonstrates a rounded pink cytoplasmic Lewy body in a neuron of the cerebral cortex from a patient with diffuse Lewy body disease, which can be a cause for dementia. Lewy bodies can also be seen in substantia nigra with Parkinson's disease. An immunoperoxidase stain for ubiquitin, seen at the right, helps demonstrate the Lewy bodies more readily.

Parkinson’s disease

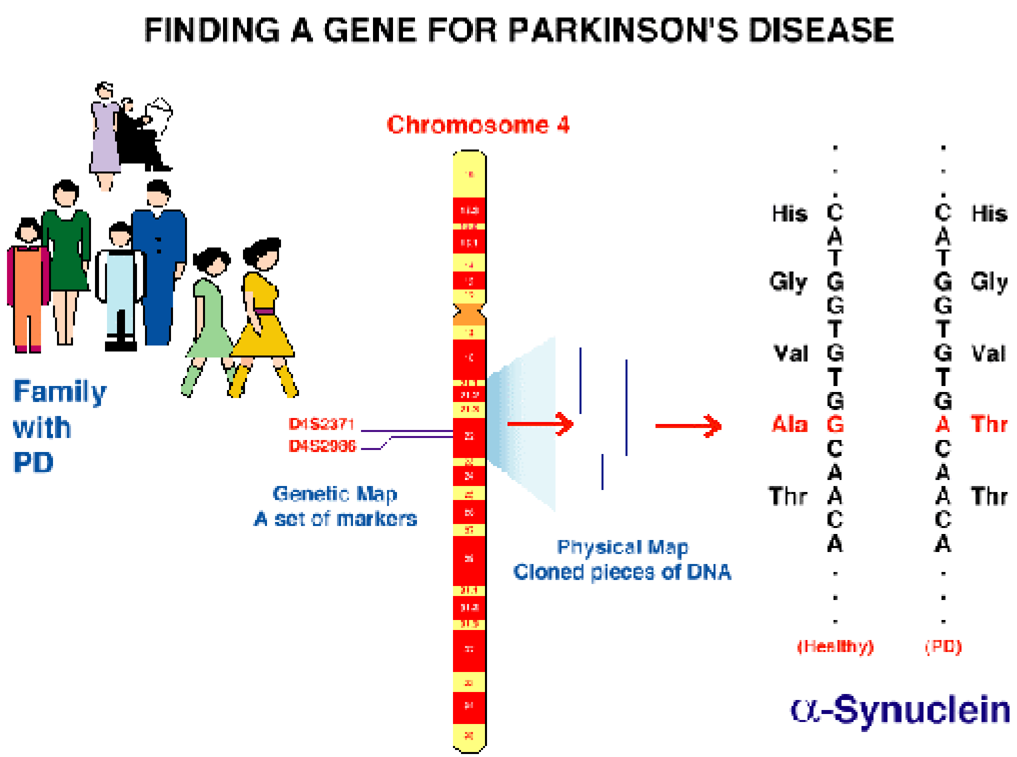
Rhythmic tremor often occurs at first in one hand, where it resembles the motion of rolling a pill between the thumb and forefinger

Leaning forward or backward when upright reflects impairment of balance and coordination.

Muscle rigidity shows itself in the cogwheel phenomenon: pushing on an arm causes it to move in jerky increments instead of smoothly.

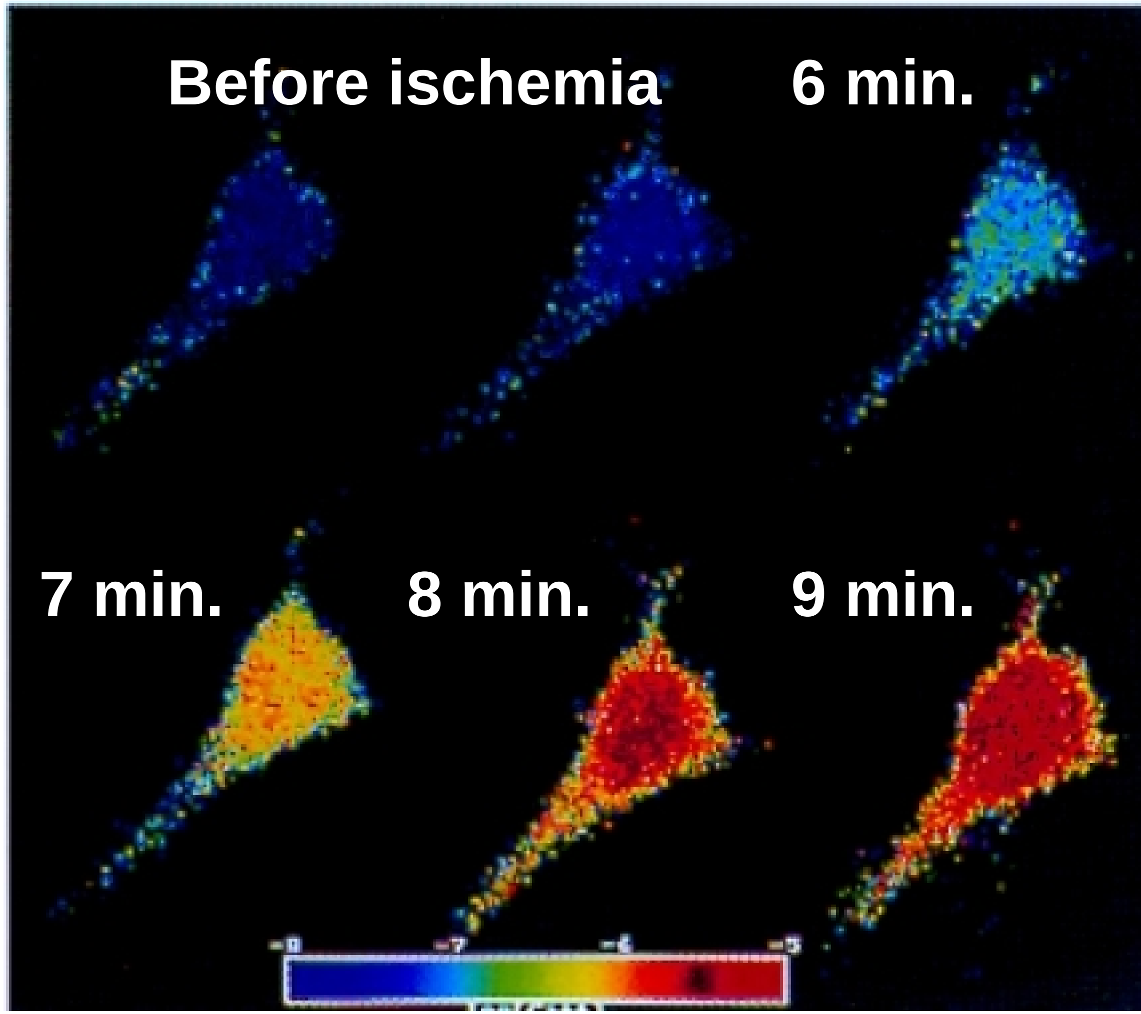
Difficulty rising from a sitting position is a common sign of disordered control over movement. Some patients report feelings of weakness and of being constrained by ropes or other forces.

