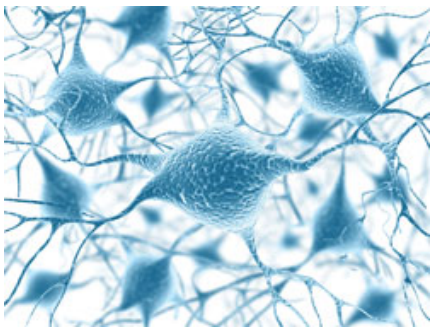
MOTOR NEURON DISEASES

Pathophysiology, genetics, proteins, therapies

Bernard Schneider
October 2024



Lecture plan

1. **Motor system**
   - Overview
2. **Motor Neuron Diseases**
   - Clinical presentation
   - Molecular pathology
3. **Amyotrophic Lateral Sclerosis**
   - Clinical presentation, epidemiology, etiology
   - Molecular pathology: RNA metabolism
   - Non-cell autonomous mechanisms

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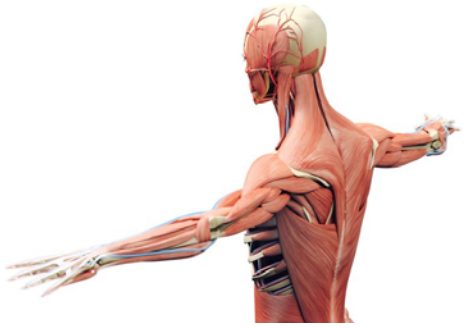
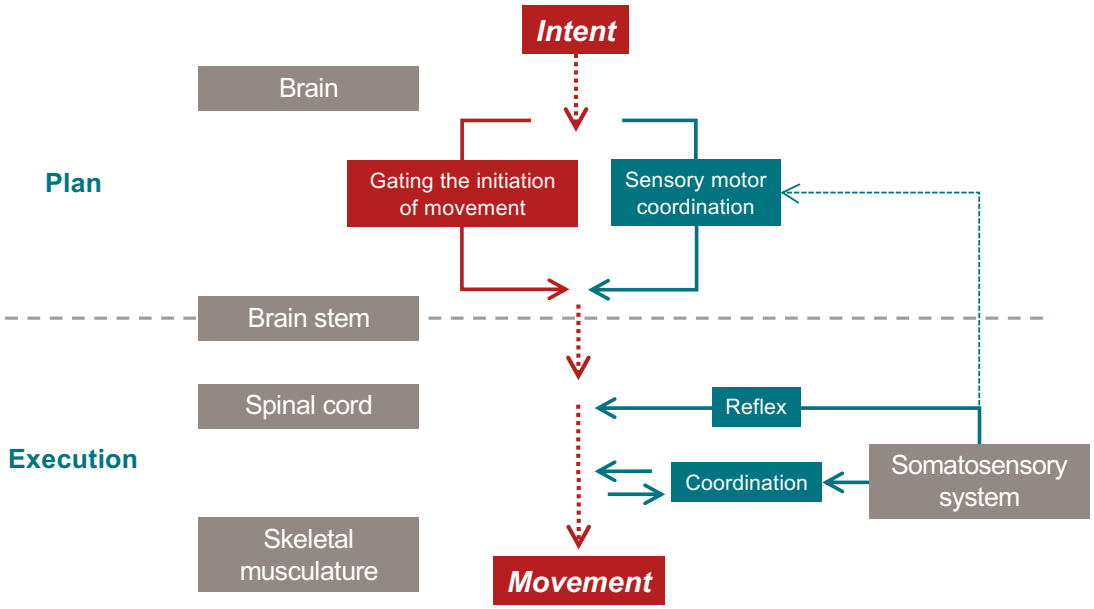
Control of voluntary movements

- Movements are among the main characteristics of living organisms
- Movements and locomotion are controlled by the nervous system
- The nervous system controls the timely contraction and relaxation of the skeletal musculature



Movement control and execution



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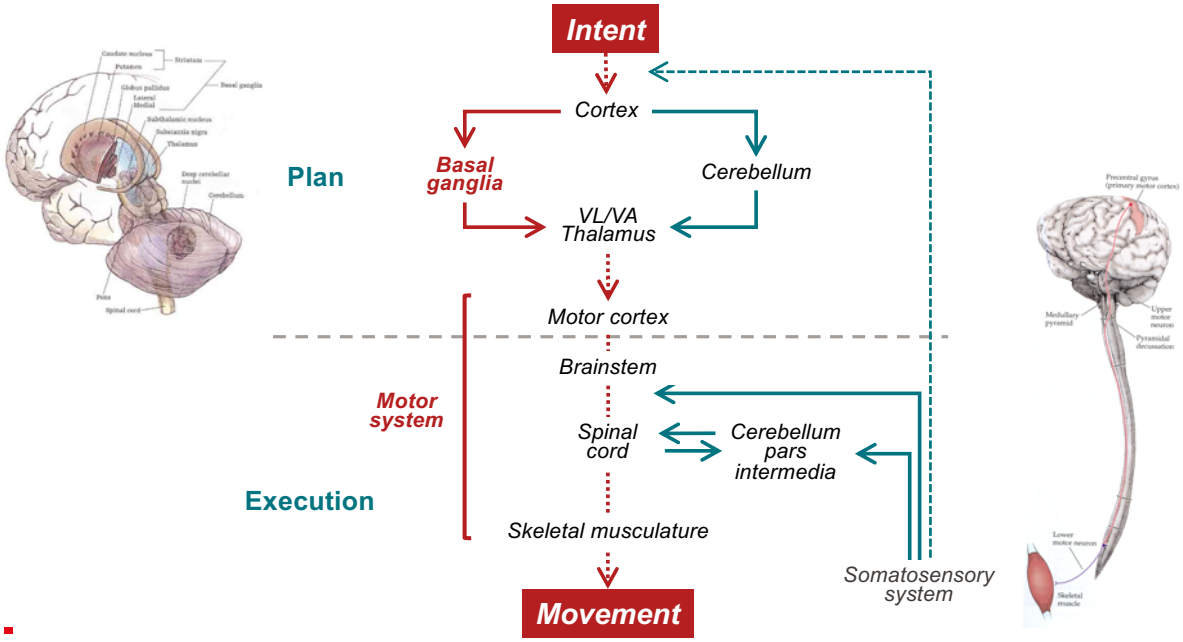
Basal ganglia and motor system



