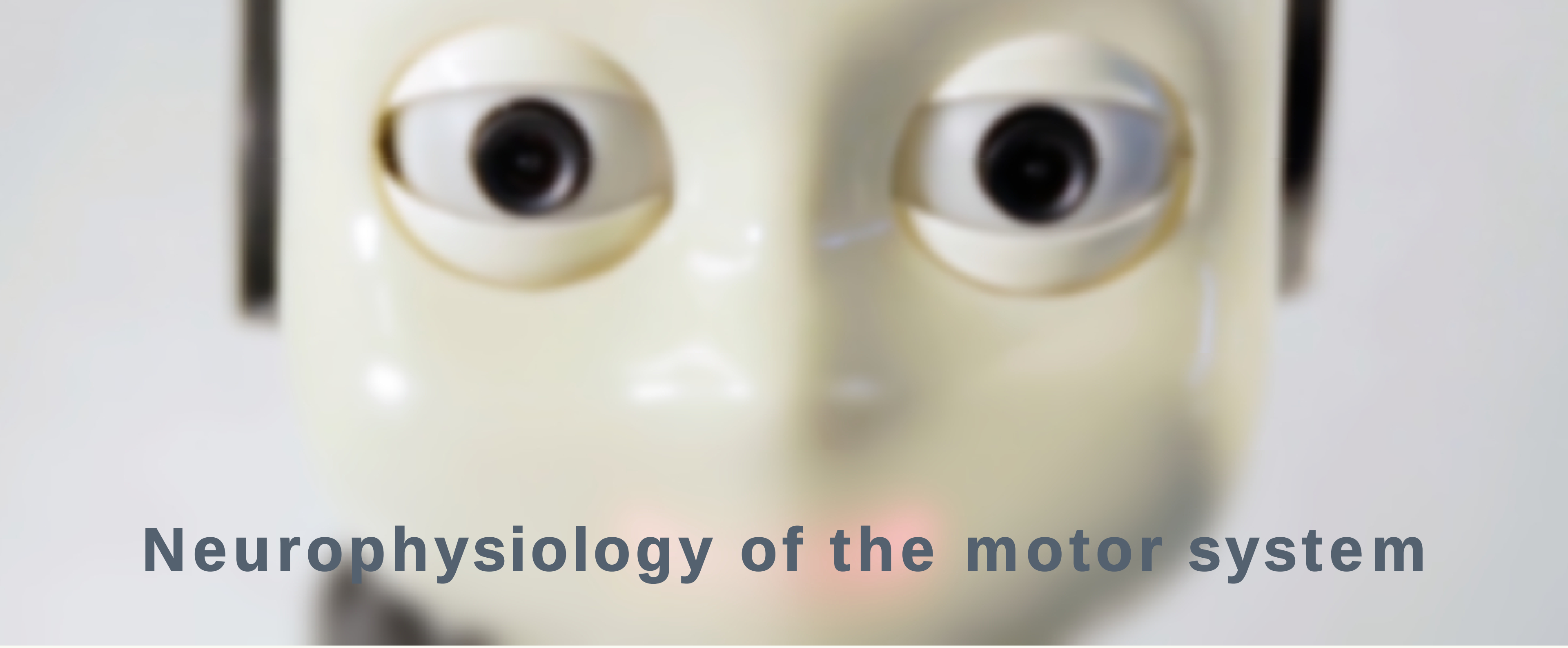

Neurophysiology of the motor system

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Resources

Most of the slides originate from the lectures "Neurophysiology of the motor system", Lecture 1-3, by

Alessandro D'Ausilio

https://sites.google.com/site/alessandrodausilio/home

With kind permission.

A lot of the material therein comes from

Kandel, E.R., Schwartz, J.H. and Jessell, T.M. eds., 2000. Principles of neural science (Vol. 4, pp. 1227-1246). New York: McGraw-hill.

This presentation is a shorter version, focusing mostly on cortical control of movement.

Some slides have been modified or added.

Outline

I) Muscle and Spinal Level

II) Sub-Cortical Level

III) Cerebral Cortex

Spinal Level

Muscle and Neuromuscular Junction

Motor Unit

Spinal Circuits, Spinal Reflexes and their Modulation

Cortico-spinal Pathways

Ascidia

Ascidia

From CONSCIOUSNESS EXPLAINED, by Daniel Dennett (parenthetical observation credited to the neuroscientist Rodolfo Llinas)

"The juvenile sea squirt wanders through the sea searching for a suitable rock or hunk of coral to cling to and make its home for life. For this task, it has a rudimentary nervous system. When it finds its spot and takes root, it doesn't need its brain anymore so it eats it! (It's rather like getting tenure.)”

Motivation

Daniel Wolpert:

- "Why don't plants have brains?“
  - "Plants don't have to move!“

“To move is all that mankind can do...for such the sole execution is muscle, whether in whispering a syllable or in felling a forest.”

Sherrington, 1924

Muscle and Neuromuscular Junction

Neurophysiology of the Motor System

Muscle Fibers

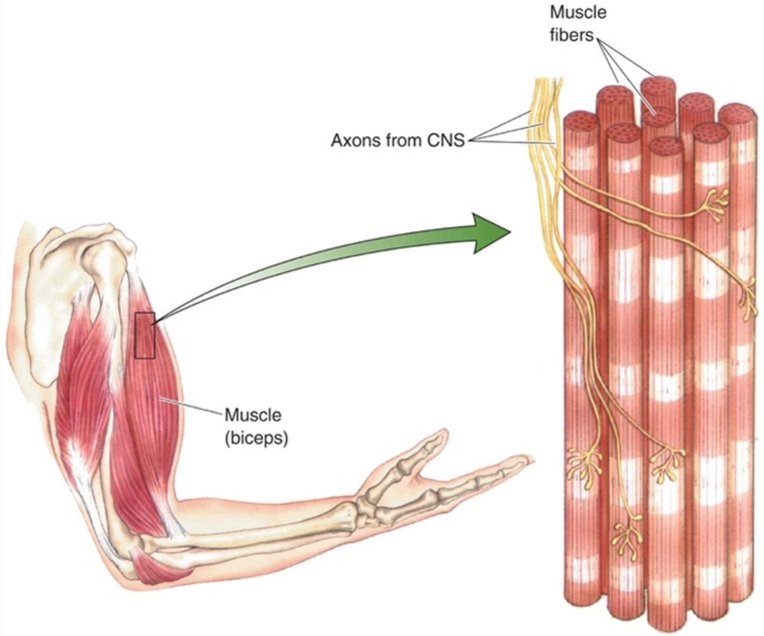
50-100μm diameter

2-6 cm length

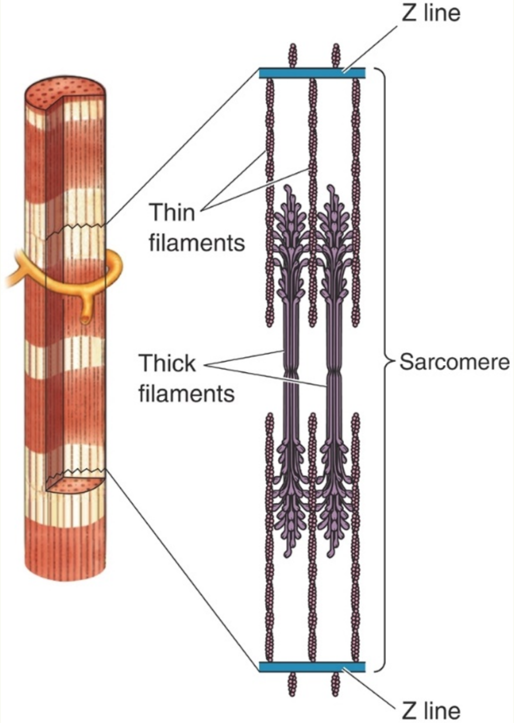
Thousands to millions each muscle

Parallel and serial in long muscles

Simultaneous activation



Sarcomere

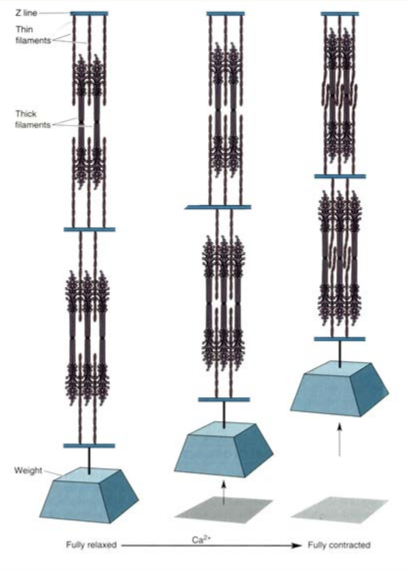


About 20000 in each muscle fiber

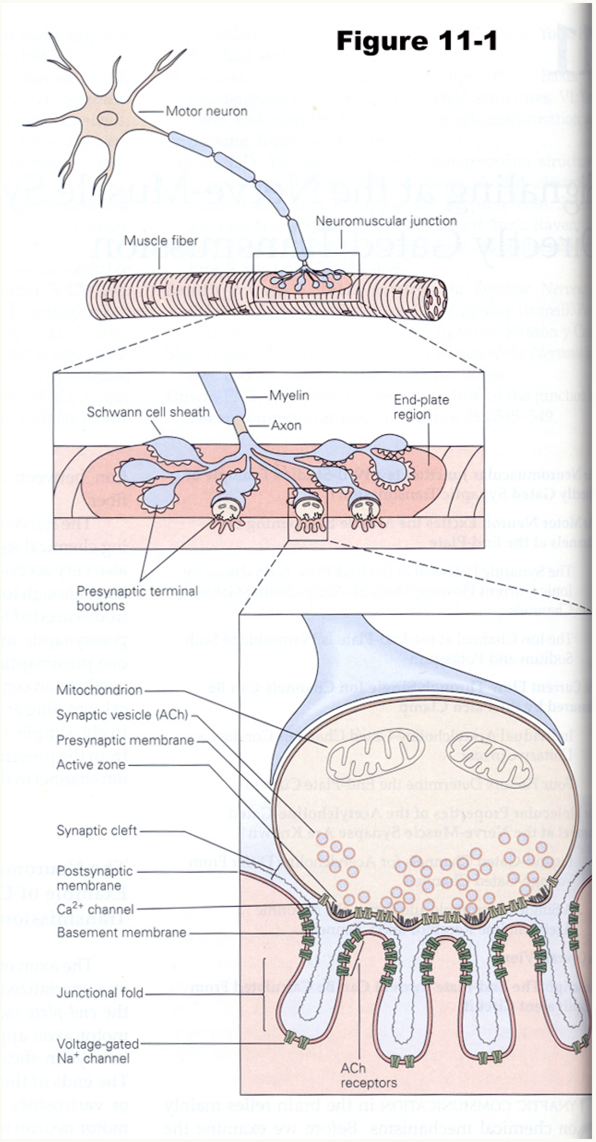
1.5 - 3.5µm length

Sacromere action:

