Diseases of the Central Nervous System

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Schedule: «Disease of the central nervous system»

Diseases of the CNS: Introduction, Stroke	13.11.2017
Neurodegenerative diseases: Parkinson's Disease	20.11.2017
Autoimmune diseases of the CNS: Multiple Sclerosis	27.11.2017

Handout & Lecture

Purves, Neuroscience, 4th edition (5th):

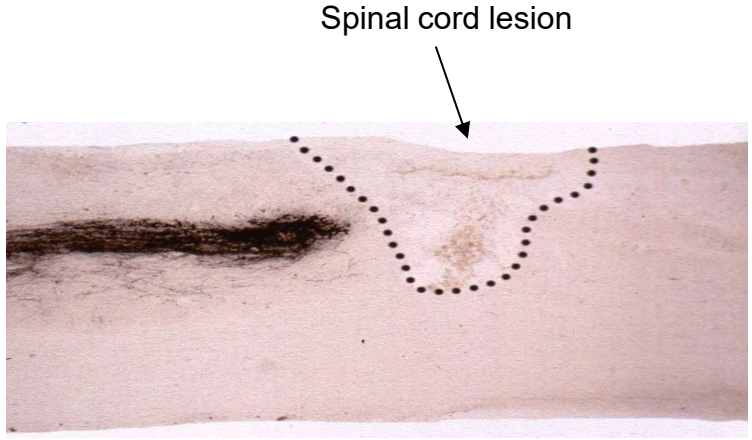
Parts of chapters 17, 19, 25, 27,
Appendix p. 833-842 (p. 735-744)

Diseases of the Central Nervous System

Most structures of our body display high capacity for tissue regeneration and compensation

- bone fracture / skin incision / muscle scissor etc.
- you can survive with 1 kidney, and <50% of your liver
- peripheral nerve fibers are capable of regeneration

The CNS has only a limited capacity for regeneration and plasticity



Physiological facts about the brain

The human brain account for only 2% of total body weight, but

- consumes **~20% of all oxygen** → continuous oxygen supply needed.

  -> cardiac arrest: unconsciousness within 10 seconds! Damage to neurons first reversible, then permanent after longer deprivation of blood supply.

- consumes ca. **25% of total energy consumption** (mainly glucose) of body

  -> neurons show a very high metabolism rate

- **Blood-brain-barrier:** maintenance of CNS homeostasis, immune-privilege

  -> limited access of systemic medications to CNS

- **No pain** receptors (nociceptors) in CNS parenchyma (only in meninges)

Stroke: Definition

WHO-Definition of Stroke Hatano (1976):

”**Stroke** is rapidly developing clinical symptoms and / or signs of focal and at times global loss of cerebral function with symptoms lasting more than twenty-four hours or leading to death with no apparent cause other than that of vascular origin.”

TIA: transitory ischemic attack (German: Streifung): symptoms similar or identical to stroke (mostly less severe). Dysfunctions are transient and disappear within < 24 hours

Stroke: epidemiology

- Stroke is the **4th largest cause of death** (behind cardiological diseases, cancer and respiratory diseases).
- 50% of stroke patients are **> 65 years old**, 10% < 40 years
- **> 4 million people** life with the consequences of stroke in the United States
- Stroke is expensive: **78 billion dollars for medication and therapy in USA in 2010**
- **15-20%** of stroke patients **die within 4 weeks**
- Surviving patients:
    - **1/3** of the surviving stroke patients **recovers well**
    - **1/3** shows deficits (hemiplegia, speech problems), but **copes well with daily life**
    - **1/3** needs **life-long care**

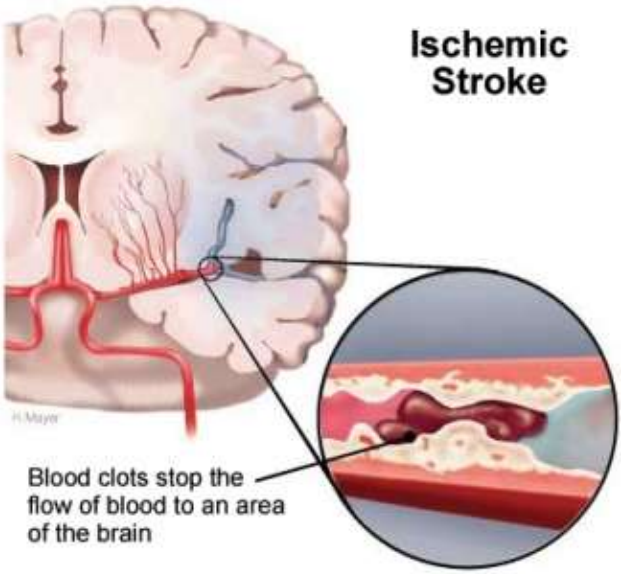
American Stroke Association (ASA) 2010

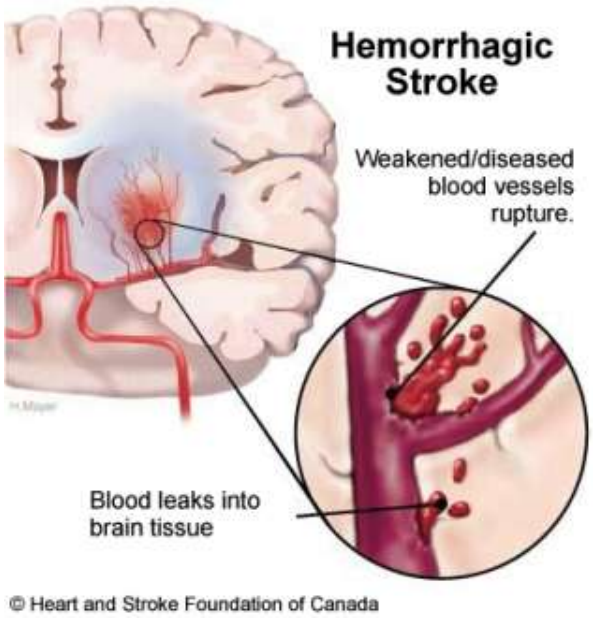
Stroke: classification of stroke types

Stroke

80% — **ischemic stroke**
- thrombotic (50%)
- embolic (30%)

20% — **hemorrhagic stroke**



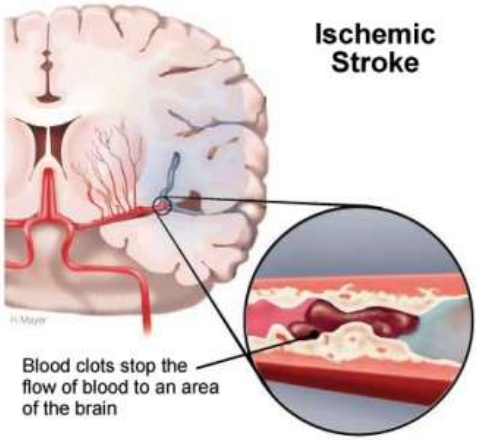


Occlusion of vessel -> infarction

Rupture of vessel -> bleeding

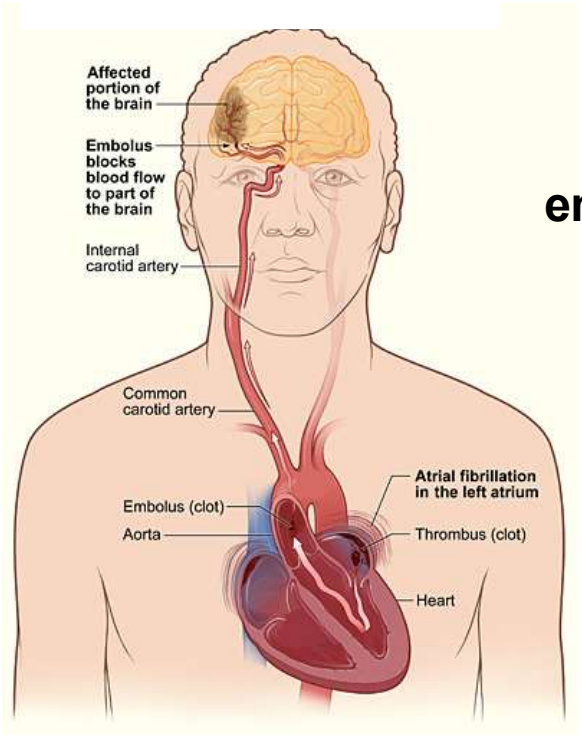
Stroke is a vascular disease!