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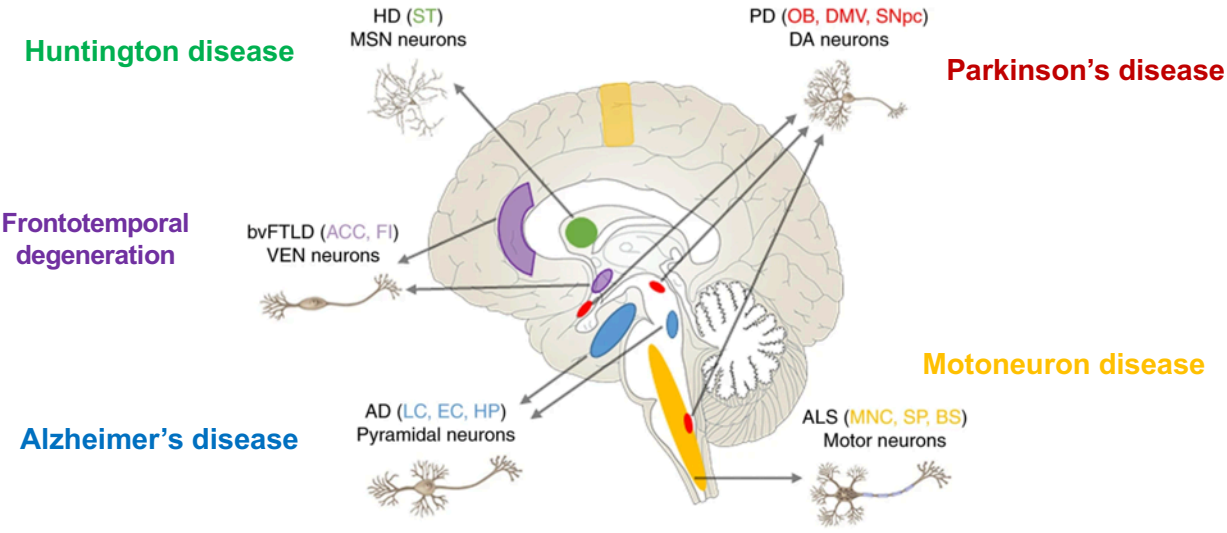
Regions and neurons that are vulnerable in neurodegenerative diseases.



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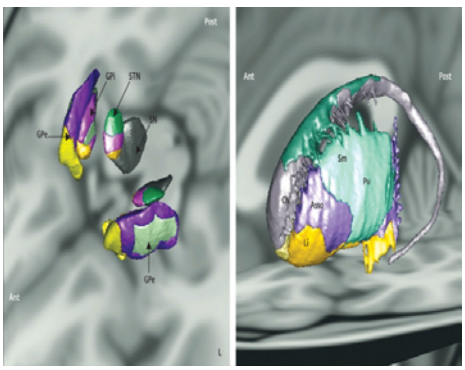
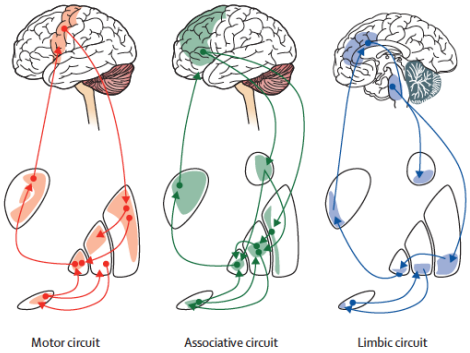
Basal ganglia: circuits

Basal ganglia: structure and function





Motor control | Cognition | Emotion Motivation Memory

- Stoessl AJ, Lancet 2014
- Obeso JA, Lancet 2014

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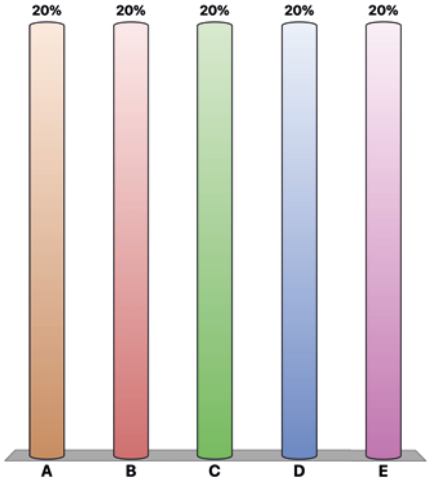
MN diseases - Question 1

For diseases affecting the function of the basal ganglia, which of the following primary symptoms would you expect?
(by order of most to least likely)

A. Paralysis
B. Cognitive deficits
C. Difficulty to initiate movement
D. Memory loss
E. Loss of movement control



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Motor system: execution of movements

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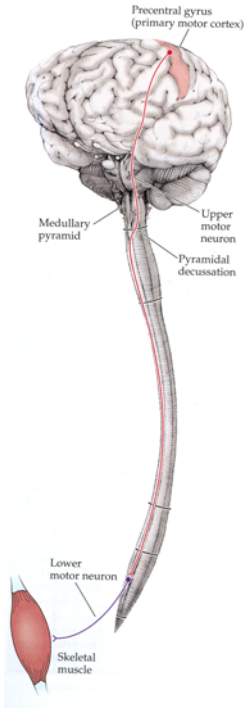
Motor system organization

In humans:

- >120,000 spinal motoneurons
- >300 bilateral muscles
- >100 mio muscle fibers



Neuroanatomy through Clinical Cases, 2nd Edition, H. Blumenfeld

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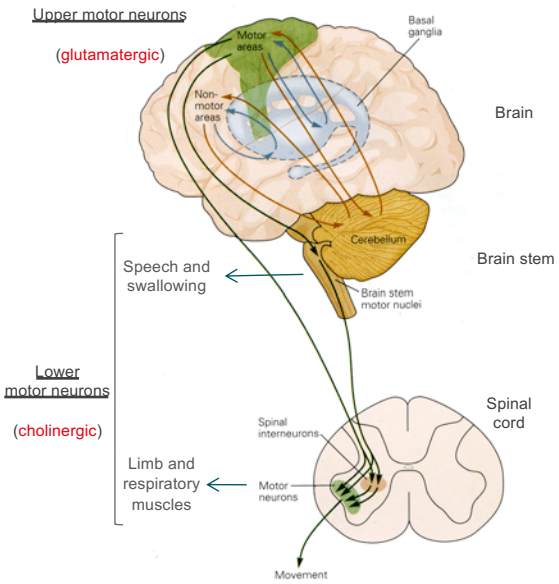
Motor system

