Development of Complex Curricula for Molecular Bionics and Infobionics Programs within a consortial* framework**

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**Molekuláris bionika és Infobionika Szakok tananyagának komplex fejlesztése konzorciumi keretben

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BEVEZETÉS A FUNKCIONÁLIS NEUROBIOLÓGIÁBA

INTRODUCTION TO FUNCTIONAL NEUROBIOLOGY

By Imre Kalló

Contributed by: Tamás Freund, Zsolt Liposits, Zoltán Nusser, László Acsády, Szabolcs Káli, József Haller, Zsófia Maglóczky, Nórbert Hájos, Emilia Madarász, György Karmos, Miklós Palkovits, Anita Kamondi, Lóránd Erőss, Róbert Gábriel, Kisvárdai Zoltán

Control of movement

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I. Neuromuscular system. Regulation of locomotion at the level of the spinal cord.

II. Regulation of posture and balance. The medial postural system.

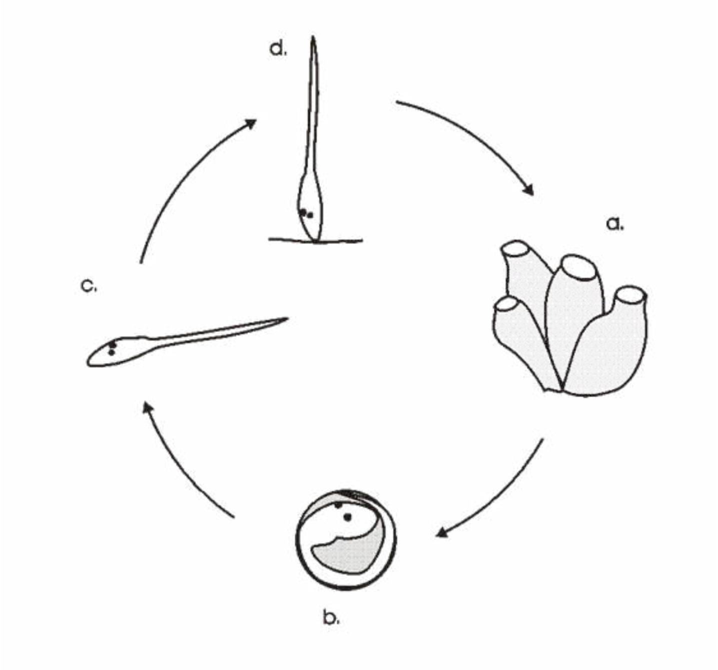
III. Regulation of fine movements. The lateral voluntary system.

Movement serves survival by enabling

- **Self-propagation - feeding**
- **Self-protection ("flight or fight")**
- **Species-propagation – reproduction**
- **Species-protection (communities, societies)**
- Biodiversity-propagation
- Biodiversity-protection

Some of the movements are **involuntary** (reflexes, fixed action patterns), some **rhythmic movements** are automatically carried out **under continuous voluntary control** (rhythmic motor patterns -locomotion) and some movements are **voluntary** (directed movements).

Locomotion – for many species the capability to change location means survival (finding new food resources, protective environment, a mate etc.)



Based on the observations on the life cycle of "sea squirt", ***Rodolfo R. Llinas*** suggested that the nervous system evolved to allow active movement of the animals.

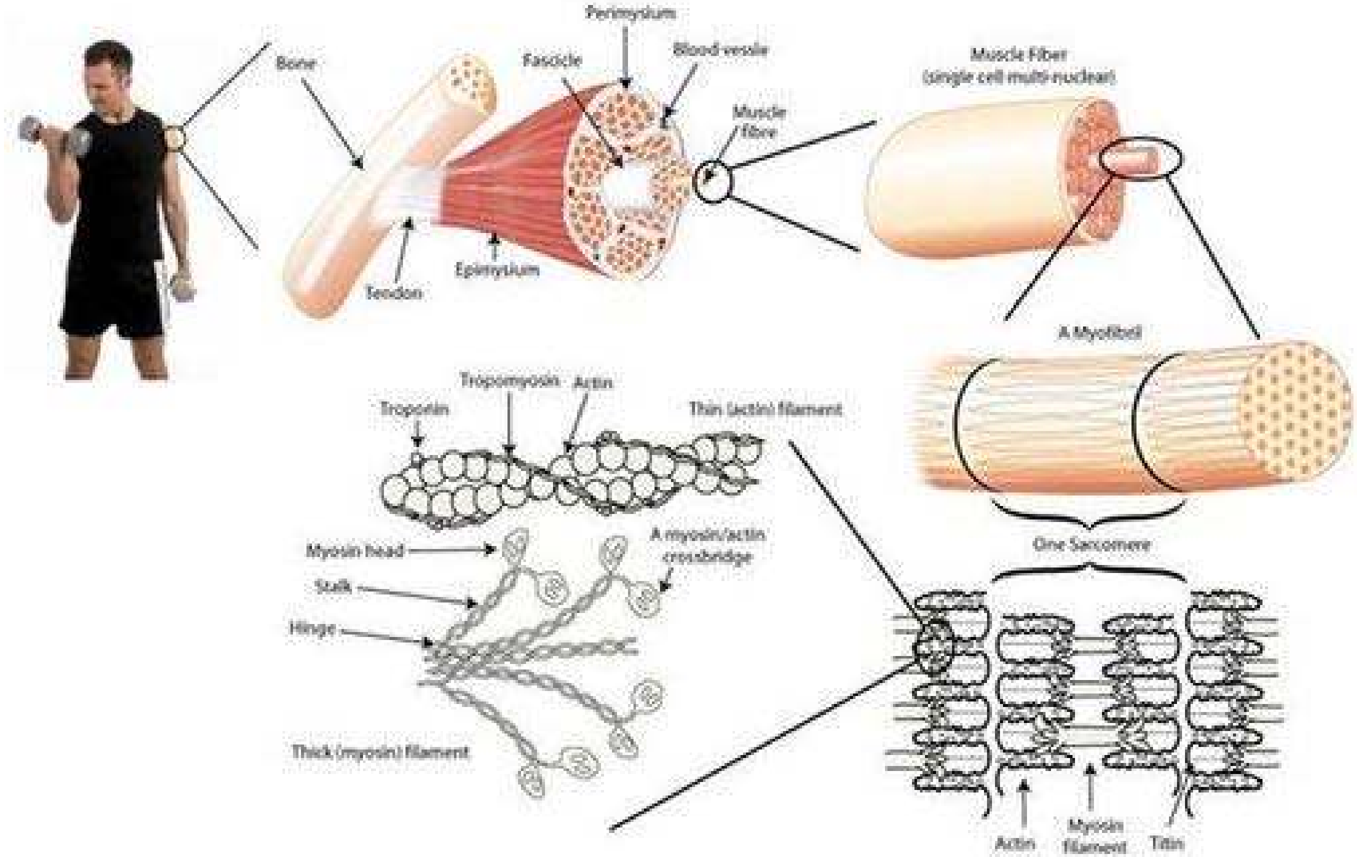
Speed, force, dimension and complexity of movement are determined by

1. Biomechanical properties of the skeleto-muscular system
2. State of the development of nervous system

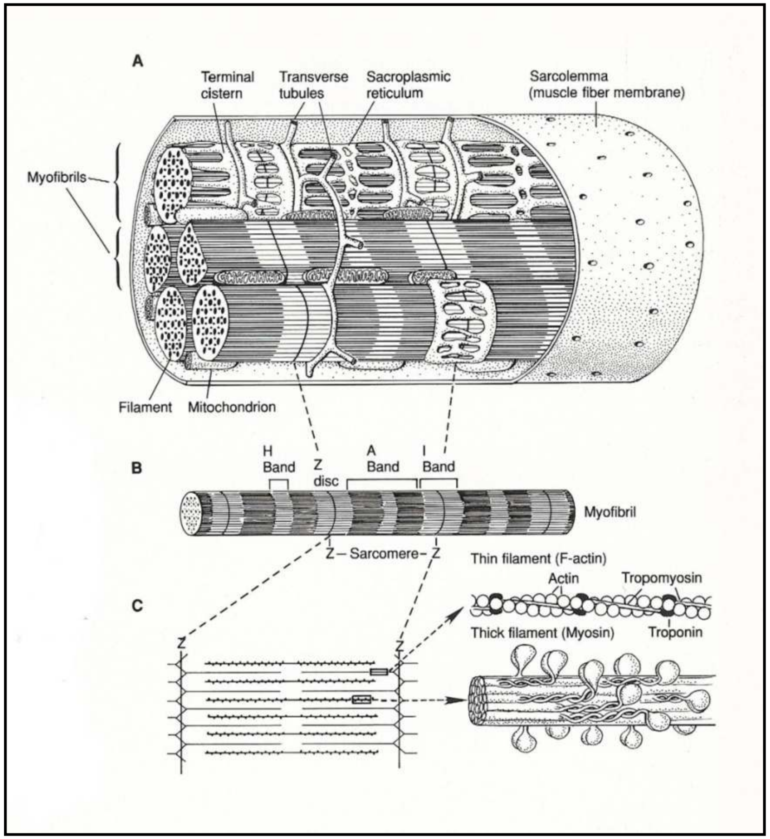
phylogenetically

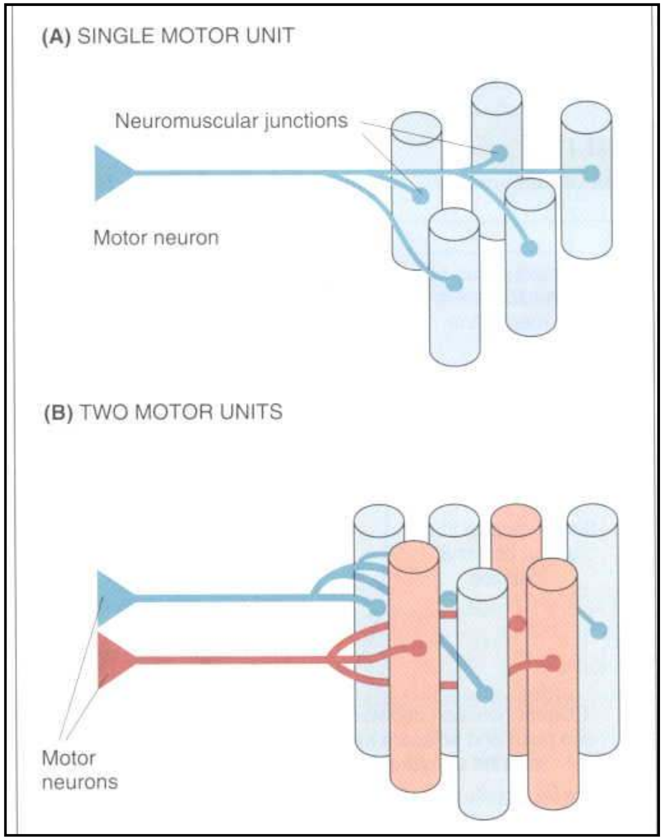
ontogenetically

1. Biomechanical properties – structure and function of skeletal muscles

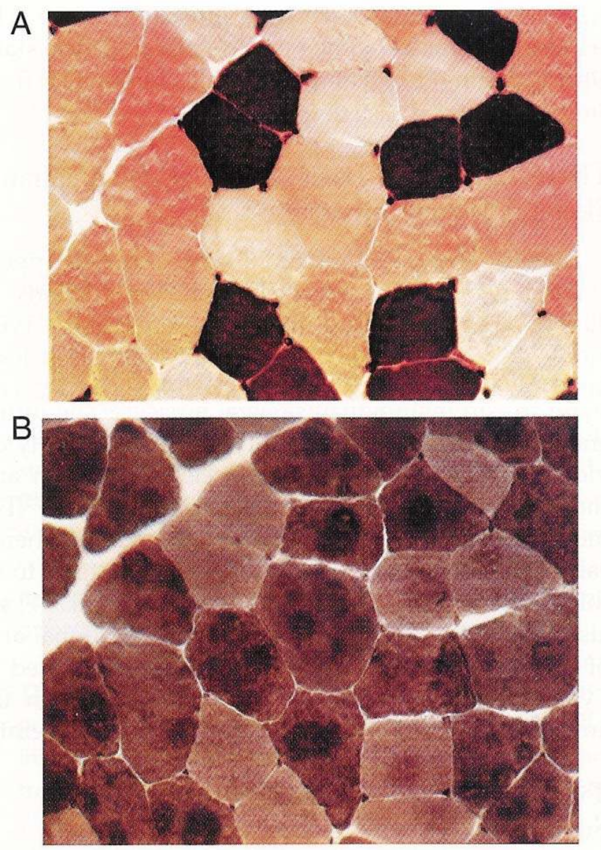


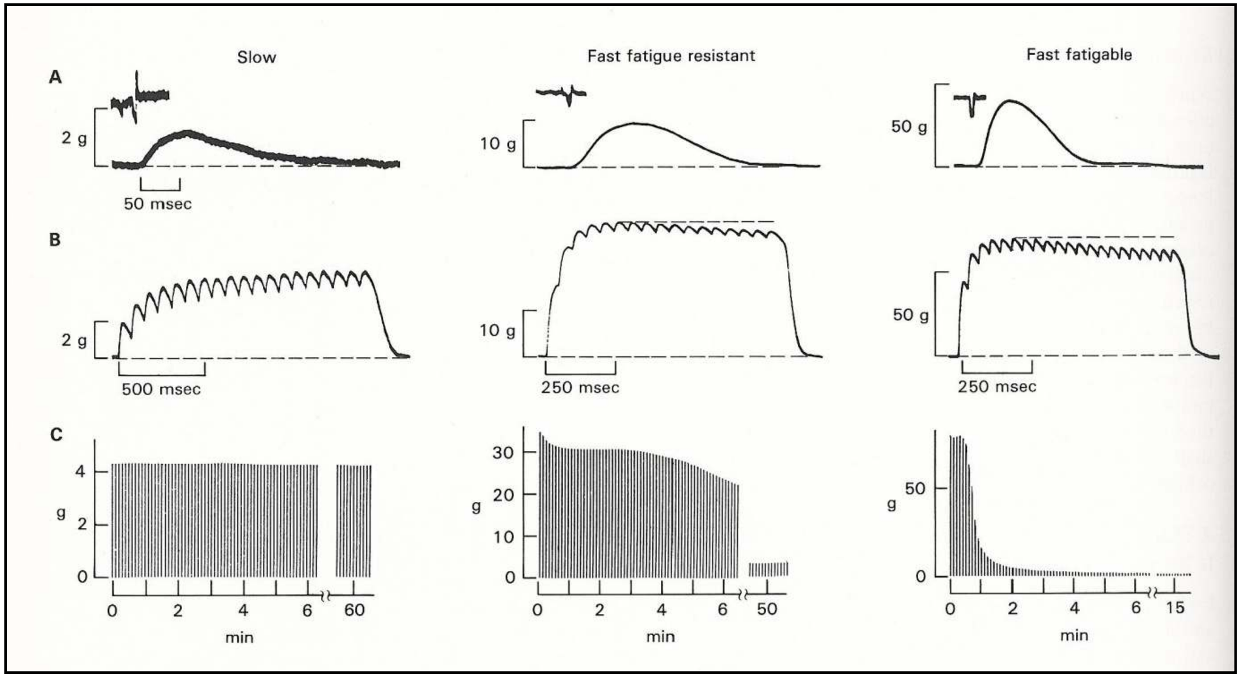
Muscle fibers contract in response to excitation. Fibers belonging to different motor units are intermingled.





Speed and force of contraction depend on the muscle fibers involved.





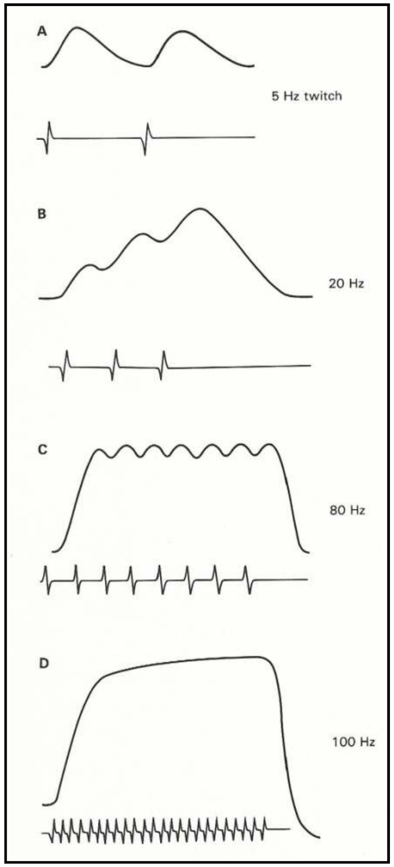
Muscle tension is regulated by motor neuron firing rate . Hierarchical and asyncronous activation of motor units!

Single MUs - **Twitch**

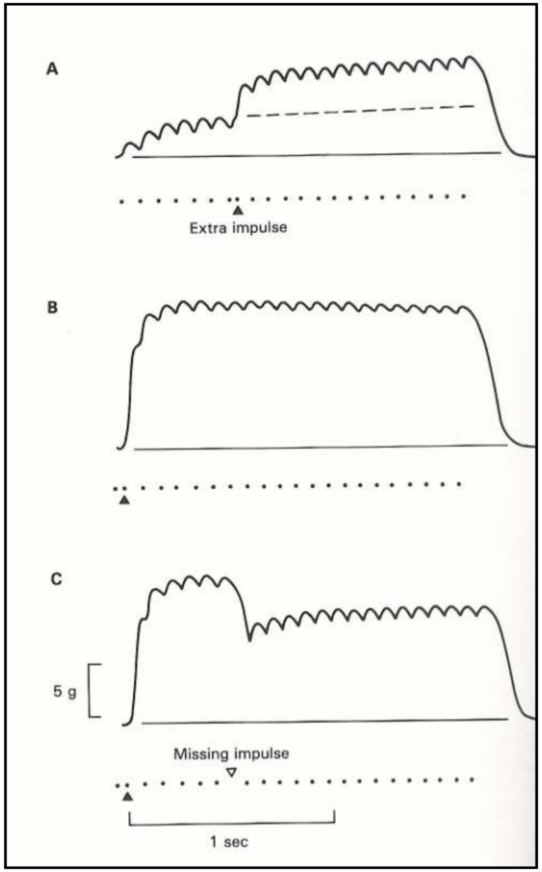
Contractile force is maintained by **Summation**

Incomplete tetanus

Tetanus

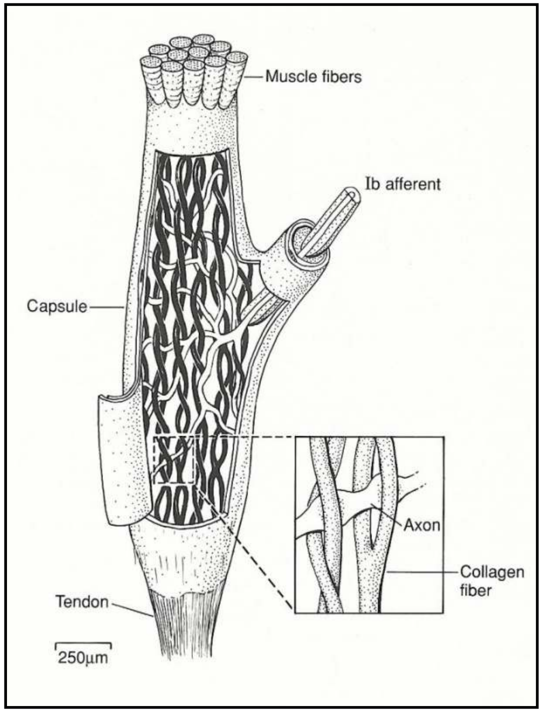


Effect of extra and missing impulses



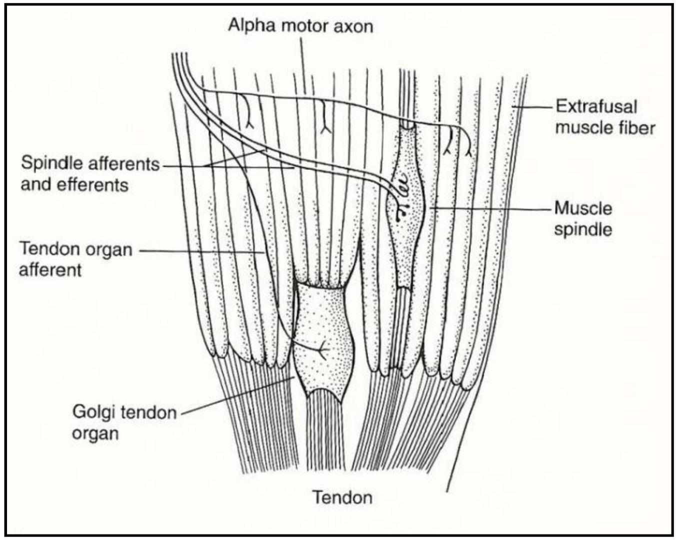
Muscle tension is modulated by receptors sensing active and passive tension, as well as static and dynamic changes during muscle contraction. Gain adjustment is possible in the muscle spindle.