Stroke: ischemia, infarction



thrombotic:

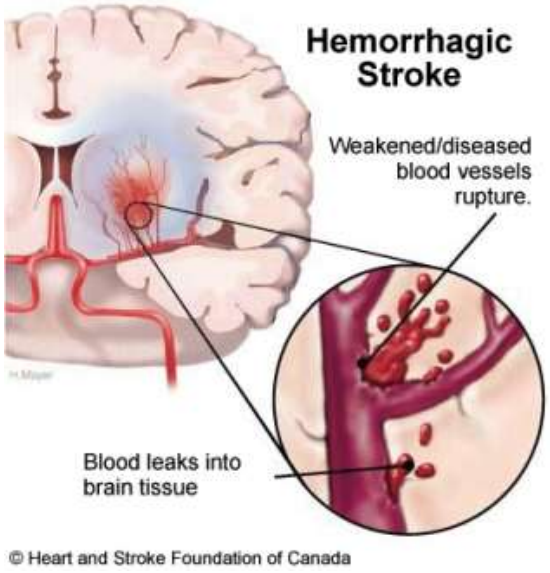
- caused by a **thrombus** (blood clot built in arteries suppling the brain with blood).
- frequently correlated with **atheroscleoris** (though e.g. high cholesterol level) and **increasing age**
- thrombotic strokes are often **preceded by TIA**

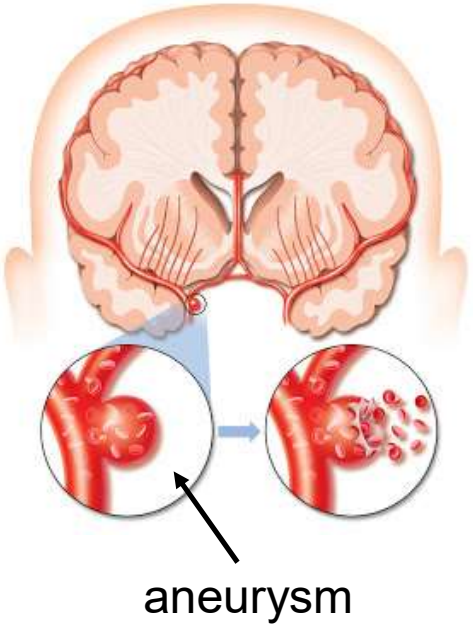


embolic:

- caused by an **embolus** (loose blood clot) which travels from the periphery (mostly from the heart) to the brain and finally occludes a cerebral vessel.
- embolic stroke often results from **heart failures** (e.g. heart dysrhythmia) or after heart surgeries.
- often occurs without sign (i.e. TIA)

Stroke: hemorrhagic





hemorrhagic:

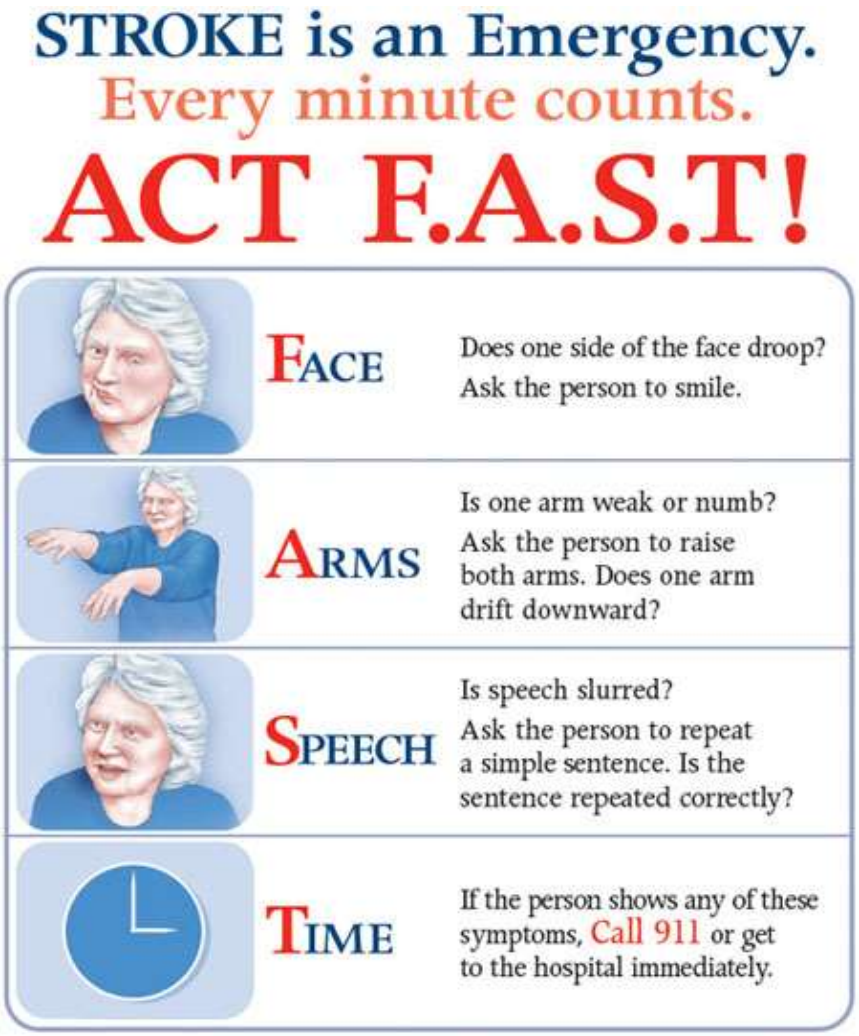
- caused by a **vessel rupture** which leads to bleeding into the brain tissue.

- Bleeding leads to **pressure and swelling** of the tissue against the skull. This can lead to mechanical damage of neurons.

- rupture of cerebral vessels can result from **hypertension,** from **aneurysms** (figure at bottom), from malformation of vessels or from direct traumatic (mechanical) injury to the vessels or the brain.

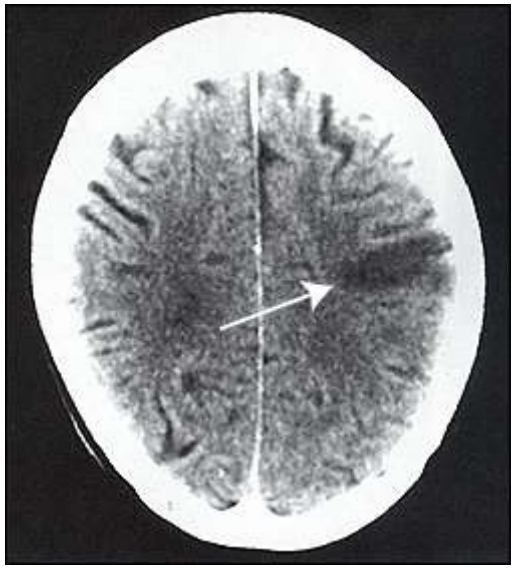
Stroke: early symptoms

Early signs:



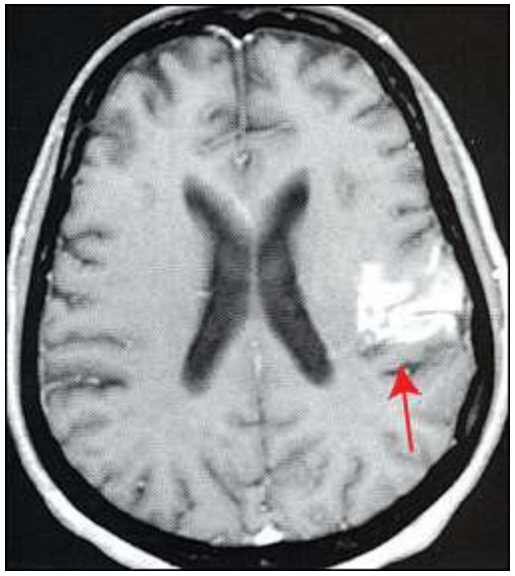
www.northwestmedicalcenter.com

Stroke: diagnosis



Computed axial tomography (CT)

- Based on x-rays
- Fast, good availability
- Less spatial resolution
- Rule out hemorrhage or tumor

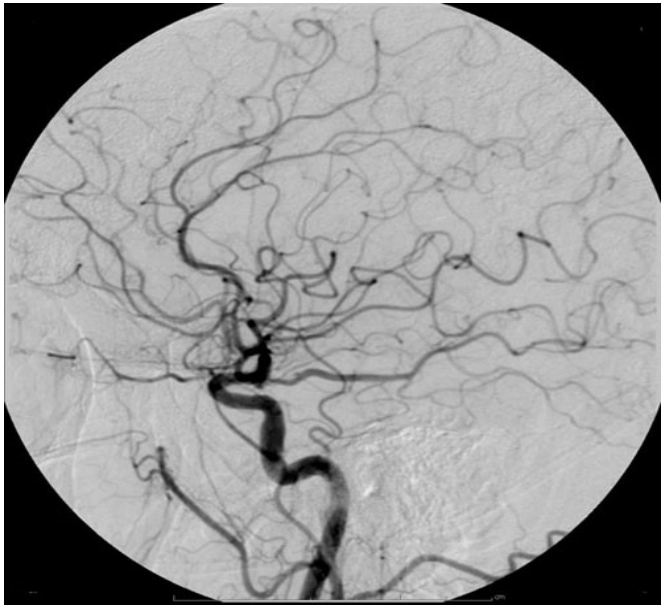


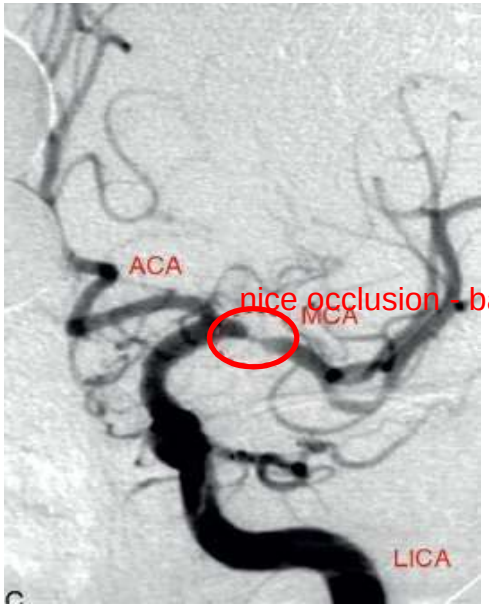
Magnetic Resonance Imaging (MRI)

- Based on magnetic fields
- Expensive, less abundant
- Good spatial resolution
- Can be used to diagnose ischemic, hemorrhagic stroke

Stroke: diagnosis

Cerebral angiography





nice occlusion - bad for patient

www.pcronline.com

- Blood vessels are normally not clearly seen in x-ray: -> injection of contrast dye to visualize vessels
- Specific investigation of occluded or ruptured vessels and visualization of structural changes: e.g. signs of atherosclerosis
- Angiography starts to be applicable to MRI

tumors are other very fast proceeding problems - has to be differentiated from strokes, using imaging techniques

- Stroke or TIA?
- Ischemic or hemorrhagic stroke?
- Location and extent of stroke?