Motor system organization

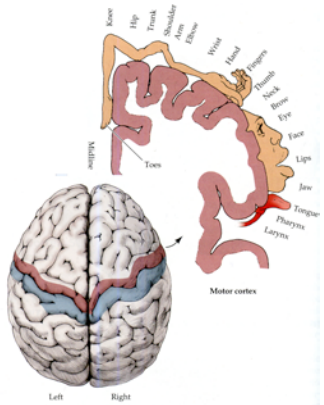
- motoneurons (MNs) are subdivided into upper and lower MNs.
- upper MNs synapse directly on lower MNs and spinal interneurons.
- lower MNs innervate skeletal muscle, co-ordinate and control movement.

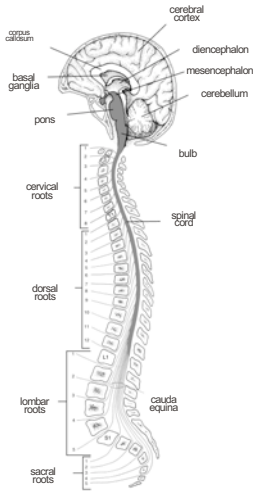


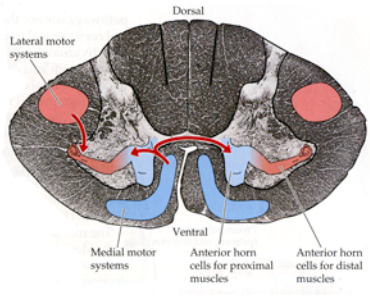
- Kandel, Schwartz, Jessell - Principles of Neural Science, 4th Edition

Motor system

Homonculus in the motor cortex	Vertical organization in the spinal cord	Linear organization at each level of brainstem and spinal cord



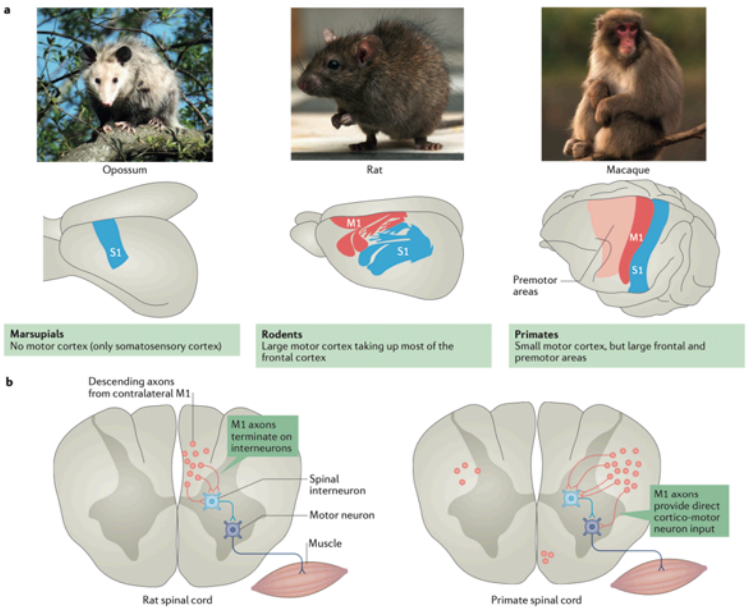




- Neuroanatomy through Clinical Cases, 2nd Edition, H. Blumenfeld

Motor system: spinal cord

Motor system organization across mammalian species



- *Ebbesen, C., Brecht, M. Motor cortex — to act or not to act?. Nat Rev Neurosci 18, 694–705 (2017). https://doi.org/10.1038/nrn.2017.119*

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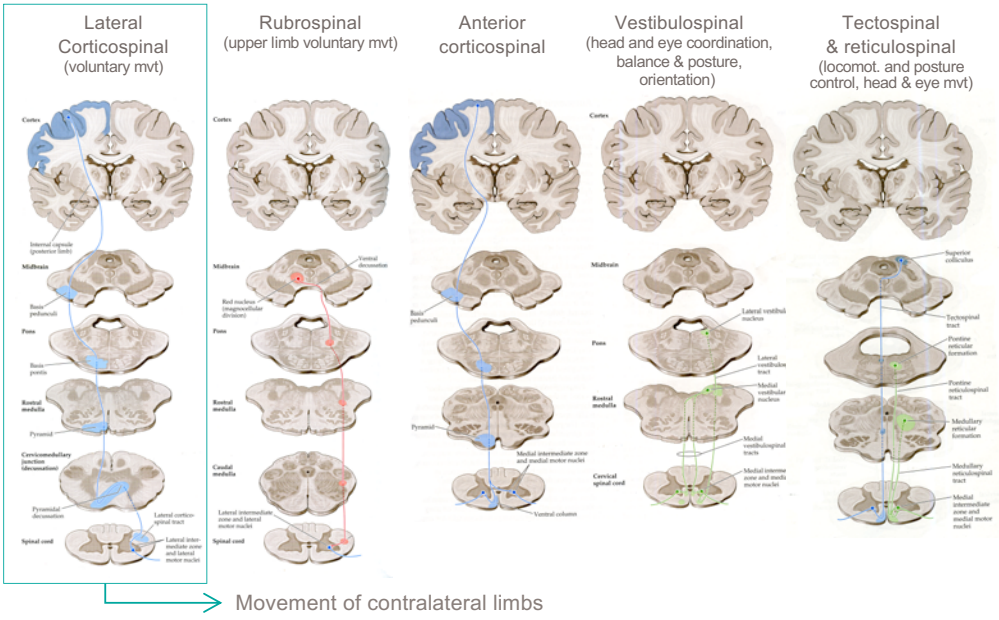
Motor system: descending tracts