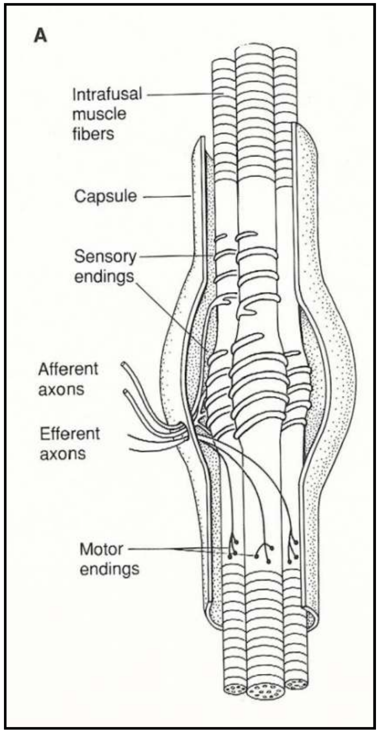
Golgi tendon organ



Muscle spindle

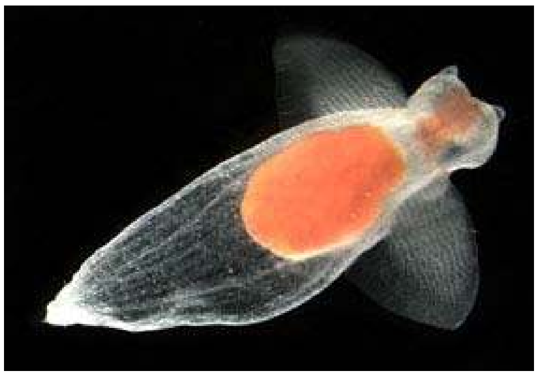
- nuclear bag
  (static and dynamic)
- nuclear chain





2. State of the development of nervous system

More advanced nervous system means higher complexity of movements. Maturation of the CNS shows species variations.



20-40. weeks

2 months

10 months

12 months

14 months

Human gait is composed of phasic and tonic components

- **the phasic component** means the rhythmic alternating contractions of limb and trunk muscles, produced mainly by central pattern generators – CPGs are functional at birth

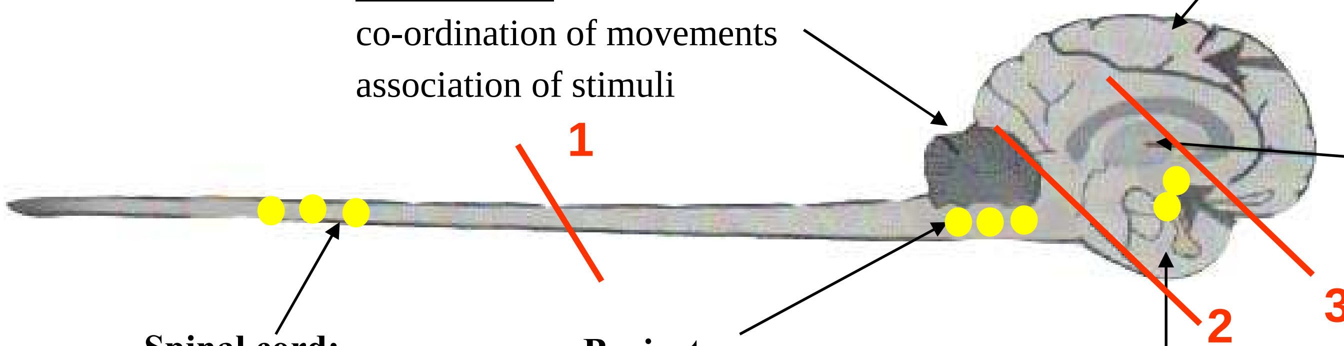
- **the tonic component** is associated with postural muscles and quite immature at birth – it becomes functional by the maturation of
  - the musculoskeletal system
  - the sensorimotor networks
  - higher brain centers
  - descending motor pathways
  - ascending sensory pathways

CPG for gait control is located in the spinal cord. Cats with total spinal cord lesion can walk on a moving platform (with supported body) after recovery from the traumatic shock.

Cerebral cortex:
speech,
hand-finger movements

Cerebellum:
co-ordination of movements
association of stimuli

Basal ganglia:
initiation of movement
behavior



Spinal cord:
protective reflexes
walking

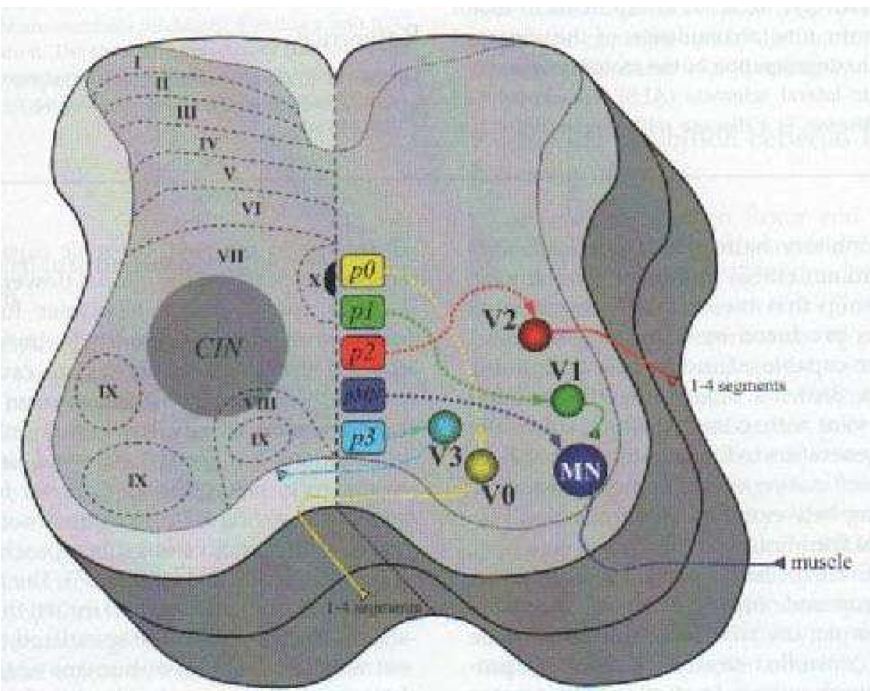
Brainstem:
chewing, swallowing,
breath taking ,
walking
eye movements

Diencephalon:
eating,
drinking

CNS lesions resulting in impairment of movements

1. **Spinal cord injury**
2. **Decerebration**
3. **Decortication**

The network responsible for controlling walking develops during the embryonic life. A dorsoventral gradient of brain morphogens trigger the expression of transcription factors, which in turn determine differentiation of neural stem cells to interneurons (V0-V3) and motoneurons (MN).



V0 - coordination of left-right alternation (contralateral)

V1 - speed of MNs output (ipsilateral inhibition)

V2 - burst robustness left-right alternation

V3 - burst robustness

A network of spinal neurons (composed of interneurons and motoneurons) generates a rhythmic motor pattern. Due to its complexity in vertebrates, it is difficult to investigate the regulating neuronal network, which is therefore largely unknown.

The major observations about the function of cellular components and the operational rules of the neuronal network generating the rhythmic motor pattern derive from studies on **organisms with relatively simple neuronal systems i.e.**

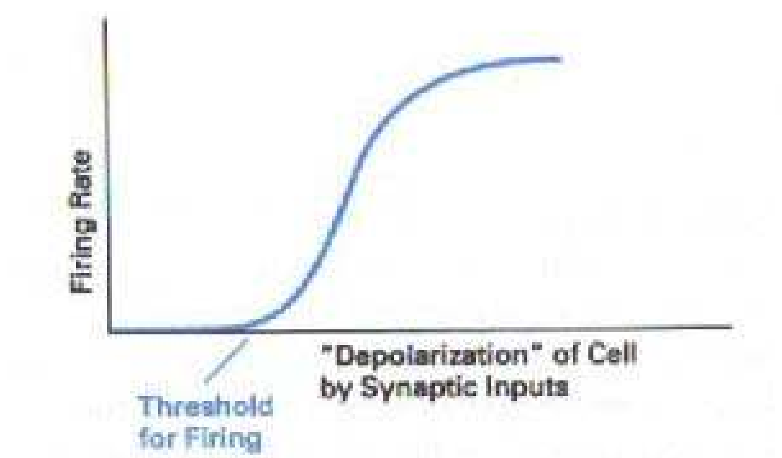
clione
lobster
leech
lamprey

Central (motor) pattern generator (CPG, MPG): Neuronal network, which is capable to maintain a rhythmic output without rhythmic sensory or central input

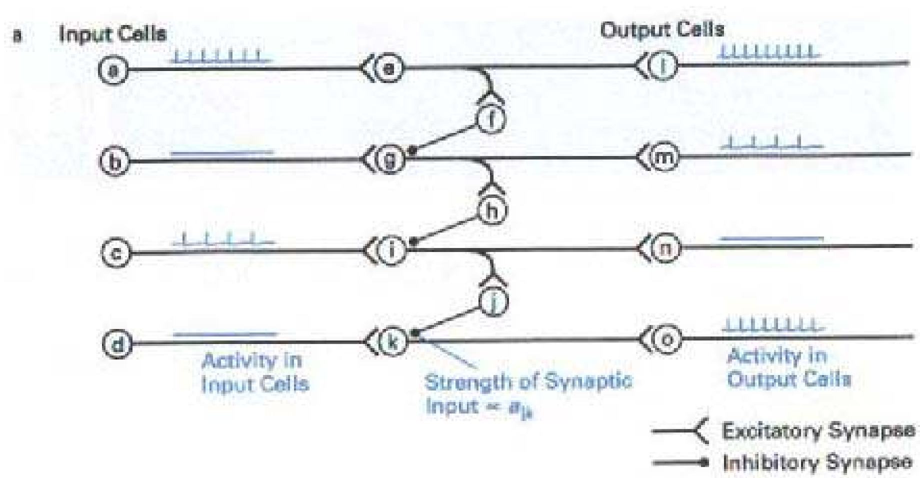
Rhythms are either generated:

- by endogenously oscillating neurons (currents) or
- by network activity of non-oscillating neurons

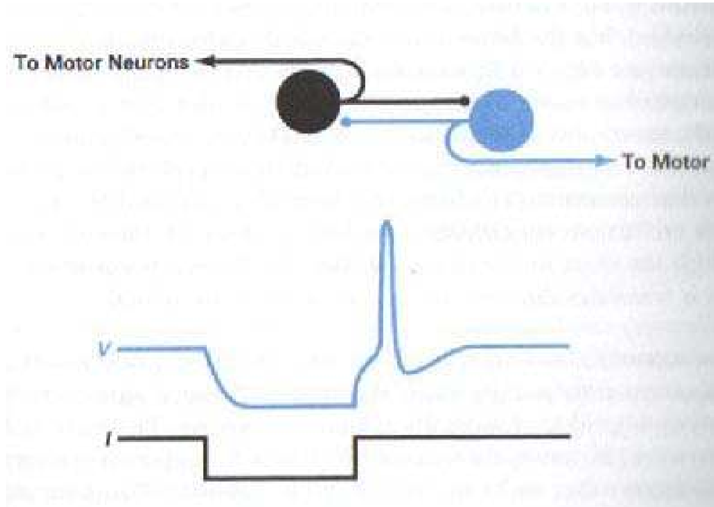
Cellular (neurons) response

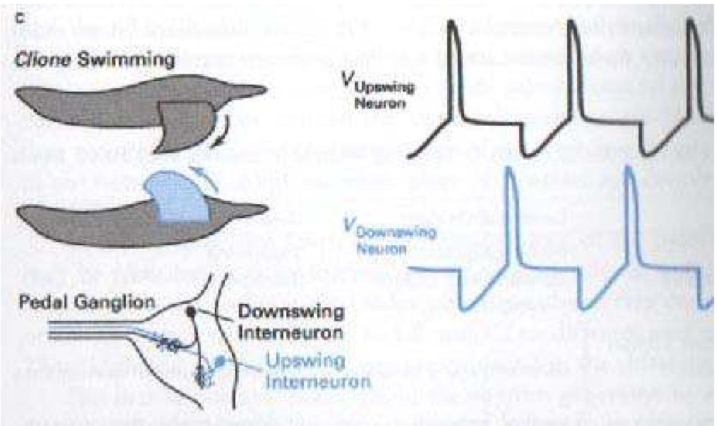


Network (model) response



Clione – two-neuron system





Half-center oscillator: Two neurons connected in reciprocal manner generate rhythms – alternating muscular contraction and relaxation

Postinhibitory rebound lead to generation of action potentials ! „anode break spike"

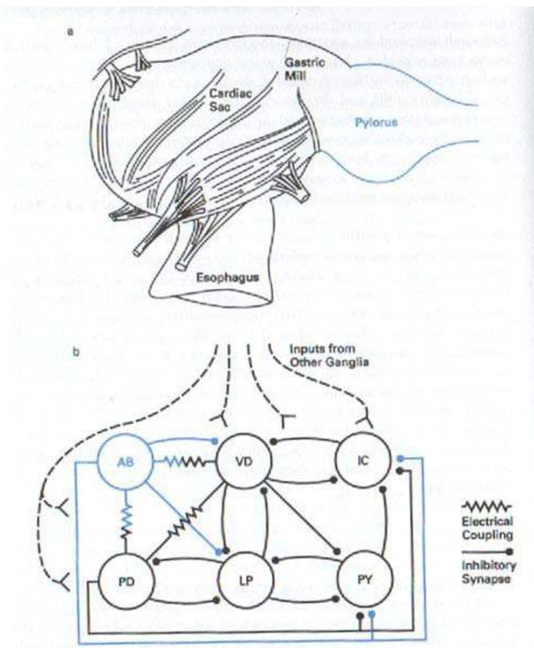
<u>**Common phenomenon**</u>: voltage-dependent Na channels or T-type calcium channels are partially inactivated at the resting potential. Transient hyperpolarization release the channels from the inactivated state. Threshold of the action potential will be lower.

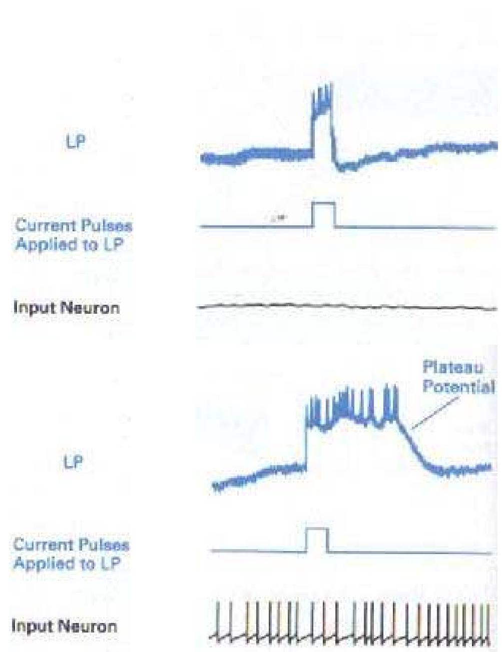
Electrical properties of the participating neurons determine

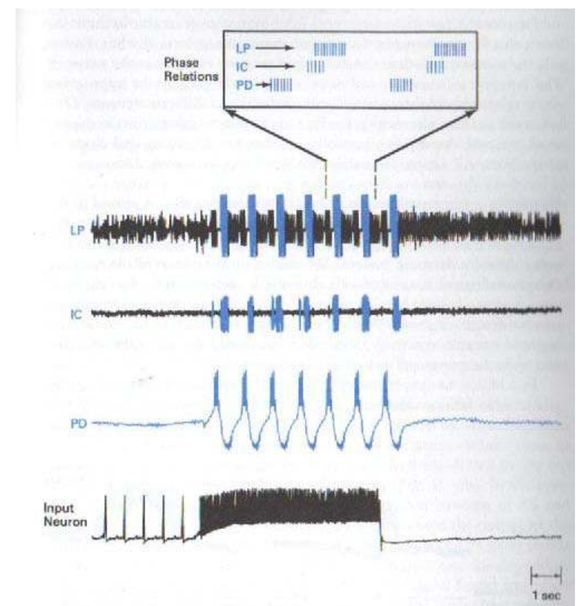
- oscillation in network output
- activity of neurons
- period of rhythms

Lobster – multi-neuron system

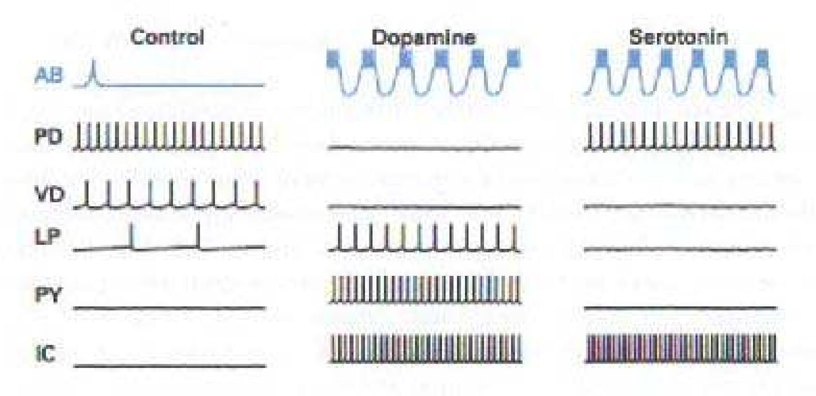
Rhythm generation is dependent on the activity of other cells – network input is essential! The released neurotransmitter alters the membrane characteristics of the neurons within the network! AB cell shows **conditional burst activity**! When it is active, a short depolarization induces a **driver (plateau) potential in** LP neuron!





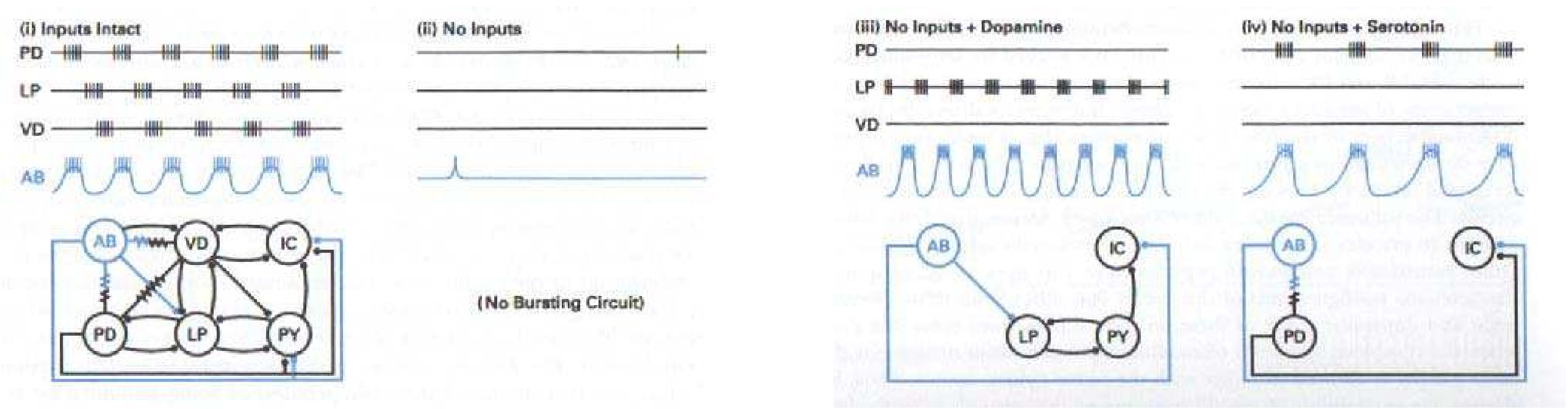


Lobster - neuromodulators alter network activity and output.