thick and thin filaments slide one over the other reducing length



Neuromuscular Junction



Biochemical Cascade

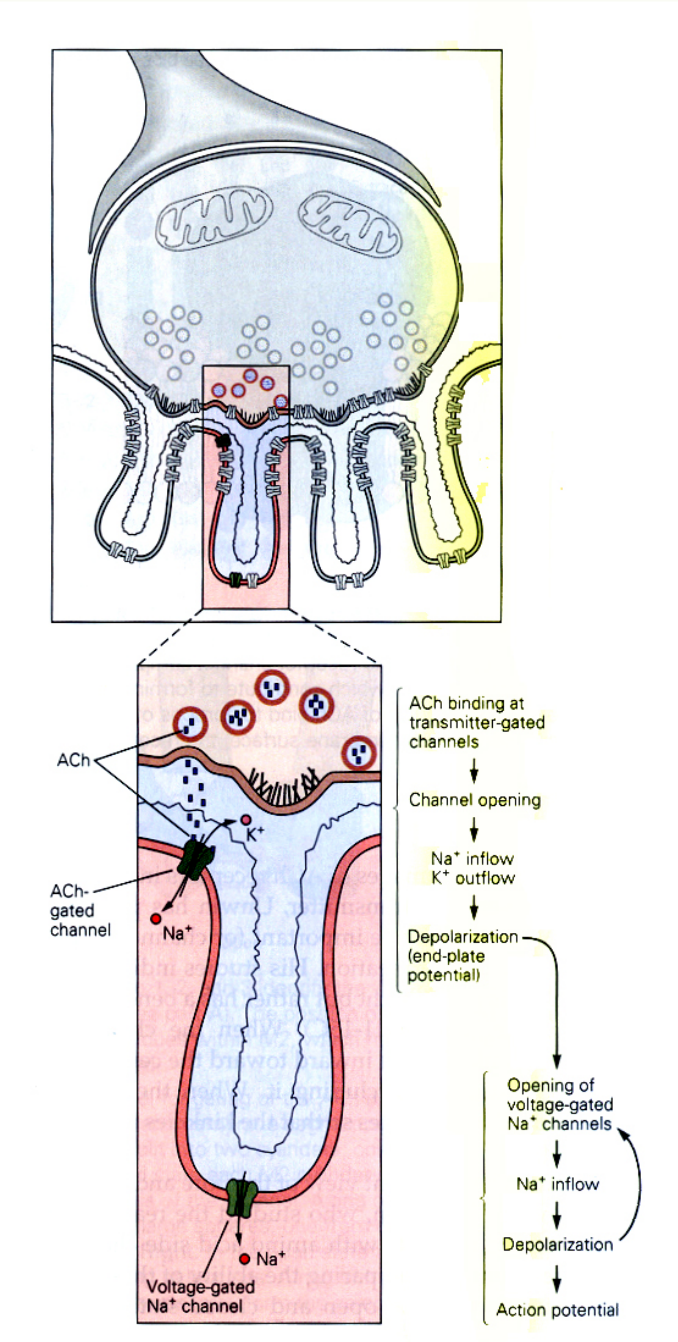
An action potential in an alpha motoneuron axon

ACh is released by the axon terminal at the neuromuscular junction (synapse between motoneuron and muscle

Nicotinic receptor channels open, Na+ enters and the membrane depolarizes

Voltage-gated Na+ channels open and an action potential is propagated down the muscle fiber

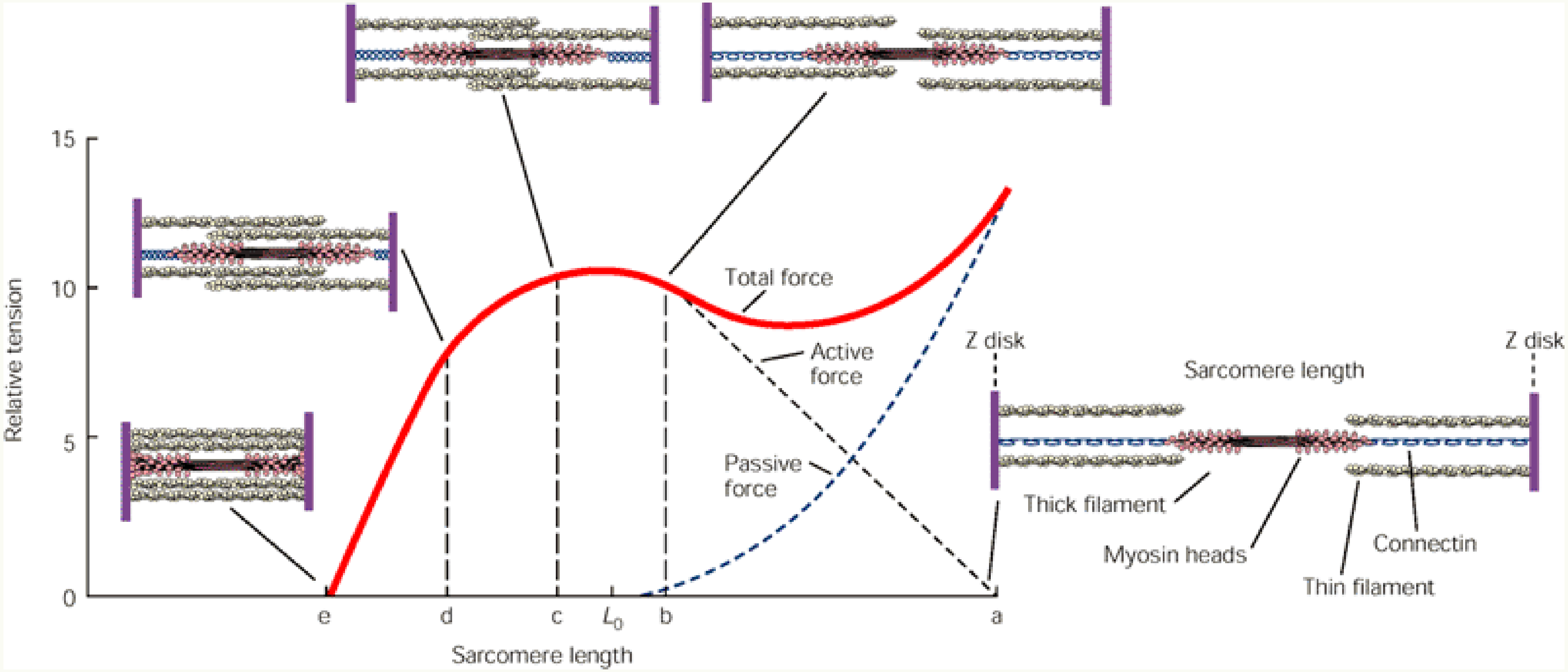
Depolarization produces Ca2+ release from intracellular stores



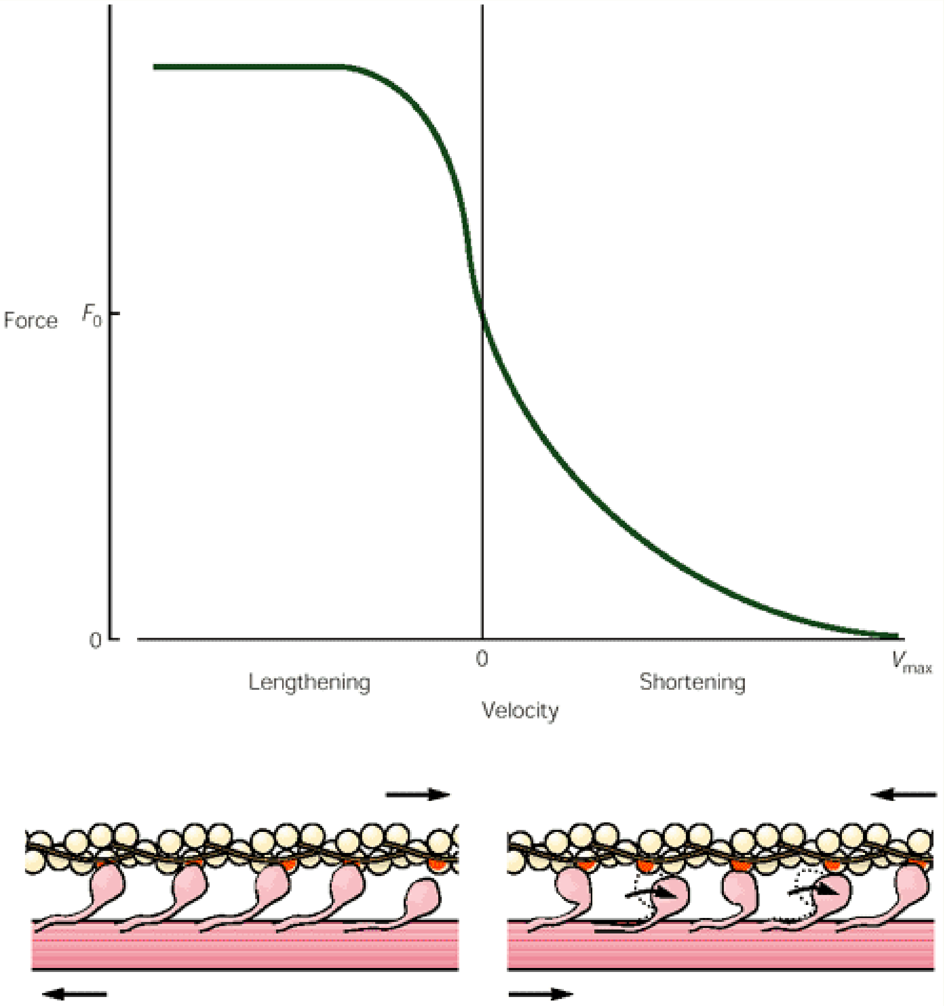
Comparison with CNS Synapse

Motor Unit	CNS Synapse
Alpha Motor Neuron	Presynaptic Neuron
Muscle Fiber	Postsynaptic Neuron
Endplate	Dendrite
NT is Acetylcholine	Many different NTs
Nicotinic Receptors	Many different receptors
Calcium enters	Sodium enters
Endplate Potential (EPP)	Excitatory postsynaptic potential (EPSP)
Muscle Contraction or Muscle Action Potential & movement	Action Potential & release of NT