- Neuroanatomy through Clinical Cases, 2nd Edition, H. Blumenfeld

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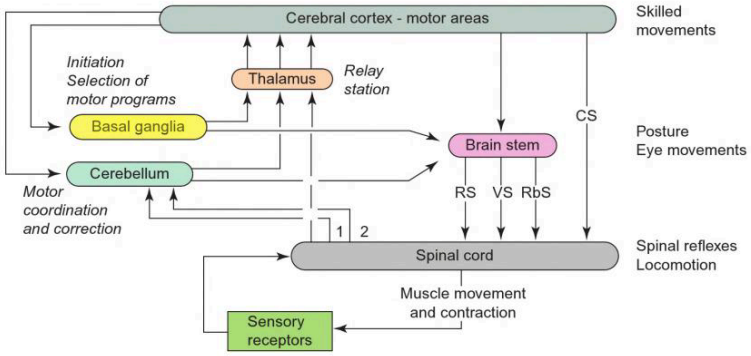
Motor system



CS: corticospinal
RS: reticulospinal
VS: vestibulospinal
RbS: rubrospinal

Basic functions of descending tracts

Cortico- and rubrospinal
1. Transmission of commands for skilled movements.
2. Corrections of motor patterns generated by the spinal cord.

Reticulospinal
1. Activation of spinal motor programs for stepping and other stereotypic movements.
2. Control of upright body posture.

Vestibulospinal
Generation of tonic activity in antigravity muscles

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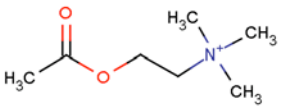
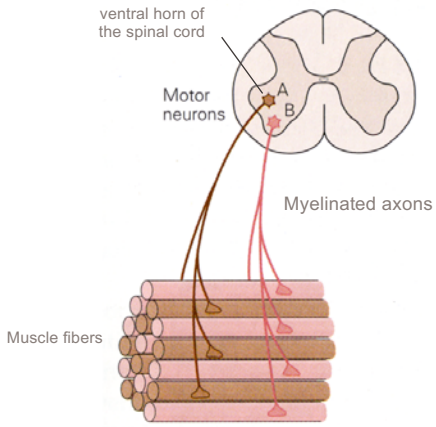
Motor system: motor unit

The neuromuscular system and the motor unit

- Neuromuscular system comprised of motoneurons, axons and muscles
- **Motor neuron + innervated muscle fibers = motor unit** (*C. Sherrington, 1925*)
- This system is responsible for the control and execution of muscle contraction
- Contact between muscles and motoneurons vital for survival of both cell types
- Neurotransmitter: *acetylcholine*





- Kandel, Schwartz, Jessell - Principles of Neural Science, 4th Edition

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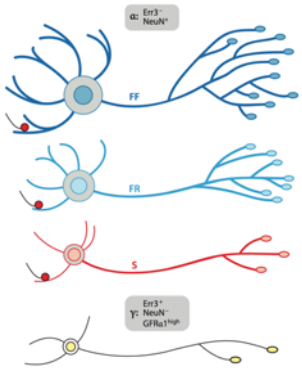
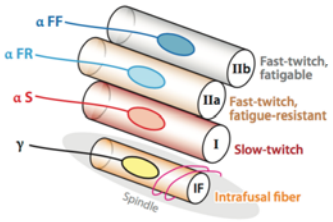
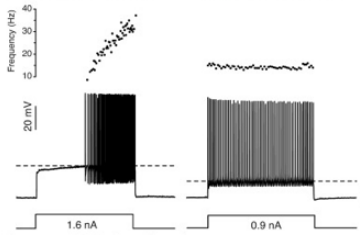
Subtypes of motoneurons in the spinal cord

- **α motor neurons** innervate extrafusal skeletal muscle: muscle contraction
  Central components of 'motor units'
  - Fast-fatigable / fatigue resistant (short-lasting forceful contraction)
  - Slow (important for posture)
- **γ motor neurons** innervate intrafusal muscle fibers (proprioception): modulate the sensitivity to stretch

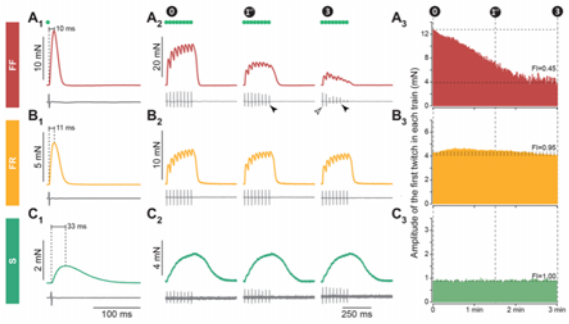




F-type motoneurons S-type motoneurons



Motor units



- Kanning KC et al, Ann Rev Neurosci 2010
  Curr Opin Physiol. 2019 Apr; 8: 23–29

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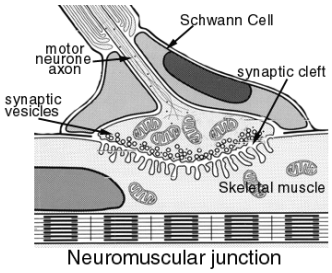
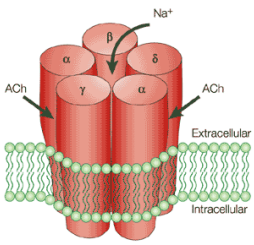
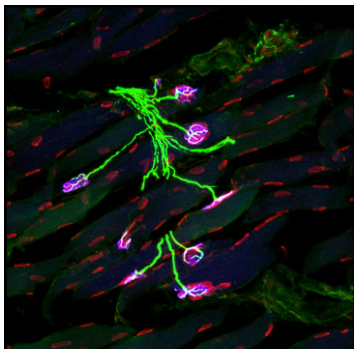
Neuromuscular junction



Neuromuscular junction



Nicotinic acetylcholine receptor



NF160 VAChT
alpha-bungarotoxin (binds AChR)