<u>Experiment:</u> Removing neuronal input (GABA, serotonin, dopamine, FMRFamide-like peptide etc.), adding neuromodulators

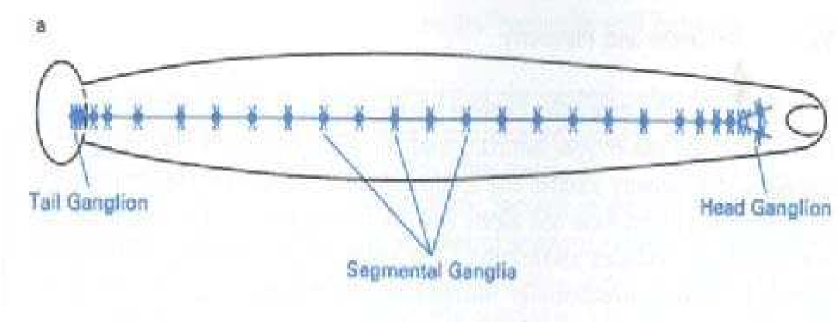
Alteration of excitability of neurons and synaptic strength within the network results in **different outputs**!

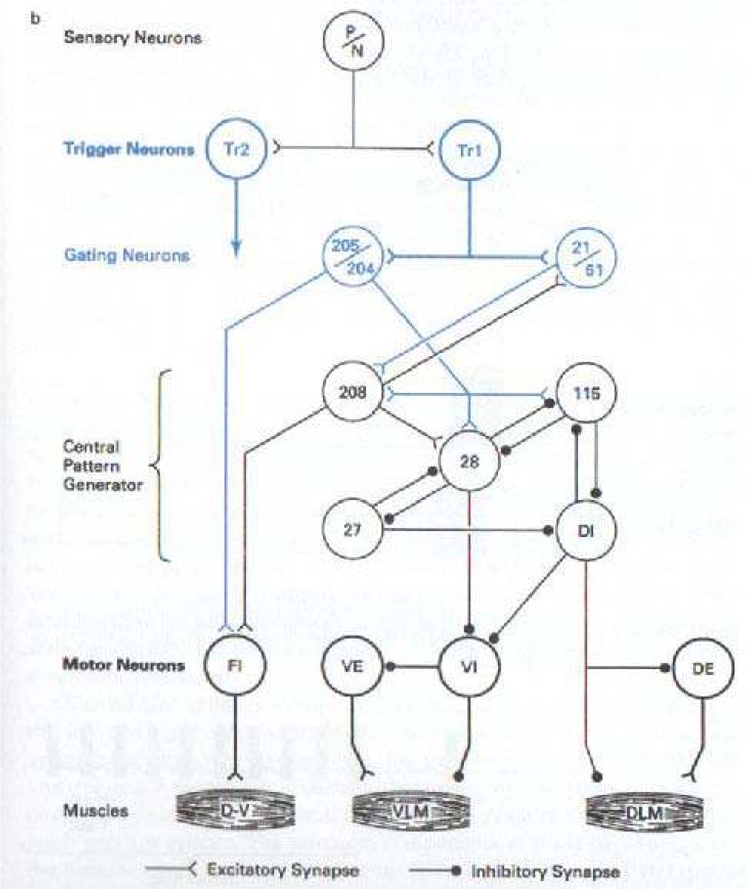


Leech - command neurons in the network activity

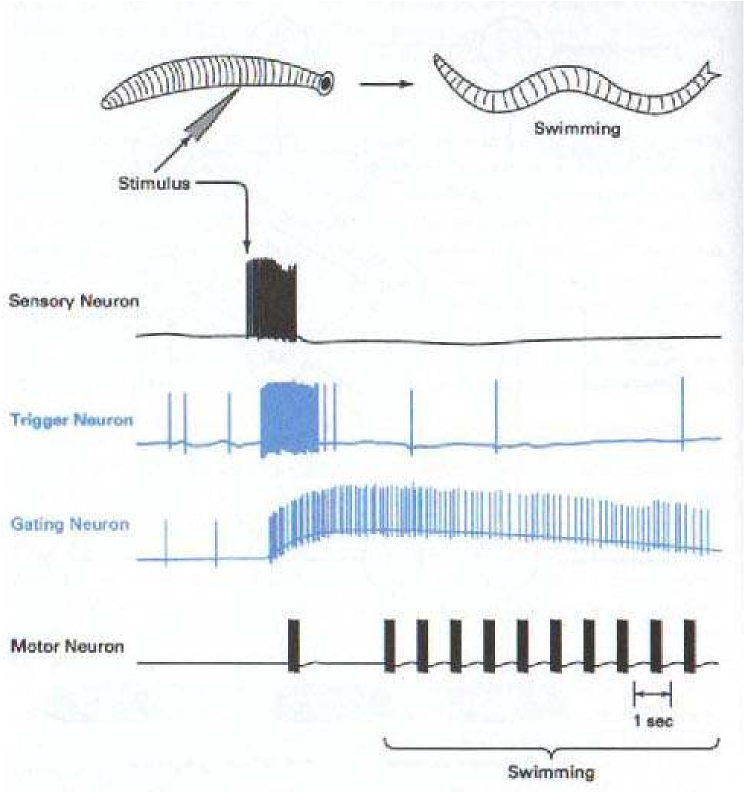
Trigger neurons receive input from sensory neurons and initiate rhythmic activity of MPGs

Gaiting neurons determine the duration of the MPGs activity – the duration of the swim





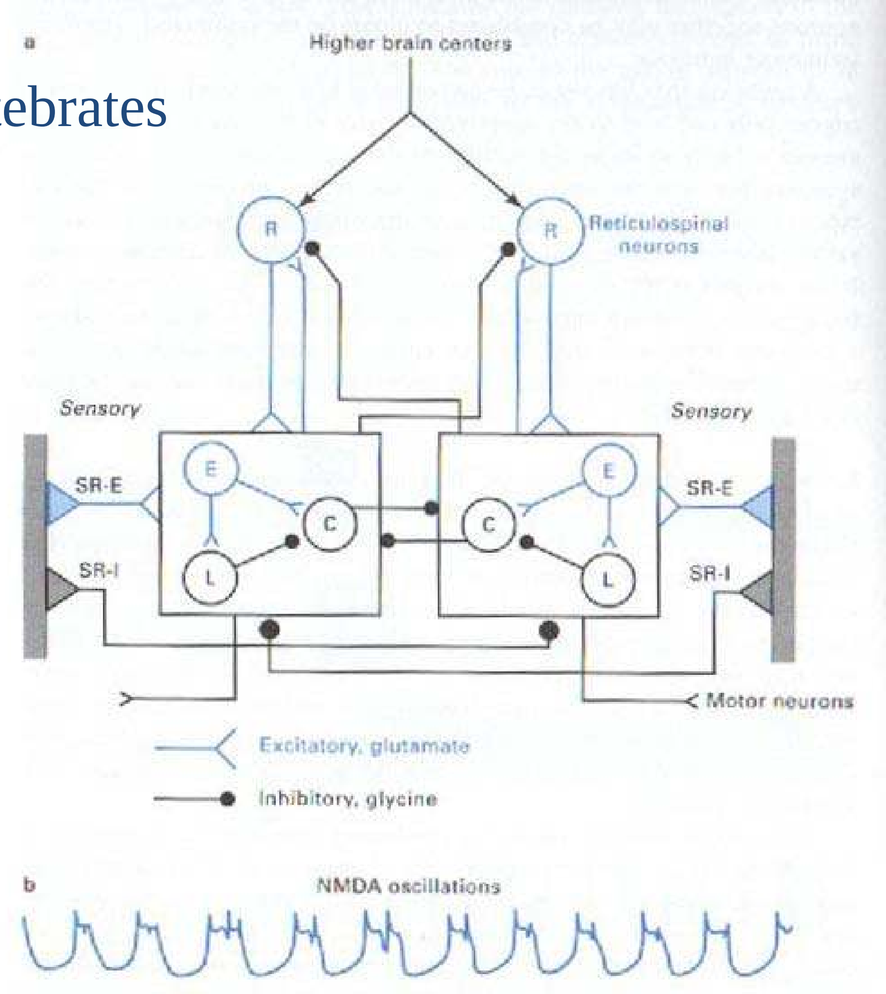
Leech - command neurons in the network activity



Short activation of the **„trigger"** neuron induces a long-lasting activation of the **„gating"** neuron, which in turn leads to a long-lasting burst activation of **CPGs** and **the motoneurons**.

Lamprey - command system of vertebrates

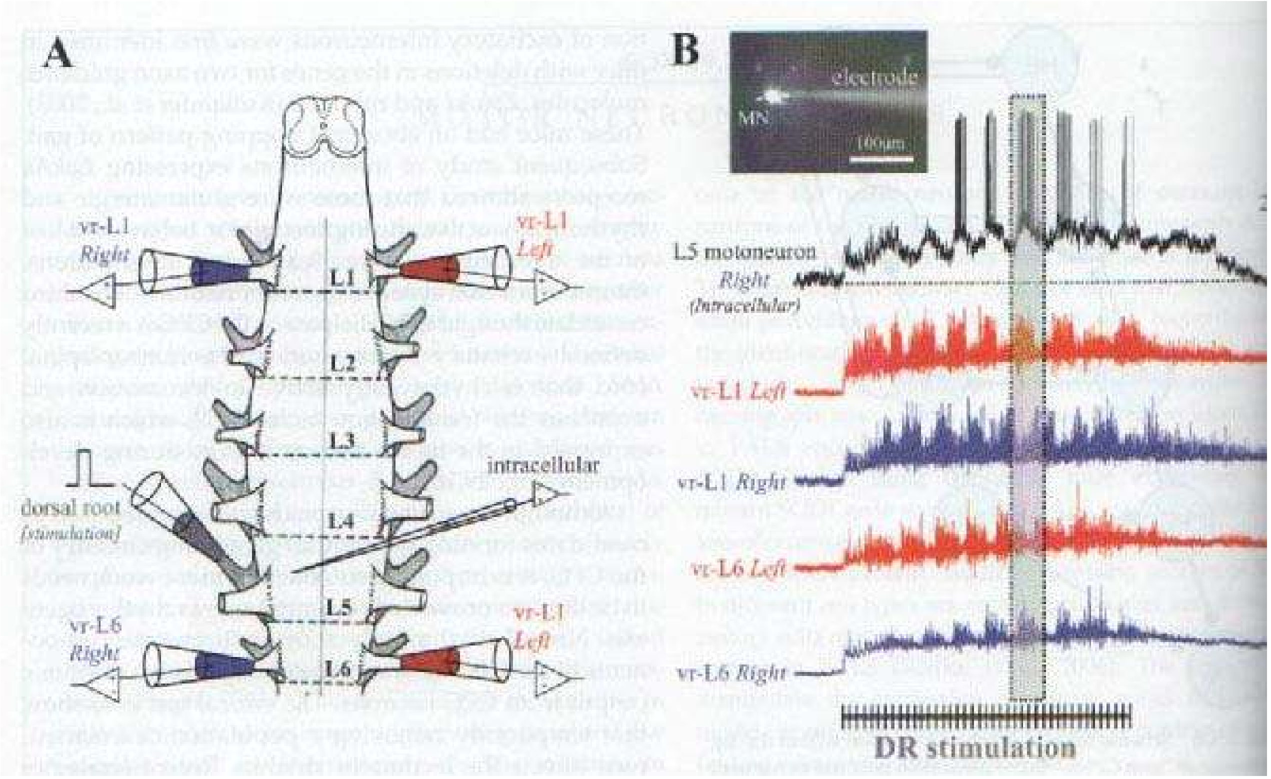
CPGs are composed of excitatory (E) and inhibitory interneurons (L&C). "C" interneurons are in reciprocal inhibition with its pair in the other half-center. Stretch receptors (SR) send excitatory and inhibitory feed-back to CPGs. Excitatory reticulospinal neurons (R) induce plateau potentials in the pattern-generating neurons. Role of NMDA receptors is to increase calcium levels, which in turn activate calcium-dependent potassium channels.



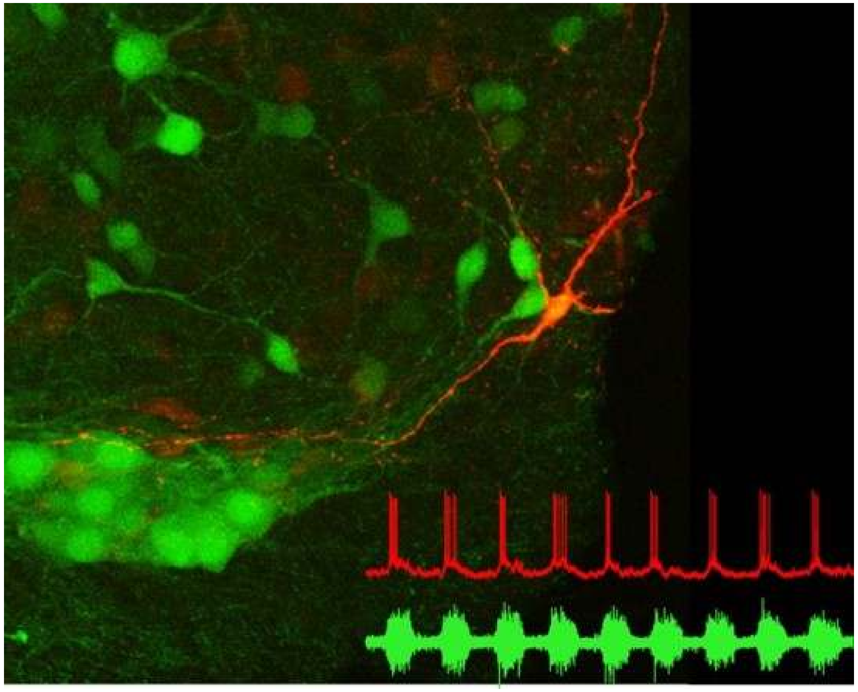
Summary – what can be predicted for the operation of MPGs in mammals (humans):

- similar membrane events (postinhibitory rebound, driver potential etc)
- similar reciprocal connection of half-centers
- neuromodulators influencing electrical properties of network elements
- cellular components brought in action determine the output signal of the network
- the existence of higher command system
- peripheral signals exert also strong influence on the MPGs

Mouse – Rhythmic burst activity of CPGs and motoneurons can be induced **by stimulating dorsal roots** for a longer period



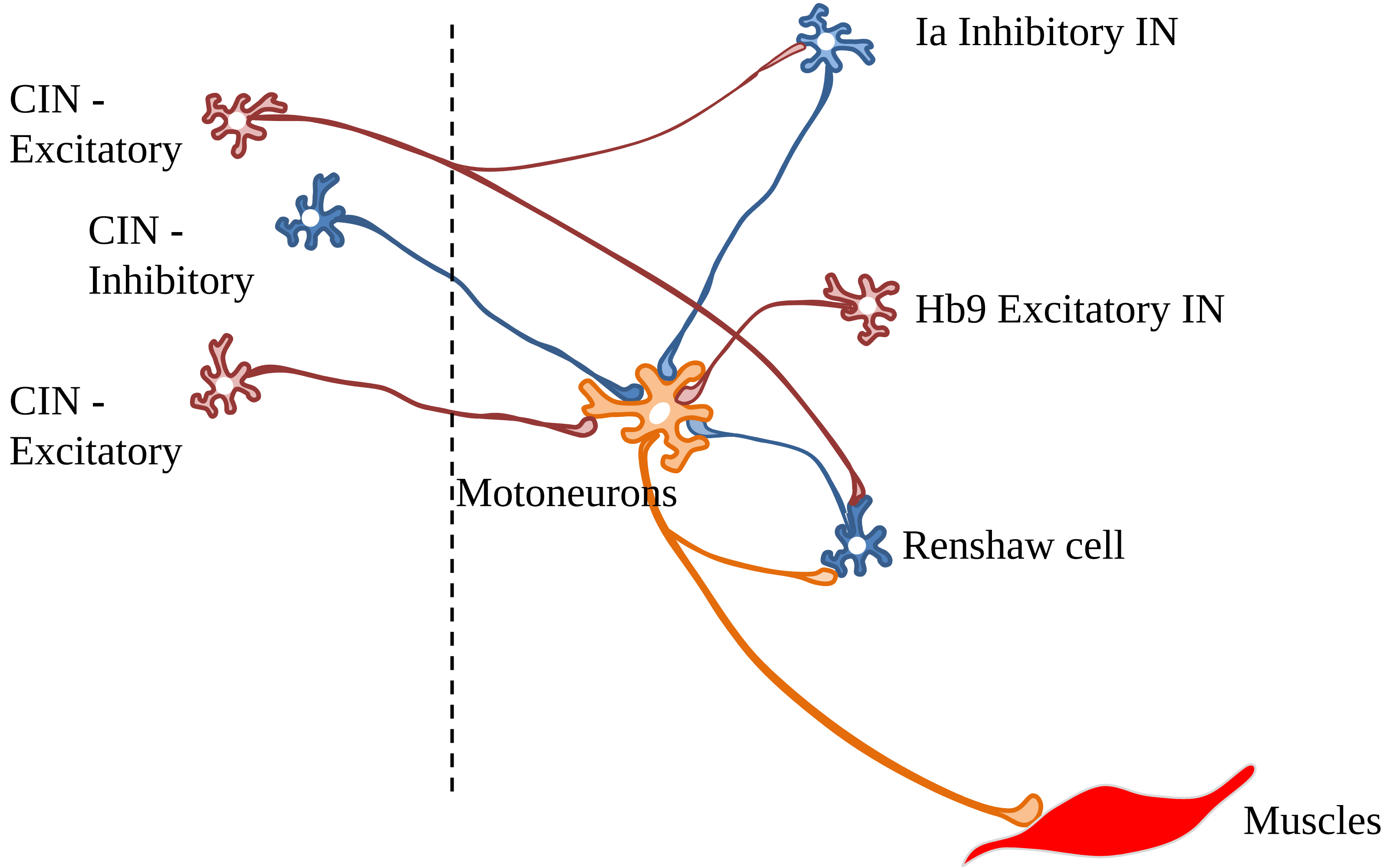
HB9 expressing spinal motoneurons and interneurons in the neonatal mouse spinal cord shown in green by the reporter fluorescein protein.
An excitatory interneuron is recorded and filled with biocytin.