Parkinson’s disease



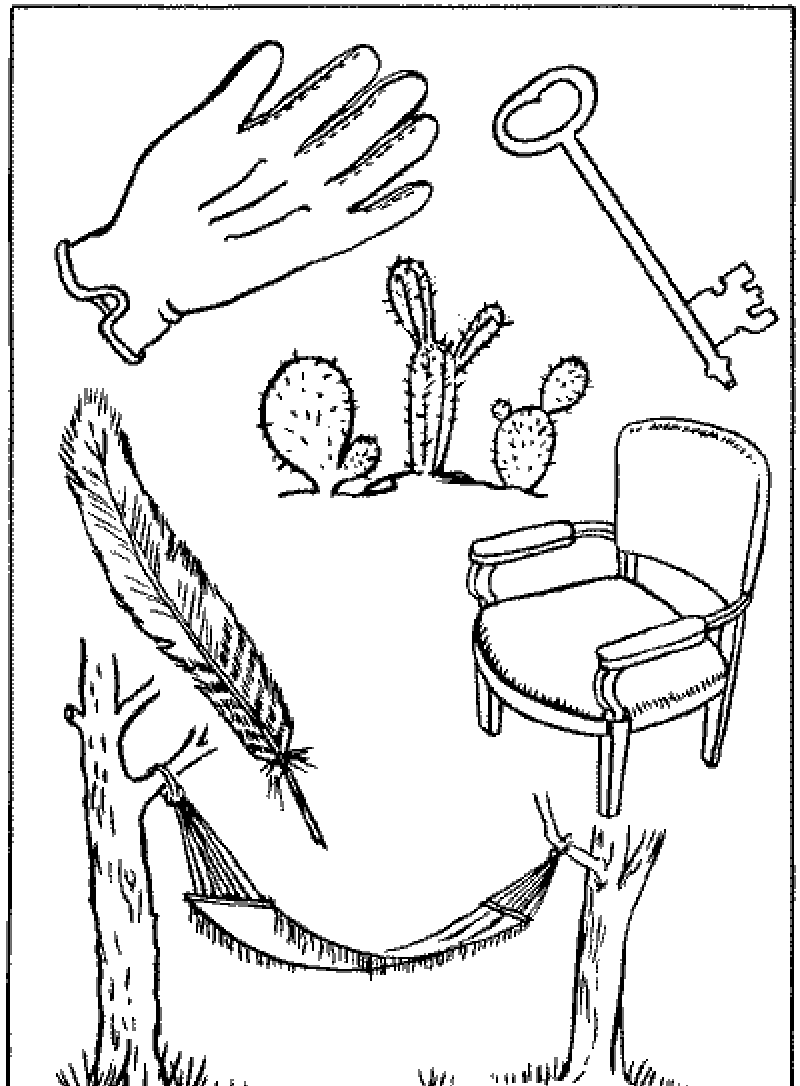
Parkinson’s disease

A pyramidal cell in the CA1 region of a rat hippocampal slice was loaded with fluo-3/fura red mixture. The neuron was then visualized using confocal laser scanning microscopy, and the ratio of the fluorescence from each probe was used to quantify intracellular calcium concentrations before and during 6, 7, 8 and 9 minutes of ischemia. Intracellular calcium increased from 60 nM to about 30 μM, *i.e.* 500 fold.