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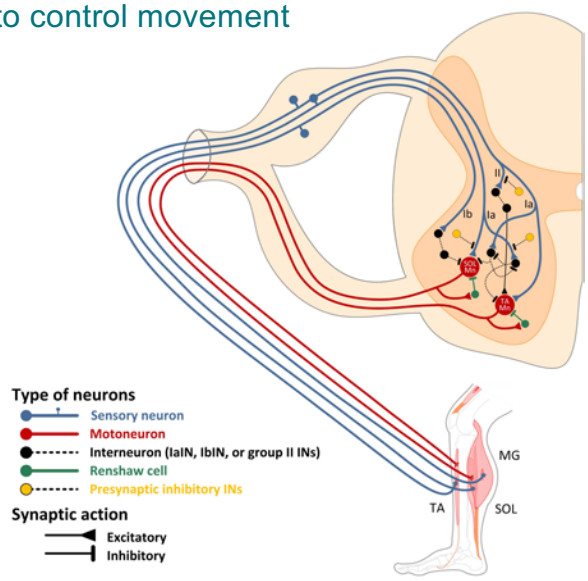
Motor system: spinal cord

Local spinal cord circuit to control movement



- Frontiers in Physiology, 2018, Vol 9 (784)

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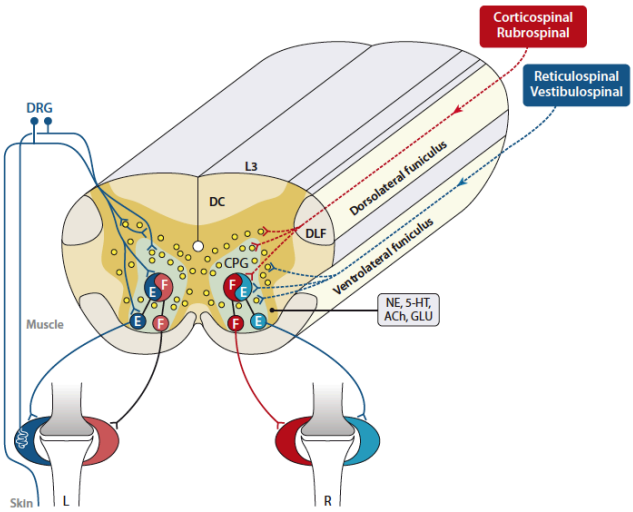
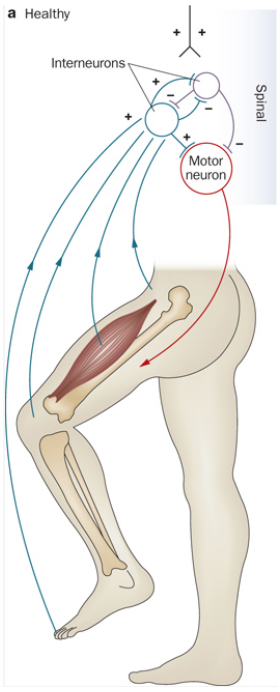
Motor system: spinal cord





Upper motor cortex regulates the activity of the local spinal cord motor circuit (supraspinal control).

- *Neuroanatomy through Clinical Cases, 2nd Edition, H. Blumenfeld*
  Rossignol S. et al., Annu. Rev. Neurosci. 2011. 34:413–40

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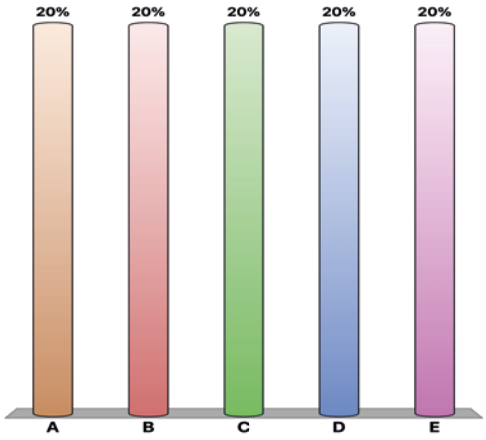
Motor neuron diseases: question 2

A neurodegenerative disease is causing the loss of **lower** motoneurons.

What are the possible symptoms ?

A. Sensory defects in the limb
B. Limb paralysis
C. Hyper reflex
D. Weakness
E. Respiratory failure



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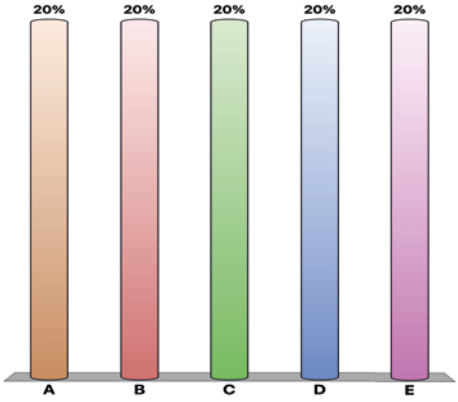
Motor neuron diseases: question 3

A neurodegenerative disease is causing the loss of **upper** motoneurons.

What are the possible symptoms ?

A. Sensory defects in the limb
B. Limb paralysis
C. Hyper reflex
D. Weakness
E. Respiratory failure



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Motor neuron diseases: definition

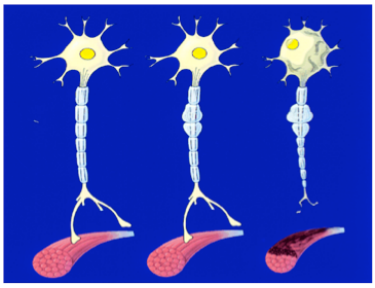
Motor neuron diseases

- **Motor Neuron Diseases**: neurological disorders affecting the **neuromuscular system.**

  [different from **Movement Disorders** = neurological disorders affecting the cerebral control of movement]