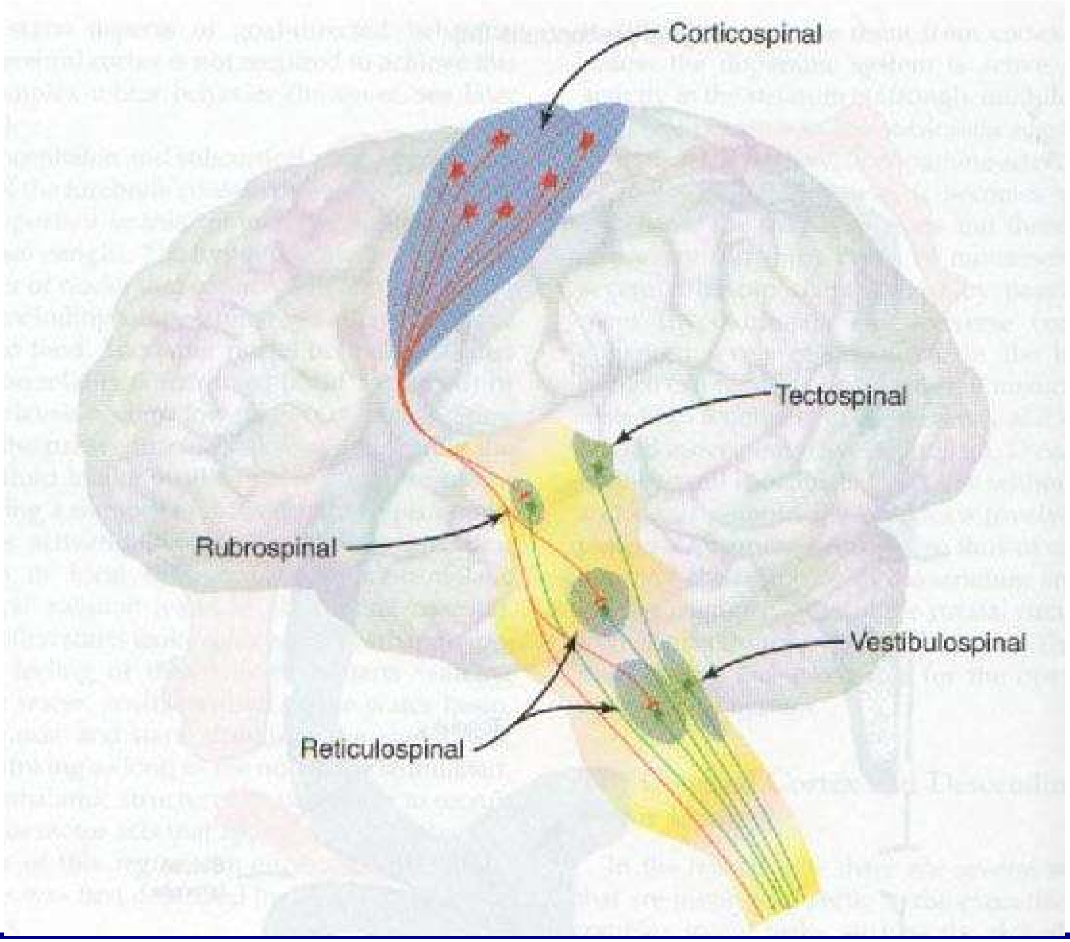
The Hb9 interneuron activity is characterized by rhythmic membrane depolarization underlying action potentials. The activity is in phase with the activity recorded from motor neurons (ventral root recording).

Hinckley et al, JNeurophysiol, 2005

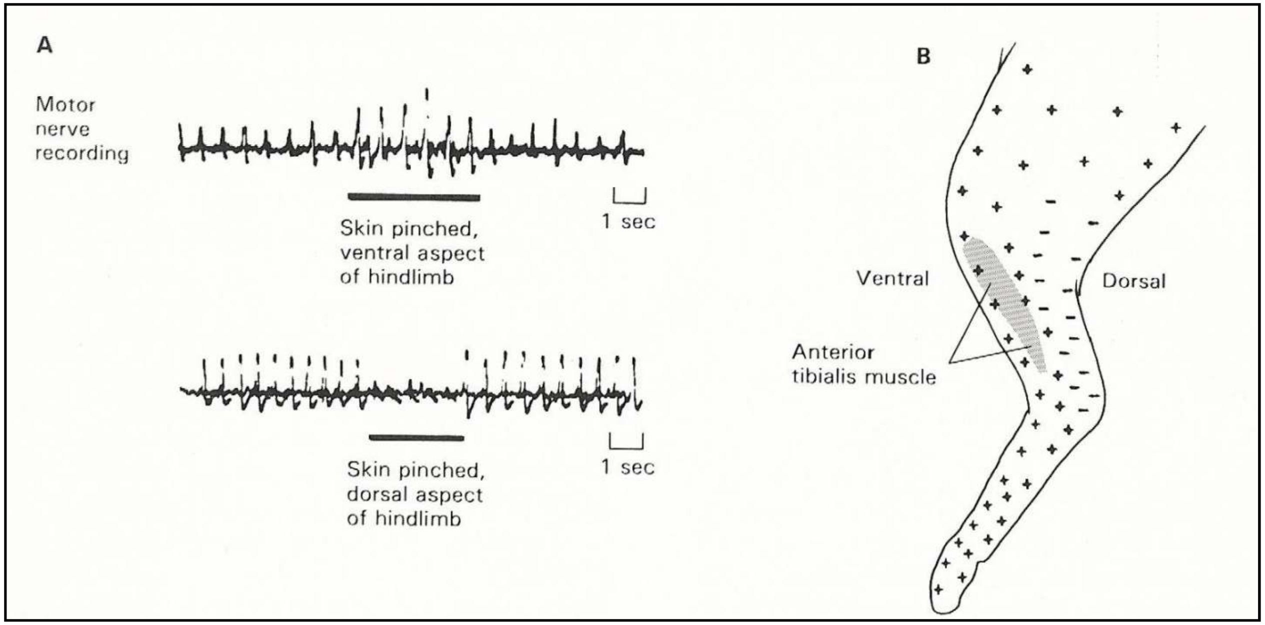
The mammalian CPGs are modulated via interneurons



Comissural interneurons (CINs) receive information from descending motor pathways



Interneurons on the ipsilateral side transfer stimulus from the skin, which **modify the motor program** and consequently the firing activity of motoneurons



Region-specific

Modality of the stimulus determines the response

Regulation of posture and balance

Posture and balance is maintained by continuous processing of sensory, vestibular and visual inputs and generation of compensatory muscular contraction.

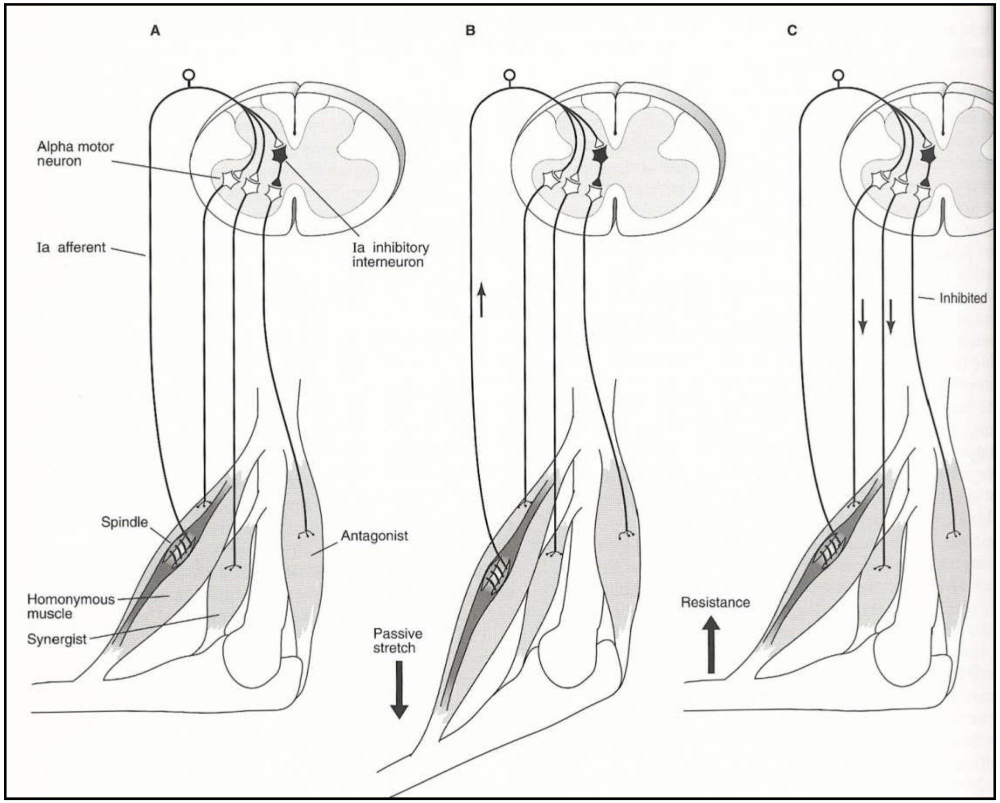
1. Sensory - proprioceptive inputs

2. Vestibular input

3. Visual input

Proprioception means the unconscious sense of self position and movement.

Changes in the physical contact of the body with the support surface trigger compensatory actions through **stretch reflexes**



This reflex

- has phasic and tonic components

-involves reciprocal innervation of the antagonistic muscles

- is characterised by motor output to all homonym and ~ 60% of synergistic muscles

- is characterised by adjustable sensitivity through setting fuzimotor fiber activity

- can be modified by presynaptic inhibition of the afferent fibers

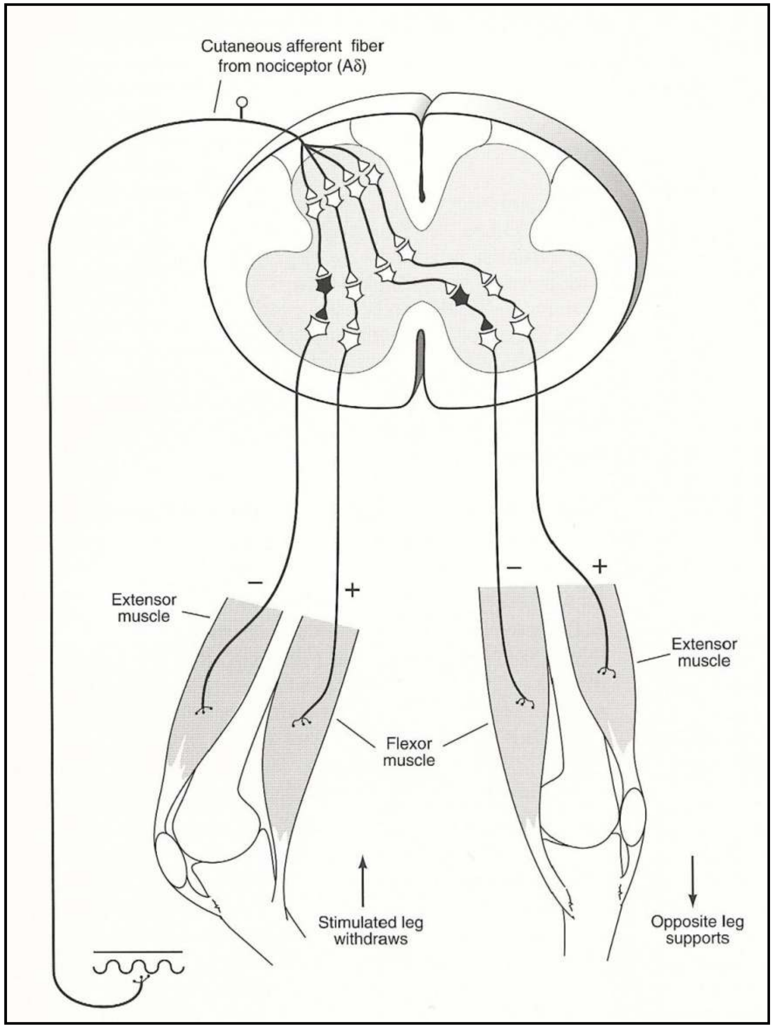
- Is characterised by direct synaptic input to MNs; the delay is 0.5-0.9 ms

Posture is maintained even, if rapid changes occur in the body support – a „built in” mechanism of the **nociceptive reflex**

Multisensory convergence –

Loss of specificity of sensory processing

Contralateral inhibition of flexor MNs

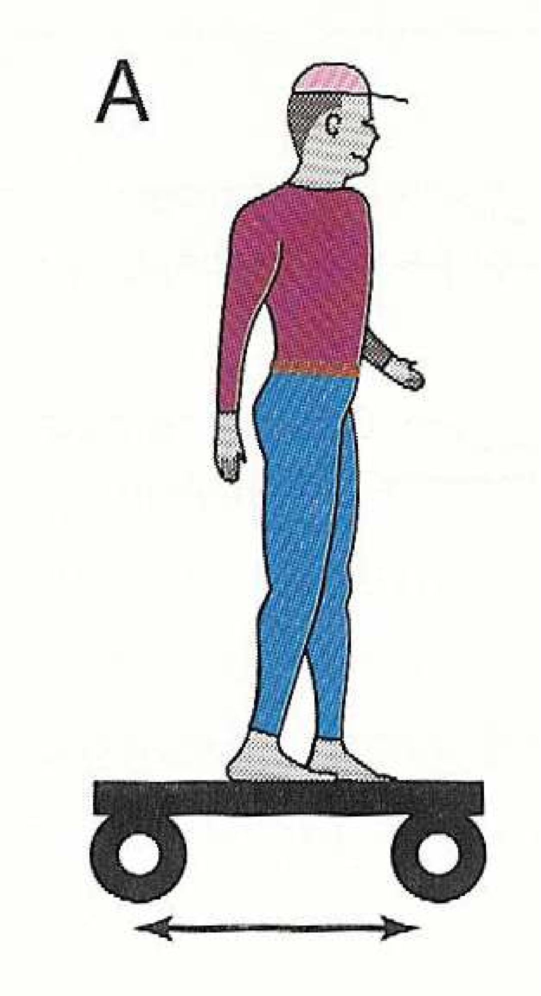


Different mechanisms are adapted to the various positional changes of the support surface

Exp: Moving platform triggers the ankle strategy - feed-back mechanism

Activation of the muscles distal to proximal direction

e.g.: forward movement of platform – backward sway: activation of TA-quadriceps muscles-abdominal muscles



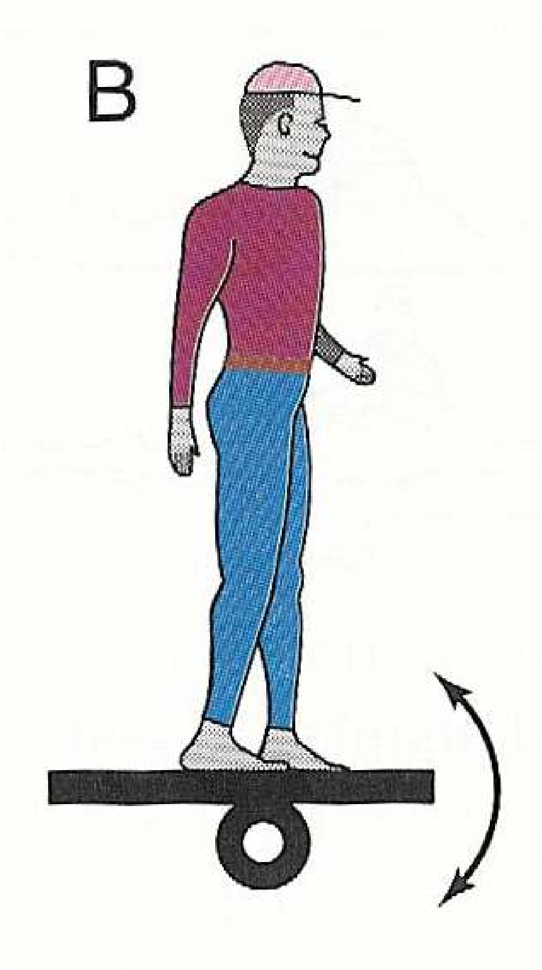
Different mechanisms are adapted to the various positional changes of the support surface

Exp: Tilting platform triggers the hip strategy - feed-back mechanism

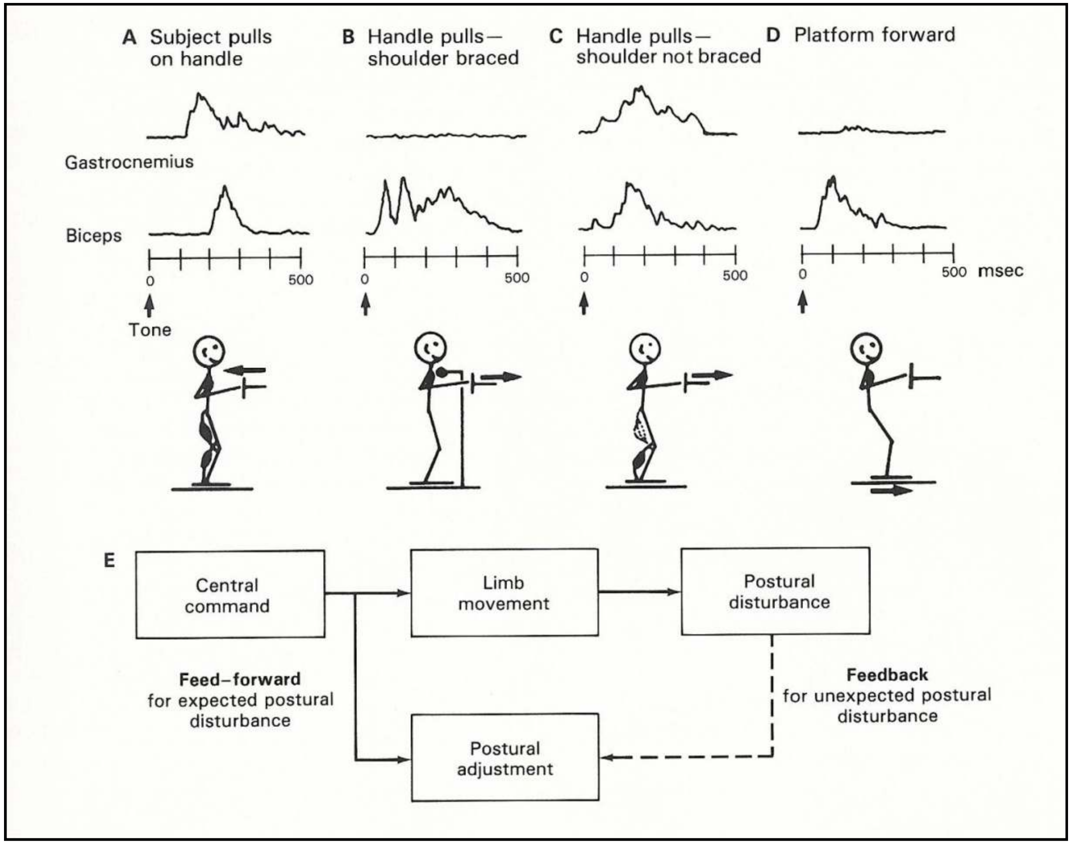
Activation of the muscles proximal to distal direction

e.g.: forward tilting – forward sway: activation of paraspinalis (erector spinae) – ham string muscles – triceps surae muscle

Similar action, when the movement of the platform is LARGER and FASTER or when the surface is COMPLIANT (soft) or NARROW