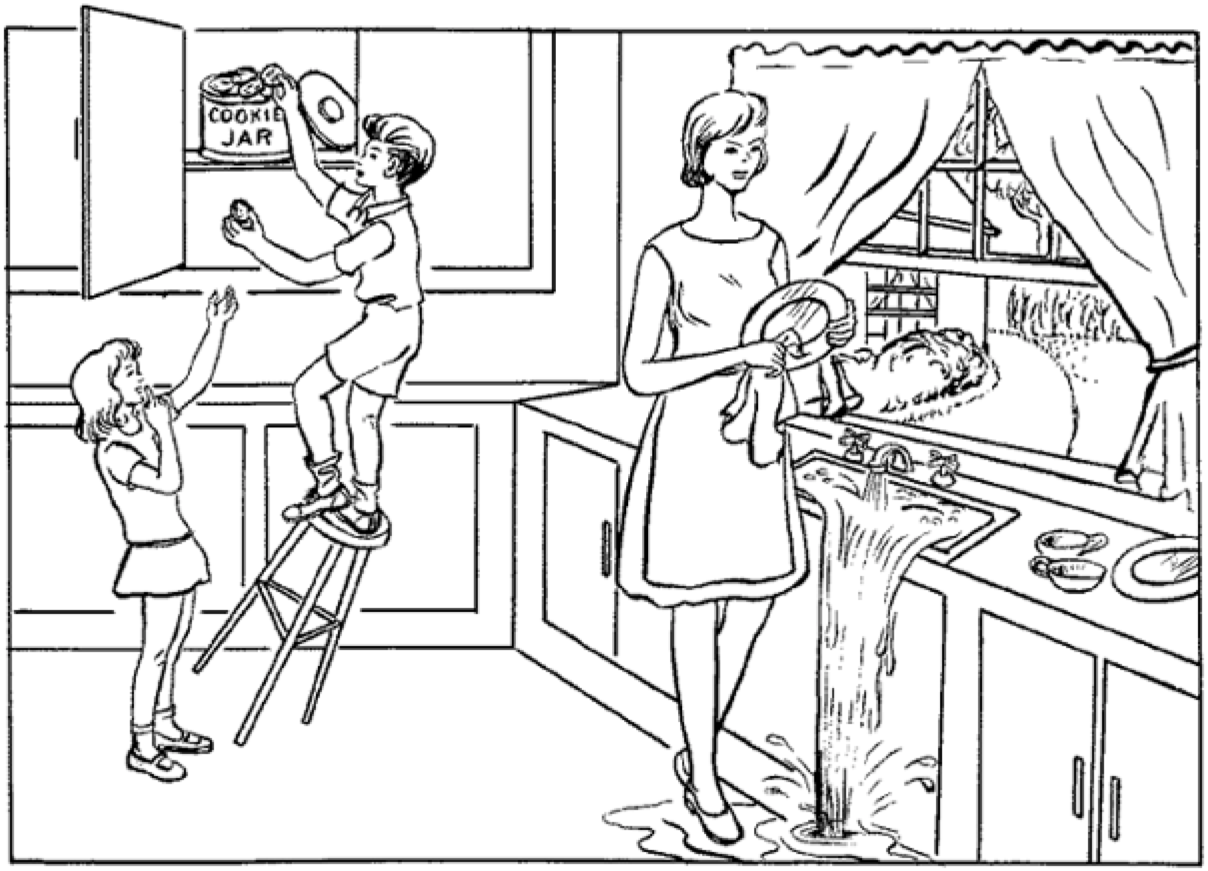


Increasing $[Ca^{2+}]$ →

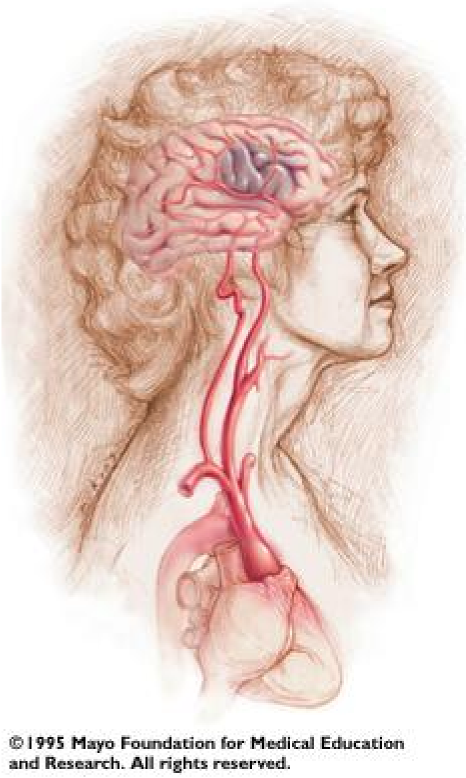
Stroke



Stroke



Stroke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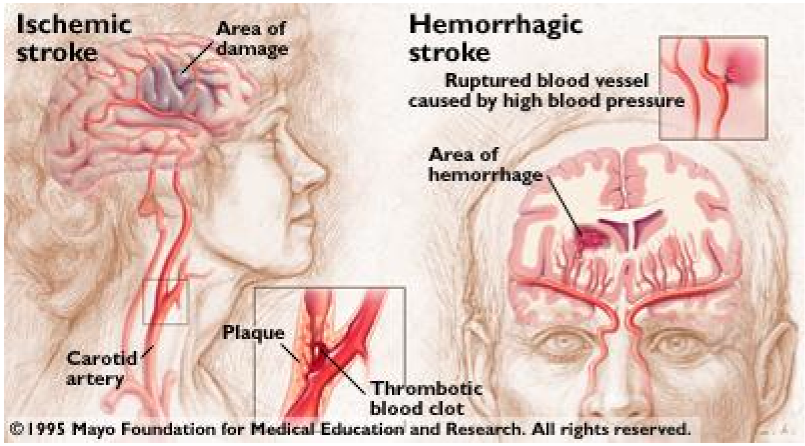
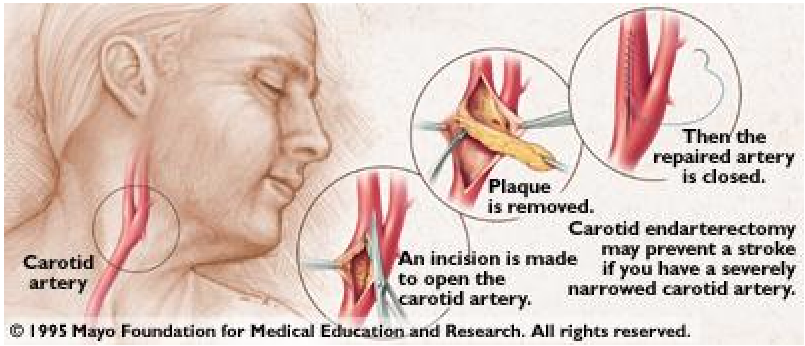
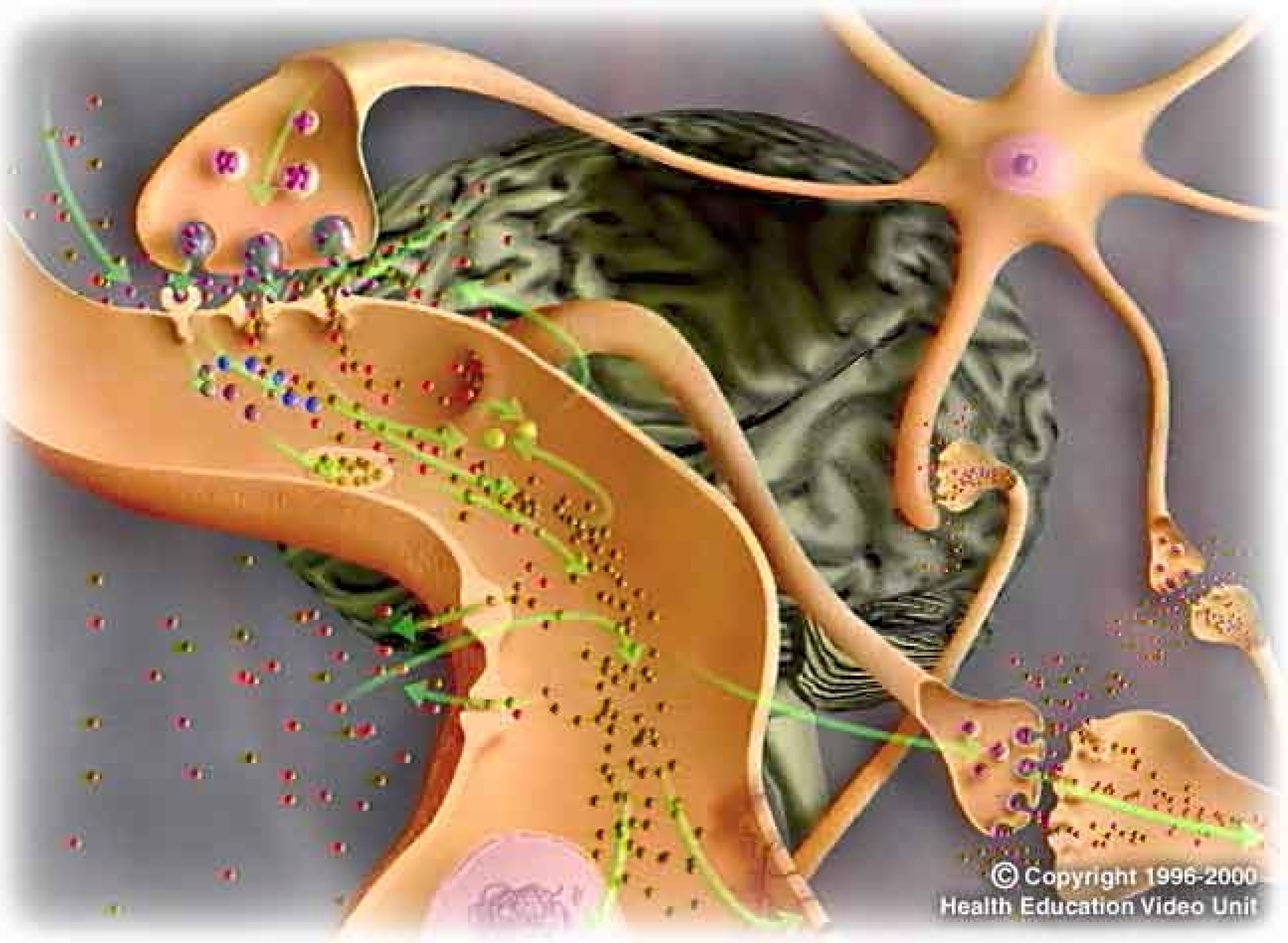

Ischemic stroke
Area of damage
Carotid artery
Plaque
Thrombotic blood clot
Hemorrhagic stroke
Ruptured blood vessel caused by high blood pressure