Force - Length



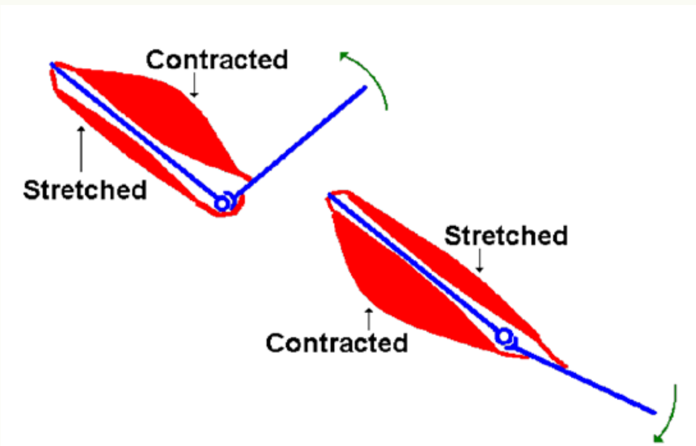
Force - Velocity

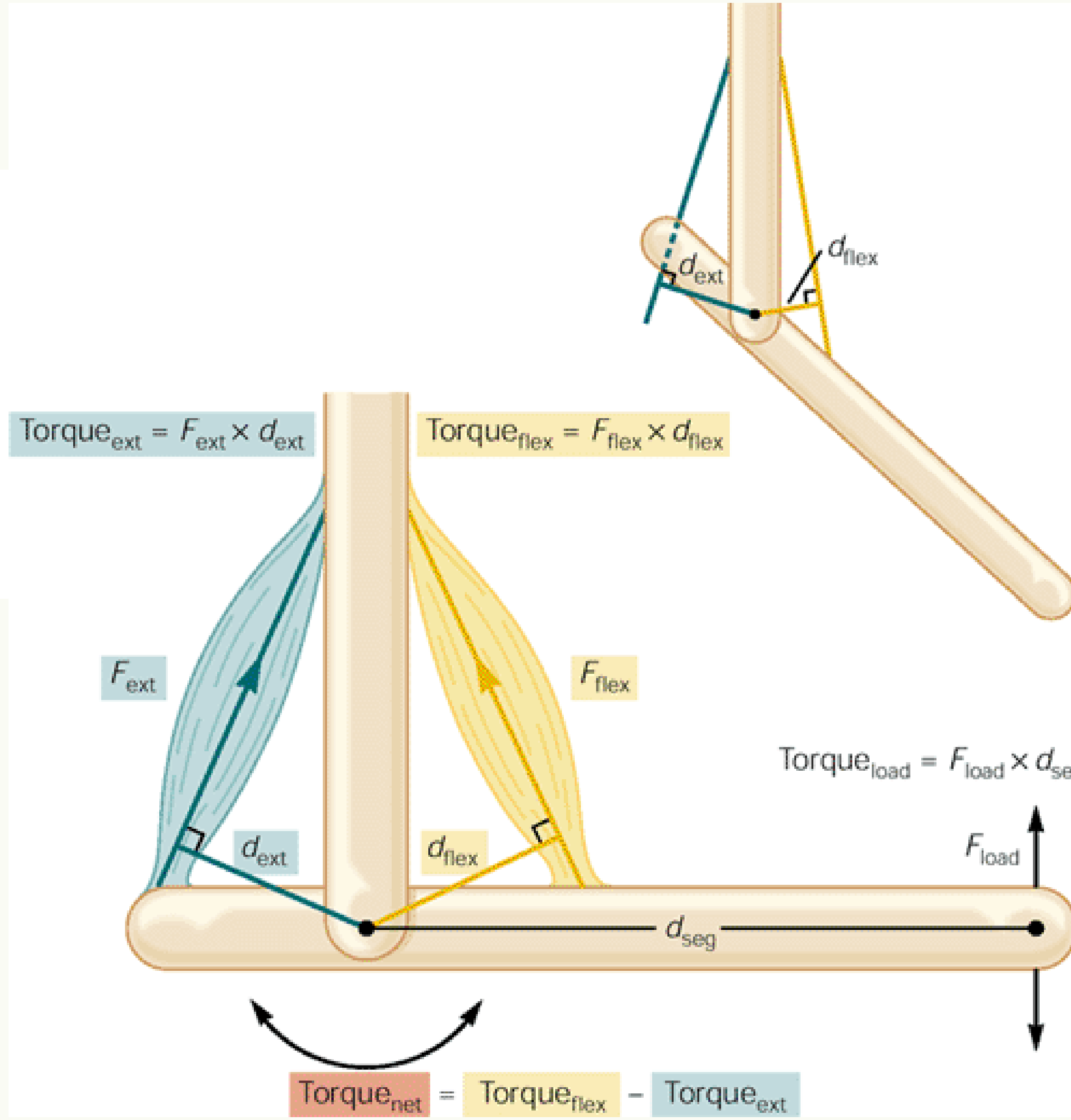


Musculoskeletal Machines

- The skeleton and muscles work together in a lever systems
- Muscles can only shorten by contraction, they cannot actively elongate
- An external force is needed to stretch a muscle back to its resting length
- Opposing muscle sets provide this external force (antagonist)

Hinge

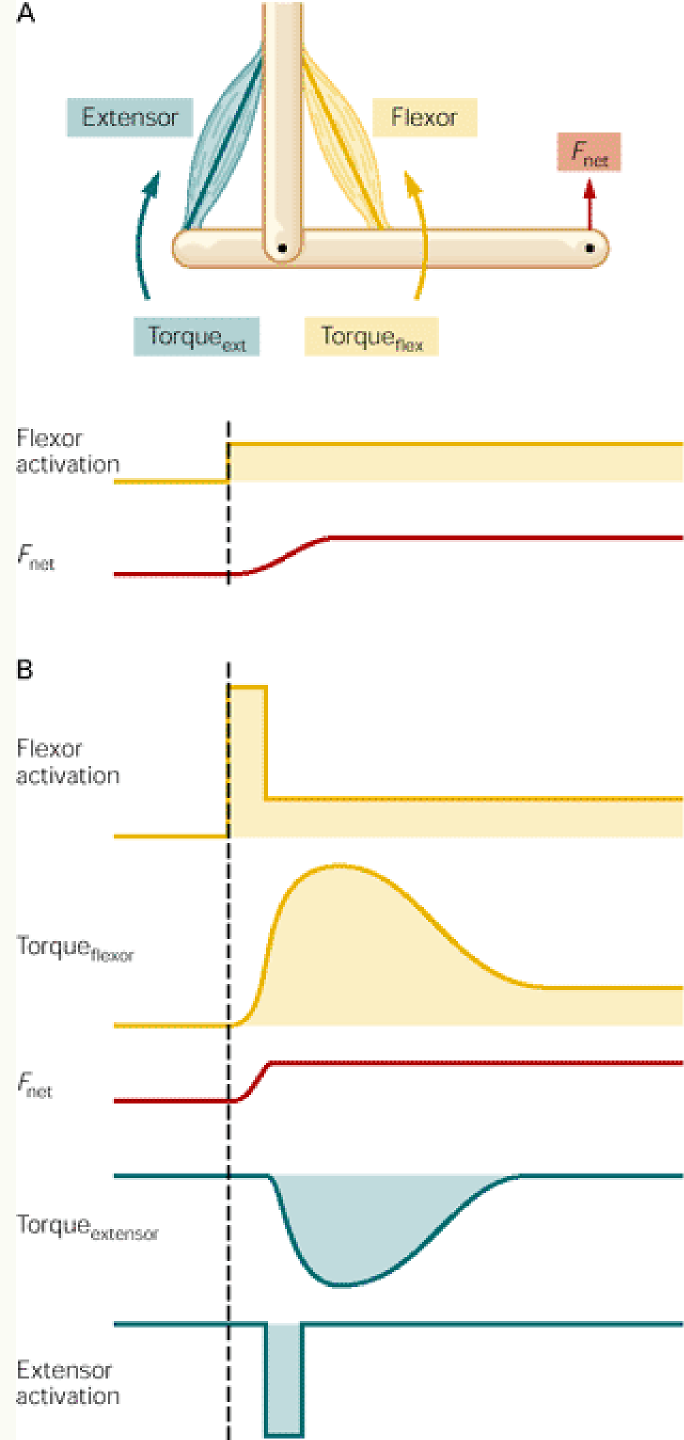

Contracted
Stretched
Stretched
Contracted


d_{ext}
d_{flex}
$\text{Torque}_{ext} = F_{ext} \times d_{ext}$
$\text{Torque}_{flex} = F_{flex} \times d_{flex}$
F_{ext}
F_{flex}
$\text{Torque}_{load} = F_{load} \times d_{seg}$
d_{ext}
d_{flex}
F_{load}
d_{seg}
$\text{Torque}_{net} = \text{Torque}_{flex} - \text{Torque}_{ext}$

Agonist-Antagonist Action

Rapid Increase of Torque

Joint Stiffness



Agonist-Antagonist Action

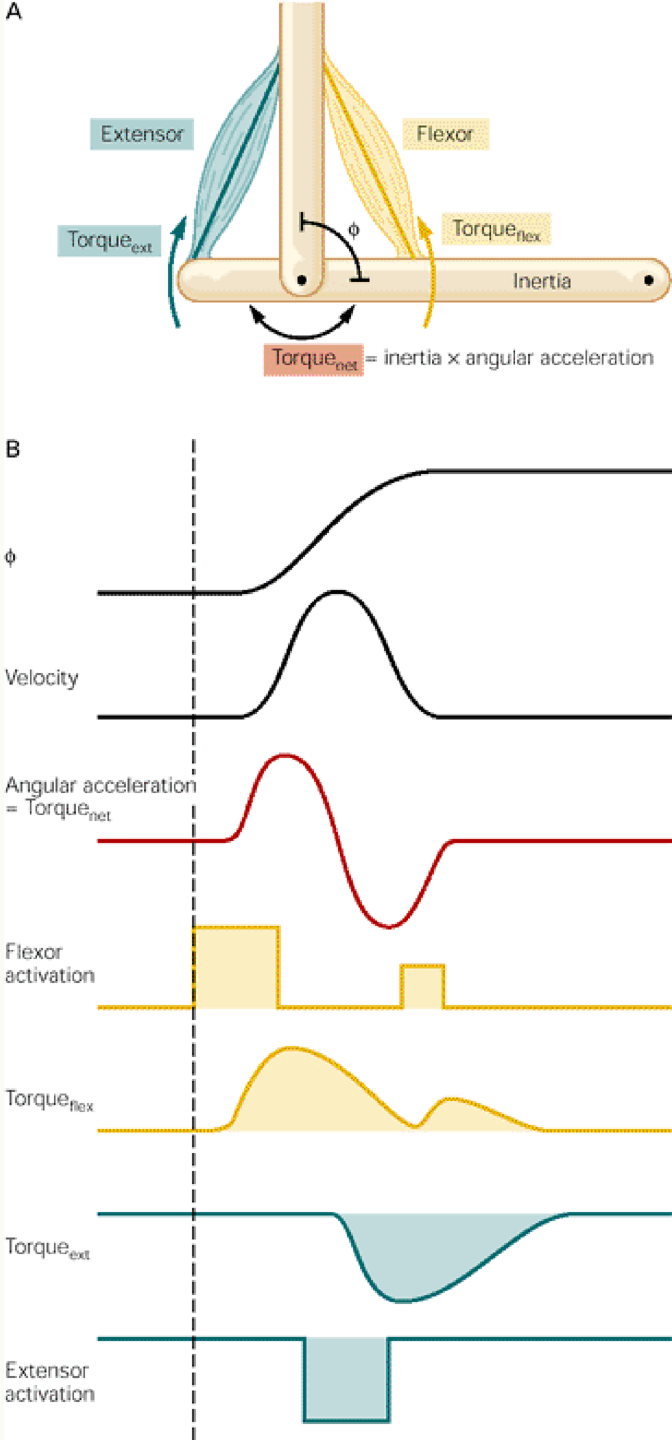
Angular velocity follows a symmetrical, bell-shaped profile

Requires equal and opposite net torque pulses to produce the corresponding acceleration and deceleration phases

The flexor and extensor muscles are activated in succession

Because of the relatively slow fall time of contractile force, the decelerating torque can overshoot

Third phase of activity is included to stop the limb on target (fast movements)

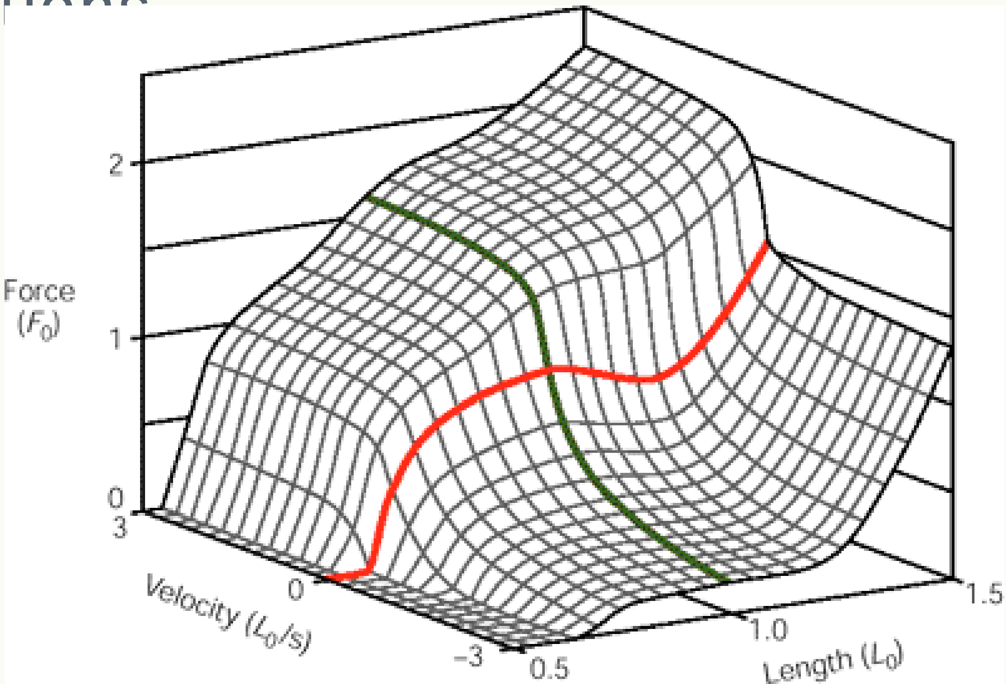


Force depends on Length / Velocity

Joint movement produces an instantaneous change in the muscle's force without any change in its state of activation

Unfortunate complication?