Stroke: primary pathomechanism

Ischemia: inadequate blood supply of an organ due to mechanical obstruction

Hemorrhage: heavy release of blood from an organ/body

Neurons in the stroke-affected brain regions are **deprived of blood,** and therefore of **oxygen and nutrients** (primarily glucose)

Stroke: primary pathomechanism

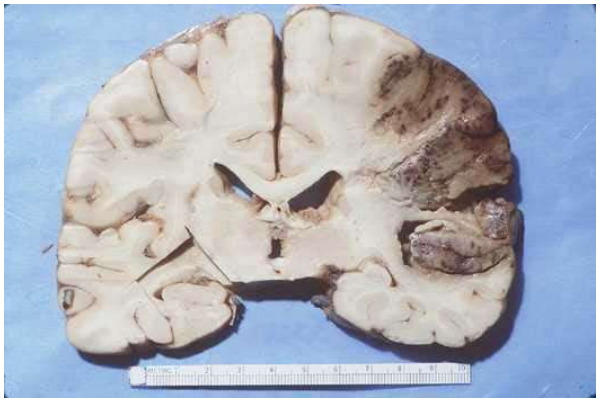
Time is brain:

Estimated Pace of Neural Circuitry Loss in Typical Large Vessel, Supratentorial Acute Ischemic Stroke

	Neurons Lost	Synapses Lost	Myelinated Fibers Lost	Accelerated Aging
Per Stroke	1.2 billion	8.3 trillion	7140 km/4470 miles	36 y
Per Hour	120 million	830 billion	714 km/447 miles	3.6 y
Per Minute	1.9 million	14 billion	12 km/7.5 miles	3.1 wk
Per Second	32 000	230 million	200 meters/218 yards	8.7 h

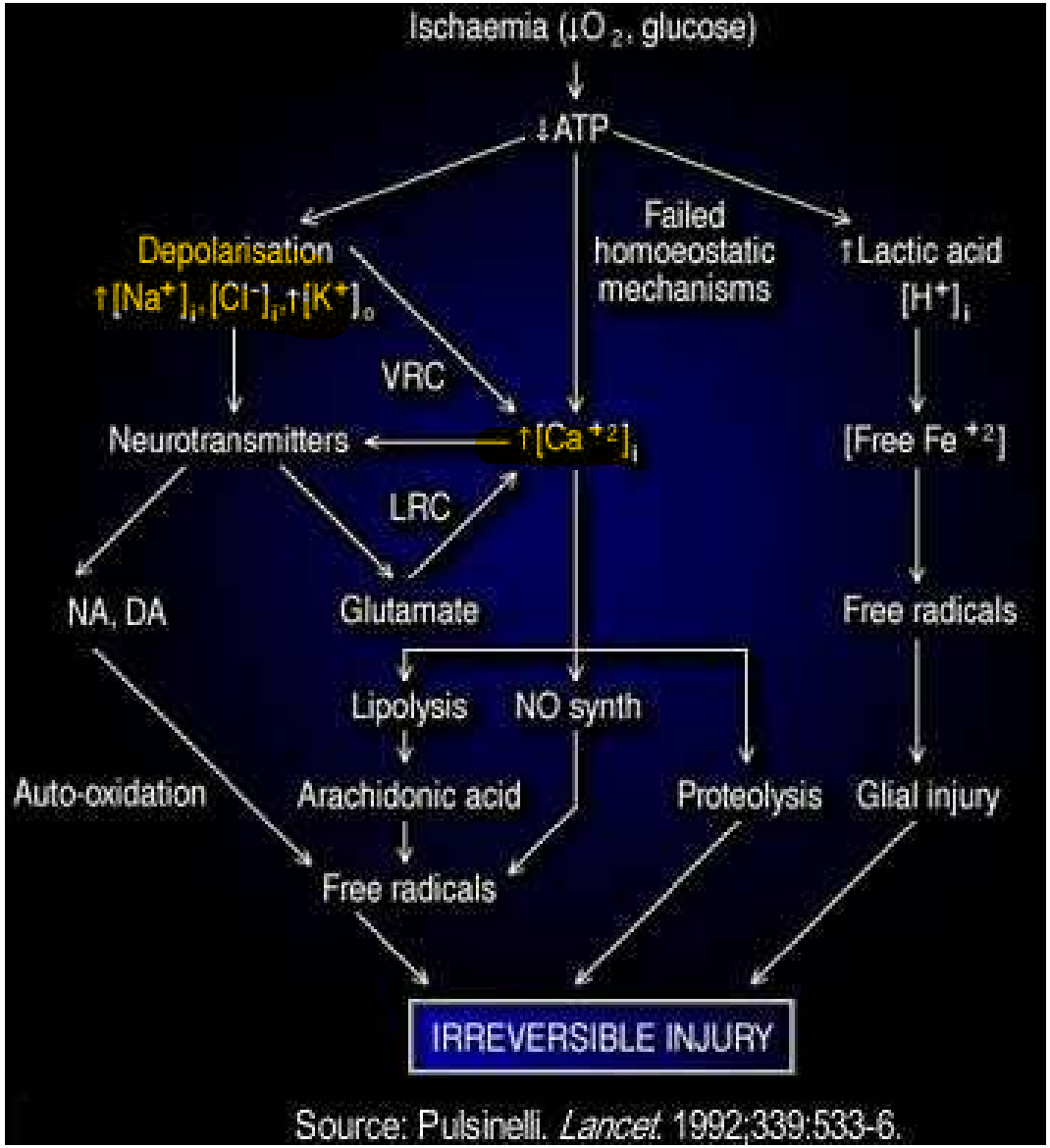
Saver, 2006, Stroke

15 mins for the brain to perform at full capacity when there is no blood supply (very short time). after 4 mins, brain shows no activity (braindead - not a death case, but brain has no detectable activity)



⇨ Stroke most frequently occurs in forebrain

Stroke: secondary pathomechanisms



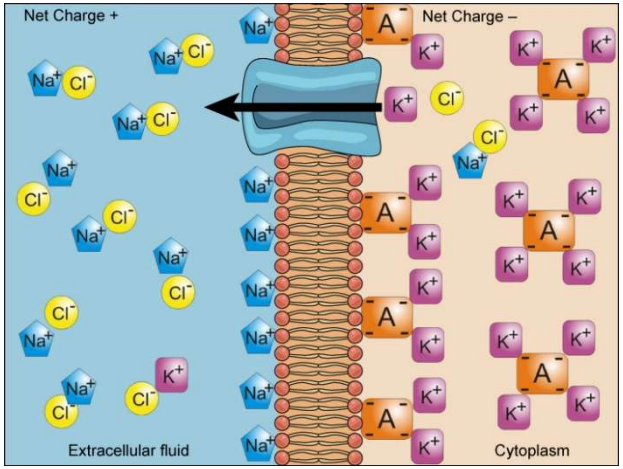
Source: Pulsinelli. *Lancet* 1992;339:533-6.

Stroke: secondary pathomechanism

Bioenergetic failure

- brain needs large amount of glucose & oxygen

  (ca. 70% to restore ionic gradients across membrane)



Na^+/K^+-ATPase

Ca^{2+}-ATPase

- 2min after global ischemia, missing ATP synthesis in mitochondria leads to:
  - membrane depolarization by passive influx (diffusion) of Na^+-ions

    -> (malfunctioning of Na^+/K^+-ATPase)

  - intracellular excess of Ca^{2+} (1. depolarization; 2. malfunctioning of Ca^{2+}-ATPase)

Stroke: secondary pathomechanism

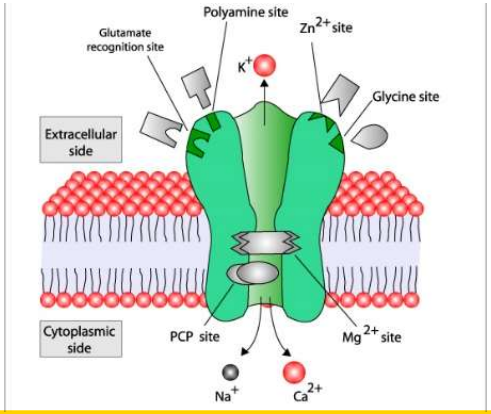
Excitotoxicity

too much excitation in the systems - caused by too much Na+ in the intracellular space

- High levels of intracellular Na^+ lead to a disturbed glutamate gradient
  - Normal situation: high Glu intracellular – low Glu extracellular
  - Ischemia: Na^+ - dependent glutamate transporters lead to destruction of gradient

⇨ Further membrane depolarization (via NMDA-, AMPA-recepotors) and increasing Ca^{2+} influx into neurons

⇨ Ca^{2+} influx leads to further neurotransmitter release



⇨ Blocking of glutamte binding sites on NMDA and AMPA-R is neuroprotective in animal models.