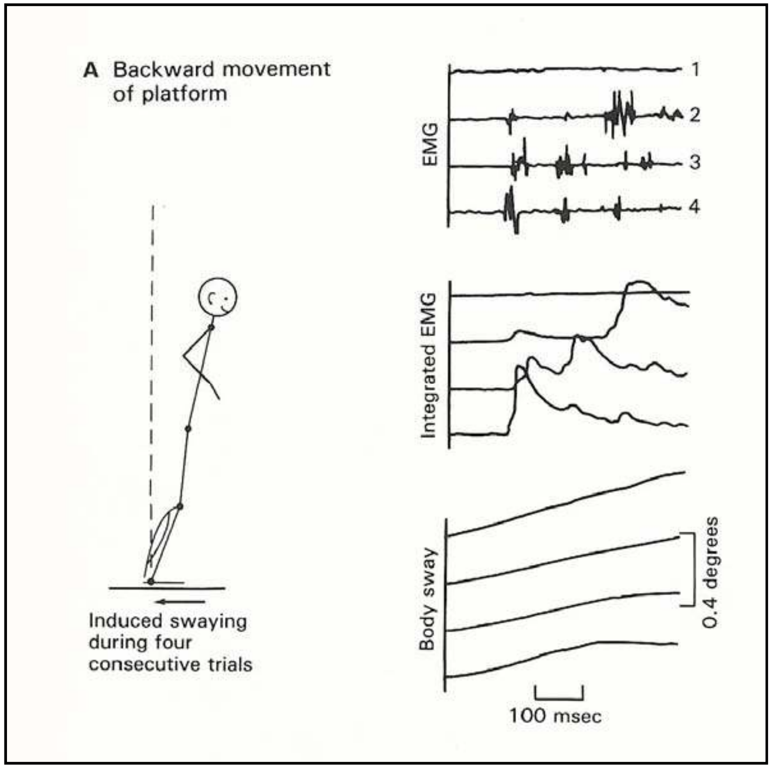


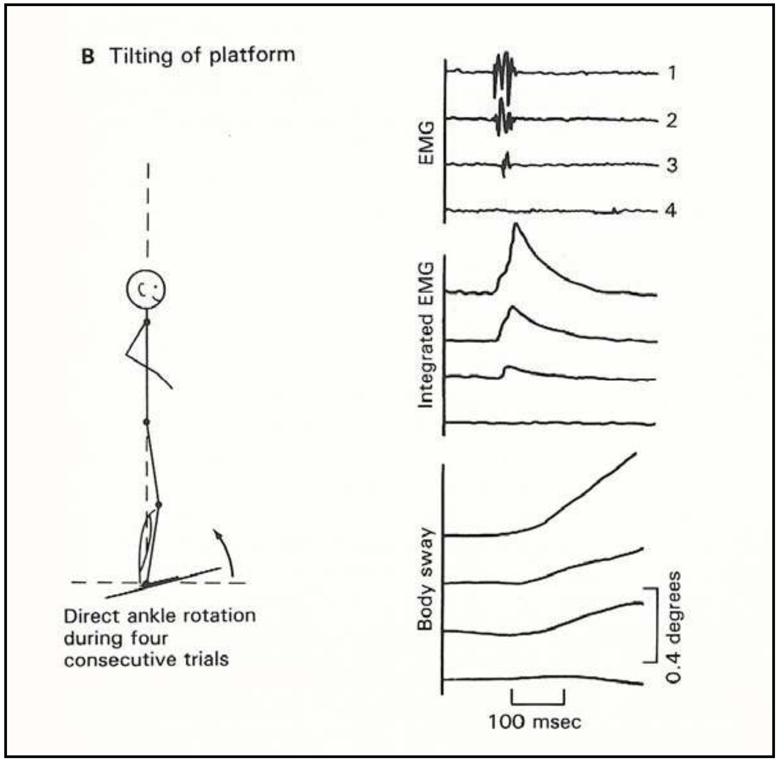
Feed-back corrections, when the postural disturbance is unexpected
Feed-forward corrections, when the postural disturbance is expected



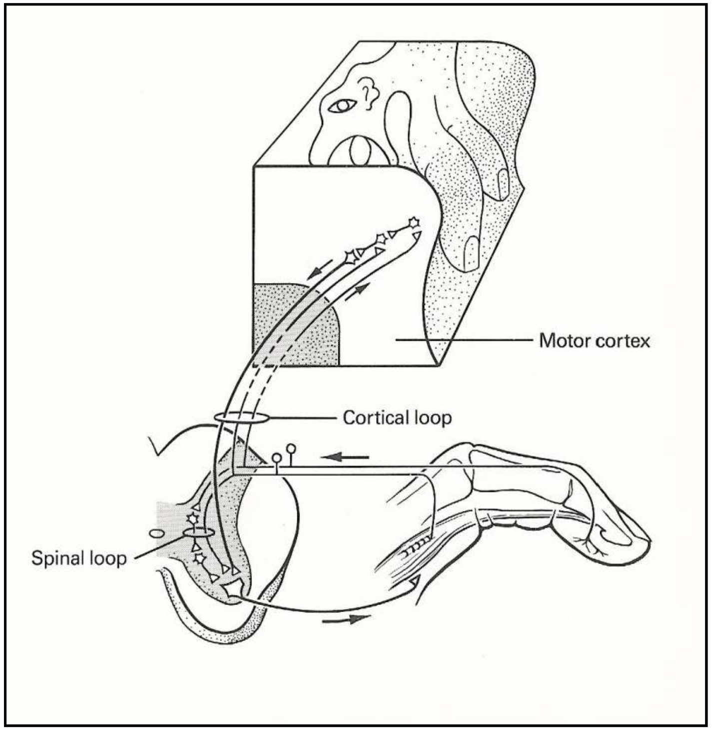
The extent of muscle contraction depends on previous experience and expectations

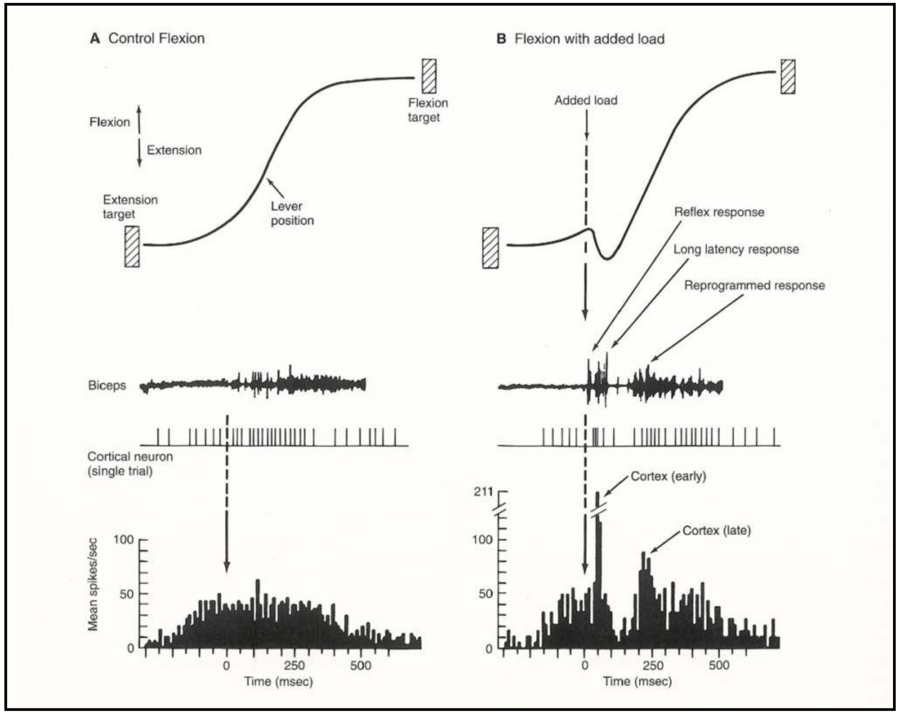
Feedforward or preventing mechanisms are triggered



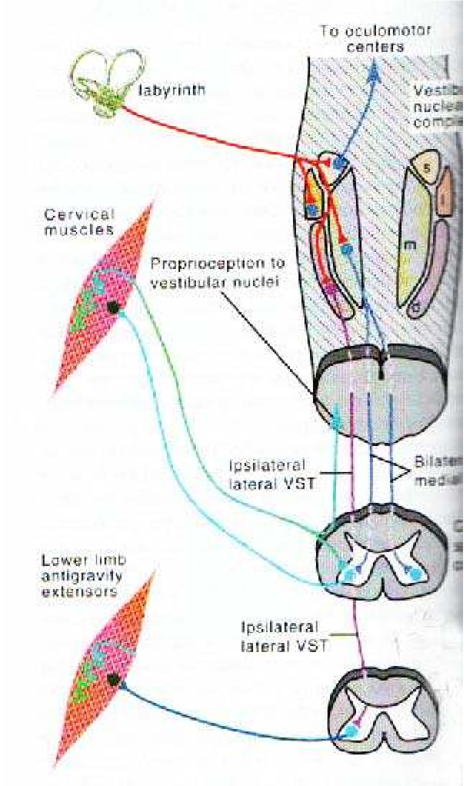


Cortical neurons respond to small disturbances



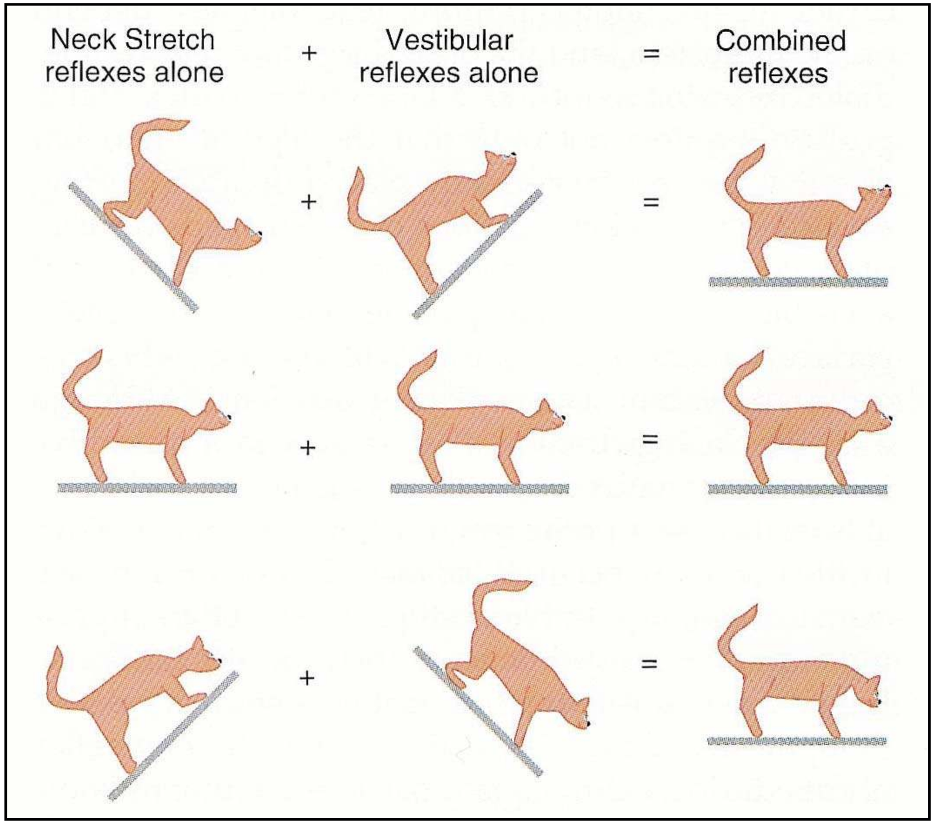


<u>The medial postural system</u> processes proprioceptive, vestibular and visual informations and conveys motor responses to the spinal cord. It innervates the axial musculature and the proximal parts of the limbs.



The vestibular nuclei are in connection with the cerebellum, which receive sensory information from the body. The medial longitudinal fascicle contains fibers of superior vestibular nucleus projecting to the motor nuclei of the eye. The lateral vestibular nucleus project to the spinal cord to activate the extensor muscles of the ipsilateral limbs.

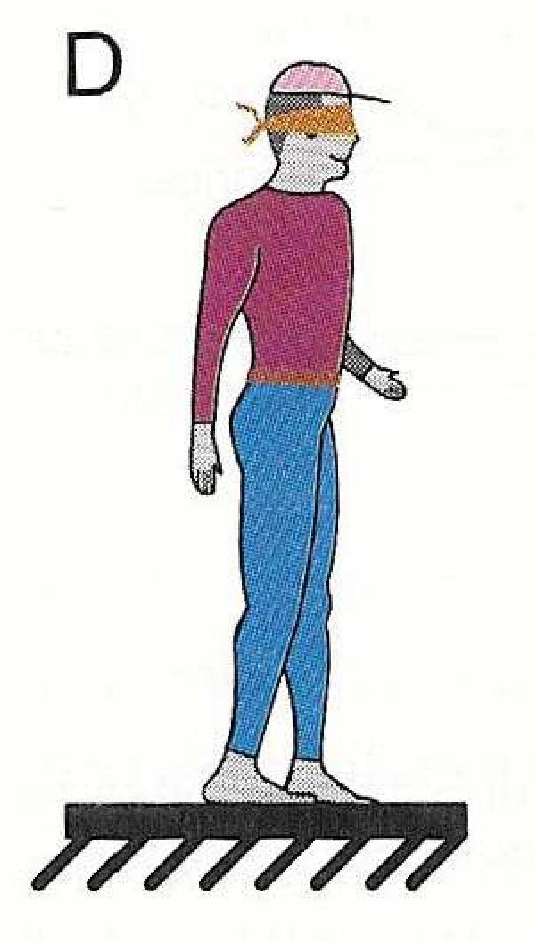
Exp: Vestibulocervical and vestibulospinal reflexes stabilize head and body posture



Stretch in the neck muscles and stimuli of the vestibular organ excite pathways that contract neck and limb muscles to oppose an undisered movement of the body.

Removal of the visual input – only the proprioceptive and vestibular sensors are in action - **Romberg test**

It is positive in the case of cerebellar, proprioceptive and vestibular damage.

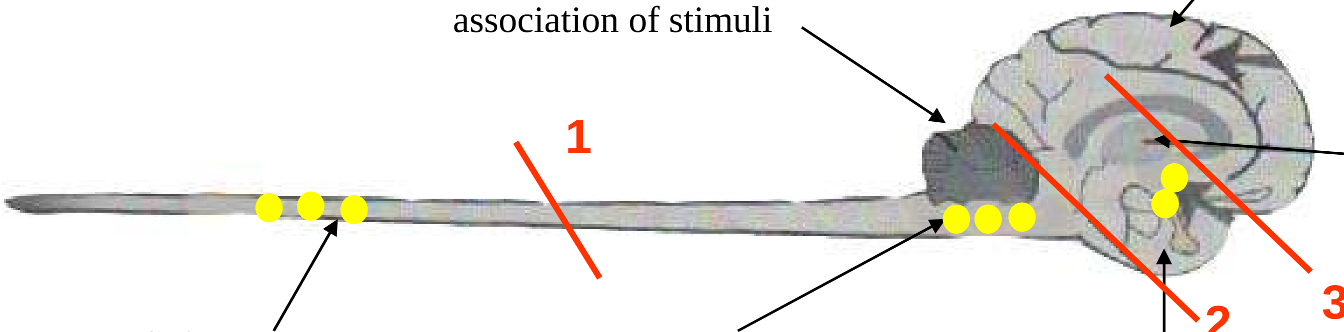


Summary

- Stability of the body is provided by feed-forward control and rapid feedback compensatory corrections
- Vestibular and neck reflexes stabilize the head and sight
- Brainstem and spinal cord mechanisms participate also in the postural control

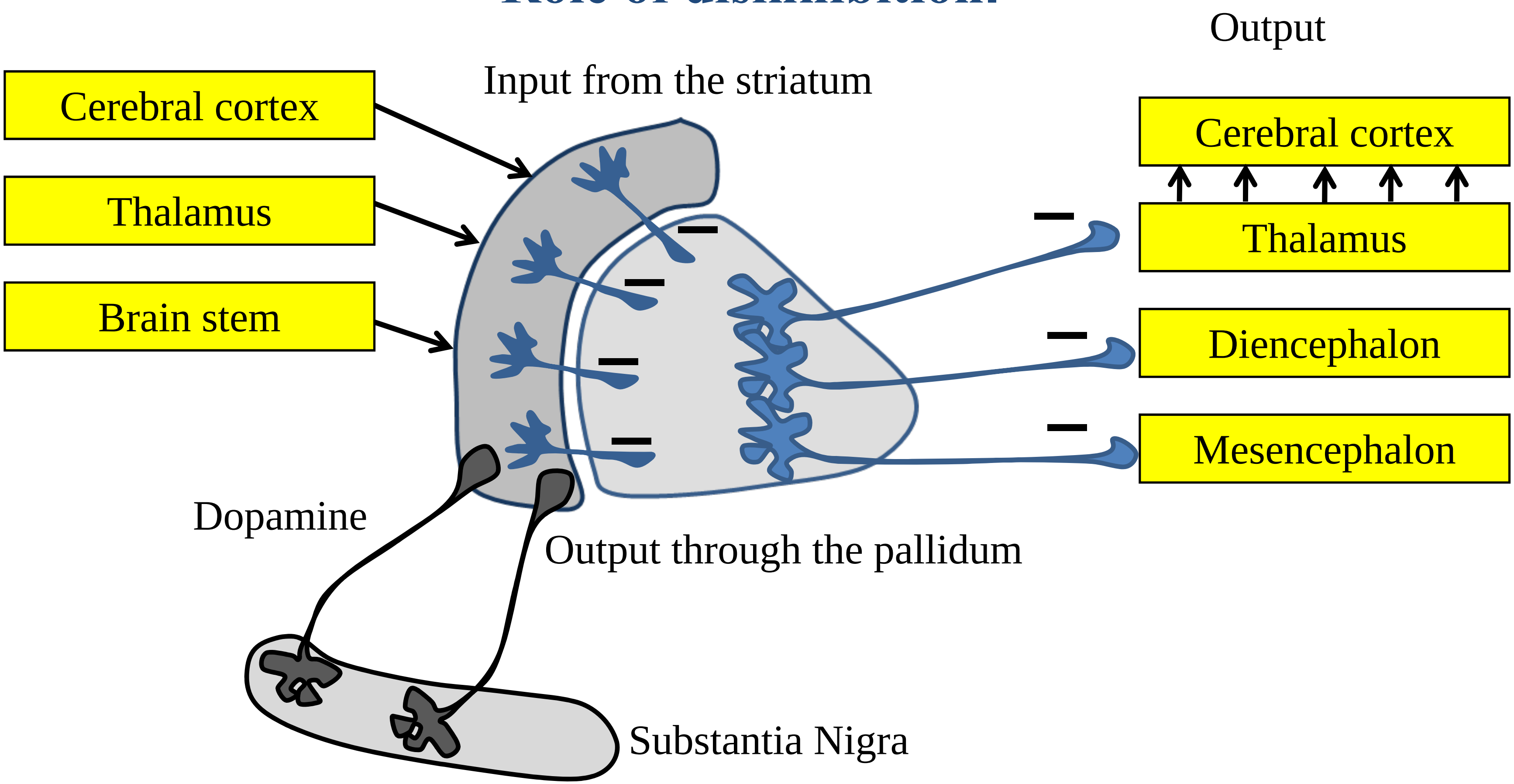
Voluntary movement

Locomotion can be initiated by the activation of many neurons distributed in several discrete regions of the brain.



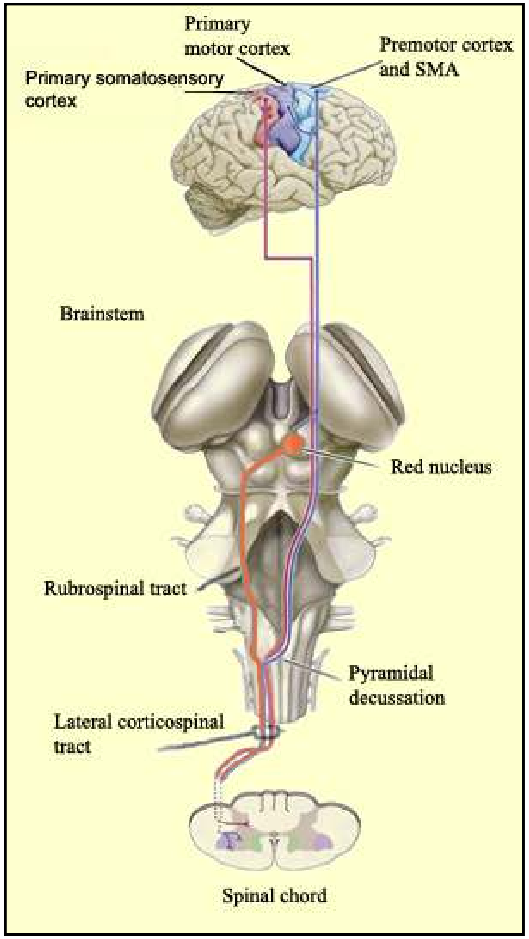
One of the principal site is in the brain stem, but tonic inhibition of this site from the basal ganglia normally prevents locomotion.