The nervous system uses these properties to great advantage in coping with unanticipated perturbations



Motor Unit

Neurophysiology of the Motor System

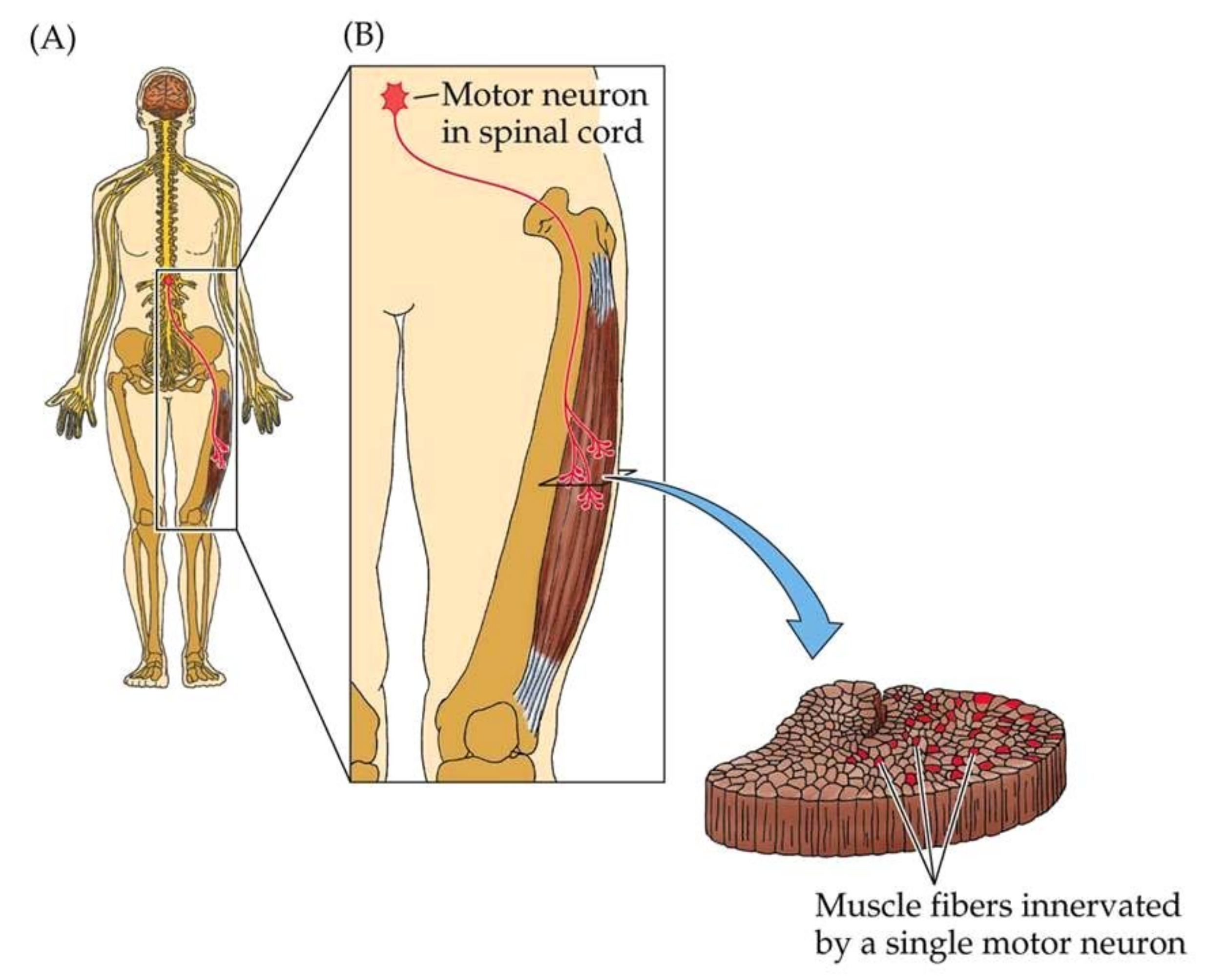
Motor Unit

Motoneuron + muscle fibers it innervates

- ...few muscle fibers (e.g. extraocular muscles)
- ...hundreds of fibers (e.g. digits)
- ...thousands of fibers (e.g. trunk and major limb segments)

Smaller motor units yield more refined control
a motor “fovea”

Motor Unit



(A)
(B)
Motor neuron in spinal cord
Muscle fibers innervated by a single motor neuron

“Motor Fovea”

- Ratio between the alpha motor neuron and the number of muscles fibers it innervates = degree of dexterity needed in the movement
  - high ratio (1:150) = contraction of large muscles
  - low ratio (1:10) = contraction of small muscles needed for fine movements
- Motor Homunculus is related to the number of alpha motor neurons needed to innervate muscles of various regions of the body

Motor Unit Activity

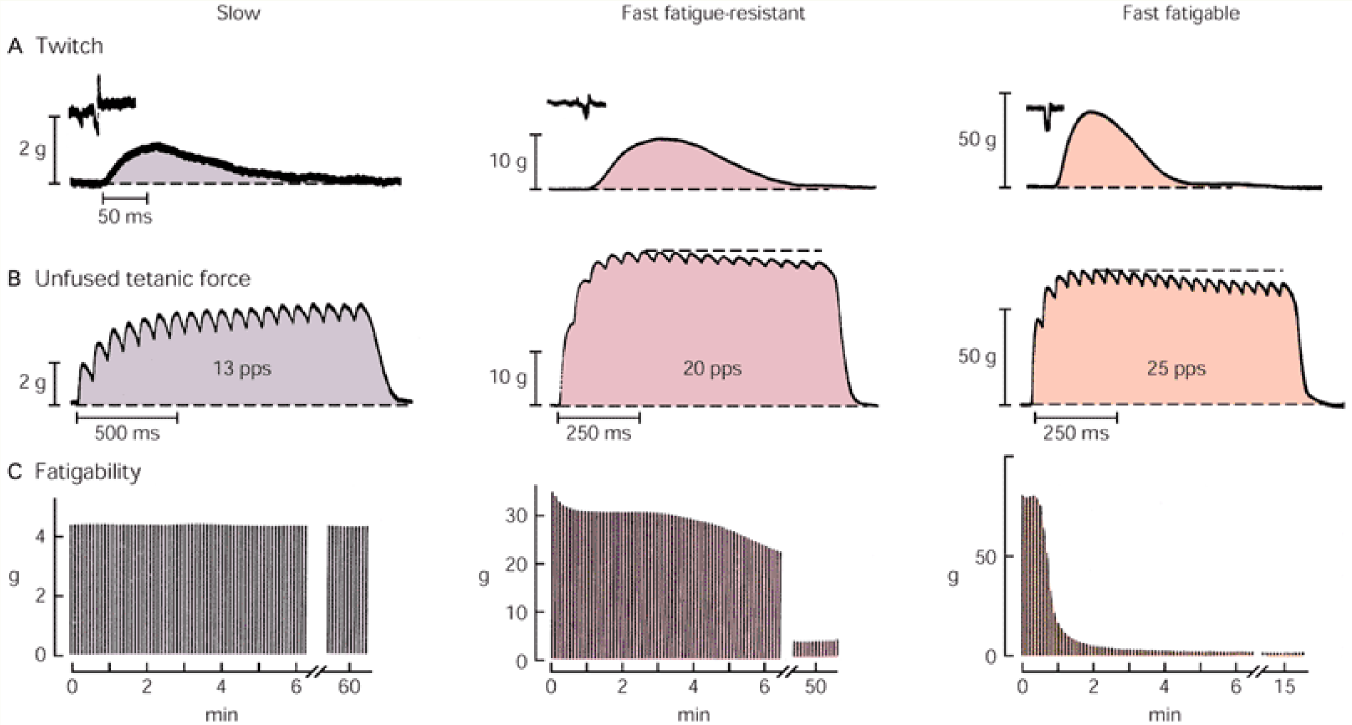
All-or-None Law (Bowditch's Law) for motor units

- Applies to individual motor units, but not the entire muscle
- Based on the difference between graded potentials and action potentials (Stimulation threshold -> A motor unit is either activated completely or is not activated at all)
- If there is enough potential to create an action potential that travels down the α-motor neuron of a motor unit, then all of the fibers in that motor unit will contract