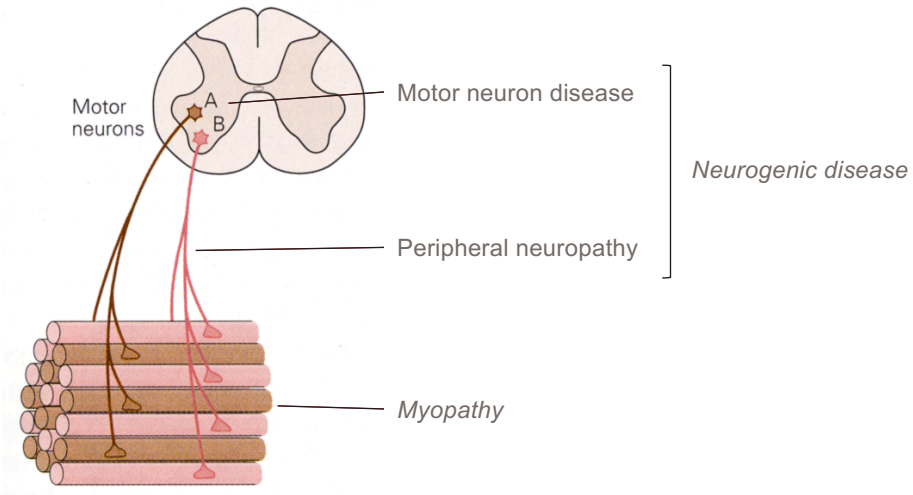
- Motoneuron degeneration that occurs **after embryological development is pathological** (consequence of either injury or disease).

- Disease results in **skeletal muscle paralysis** but range significantly in both aetiology as well as clinical aspects such as severity, duration, and fatality.



Motor neuron diseases: definition

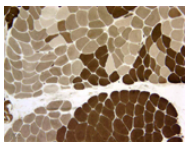
Classification of the diseases affecting the motor unit



Motor neuron diseases: pathological signatures

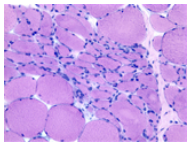
Distinction between neuropathies and myopathies

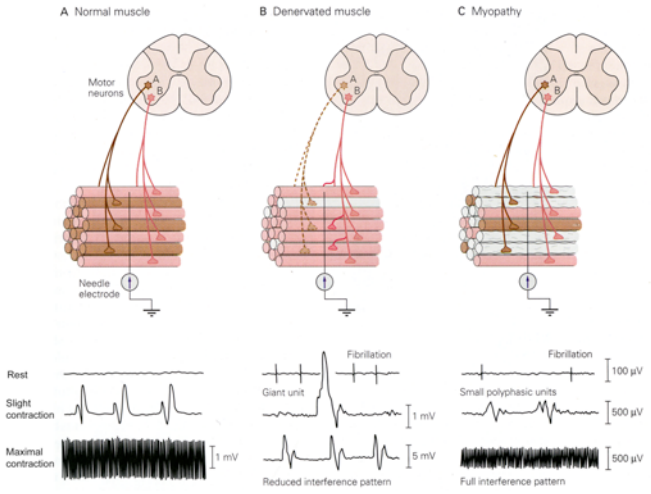
Grouping of muscle fiber types



Myofibrillar ATPase
(more abundant in type II)

Muscle atrophy

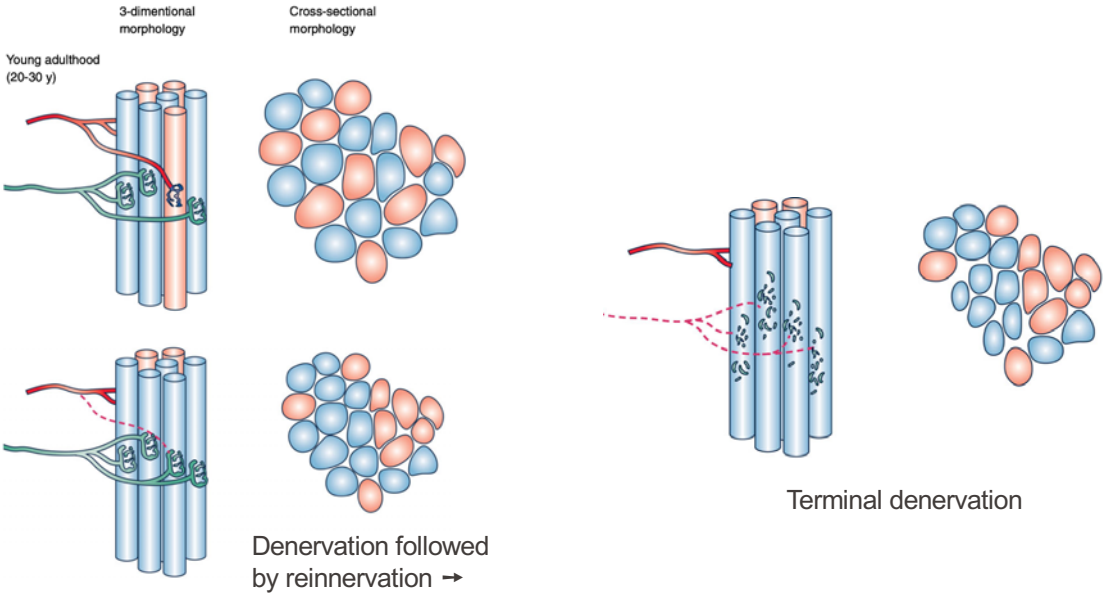




Muscle potentials measured by electromyography.

- Kandel, Schwartz, Jessell - Principles of Neural Science, 4th Edition

Motor neuron diseases: pathological signatures



Denervation followed by reinnervation → fiber type grouping

Terminal denervation

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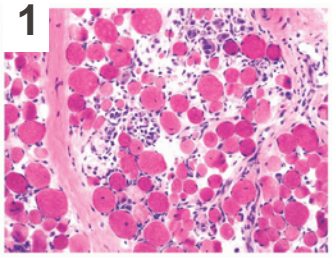
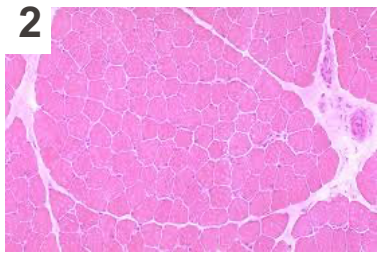
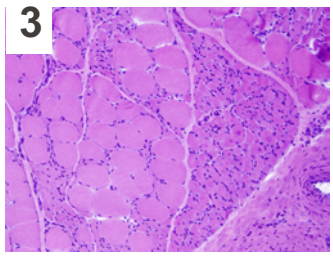
MN diseases - Question 4

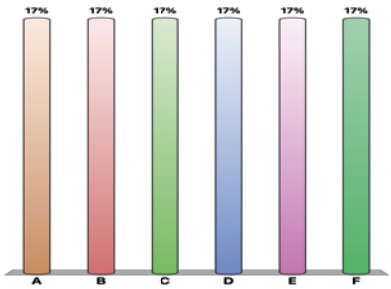
Here are three images characteristics of skeletal muscle in various conditions.
Put these images in the order: normal – myopathy (Duchenne) – neuromuscular disease (SMA) and define the correct answer.