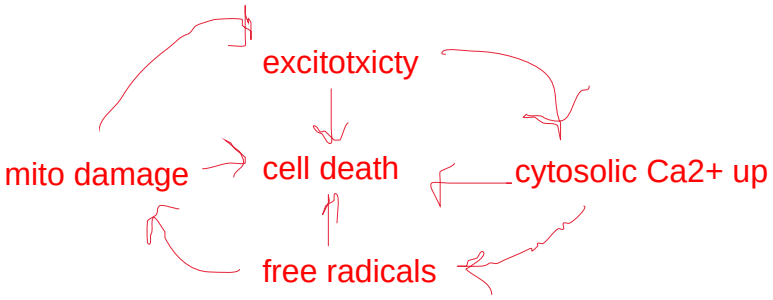
Stroke: secondary pathomechanism

Excitotoxicity II

- High levels of intracellular Ca^{2+} lead to:

1. Facilitated neurotransmitter release (excitatory)
2. Activation of Ca^{2+}-dependent proteases, lipases and DAases

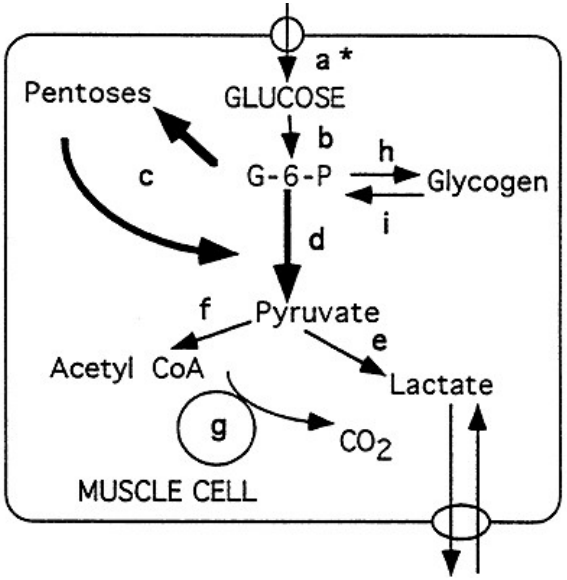
   -> protein degradation, membrane lysis (cytotoxic edema), cell death
3. Production of free radicals and reactive oxygen species (ROS)



Stroke: secondary pathomechanism

Acidosis

- Anaerobic metabolism through ischemia
- Lactate production decreases pH in environment
- Activation of Na^+-selective acid-sensing ion channels (ASICs) by extracellular protons



⇨ ASICs are permeable to Ca^{2+}

➡ Selective ASIC blocker has been shown to reduce lesion volume in animal models

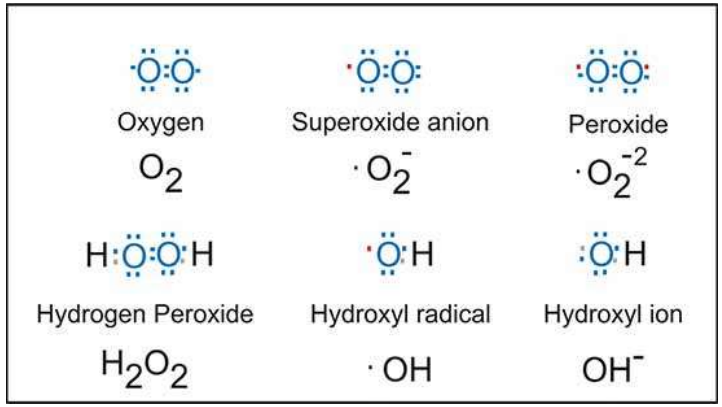
- Acidosis leads to production of free radicals

Stroke: secondary pathomechanism

Oxidative stress (and nitrative stress)

- High levels of intracellular Ca^{2+}, Na^{+} and ADP

⇨ mitochondria produce a lot of reactive oxygen species (ROS)

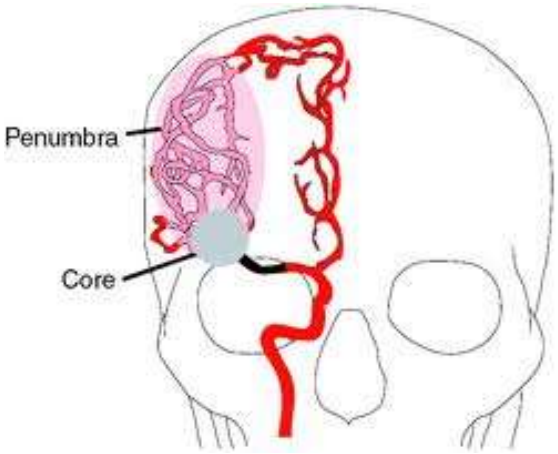


- Brain has low levels of endogenous antioxidants -> vulnerable to ROS
- ROS cause destruction of cellular macromolecules and induce apoptosis
- Ischemia activates nitric acid synthase (NOS):

⇨ NOS produces nitric oxide (NO)

Stroke: core zone and penumbra

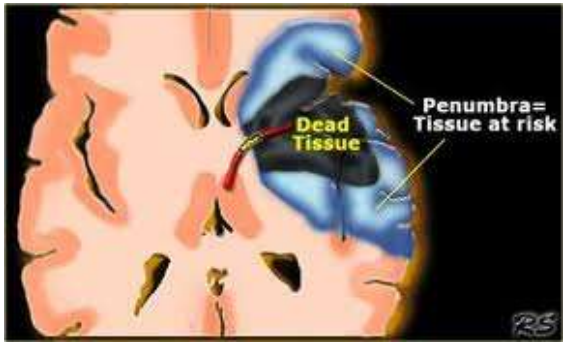
Ischemic core zone and penumbra



www.ajnr.org

Core zone:

results in fast necrosis of neurons and glial cells and irreversible damage



rad.desk.nl

Ischemic penumbra (peri-infarct area):

ischemica tissue potentially destined for infarction but not yet irreversibly injured and the target of acute therapies

this zone can still be recovered

Stroke: early treatment

Two main strategies

- **Reperfusion**: restoration of normal blood supply

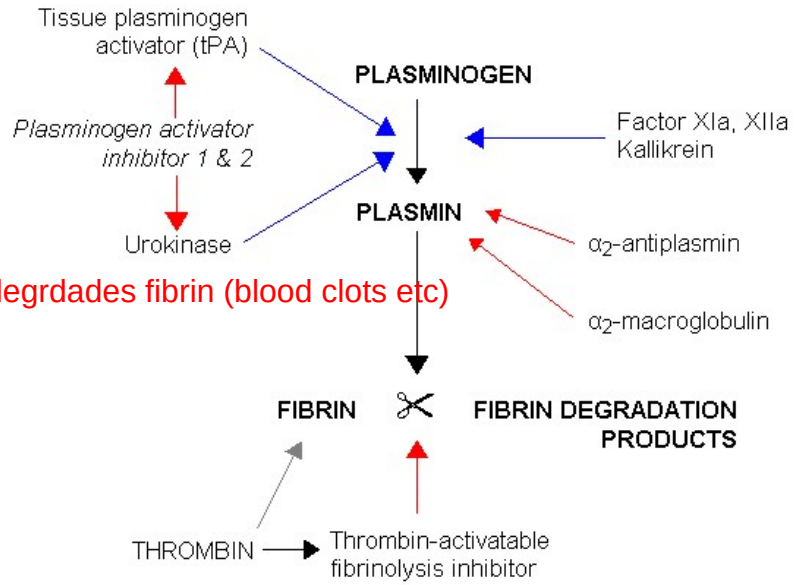
- **Neuroprotection**: protect ischemic tissue (penumbra)

Remember: **TIME IS BRAIN**

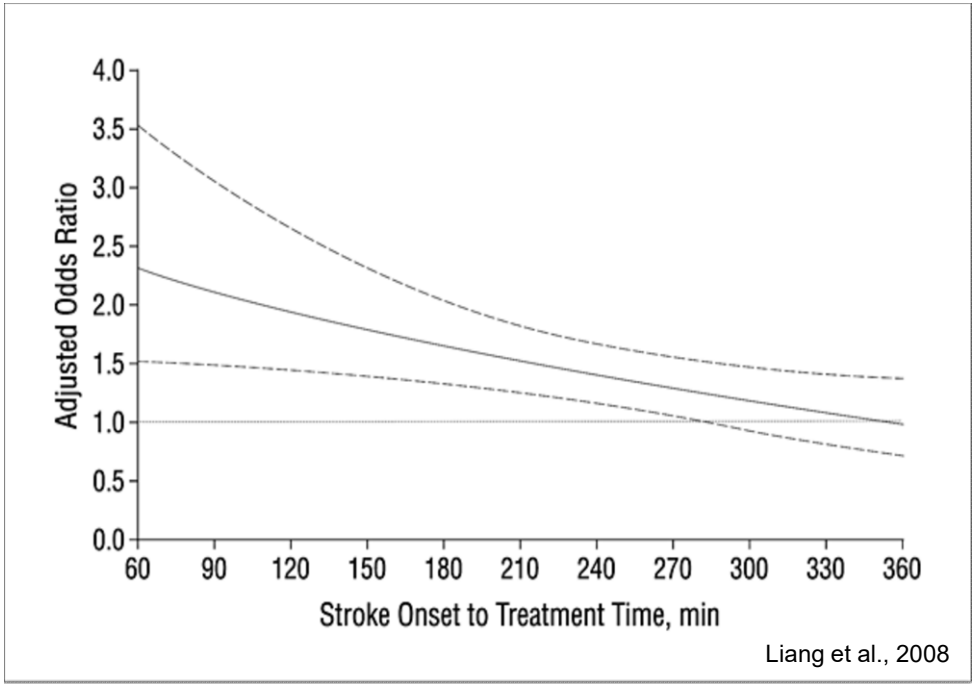
Every 30 minutes delay in reperfusion is a 10% relative reduction in the probability of good clinical outcome

Stroke: early treatment-thrombolysis

Tissue plasminogen activator: t-PA



plasmin degrdades fibrin (blood clots etc)