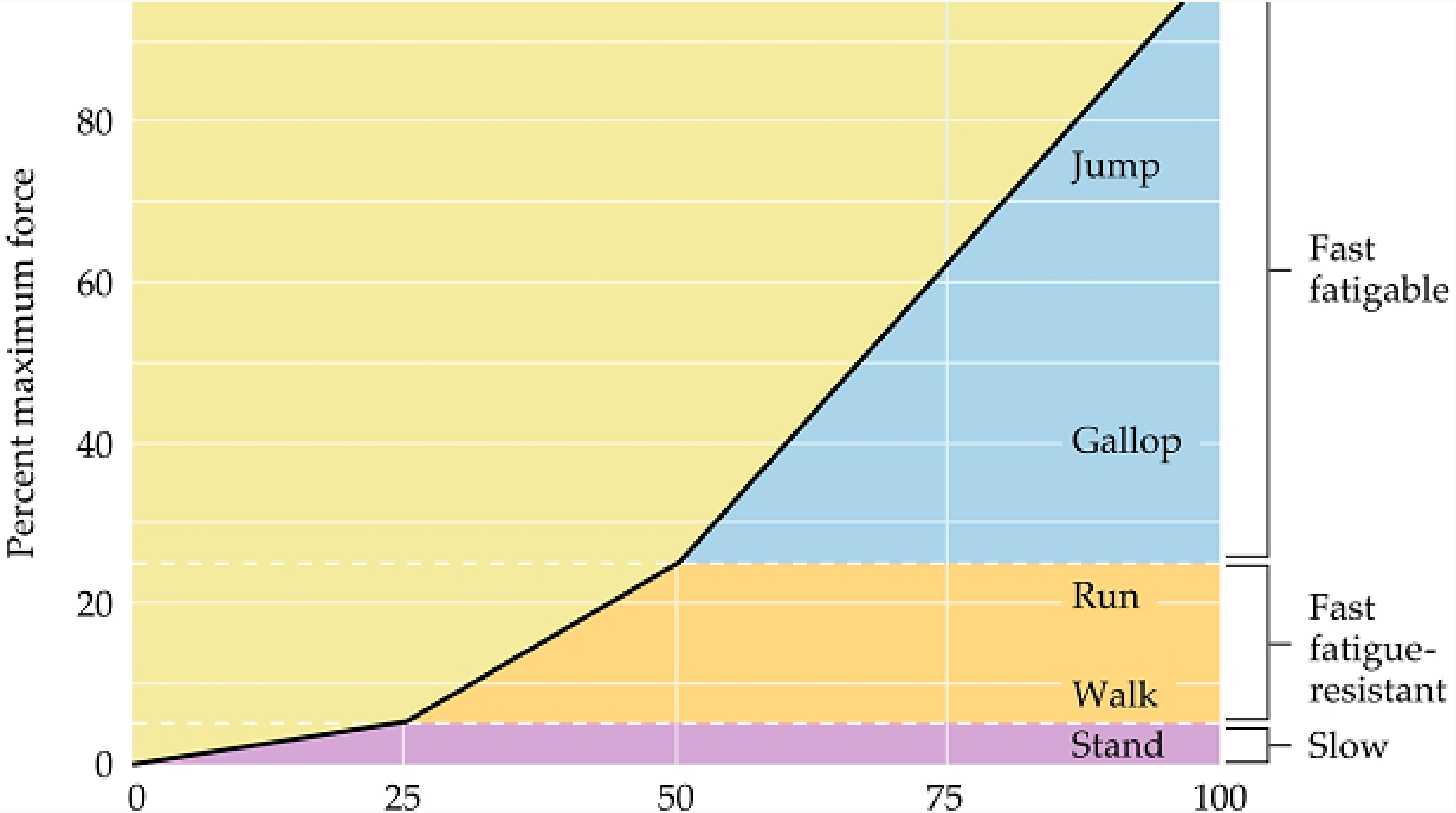
Fatigue

One motor neuron innervates only 1 type of fibers

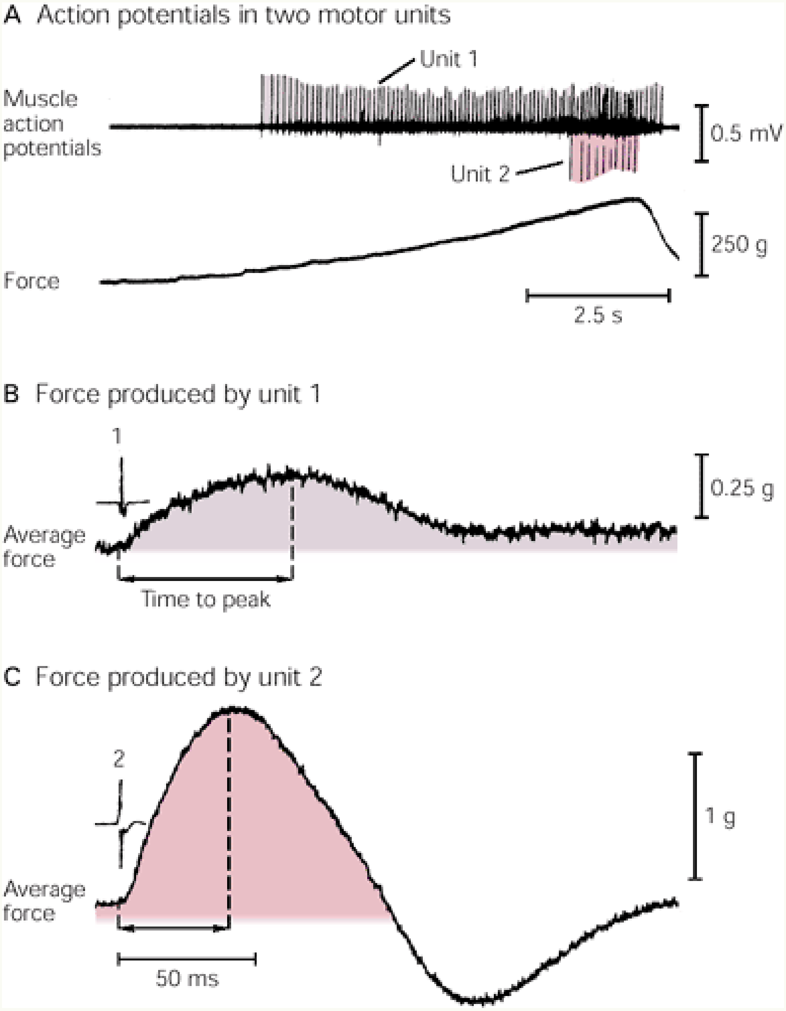
- Slow (type I)
- fast fatigue-resistant (type IIa)
- fast and fatigable (typeIIb)



Fiber Type Recruitment



Example

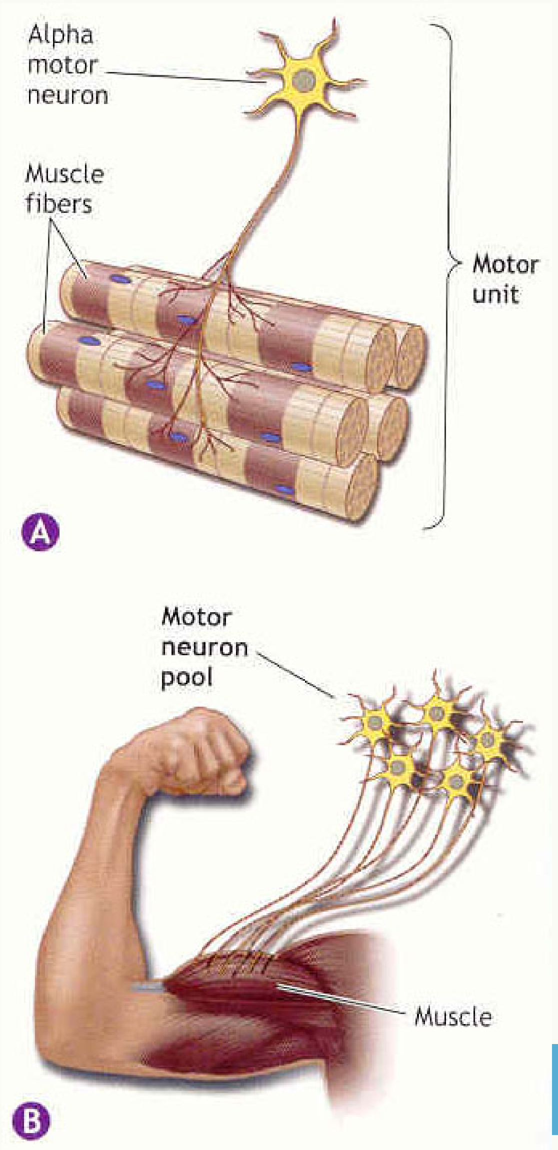


A Action potentials in two motor units
Unit 1
Muscle action potentials
Unit 2
0.5 mV
Force
250 g
2.5 s
B Force produced by unit 1
1
Average force
0.25 g
Time to peak
C Force produced by unit 2
2
Average force
1 g
50 ms

Gradation of Muscle Force

Two neural mechanisms:

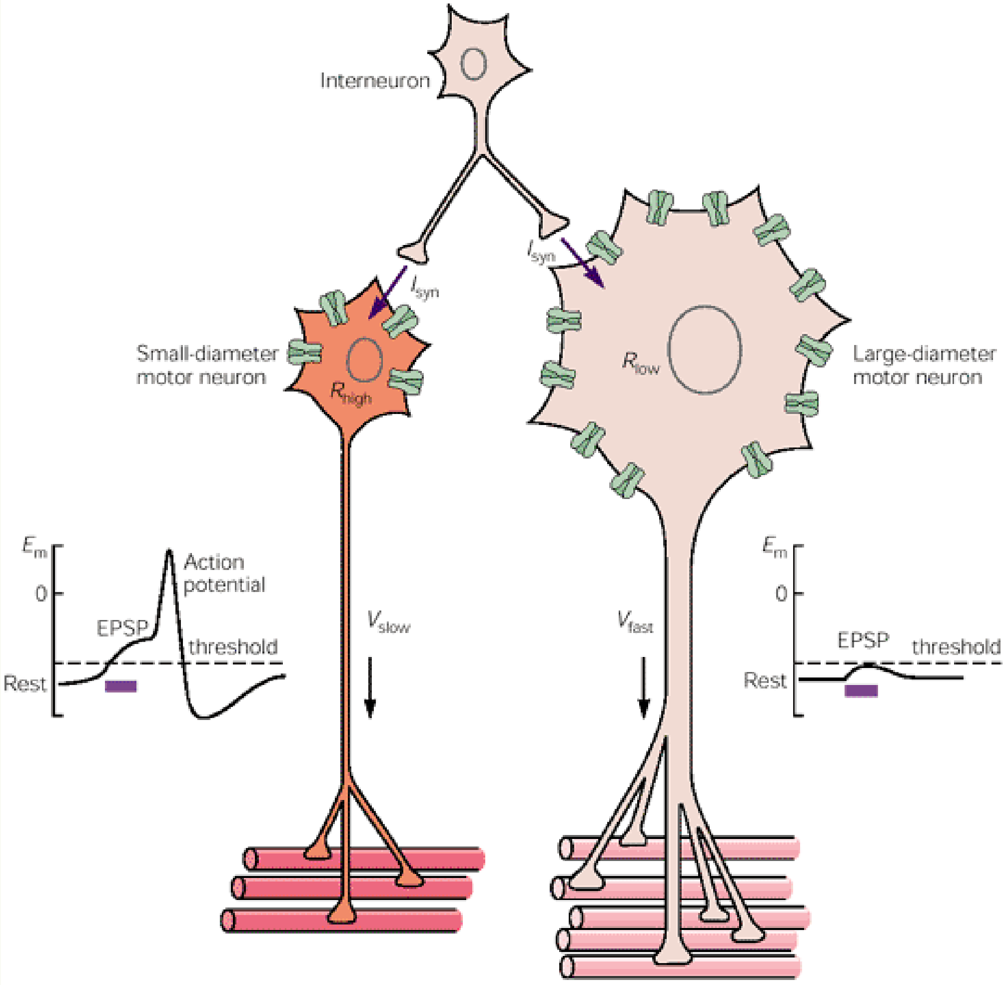
- Recruitment
  - Spatial summation
- Rate coding
  - Temporal summation



Recruitment

The “size principle”

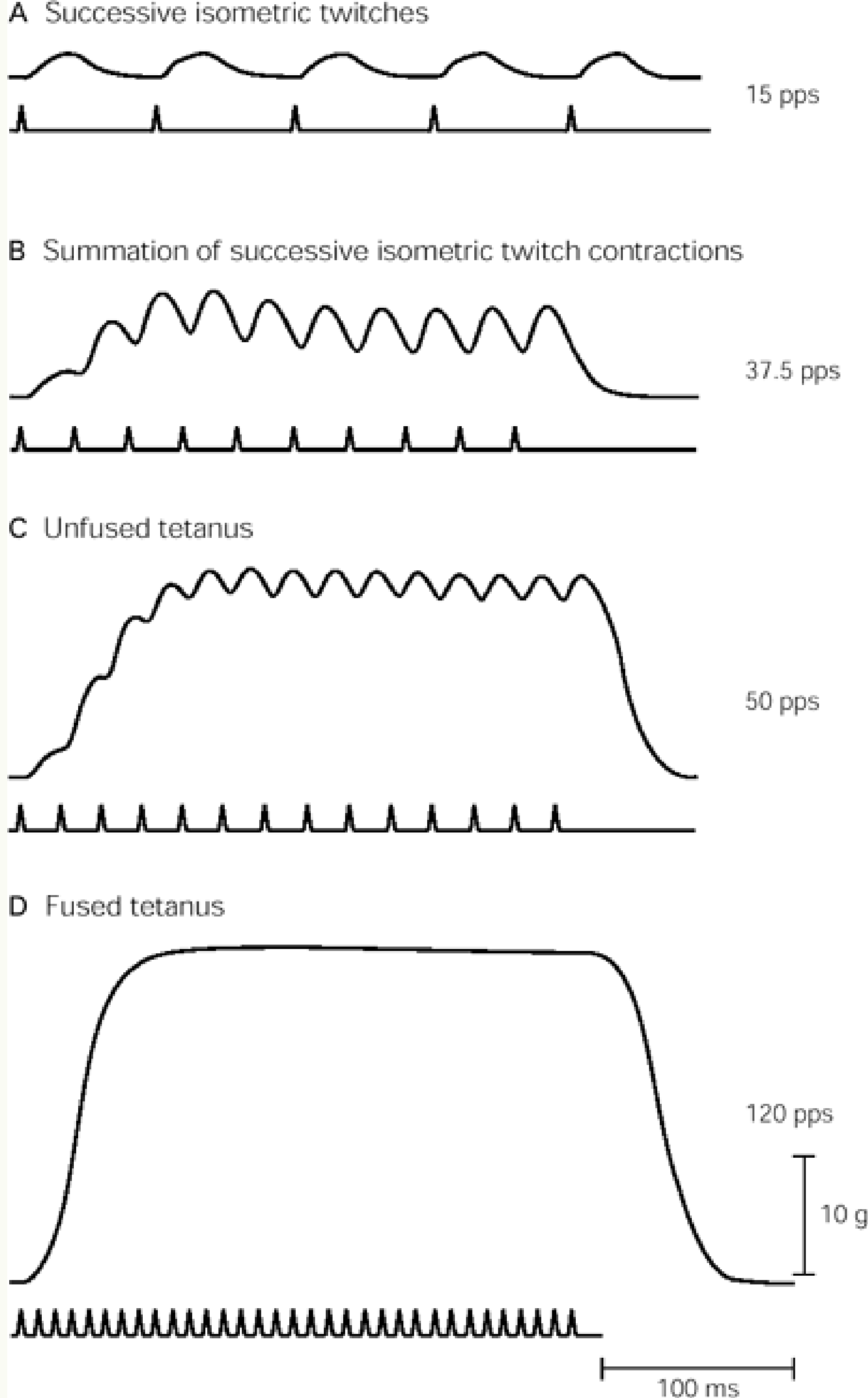
- Bigger neuron -> higher threshold -> recruited later
- Bigger neuron -> Typically innervate type 2 -> more force
- Bigger neuron -> more fibers -> bigger muscles
- Bigger neuron -> larger axons -> faster