Area of hemorrhage
©1995 Mayo Foundation for Medical Education and Research. All rights reserved.

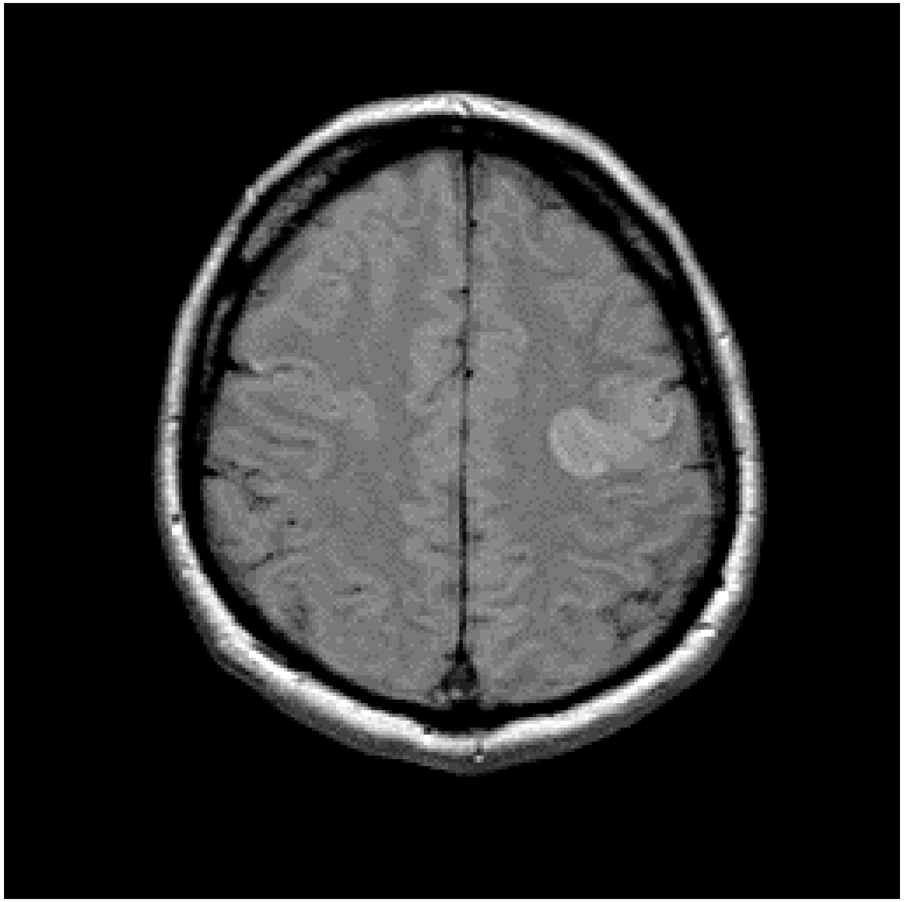

Carotid artery
An incision is made to open the carotid artery.
Plaque is removed.
Then the repaired artery is closed.
Carotid endarterectomy may prevent a stroke if you have a severely narrowed carotid artery.
© 1995 Mayo Foundation for Medical Education and Research. All rights reserved.