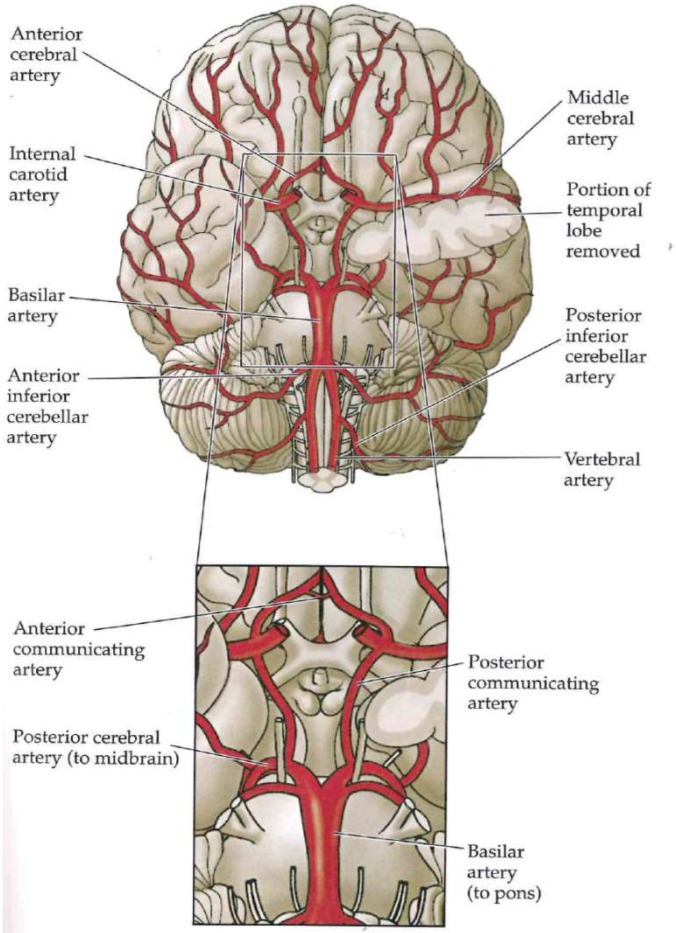
Liang et al., 2008

- t-PA is the **only approved treatment** for acute ischemic stroke
- has to be applied within 4.5 h after stroke onset (USA: 3 h)

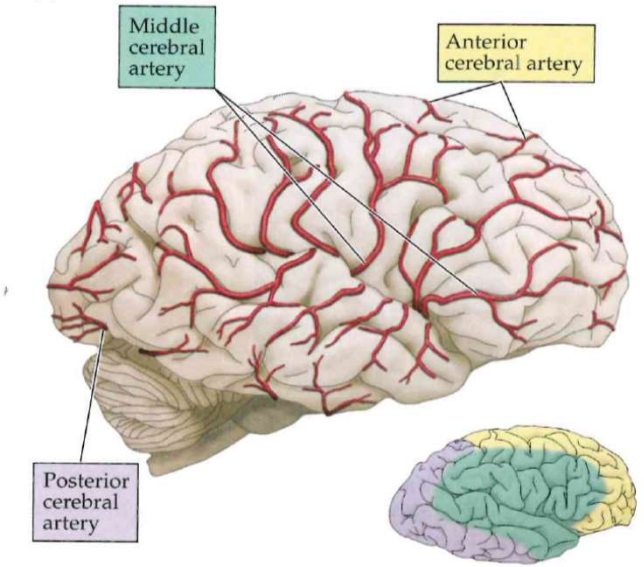
  -> only a few patients (ca. 5%) qualify for this treatment due to the narrow time window
- Only for ischemic stroke, not hemorrhagic stroke (increases bleeding actually, but we want to seal the rupture, so dont do it)

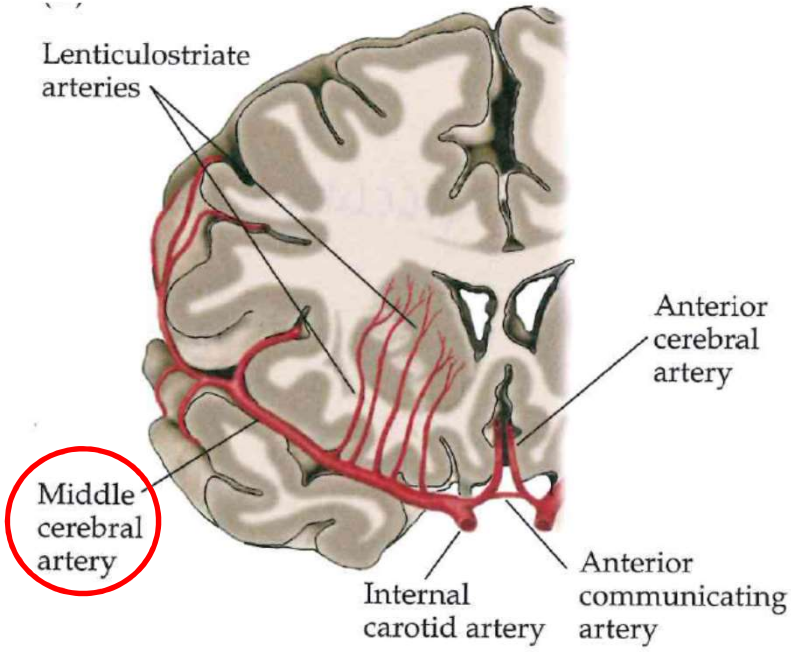
  -> obligate imaging with CT (computed tomography) or MRI (magnetic resonance imaging)

Stroke: cerebrovascular system



Purves, major vessels, p 835, 836



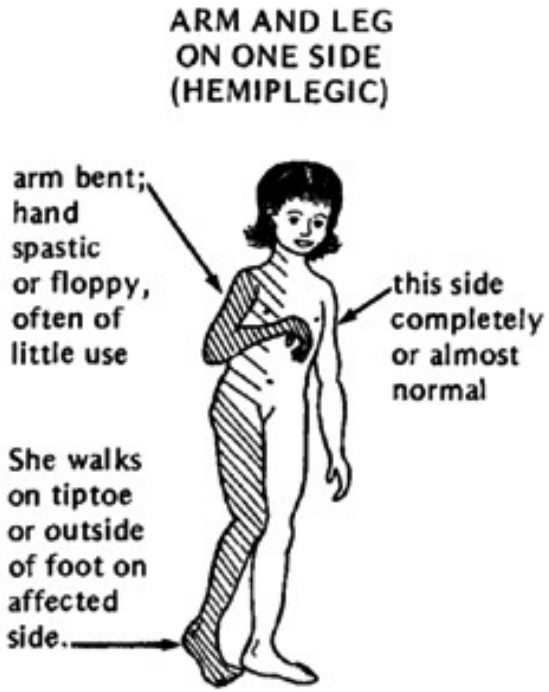


Middle cerebral artery (MCA) is most often occluded in human stroke

→ **Distal** occlusion of MCA: Damage restricted to cerebral cortex

Stroke: hemiplegic gait

Hemiparetic gait: One affected body side, 1 nearly-intact body side

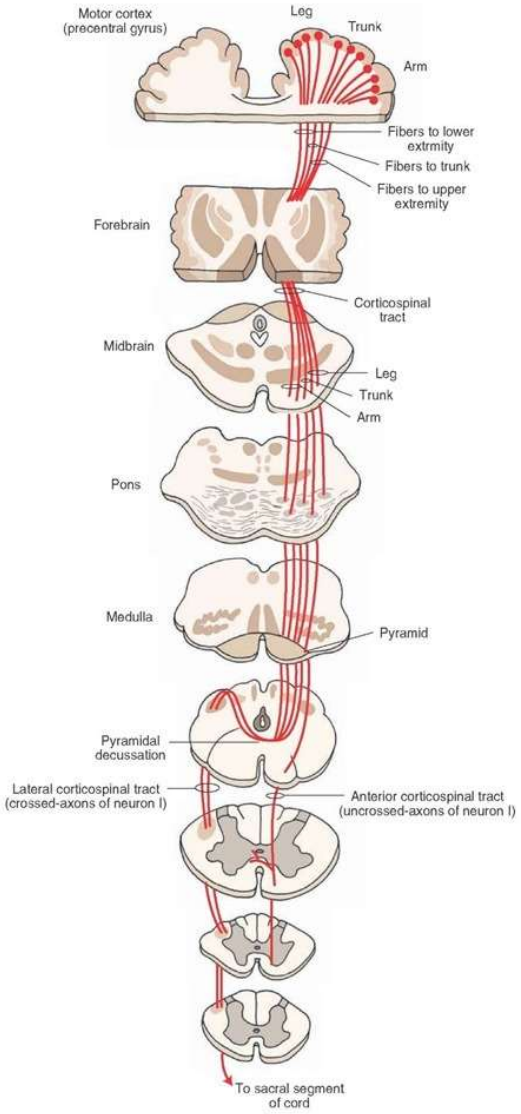


Leg:

- Extension (spastic, stiff) mostly of distal joints (knee, ankle)
- Internal rotation
- Circumduction of leg