Rate Coding

Rate coding refers to the motor unit firing rate

- Active motor units can discharge at higher frequencies to generate greater tensions

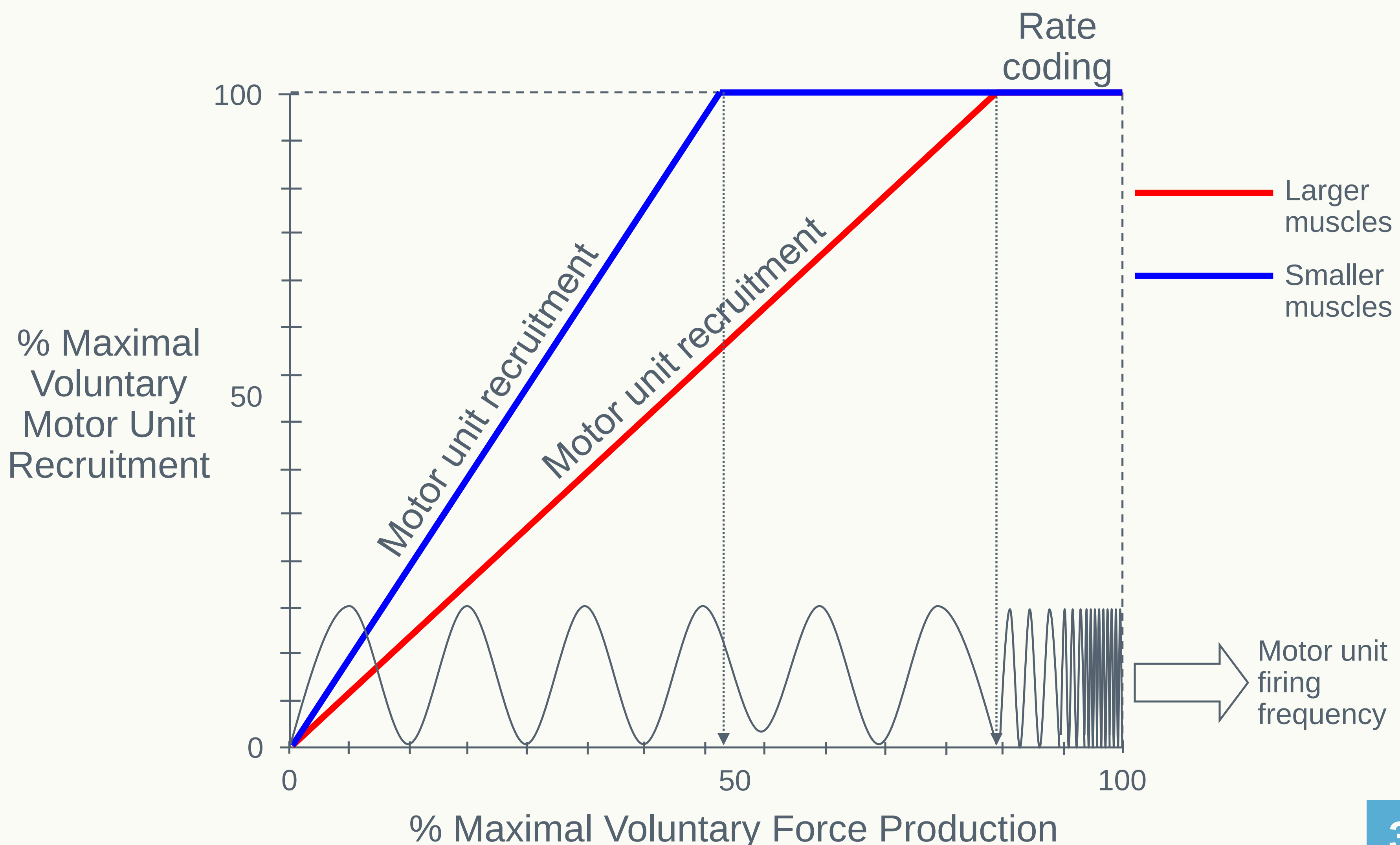


Spatial Vs. Temporal Summation

Recruitment vs. Rate coding

- Smaller muscles (ex: first dorsal interosseous) rely more on rate coding
- Larger muscles (ex: deltoid) rely more on recruitment

Rate Coding



Rate
coding
100
50
0
% Maximal
Voluntary
Motor Unit
Recruitment
Motor unit recruitment
Motor unit recruitment
Larger
muscles
Smaller
muscles
Motor unit
firing
frequency
0
50
100
% Maximal Voluntary Force Production

Spinal Circuits, Reflexes and their modulation

Neurophysiology of the Motor System

Spinal Circuits

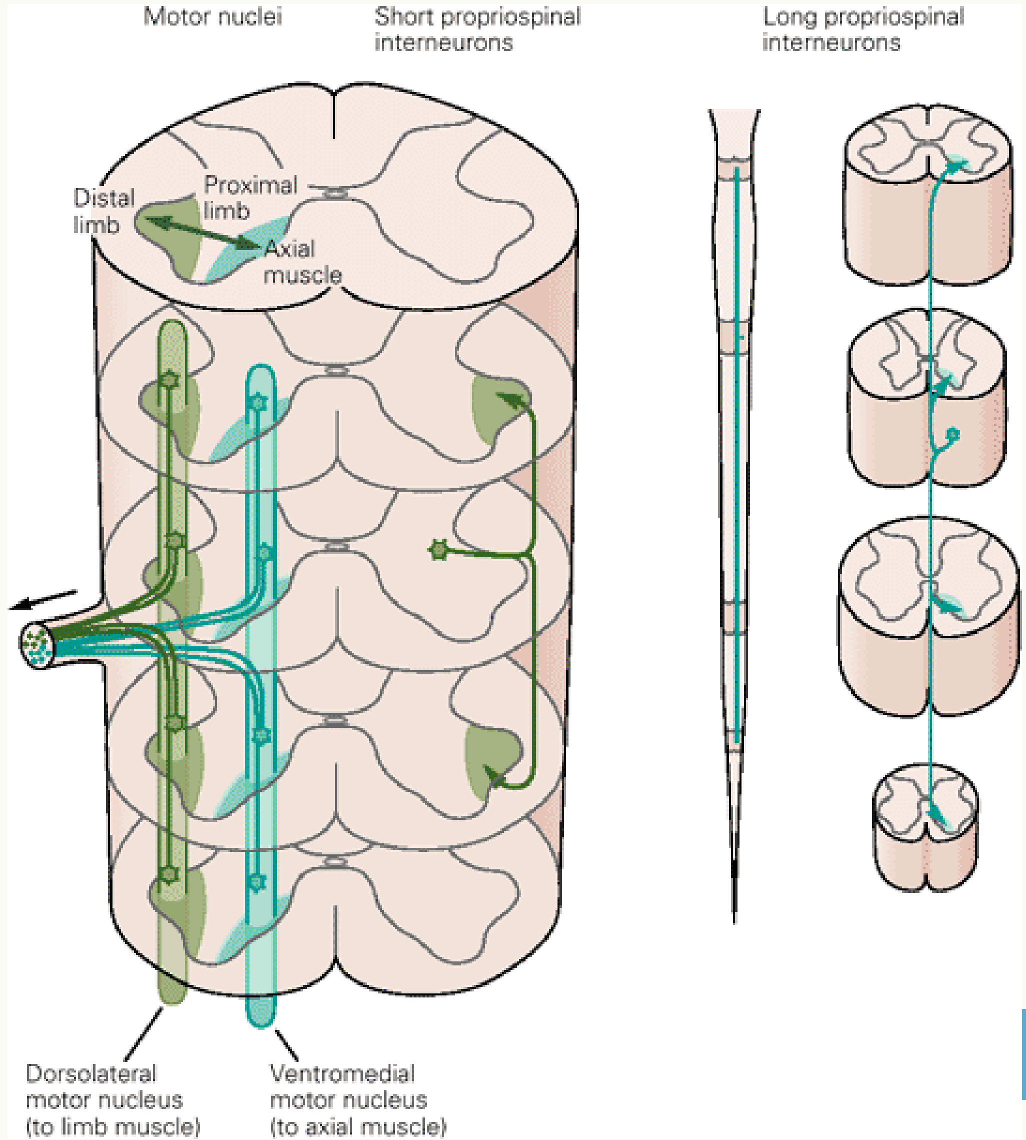
Medial nuclei contain the motor neurons innervating axial muscles

Lateral nuclei

- the most medial innervate proximal
- the most lateral innervate distal muscles

The medial motor nuclei are interconnected across several segments

The lateral nuclei are interconnected across fewer segments



An introduction to reflexes

Reflexes are rapid and automatic responses to stimuli (old view)