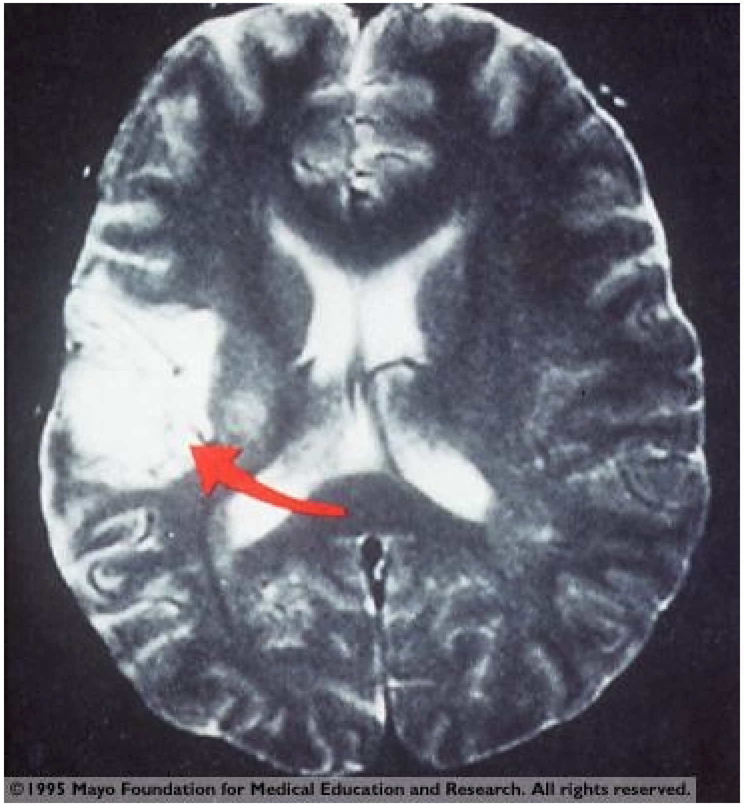
Stroke



Stroke

Stroke

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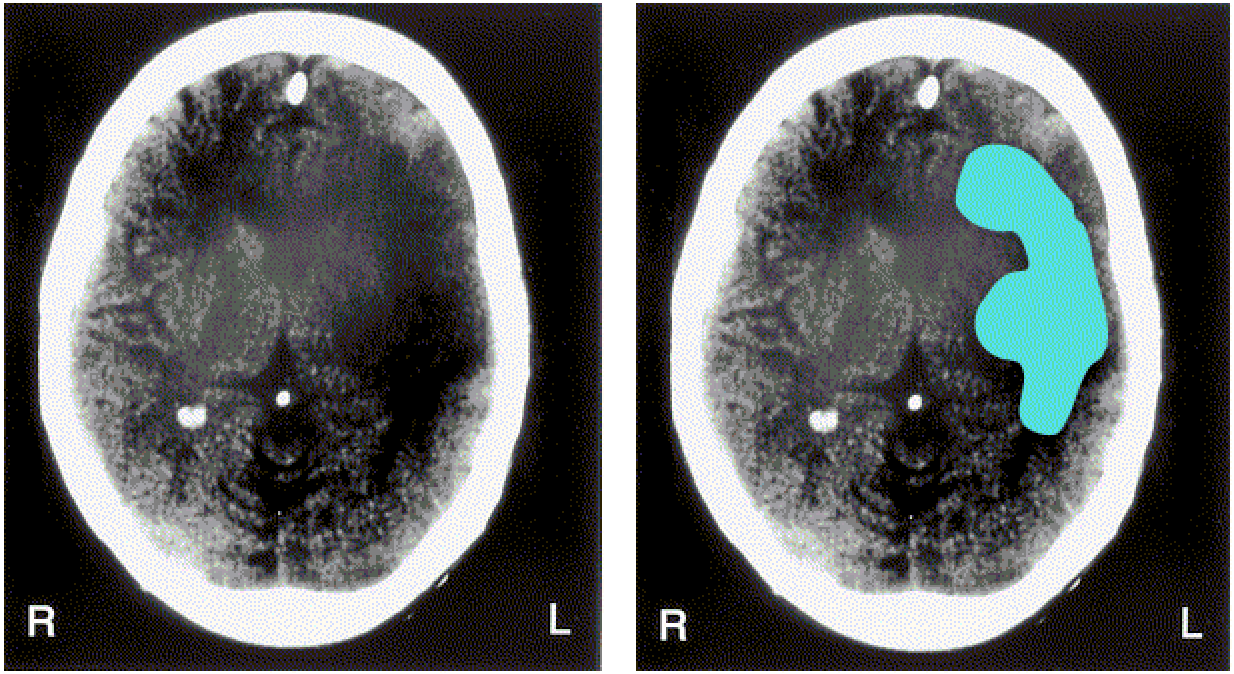
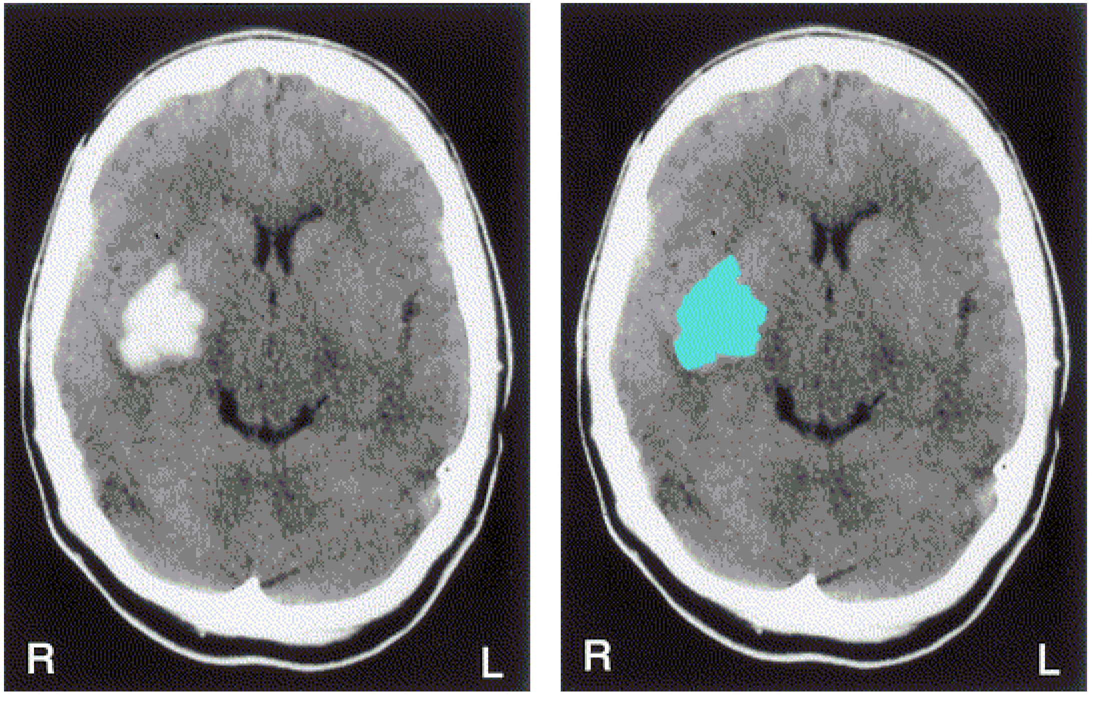
Stroke