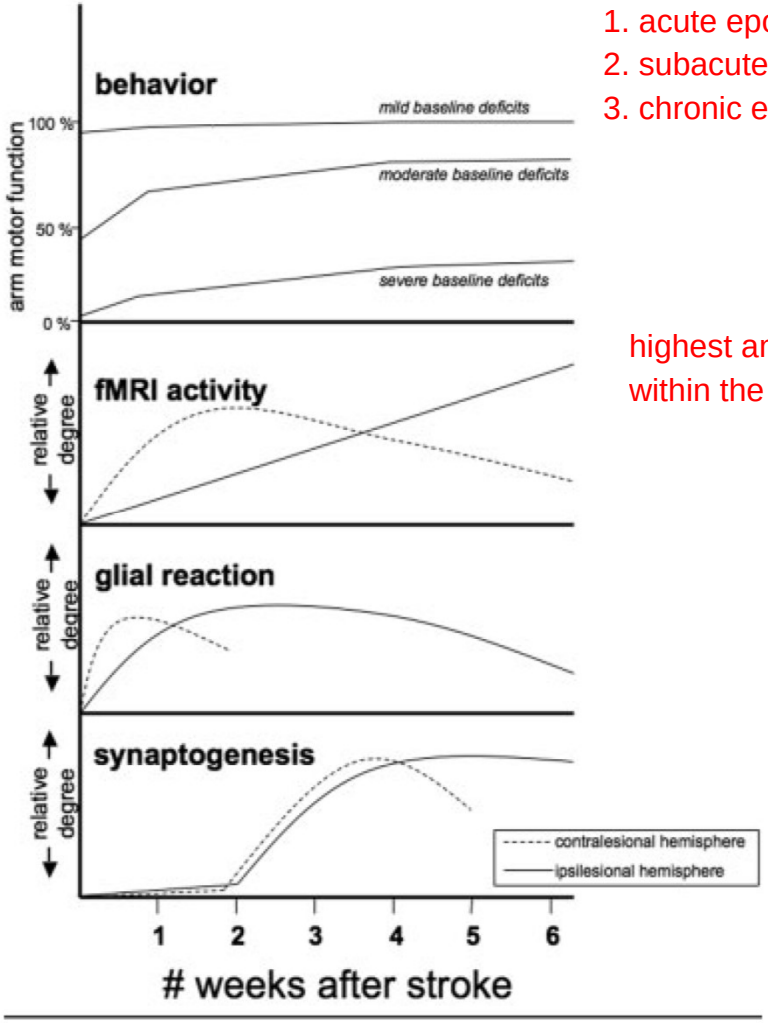
Arm:

- Shoulder adducted
- Elbow flexed
- Pronation of wrist



nsmec.wordpress.com

Stroke: spontaneous functional recovery

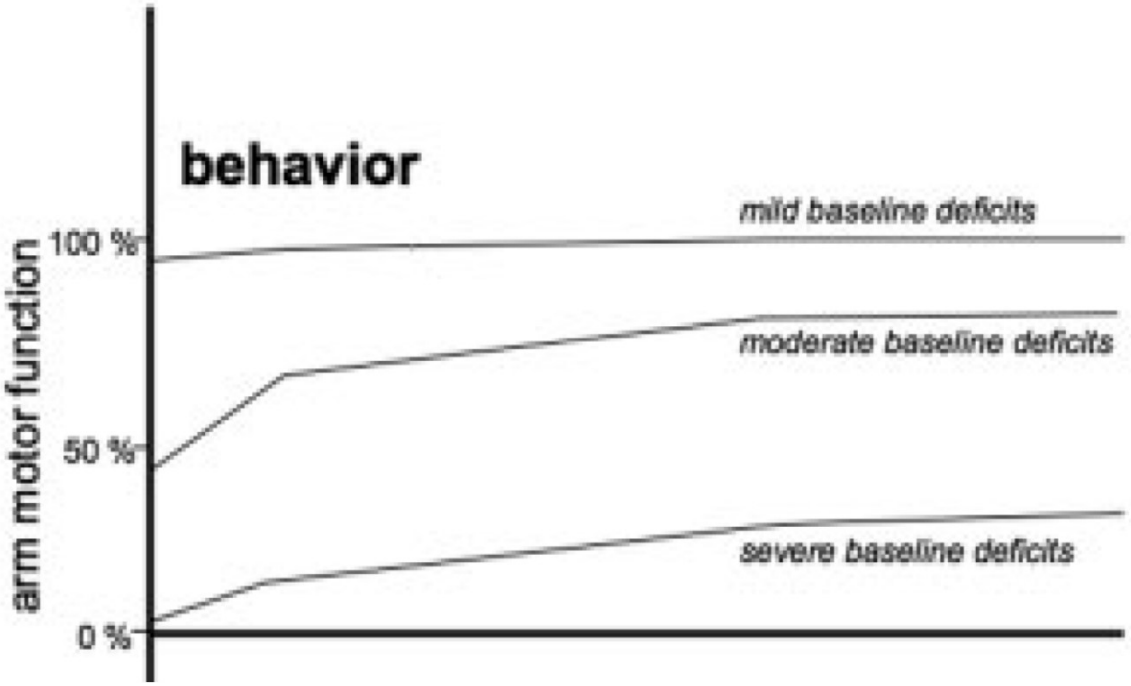


usually some degreeof spontaneous functional recovery
three epochs of functional recovery:
1. acute epoch: inital hours after stroke
2. subacute epoch: first days to weeks after stroke
3. chronic epoch: weeks to months after stroke

highest amount of spontaneous sensorimotor recovery usually takes place within the first 3 weeks after stroke

Cramer SC, 2008

Stroke: spontaneous functional recovery



Cramer SC, 2008

mild deficits show faster recovery of functions
most improvement occurs within 30 days after stroke
more severe deficits can take up to 90 days to recovery
DAY 7 clinical assessment is most predictive of final outcome

80% of patients showed max revoery around 3 weeks (plateau)
95% showed max recoery aroiund 6 weeks (plateau)

http://www.homehealthofmontana.com

Stroke: mechanisms of spontaneous recovery

Molecular and cellular level:

- Data mainly from preclinical studies (animal models) due to invasive methodology

- Associated with recovery of secondary pathomechanisms (discussed before)

Table 1. **Repair-Related Molecular and Cellular Changes after Stroke**

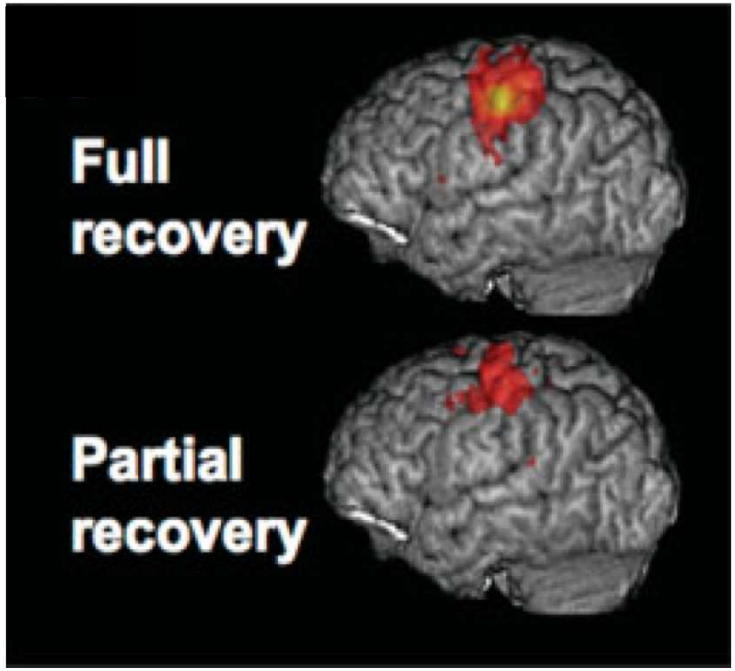
↑ Inflammatory markers
↑ Growth-associated proteins
↑ Cell-cycle proteins
↑ Growth factors
GABA receptor downregulation
↑ *N*-methyl-D-aspartate receptor binding
↑ Angiogenesis
Hyperexcitability, with facilitation of long-term potentiation
↑ Synaptogenesis
↑ Dendrite branching/spine density
↑ Neuronal sprouting
↑ Cortical thickness

Cramer SC, 2008

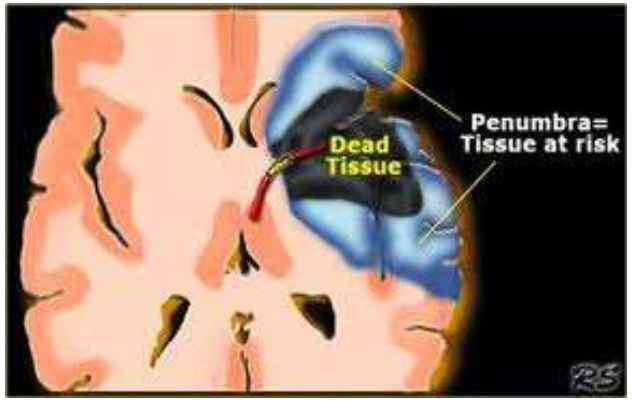
Stroke: mechanisms of spontaneous recovery

Neural network level: <u>restoration</u> of function in ischemic brain area

<u>1. Reduced neural activity locally (at or close to infarct area)</u>



Functinoal MRI study: Zemke et al., 2003



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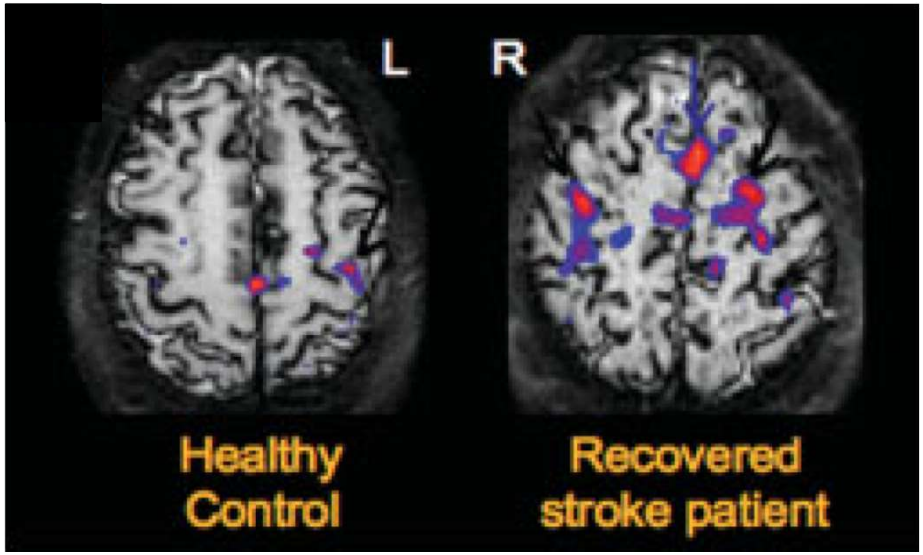
Stroke: mechanisms of spontaneous recovery