Initiation of movement from the basal ganglia. Role of disinhibition.



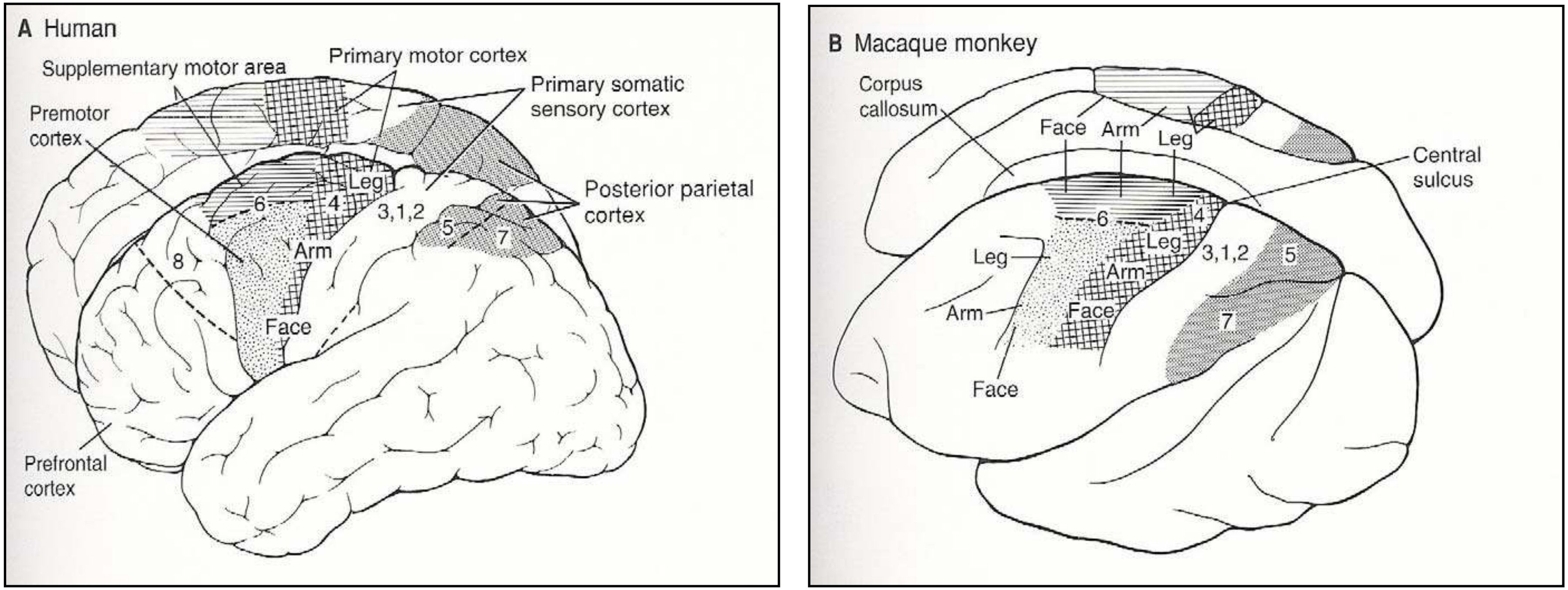
The lateral voluntary system

The corticospinal pathway
The (cortico-) rubrospinal pathway



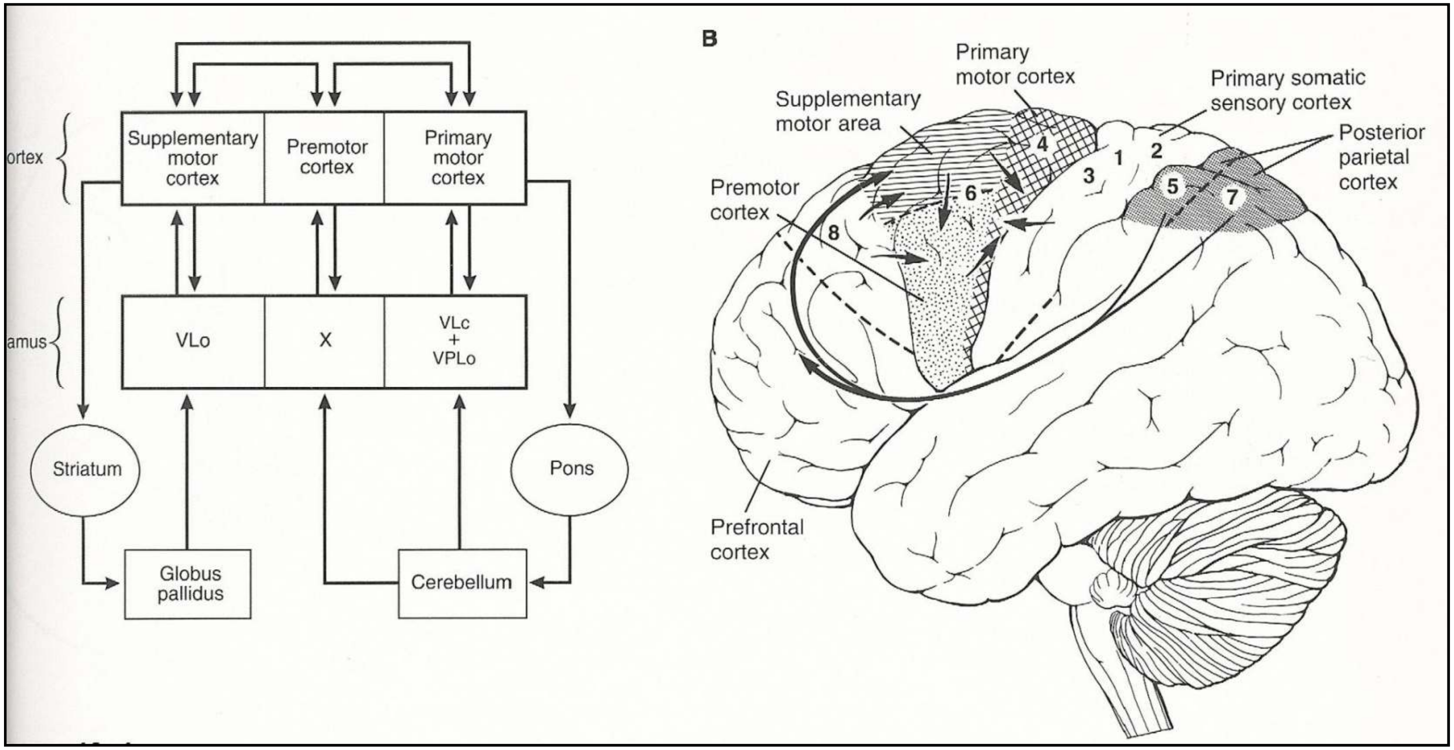
Cortical areas involved in motor control

Their ablation results in deficits in movements, their stimulation induces or alters movements
Cytoarchitectonic areas 4 and 6 Brodman (and areas 1, 2, 3, 5, 7 and 24)



They communicate with other motor structures and receive area-specific subcortical (thalamic and basal ganglia) and cortical afferents.

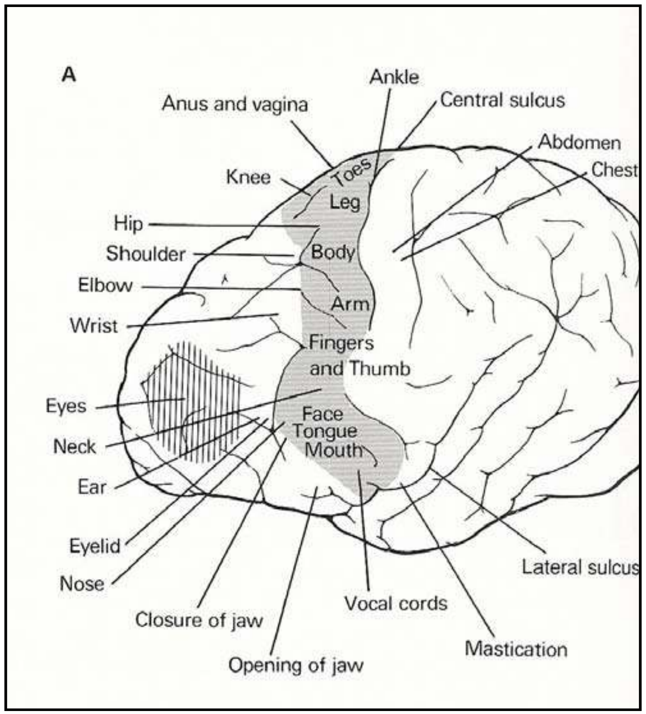
Motor cortical areas receive input from other cortical areas, as well as subcortical areas

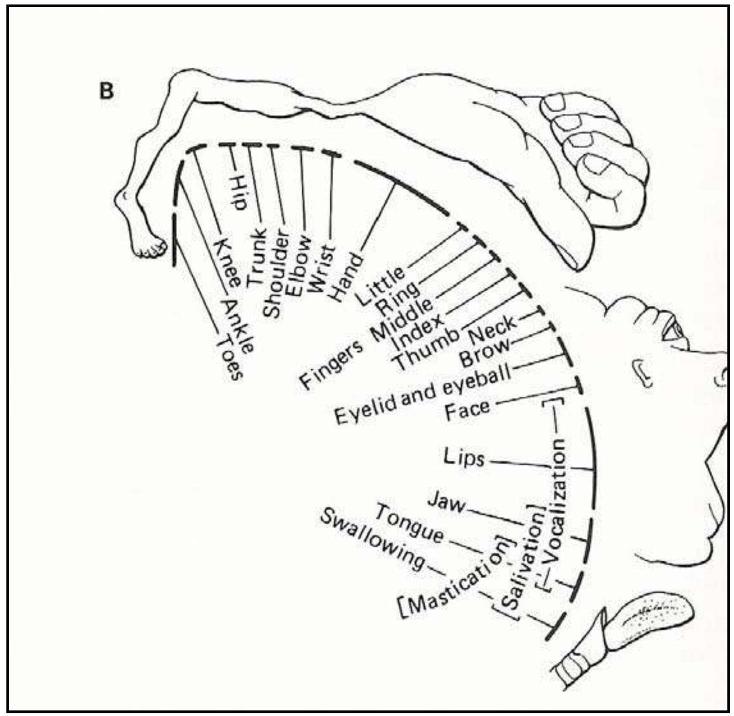


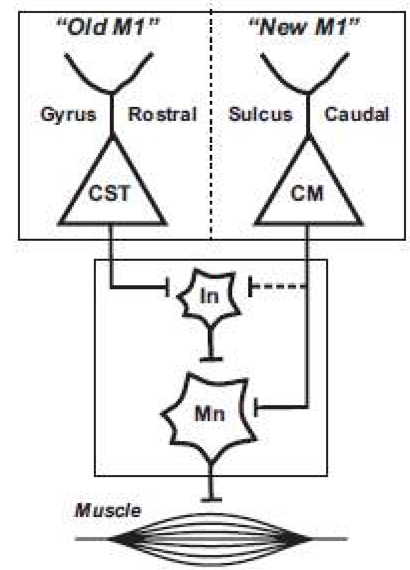
Somatotopic representation in monkeys and humans

A large overlap in the representation fields of body parts, muscles or movements!

″New ″ M1 bypasses spinal cord mechanisms and enables novel patterns of motor output



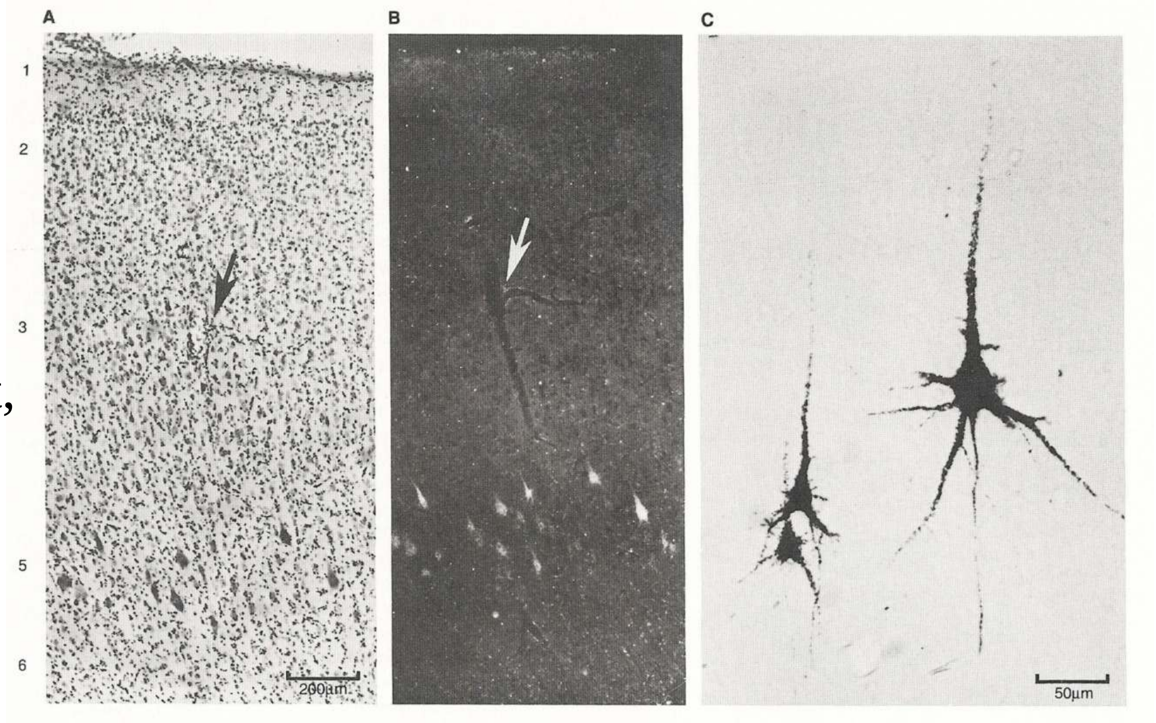




Rathelot, PNAS, 2009

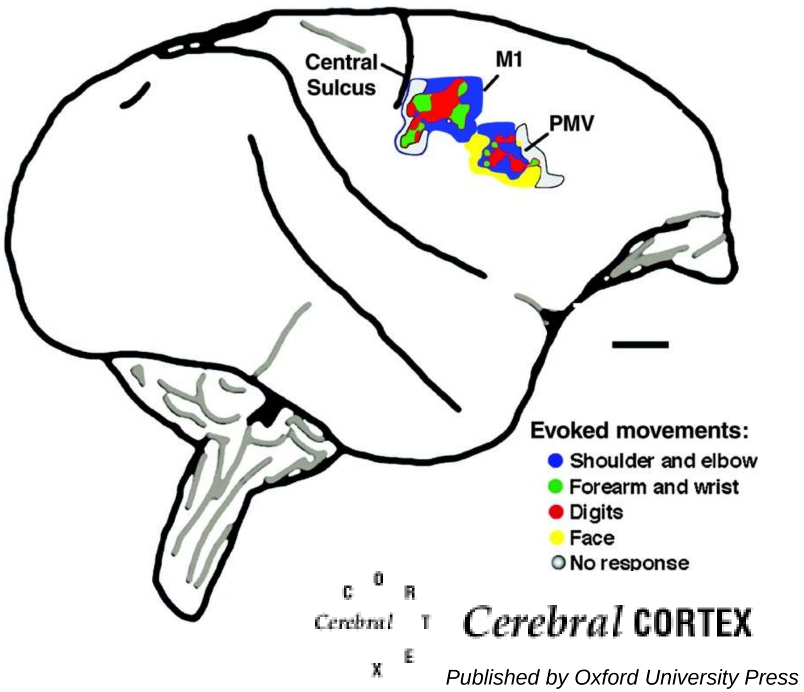
The primary motor cortex is agranular – predominantly there are pyramidal cells at this site

Layer 4 is reduced or absent,
no internal granular layer!

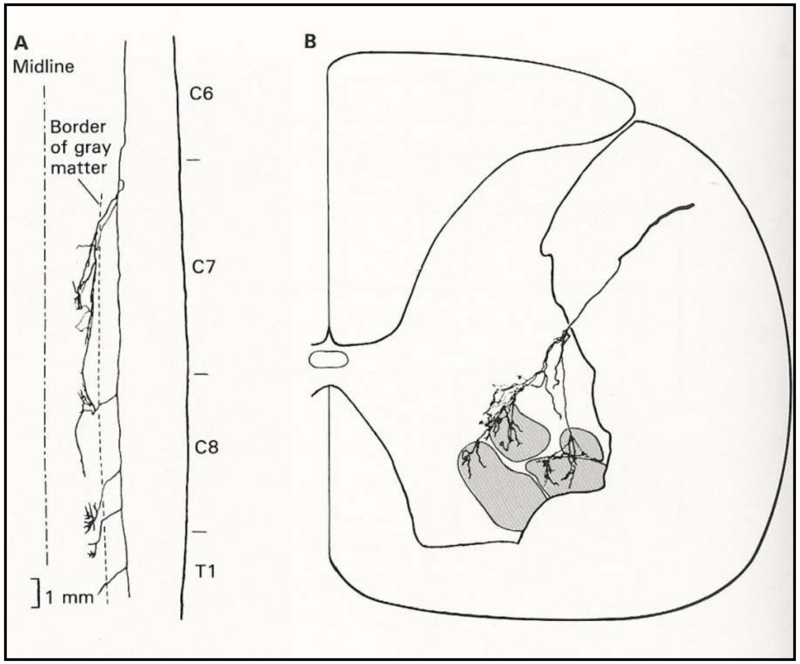


Convergence and divergence characterize the M1 neurons

Convergence – they are distributed in complex mozaik arrangement



Divergence – they ramify in multiple spinal segments

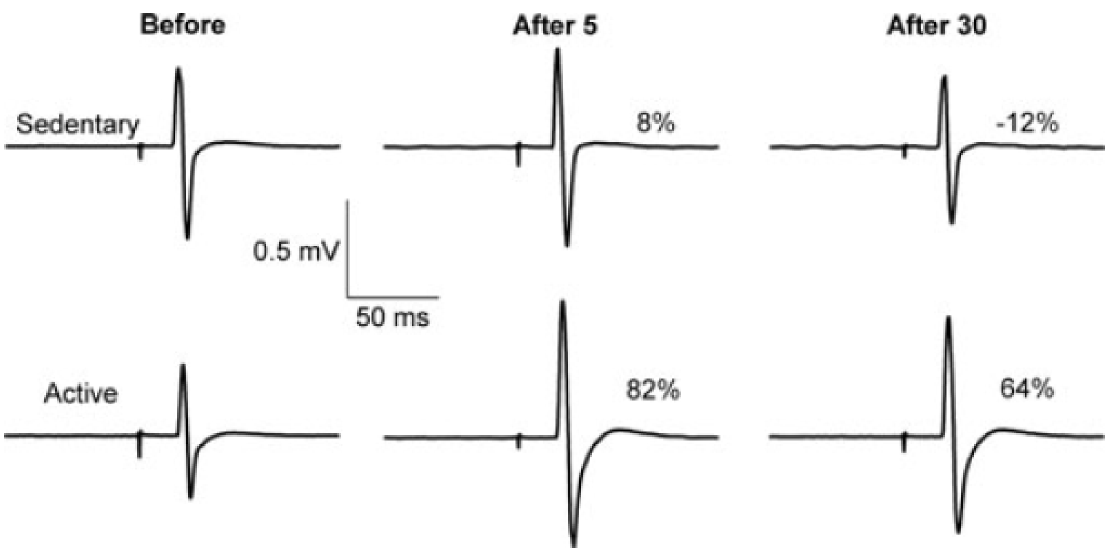


Dancause N et al. Cereb. Cortex 2006;16:1057-1068

Plasticity of the motor cortex

It occurs:

- after denervation of one part of the body
- when a muscle is stretched passively – rehabilitation after stroke
- when muscles are used intensively for prolonged period

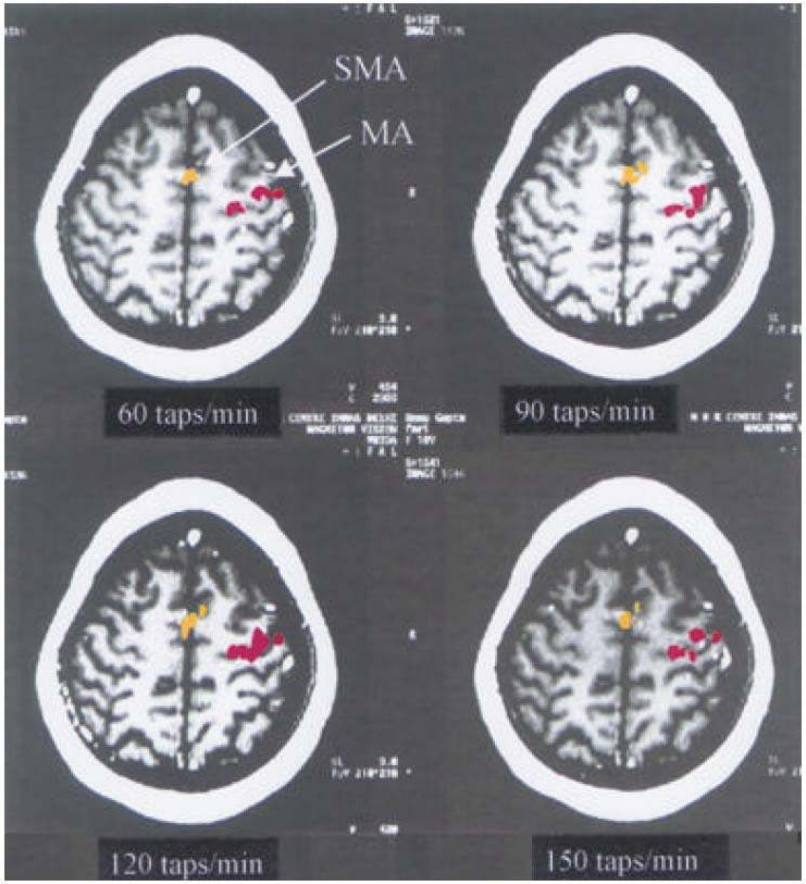


Paired associative stimulus (electric stimuli of Median Nerve followed by TMS)

Motor-evoked potential (MEP) amplitudes are substantially larger in active subjects!