Obvious findings of cerebral infarction on CT scan. A CT scan of the brain shows a large left middle cerebral infarct, indicated by the hypodensity or dark color (a); the size of the infarct is indicated by the blue color (b). This infarct will be associated with a contralateral hemiplegia, homonymous hemianopsia, and a hemisensory defect, all of which likely will be permanent.



Clear pathology of intracerebral hemorrhage on CT scan. CT scan shows a large right putaminal hemorrhage (a), schematically shown in blue (b). Criteria for hematoma evacuation remain uncertain. Hemorrhages greater than 80 ml (estimated by multiplying the height, width [as measured on the CT], and depth [CT-slice thickness] of the hemorrhage and dividing by two) are usually lethal. Surgery appears contraindicated, particularly if the patient is in deep coma.



CT scan shows gross subarachnoid hemorrhage, with the blood indicated as white, or increased signal intensity (a). The massive hemorrhage fills the subarachnoid space by outlining the interhemispheric fissure anteriorly, the temporal fossae laterally, the suprachiasmatic cistern in the middle, and the paramesencephalic cistern posteriorly. The enormous amount of bleeding is shown in blue (b). This amount of bleeding is usually lethal. Patients with such bleeding usually present in coma.

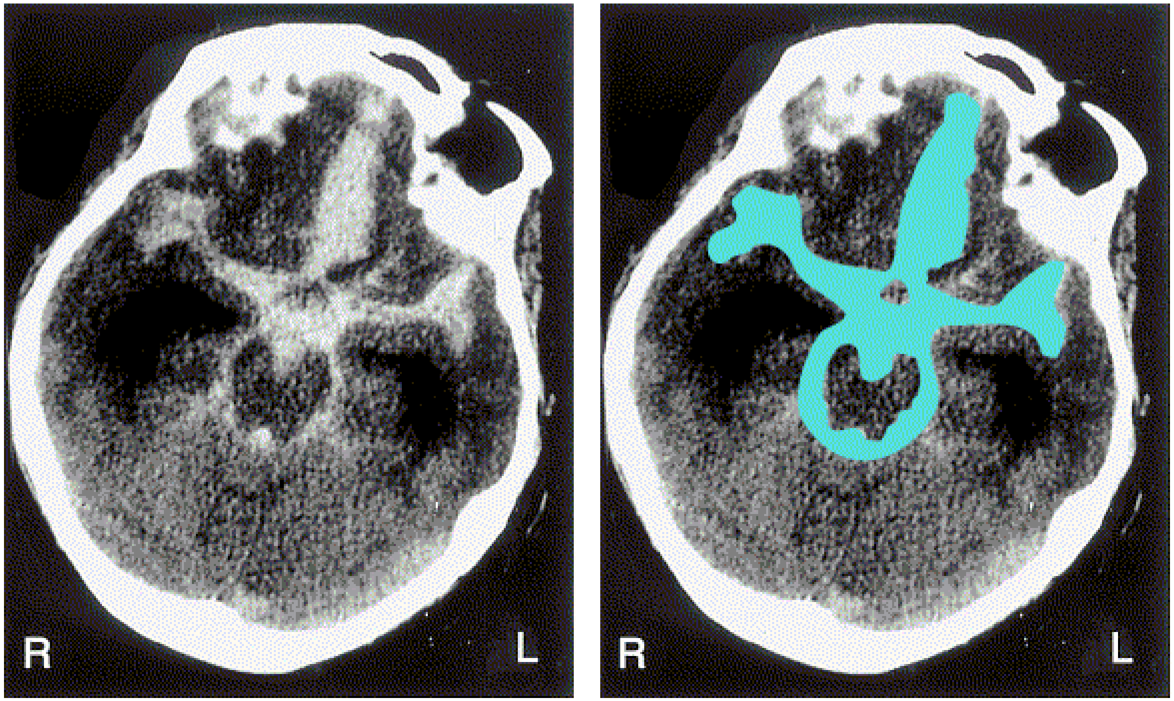
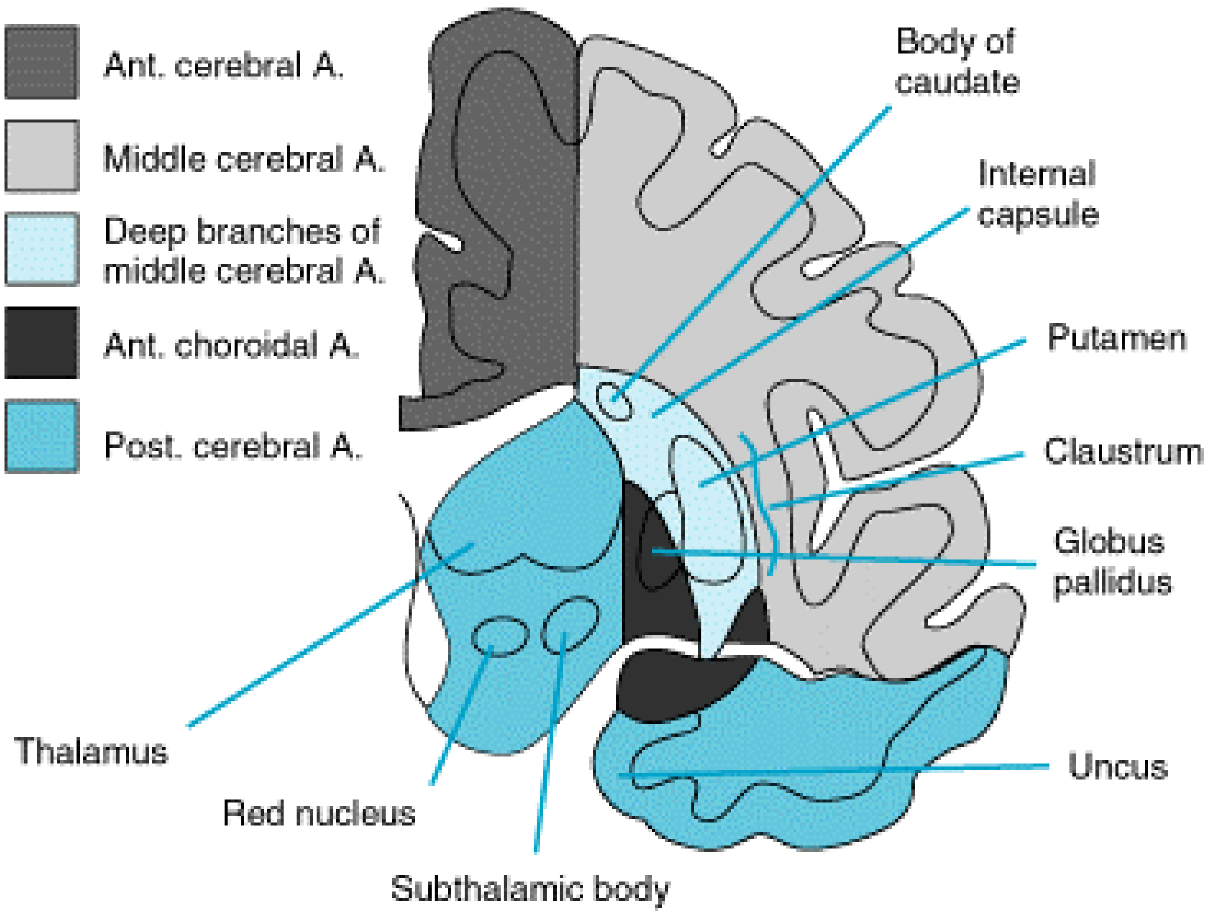
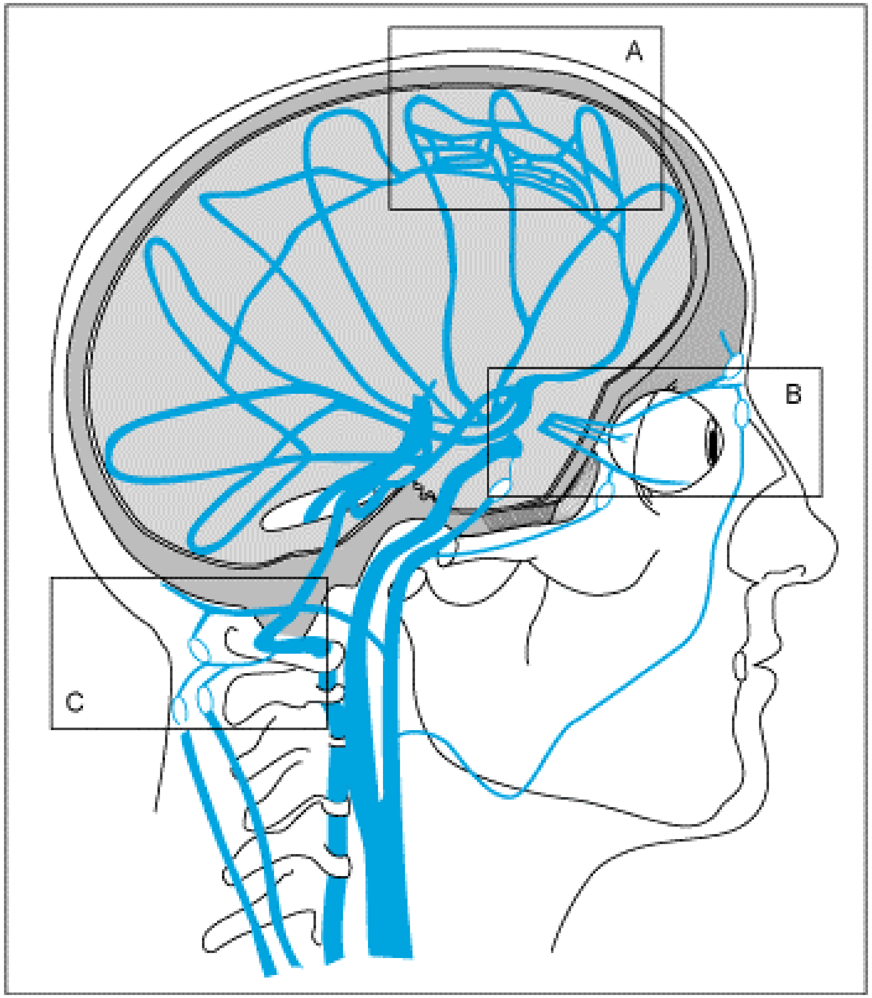
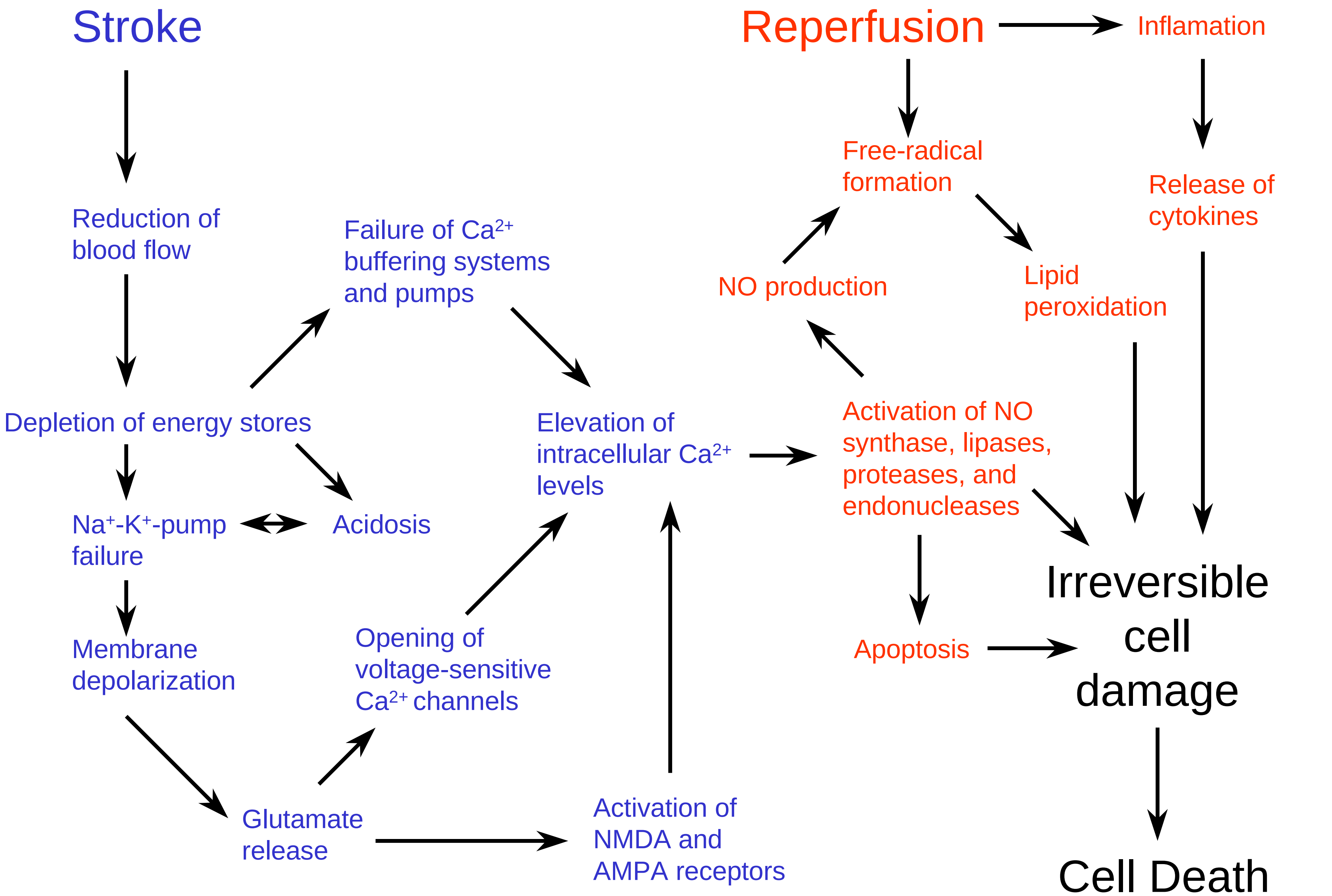