Neural network level: <u>compensation</u> of function by secondary brain areas

<u>2. Increased neural activity at areas distant from core zone</u>

i) Enhance activity in CNS areas distant from, but connected to core zone:



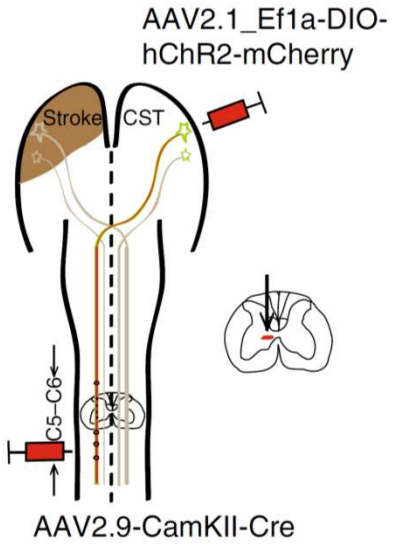
Functinoal MRI study: Cramer et al., 1997

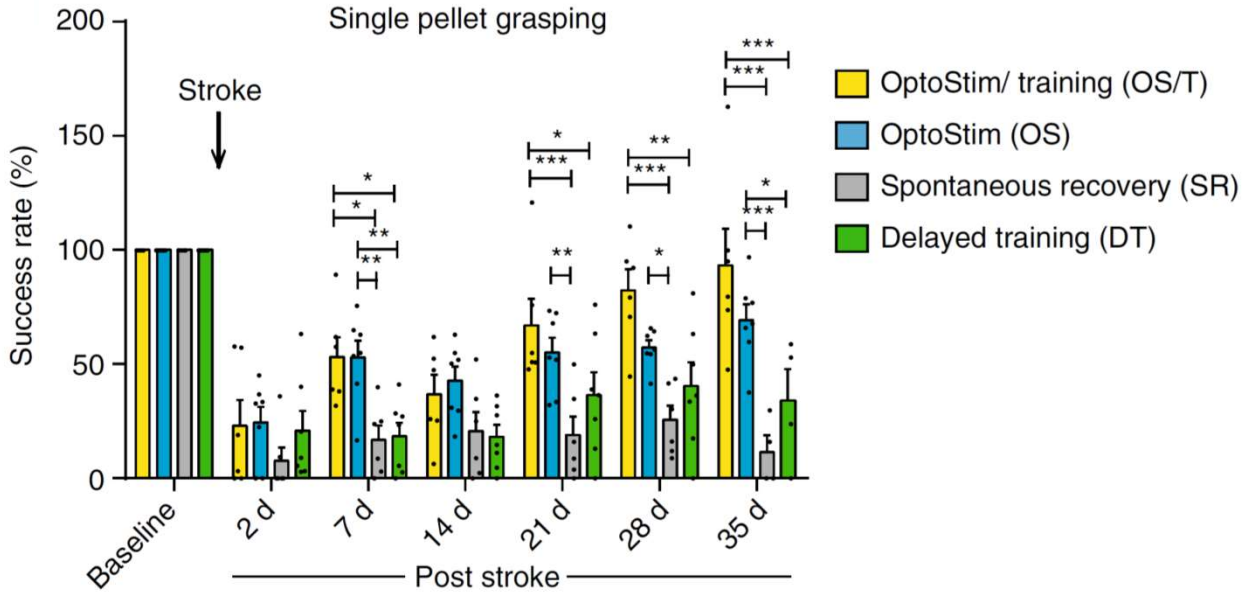
Stroke: mechanisms of spontaneous recovery

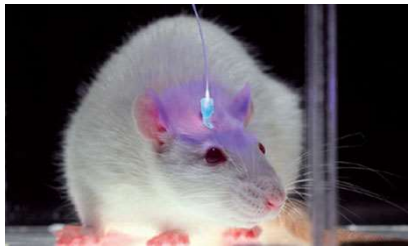
Neural network level: <u>compensation</u> of function by secondary brain areas

2. Increased neural activity at areas distant from core zone

ii) Reduced laterality of neural motor control (more contralesional activity after stroke)







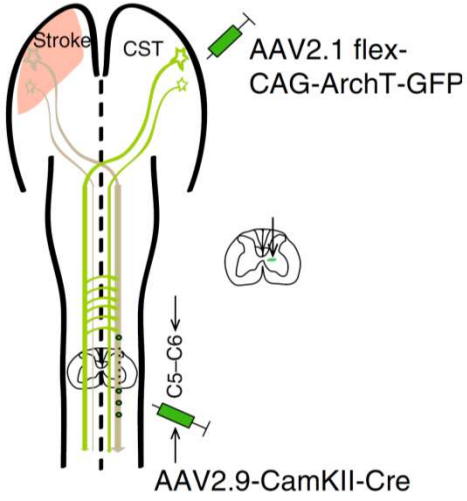
Wahl et al., 2017

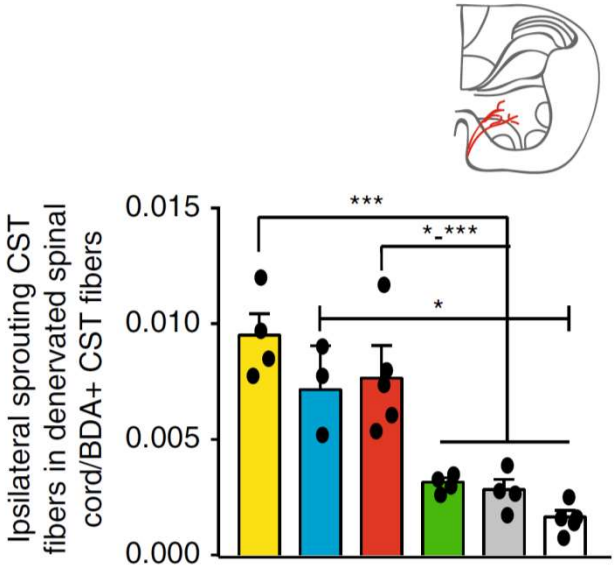
Stroke: mechanisms of spontaneous recovery

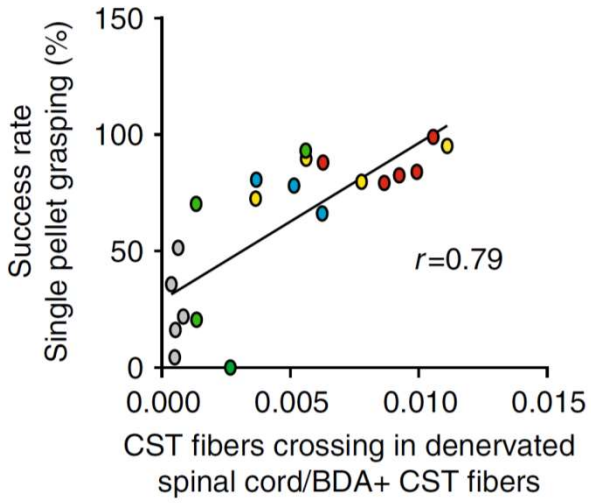
Neural network level: <u>compensation</u> of function by secondary brain areas

2. Increased neural activity at areas distant from core zone

ii) Reduced laterality of neural motor control (more contralesional activity after stroke)







Wahl et al., 2017

Stroke: mechanisms of spontaneous recovery

Neural network level: <u>compensation</u> of function by secondary brain areas

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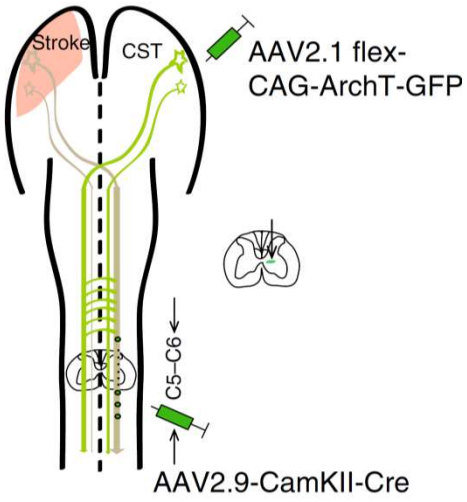
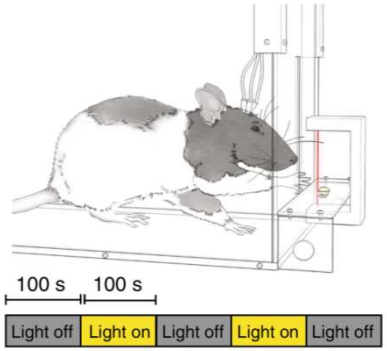
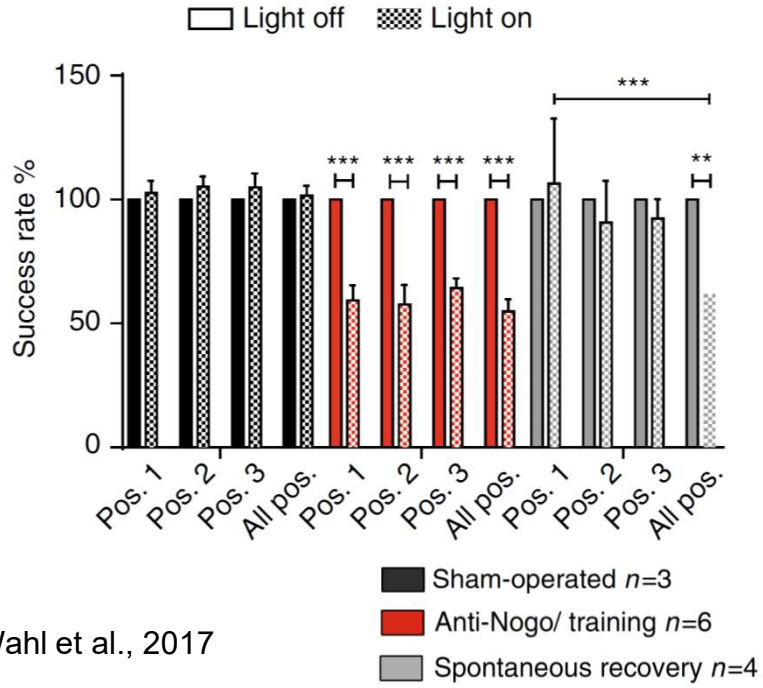