Cirillo J, J.Physiol., 2009

Several cortical areas are activated during planning and execution of voluntary movements.



By complex hand movements bilateral activation of the:

- Sensorimotor areas
- Supplementar motor area
- Ventrolateral premotor area

contralateral activation of the:

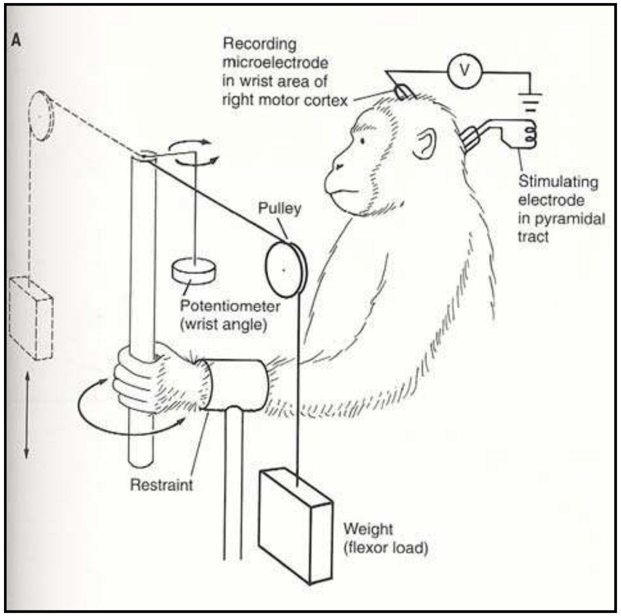
- Dorsolateral premotor area
- Medial cortical areas rostral to the SMA

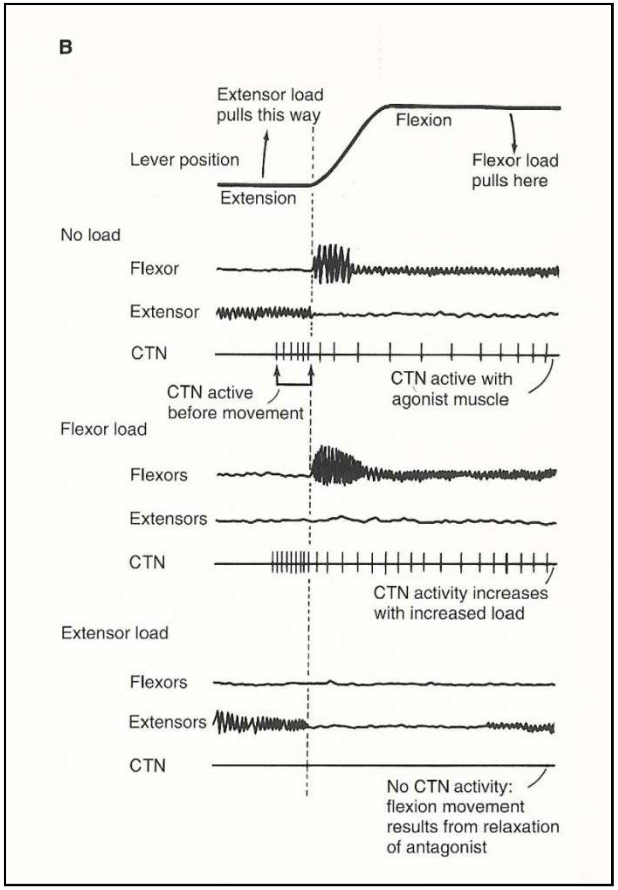
Cortical electrical potentials 1s prior to movement!

Khushu, J.Biosci, 2001

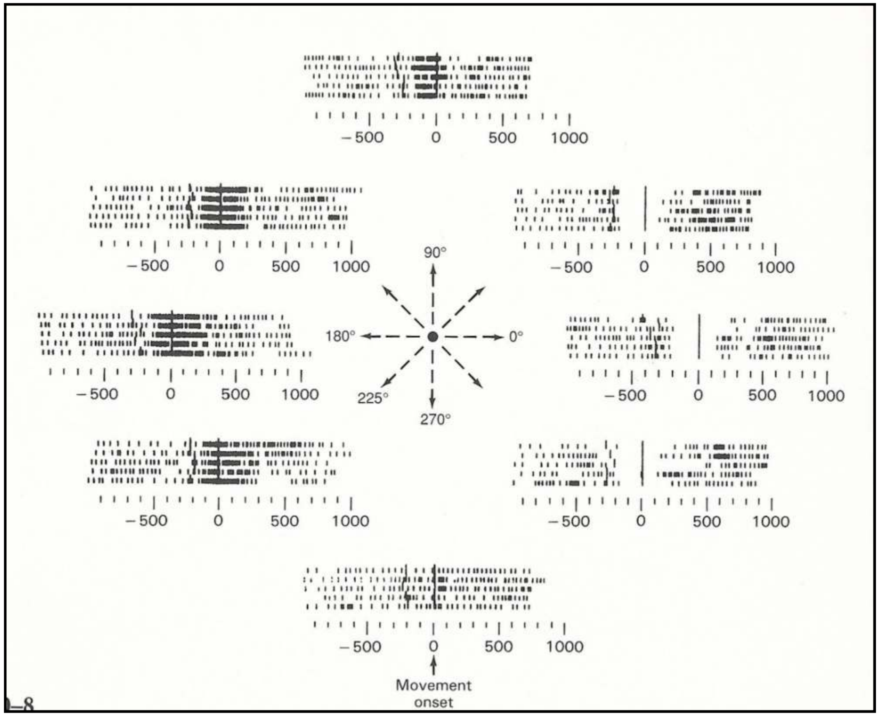
M1 neurons regulate kinematics and dynamics of movement

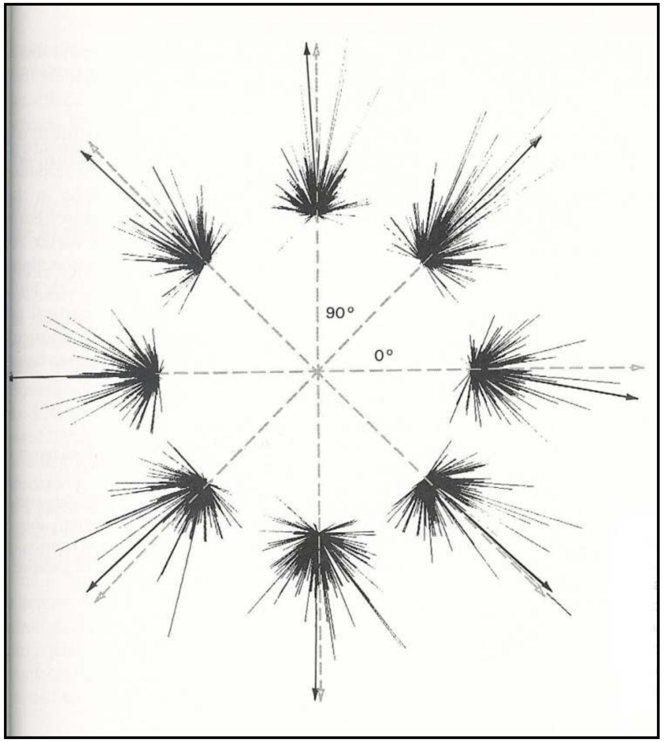
Discharge of neurons is correlated with force, direction of the movement, position of the joints and velocity. Single cell recording.



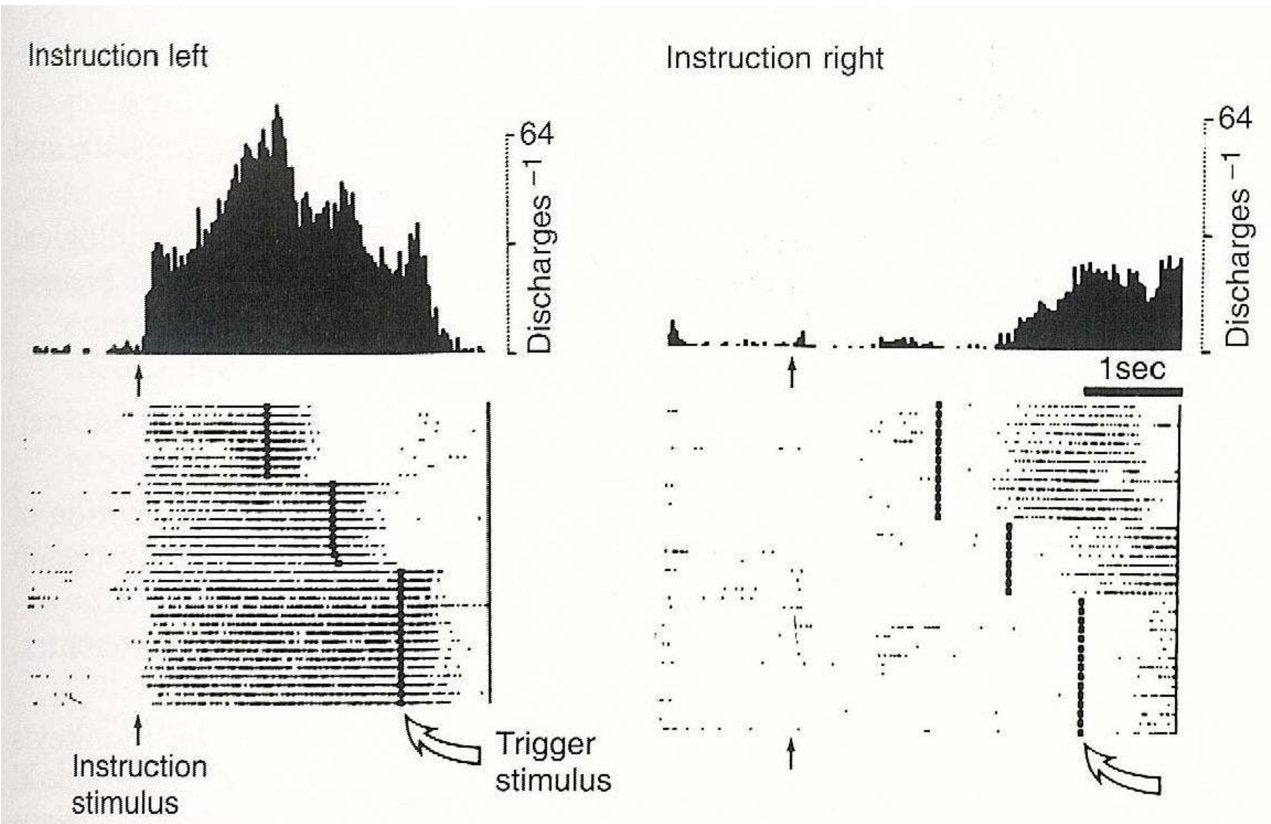


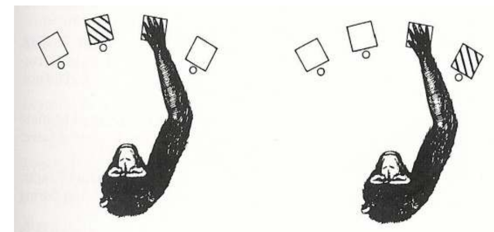
Ensemble activity of a large population of cortical neurons is tuned for a particular direction of movement





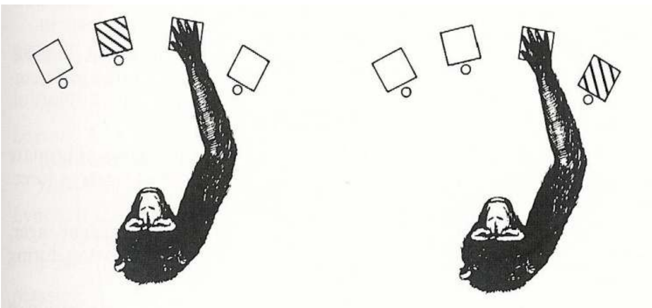
Cells in the premotor area encode the direction of the the planned movement





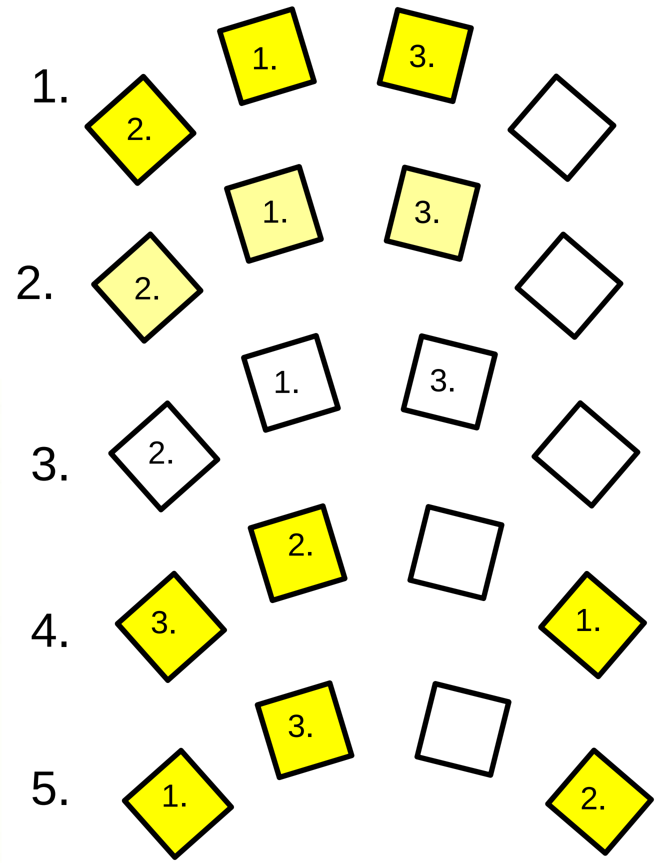
Wise and Strick, 1996

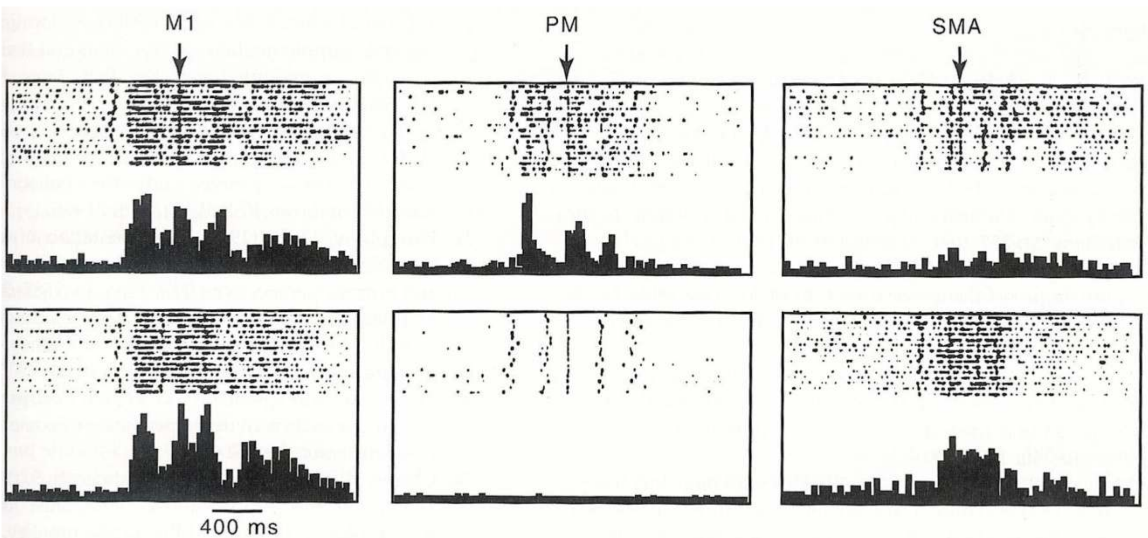
Internal cues activate cells in the SMA, whereas cells in the premotor area are active in response to visual cues