Diagram of a cerebral hemisphere in coronal section showing the territories of the major cerebral vessels.





Arrangement of the major arteries of the right side carrying blood from the heart to the brain. Also shown are vessels of collateral circulation that may modify the effects of cerebral ischemia (A, B, C). Not shown is the circle of Willis, which also provides a source for collateral circulation. A. The anastomotic channels between the distal branches of the anterior and middle cerebral artery, termed border-zone or watershed anastomotic channels. Note that they also occur between the posterior and middle cerebral arteries and the anterior and posterior cerebral arteries. B. Anastomotic channels occurring through the orbit between branches of the external carotid artery and ophthalmic branch of the internal carotid artery. C. Wholly extracranial anastomotic channels between the muscular branches of the ascending cervical arteries and muscular branches of the occipital artery that anastomose with the distal vertebral artery. Note that the occipital artery arises from the external carotid artery, thereby allowing reconstitution of flow in the vertebral from the carotid circulation.


Stroke
Reperfusion
Inflamation
Free-radical formation
Release of cytokines
Reduction of blood flow
Failure of Ca2+ buffering systems and pumps
NO production
Lipid peroxidation
Depletion of energy stores
Elevation of intracellular Ca2+ levels
Activation of NO synthase, lipases, proteases, and endonucleases
Na+-K+-pump failure
Acidosis
Irreversible cell damage
Apoptosis
Membrane depolarization
Opening of voltage-sensitive Ca2+ channels
Glutamate release
Activation of NMDA and AMPA receptors
Cell Death

Stroke