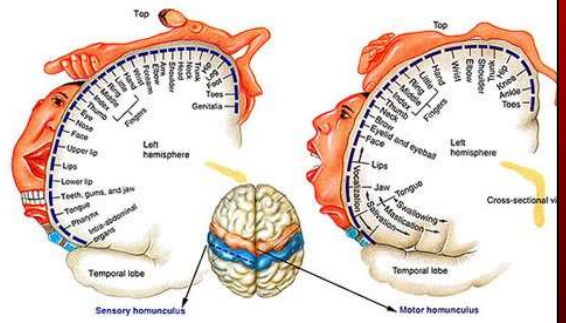
Wahl et al., 2017

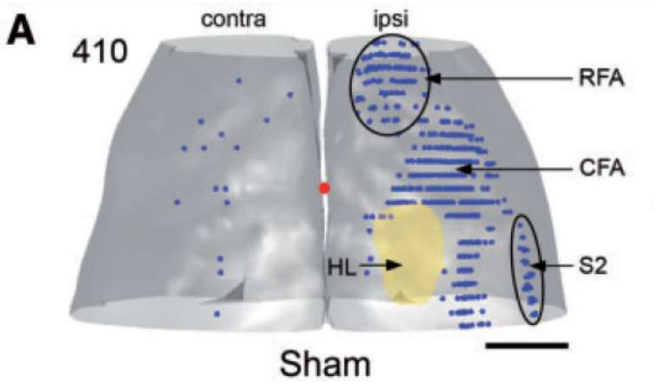
Stroke: mechanisms of spontaneous recovery

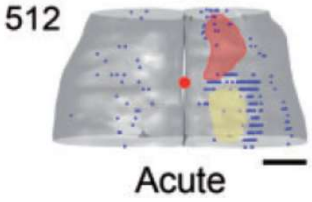
Neural network level: <u>compensation</u> of function by secondary brain areas

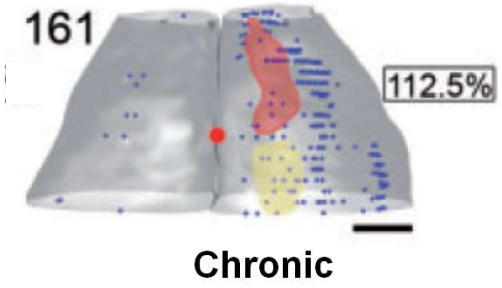
2. Increased neural activity at areas distant from core zone

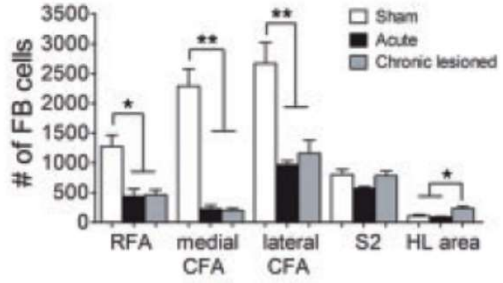
iii) Reorganization of somatotopic maps after stroke

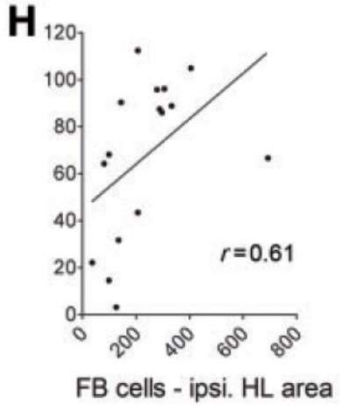


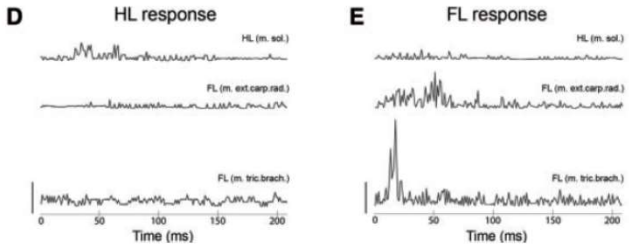












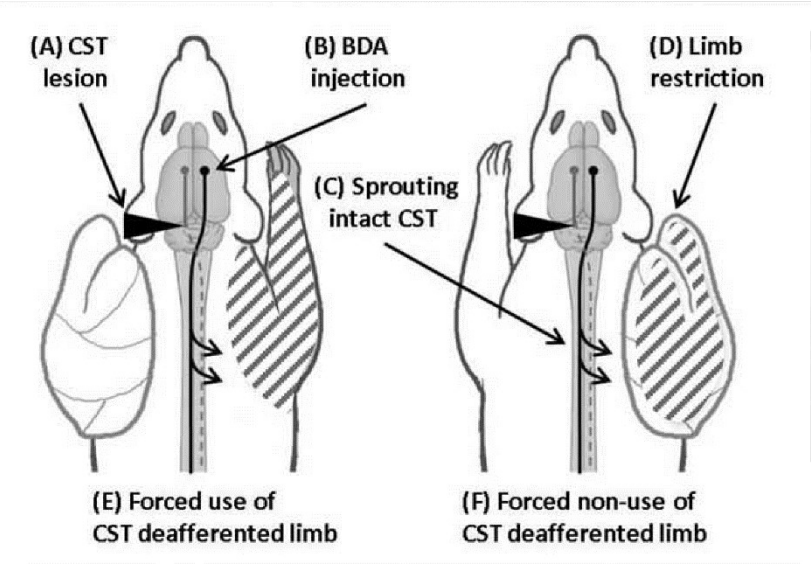
Starkey et al., 2012

Stroke: later treatment – rehabilitative training

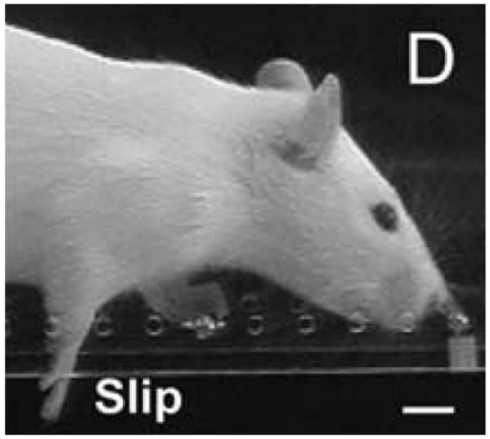
Depending on deficits:

- **Physiotherapy**
- Occupational therapy
- Speech therapy
- Psychological care

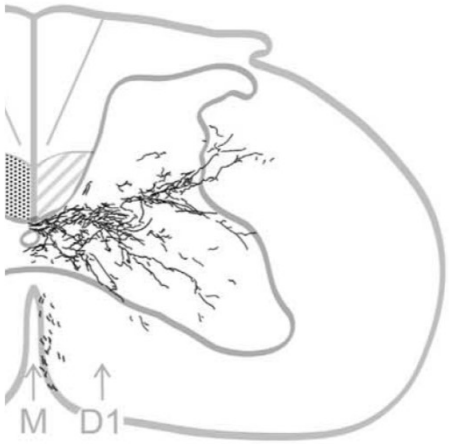
Stroke: constraint-induced movement therapy



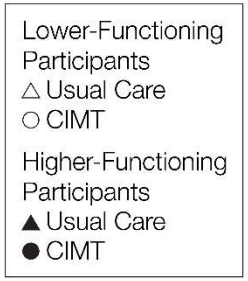
Maier et al., 2008

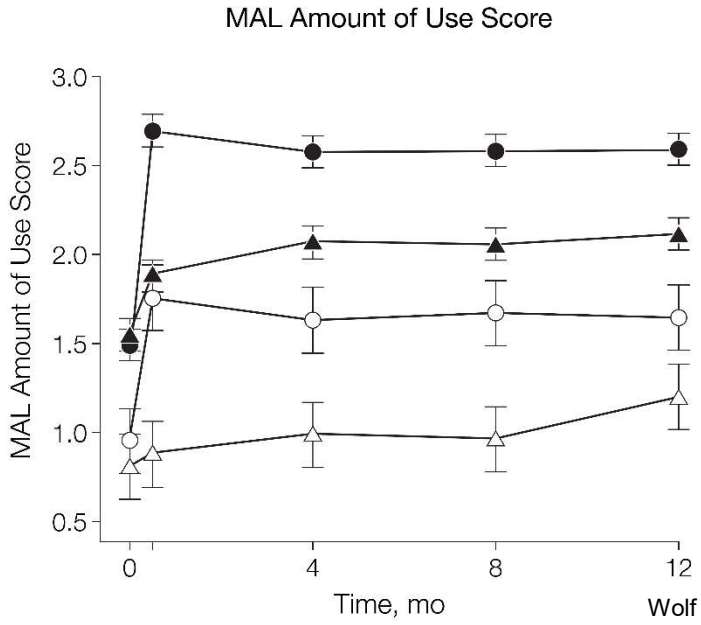


Improvement forelimb function



Increase corticospinal fibers in denervated spinal cord





Wolf et al., 2006