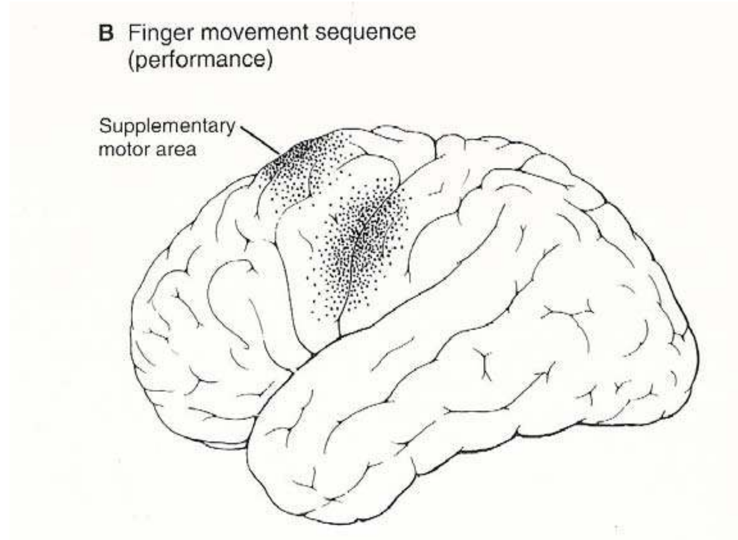
Internal cues 1-3

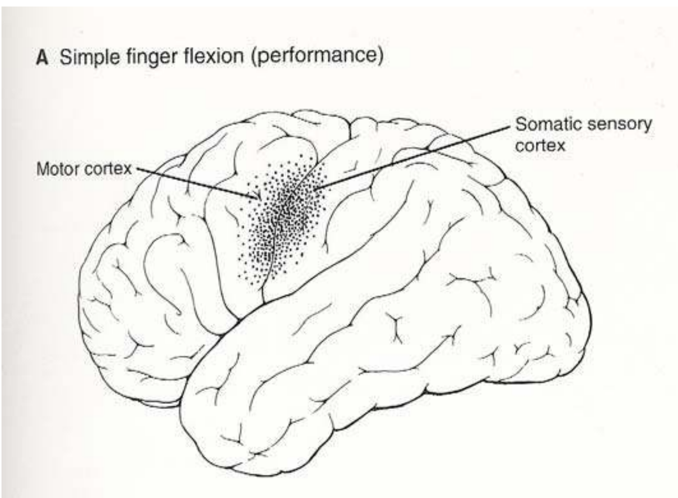
External cues 4-5

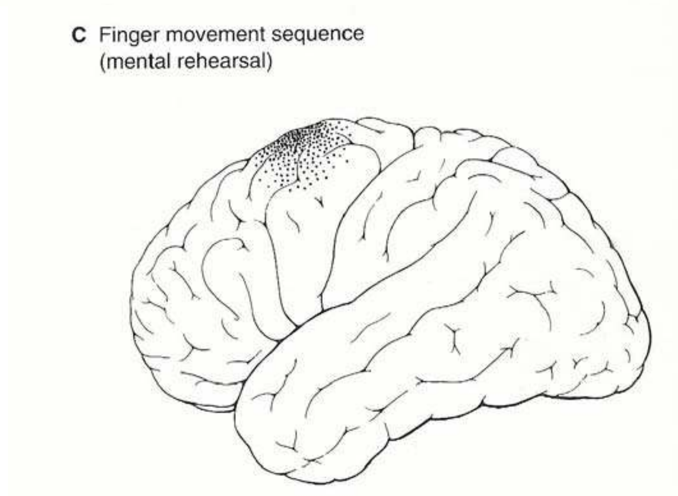




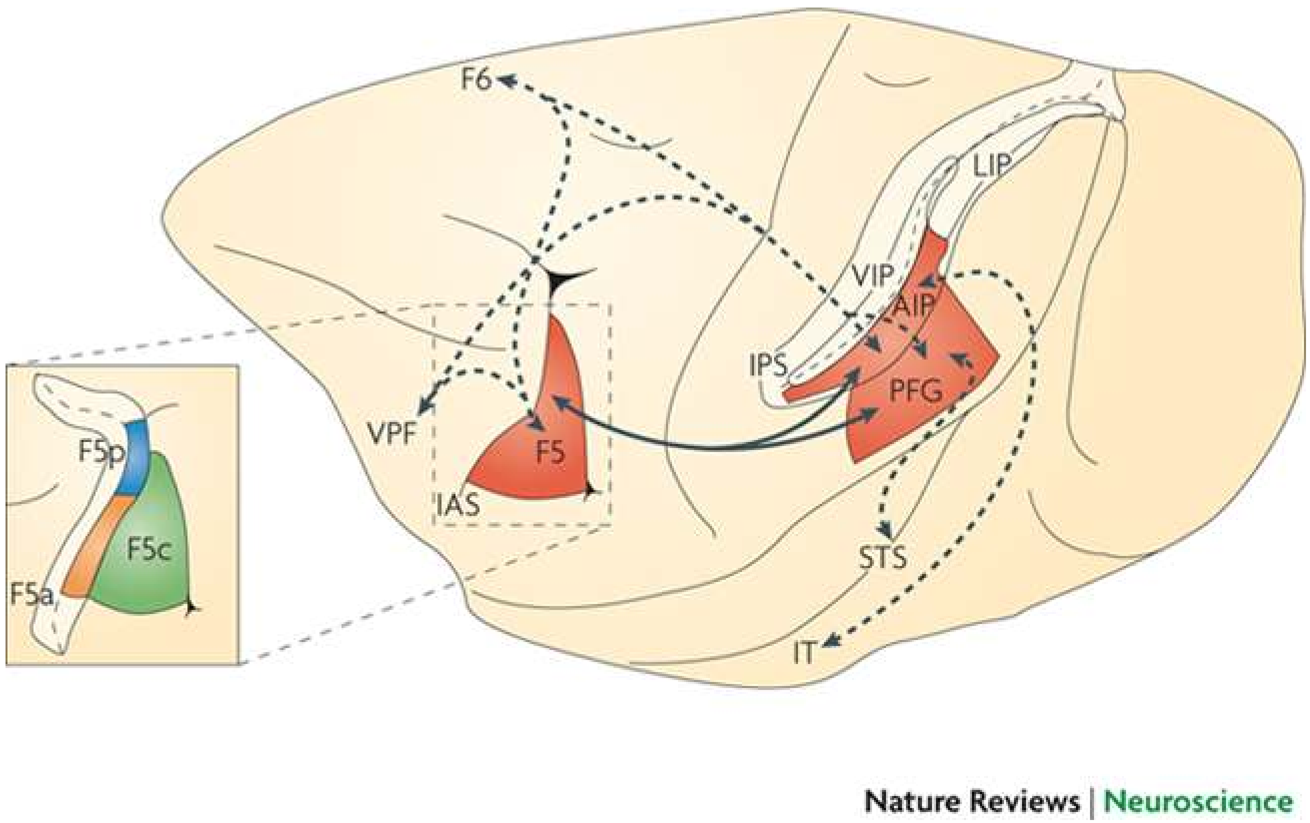
Local increase in blood flow shows also the role played by the supplementer motor area during mental rehearsal of motor tasks





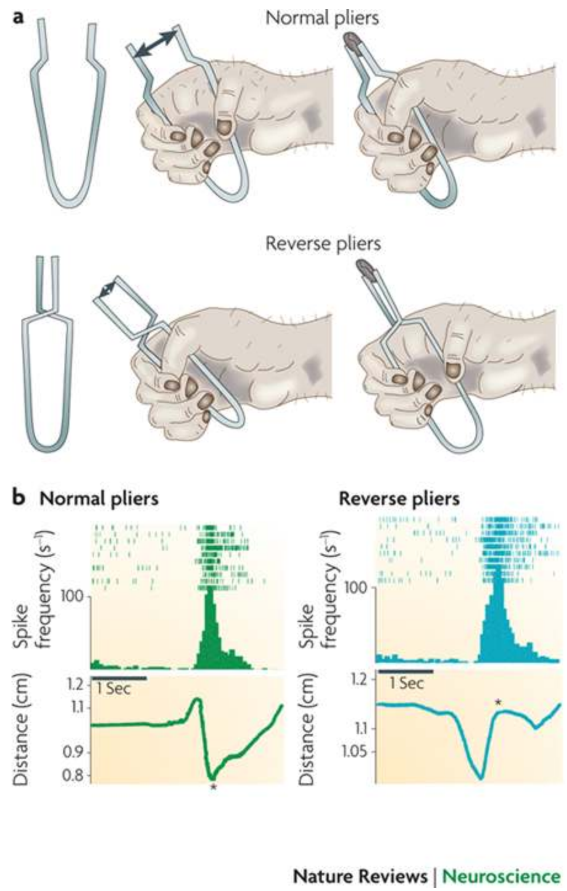


Parieto-frontal mirror neuronal circuit



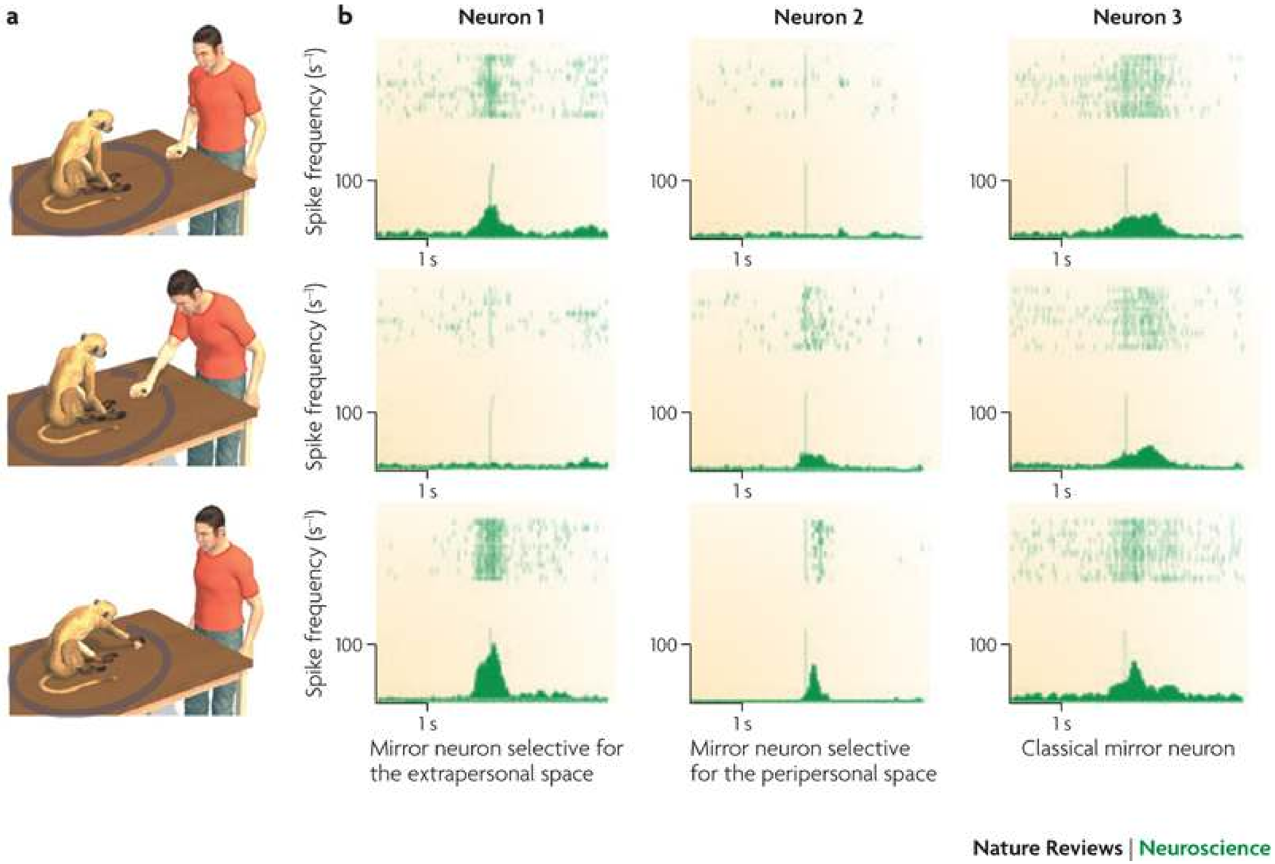
Nature Reviews Neuroscience **11**, 264-274 (April 2010)

The premotor neurons encode the goal of the movement



Nature Reviews Neuroscience **11**, 264-274 (April 2010)

Mirror neurons may encode the goal of the motor acts of another individual in an observer-centred spatial framework.



Nature Reviews Neuroscience **11**, 264-274 (April 2010)

Functions of the premotor cortex -Summary

1. Orchestration of proximal muscles during limb movements.
2. Control of visual and acoustic stimuli induced voluntary movements.
3. Preparation of movements and setting the postural positions to carry out movements.
4. Activation of premotor area to enhance the subsequent motor response.

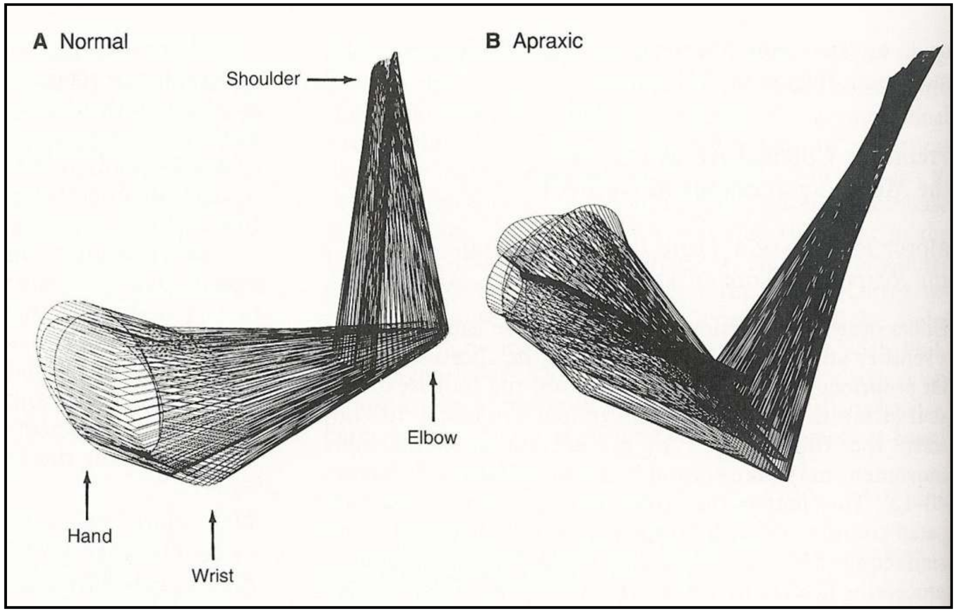
Functional disturbance of M1 and the premotor area

Lesions in the primary motor cortex result in weakness in the contralateral side of the limbs. In contrast, lesions in the premotor areas cause impairment of strategic plans to carry out the movements.

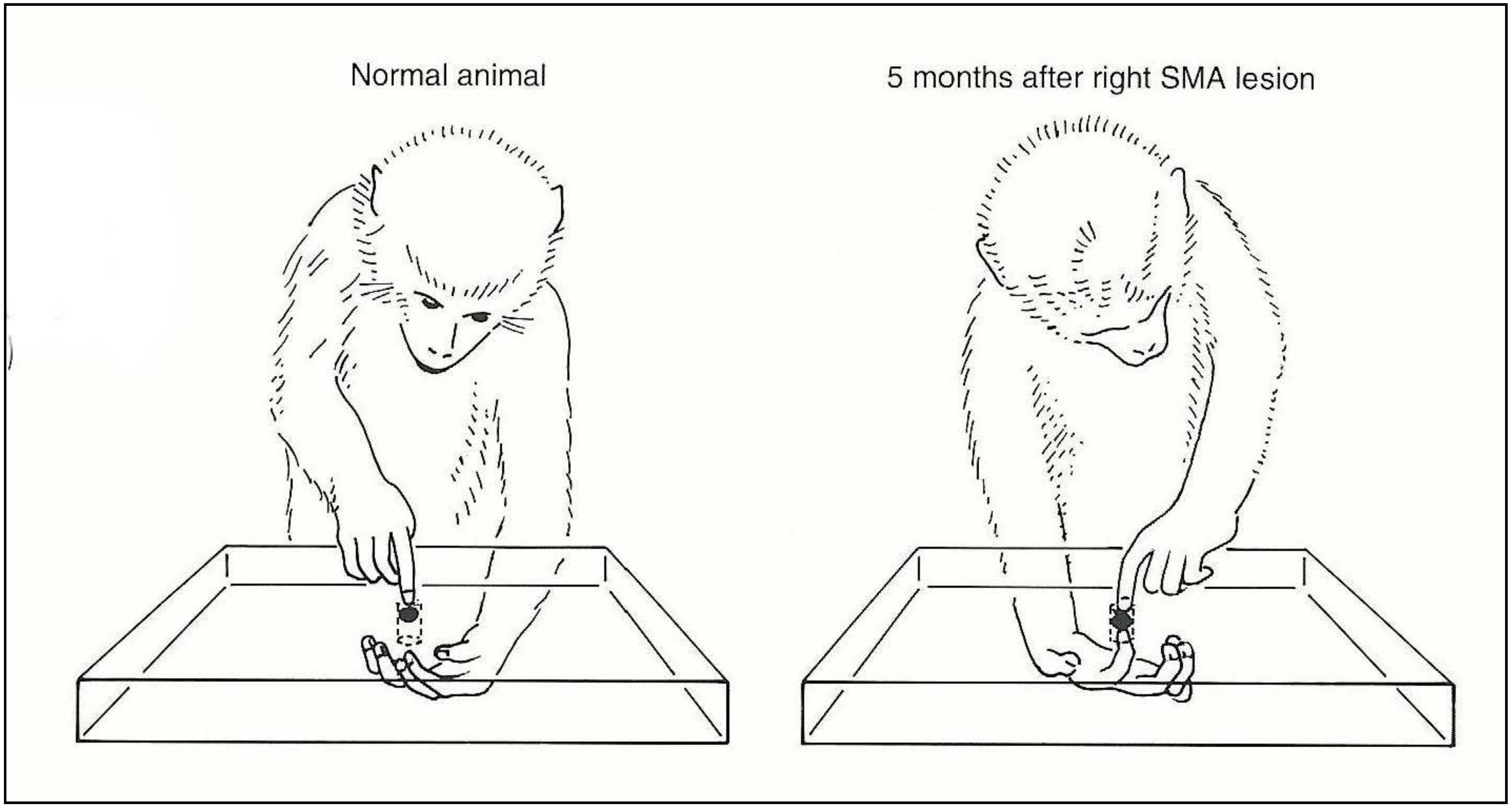
Akinetic mutism: Serious damage leads to akinetic mutizm. Patient do not move and do not speak.

Apraxia: Damage of left parietal lobe, PMA and SMA

Movements of the apraxic patients are tentative and irregular.



Lesion of the supplementer motor area results in a deficit in the bimanual coordination.



Functions of the supplementer motor area - Summary

1. Planning of movements – control of planned movements
2. Initiation of **speech** by activating the motor speech areas
3. Orchestrating center of cortico-subcortico systems of movement initiation
4. It organizes the orientation of attention to stimuli.
5. It influences the brainstem and spinal cord motoneurons via neuronal connections
6. It plays important role in coordinating posture and voluntary movements.

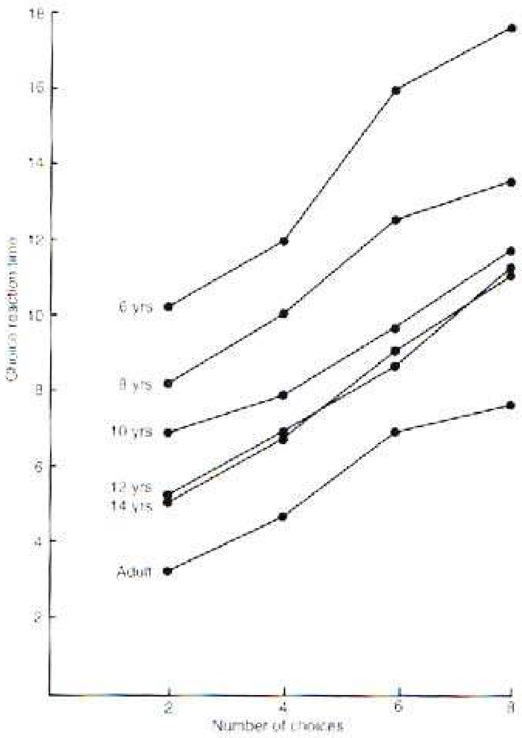
Functional disturbance of the posterior parietal cortex

1. Severe attentional disturbances.
2. Mistakes, when locating objects in space.
3. Inability to recognise complex objects or to draw in 3D.
4. Patients can not perform complex gestures.
5. Neglect of tactile or visual stimuli on the contralateral side of the body.

Processing of visual information – external cues - PM

Simple reaction time ~160 ms

Choice reaction time is increasing with the number of alternative responses and with age!



Summary: voluntary movement

Motor areas are characterized by somatotopic organization

Neurons in the primary motor cortex encode the direction of the force during movement

The premotor and supplementer cortical areas prepare the motor system for the movement

The posterior parietal lobe provides the visual information for the targeted movements