A. 1-2-3
B. 3-2-1
C. 2-1-3
D. 1-3-2
E. 2-3-1
F. 3-1-2



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Motor neuron diseases: etiology

Common pathology ?

- **Multiple pathogenic causes**, and **some common mechanisms** have been proposed to explain the aetiology of motor neuron diseases.
- Many genes implicated in ALS are in genes that are **ubiquitously expressed** in human tissues.
- **Selective vulnerability**: morphology and energy requirements of motor neurons make then particularly susceptible to disruptions in cellular energetics and transport systems.

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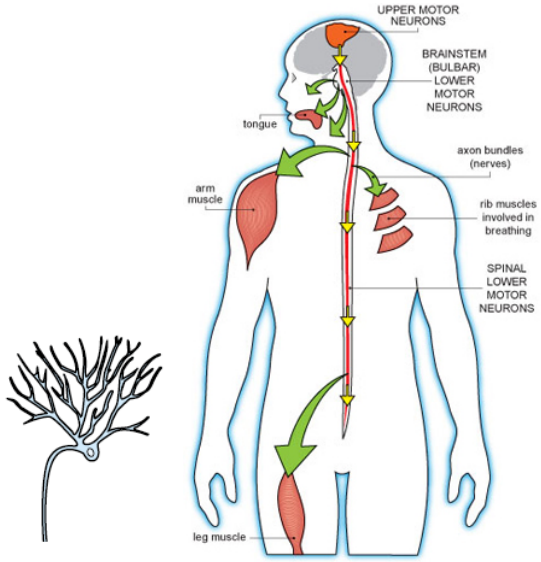
Motor neuron diseases: etiology

Intrinsic vulnerability of motor neurons

- Motor neurons have large metabolic demands
- Axons can project for up to 1 meter
- Large neuronal soma (> 50µm)
- Ca^{++} homeostasis is critical
- Exposure to oxidative stress
- Efficient energy production and axonal transport are essential



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MN diseases - Question 5

You are developing implantable electrodes to stimulate the local motor circuit in the spinal cord.

Rank the following applications according to their chance to be addressable by your technology (from most likely to least likely)

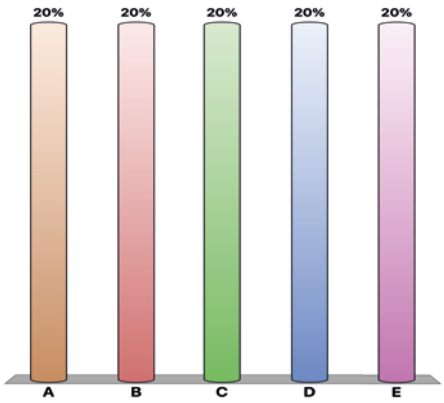
A. Disease leading to neuronal degeneration of the sensory system

B. Myopathy

C. Partial spinal cord injury

D. Disease leading to motoneuron degeneration

E. Complete spinal cord transection



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Motor neuron diseases

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Motor Neuron Diseases include…

- Primary Lateral Sclerosis
- Hereditary Spastic Paraplegia
- Charcot Marie Tooth disease
- Kennedy's disease (CAG extension in androgen receptor)
  X-linked spinobulbar muscular atrophy
- **Spinal Muscular Atrophy (SMA)**
- **Amyotrophic Lateral Sclerosis (ALS)**

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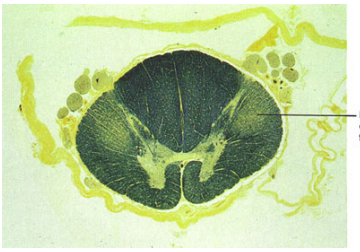
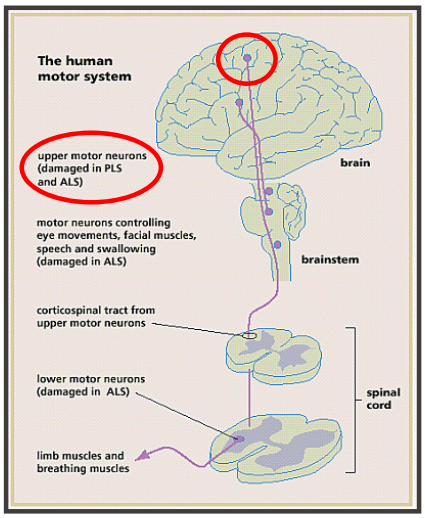
Motor neuron diseases: primary lateral sclerosis

- Degeneration of upper MNs in the motor cortex only
- Non fatal
- Non inherited
- Progressive **muscle weakness**
- Arms, legs and face affected
- **Spasticity**
- No muscle wasting
- Symptomatic treatment (muscle relaxants) to reduce spasticity



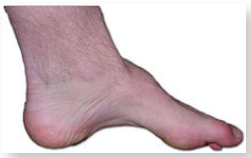


Motor neuron diseases: Charcot Marie Tooth

- Named after 3 physicians who described the condition (*Jean-Martin Charcot, Pierre Marie, Howard Henry Tooth*)



- Most common inherited neuromuscular disorder (prevalence: 17-40/100,000)
- **Peripheral neuropathy**, affects sensory & motor nerves
- Clinically and genetically heterogeneous **hereditary neuropathies**
- Mainly **weakness of extremities** (often legs first), limbs can be affected
- Predominantly motor deficits ↔ Predominantly sensory deficits
- Blood test diagnosis



Motor neuron diseases: Charcot Marie Tooth

Genetic causes

>30 loci, approx. 20 causative genes

Inheritance can be autosomal dominant, X-linked or autosomal recessive

Electrophysiological criteria → classification in two groups

- **Demyelinating type** (Schwann cells)
- **Axonal type** (axonal loss)