…are integrated by CNS commands

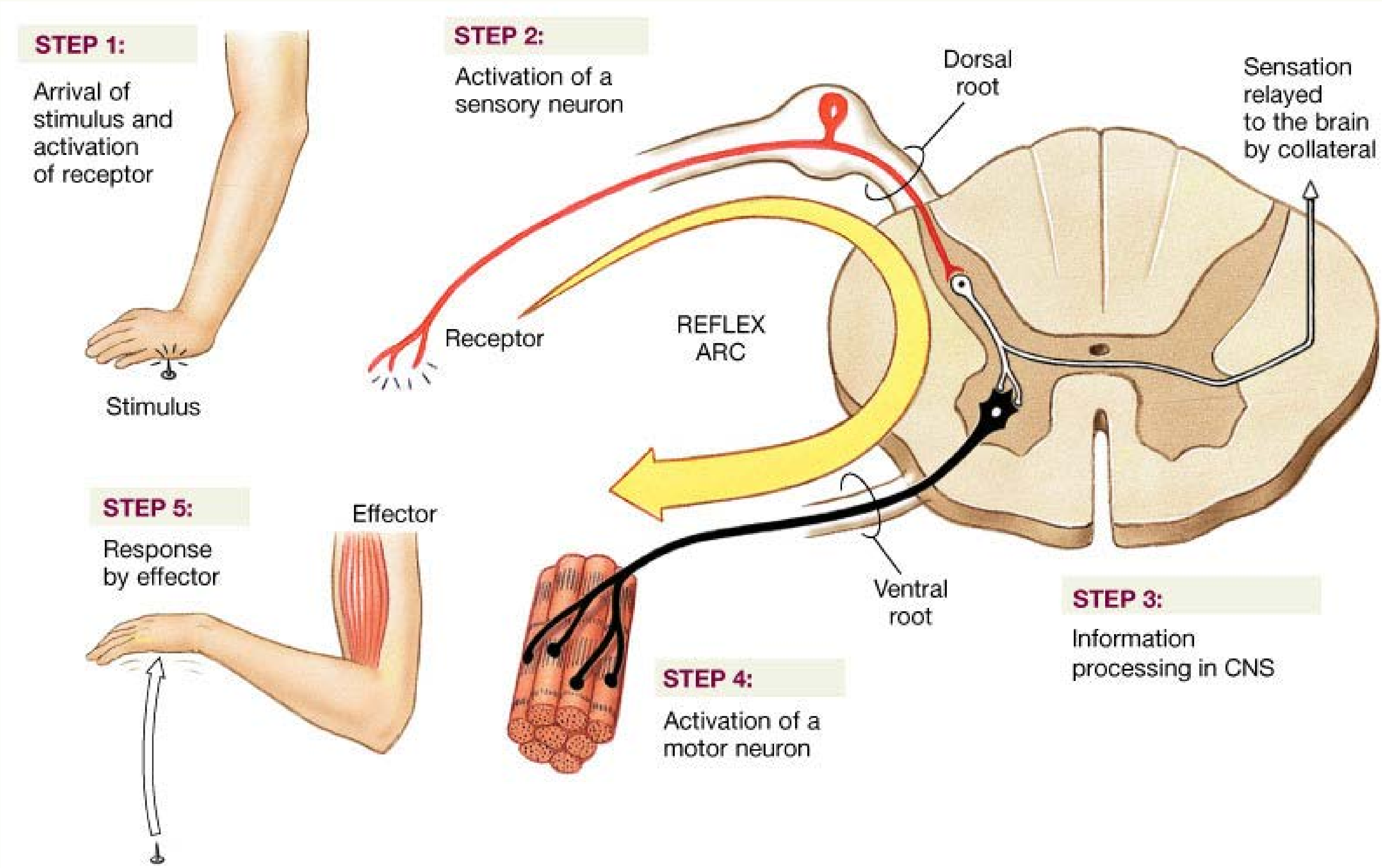
Reflex arc

Wiring of a neural reflex

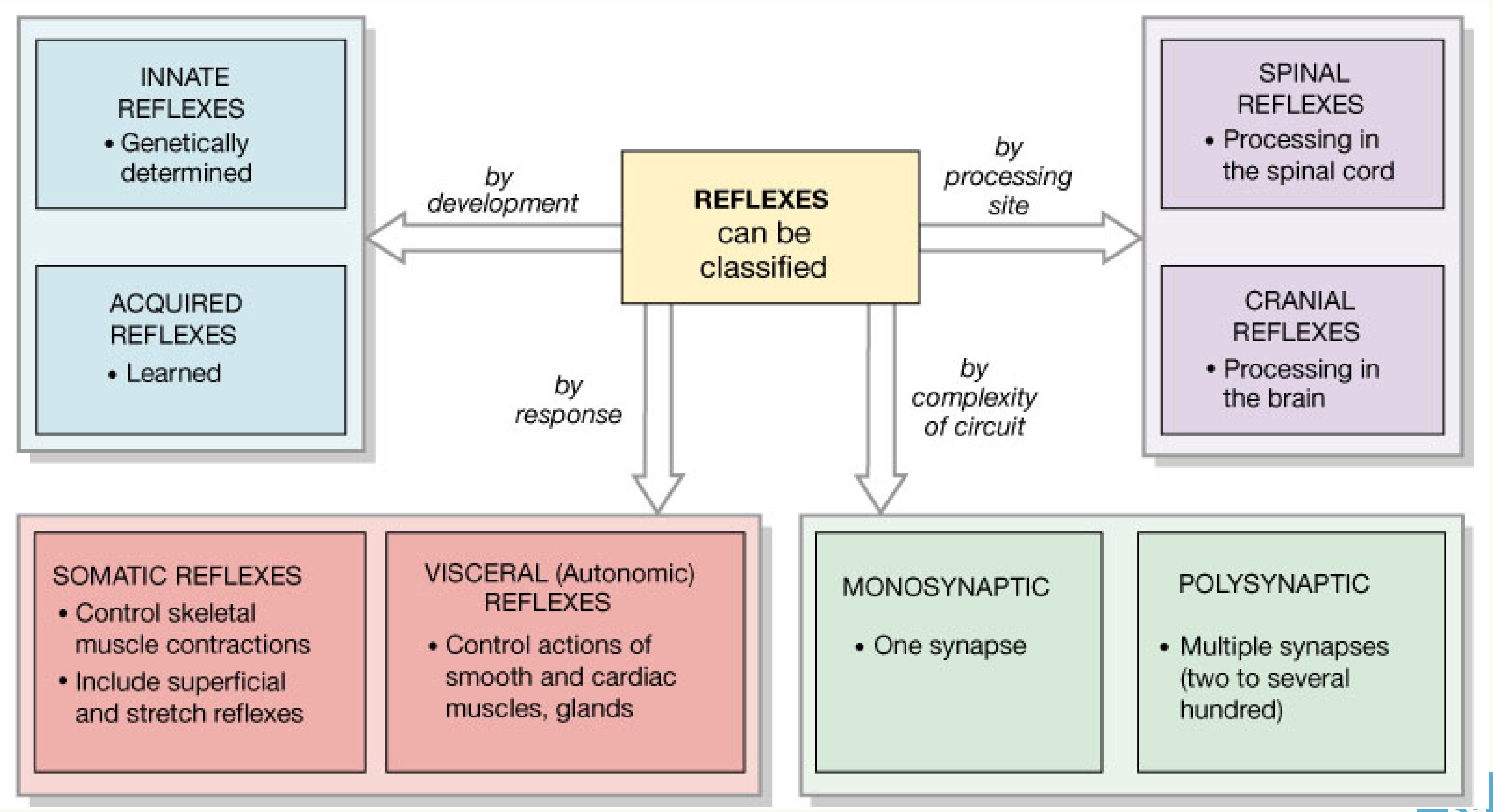
Five steps

- Arrival of stimulus and activation of receptor
- Activation of sensory neuron
- Information processing
- Activation of motor neuron
- Response by effector

Components of the Reflex Arc



Reflex classification



More on Reflex Classifications

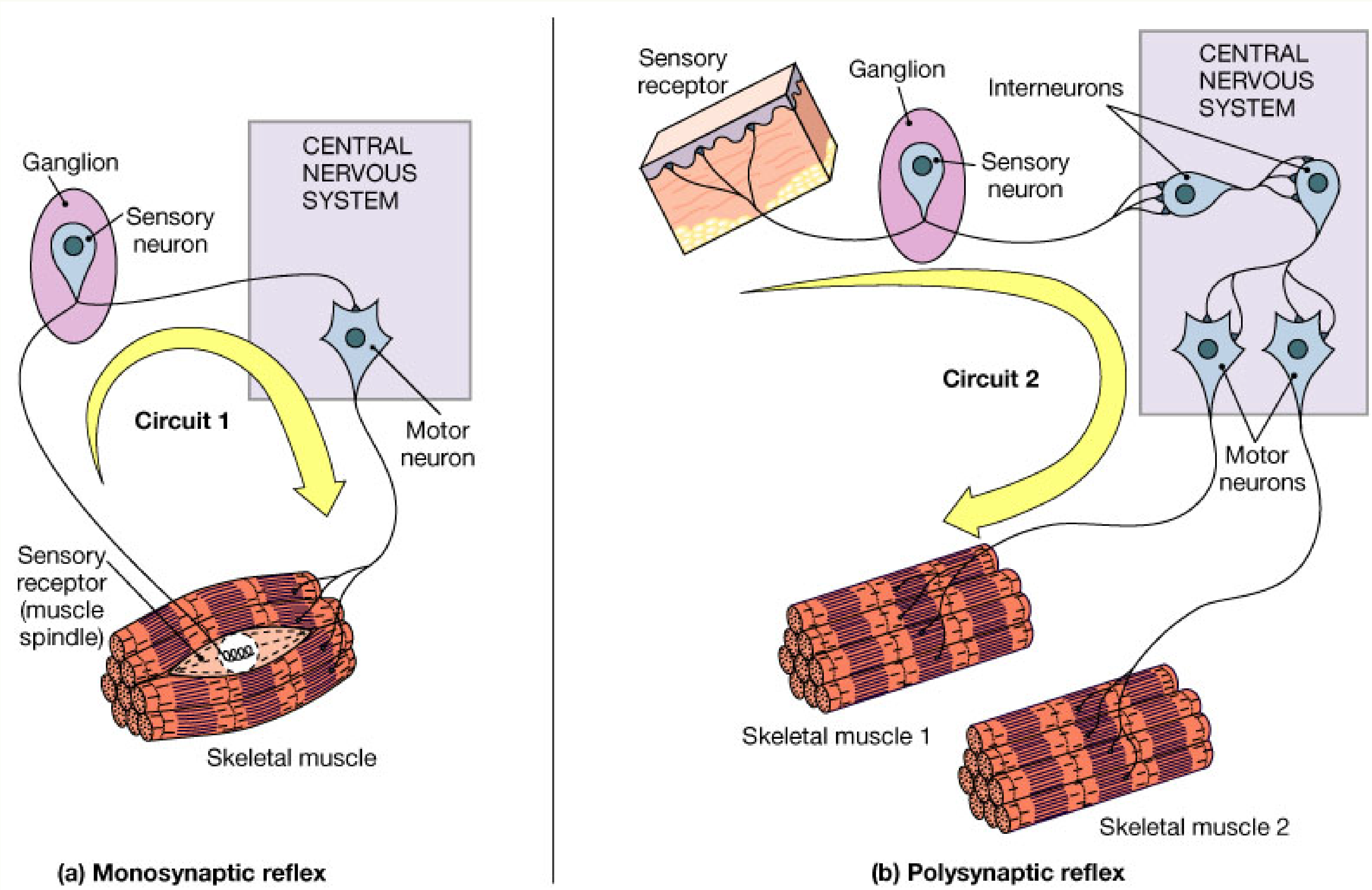
Monosynaptic reflex

– Sensory neuron synapses directly on a motor neuron

Polysynaptic reflex

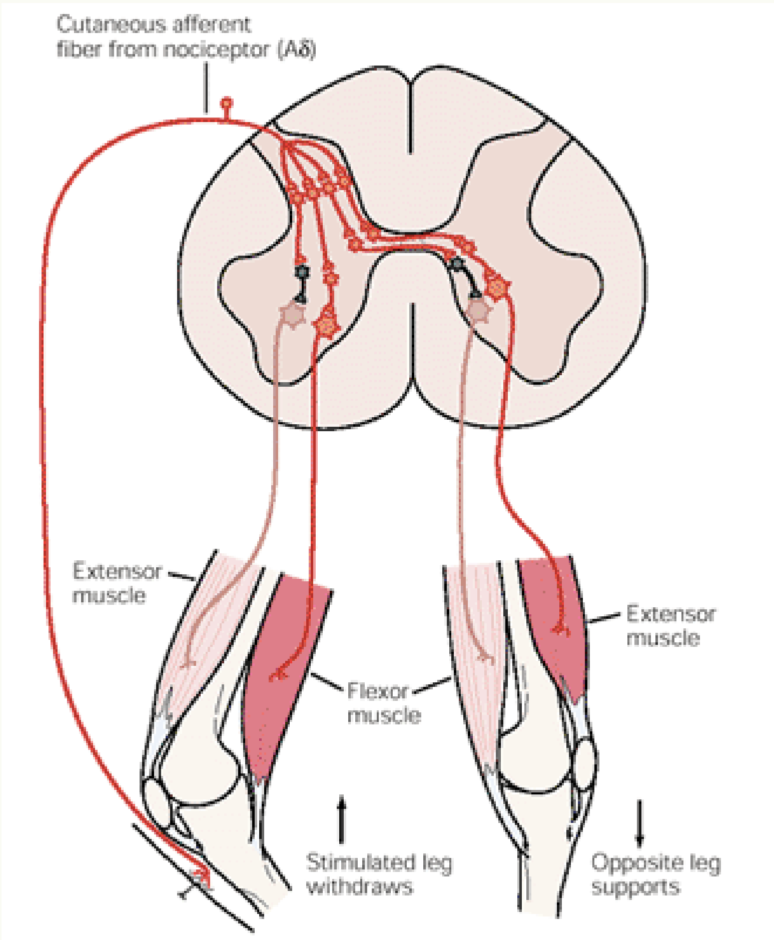
– At least one interneuron between sensory afferent and motor efferent
– Longer delay between stimulus and response