Involved gene functions:

- Mitochondrial fusion/fission and transport
- Myelination
- Axonal transport
- RNA processing
- etc…

Motor neuron diseases: spinal muscular atrophy

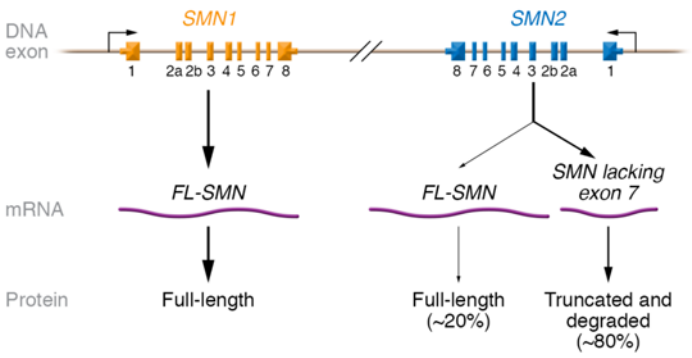
Spinal muscular atrophy (SMA)

- 2nd most common autosomal recessive genetic disorder
- first genetic cause of death during childhood
- carrier frequency: 1:30-50
- incidence: 1:10,000 births/year
- age of onset: before 6 months
- disease course: 2 years
- bodies outgrow the ability to innervate the muscles.
- no cognitive deficits

SMA type I
(Werdnig-Hoffmann disease)

Hypotonia = low muscle tone
« floppy baby »

SMN1 / *SMN2* genes



SMN complex:

- Role in RNA metabolism, actin dynamics
- Key for axonal outgrowth and stabilization of neuromuscular junctions

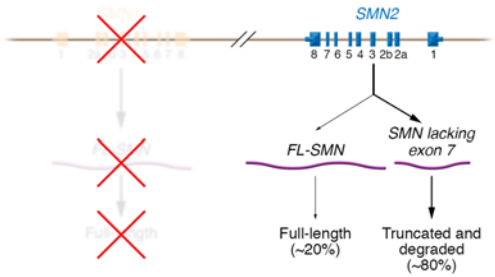
Cell, Vol. 80, 155–165, January 13, 1995, Copyright © 1995 by Cell Press

Identification and Characterization of a Spinal Muscular Atrophy–Determining Gene

- J Clin Invest. 2018;128(8):3219-3227

Disease etiology

- SMA is due to the loss of the SMN1 gene.
- A second gene present in humans, SMN2, can partly rescue SMN1 function.
- The number of SMN2 copies varies between 1 and 4 or even more.



SMA type	Age of onset	Death	Motor abilities / defects	SMN1	SMN2 copies	Frequency
I	0-6 months	< 2 yrs	Never sit	Deleted/ mutated		60%
II	7-18 months	> 2 yrs	Sit, never walk			20-30%
III	> 18 months	Adult	Stand and walk Scoliosis Weakness			10-20%
IV	10-30 yrs	Adult	Walk during adulthood Weakness			rare

Motor neuron diseases: SMA

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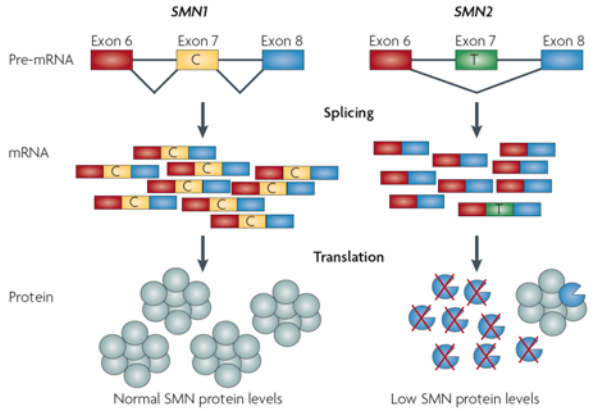
The SMA phenotype is caused by deletion or mutations of the SMN1 gene

The SMN2 gene regulates the phenotypic variability of the disease

SMN2: C→T mutation that leads to a lack of Ex7 in the transcript → Loss of Ex7 amino acids results in SMN protein with reduced oligomerization efficiency and stability, rapidly degraded



- Burghes AHM & Beattie CE, Nat Rev Neurosci 10 597-609 (2009)

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Motor neuron diseases: SMA

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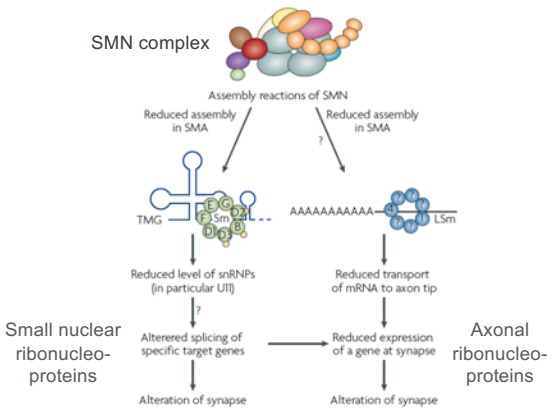
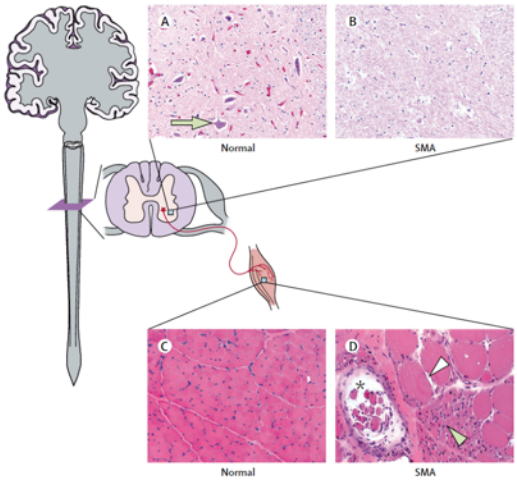
Two main functions proposed for SMN complex:

- mRNA splicing (snRNPs)
- Axonal transport (axonal ribonucleoproteins)





- Lunn MR & Wang CH, Lancet 371 (2008)
  Burghes AHM & Beattie CE, Nat Rev Neurosci 10 597-609 (2009)

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Exercise 1