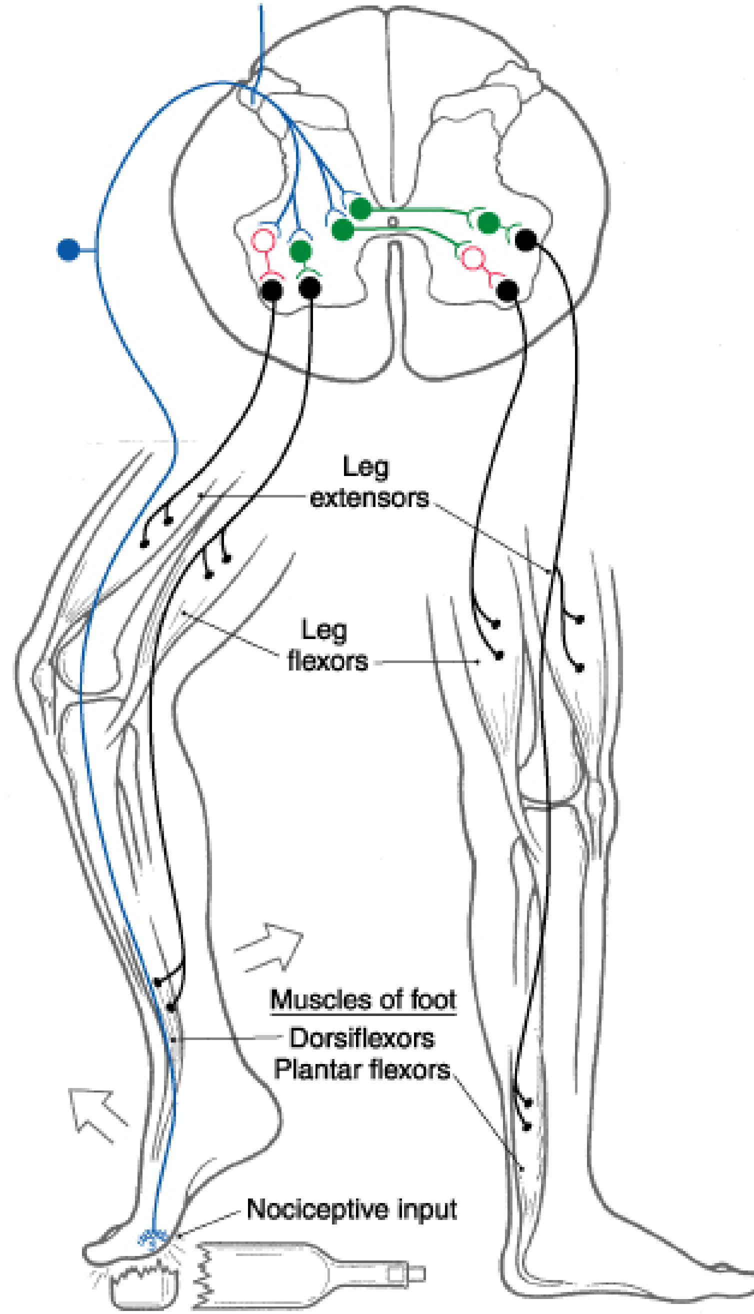
Reflexes



Ganglion
Sensory neuron
CENTRAL NERVOUS SYSTEM
Circuit 1
Motor neuron
Sensory receptor (muscle spindle)
Skeletal muscle
(a) Monosynaptic reflex
Sensory receptor
Ganglion
Interneurons
CENTRAL NERVOUS SYSTEM
Sensory neuron
Circuit 2
Motor neurons
Skeletal muscle 1
Skeletal muscle 2
(b) Polysynaptic reflex

Flexor Reflex

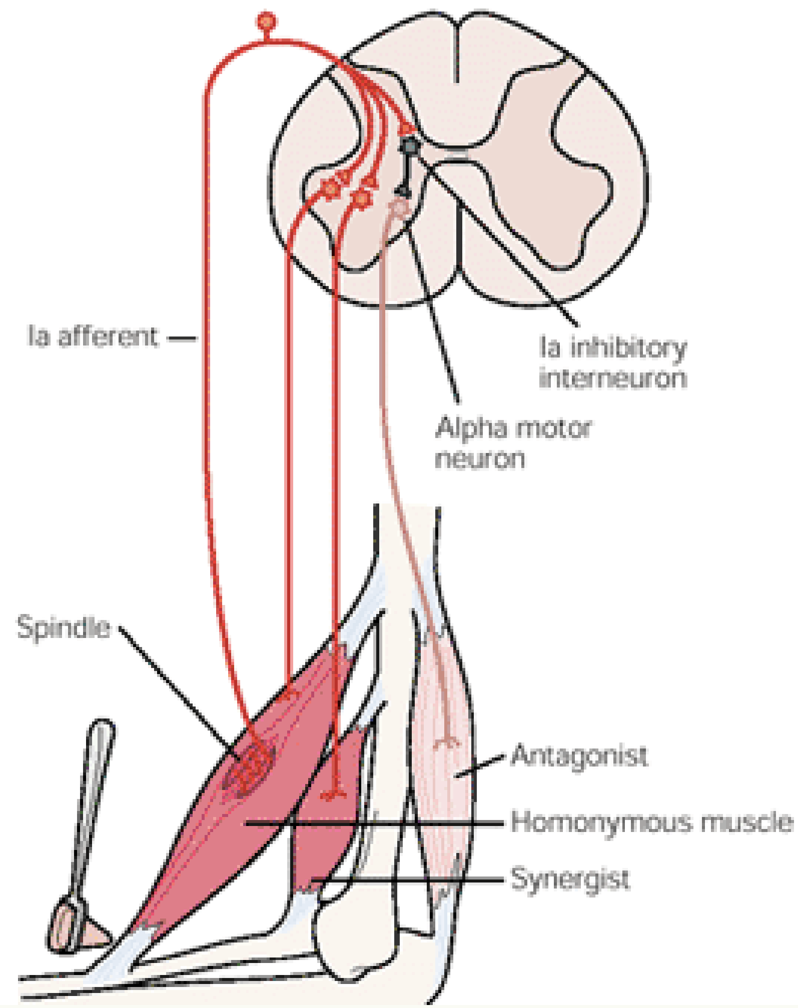


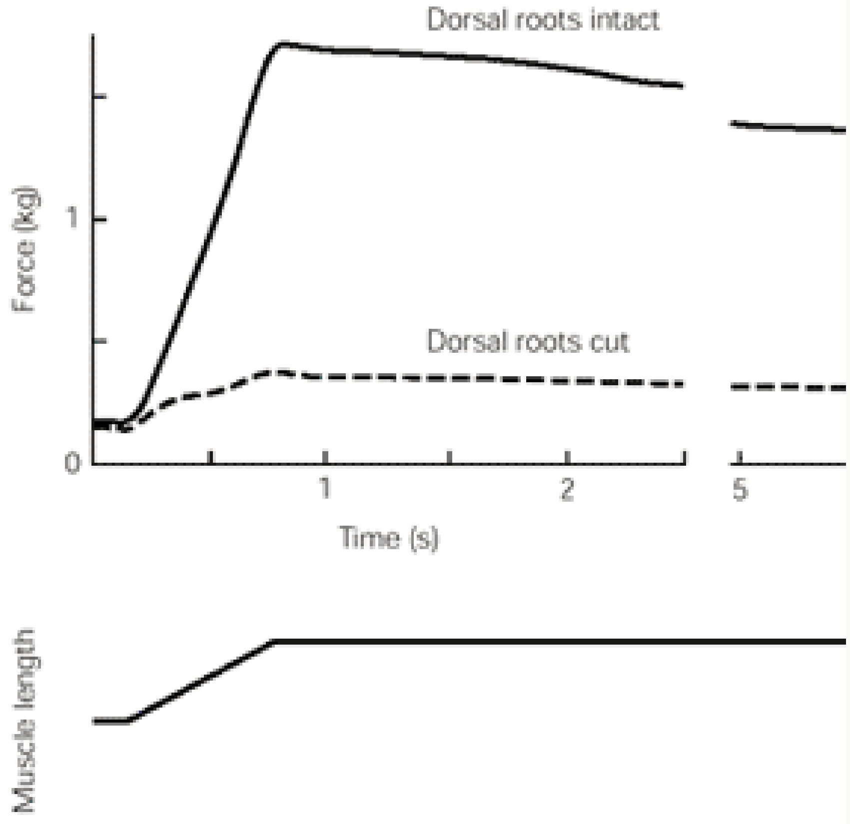


Polysynaptic Reflexes: Flexor Reflex

- Involve pools of interneurons
- Sensory receptors are nociceptive sensors
- Intensity and duration depends on intensity of stimulus
- Are intersegmental in distribution
- Involve reciprocal inhibition
- Function: body protection and postural adjustment

Stretch Reflex





Monosynaptic Reflexes: Stretch Reflex

Automatically monitors skeletal muscle length and tone

Sensory receptors are muscle spindles

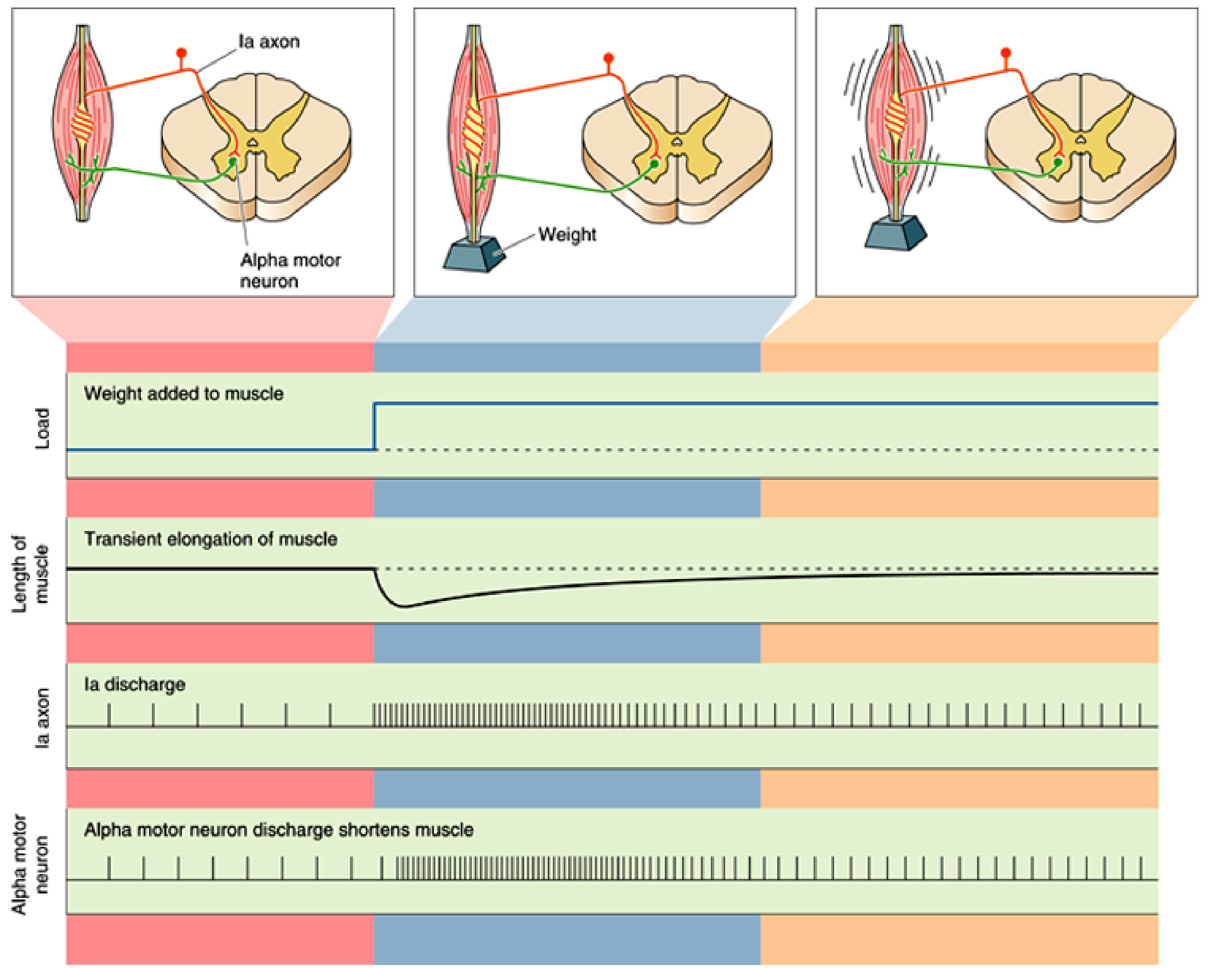
Mediated by:

- Ia afferent fibers
- Ia inhibitory interneurons

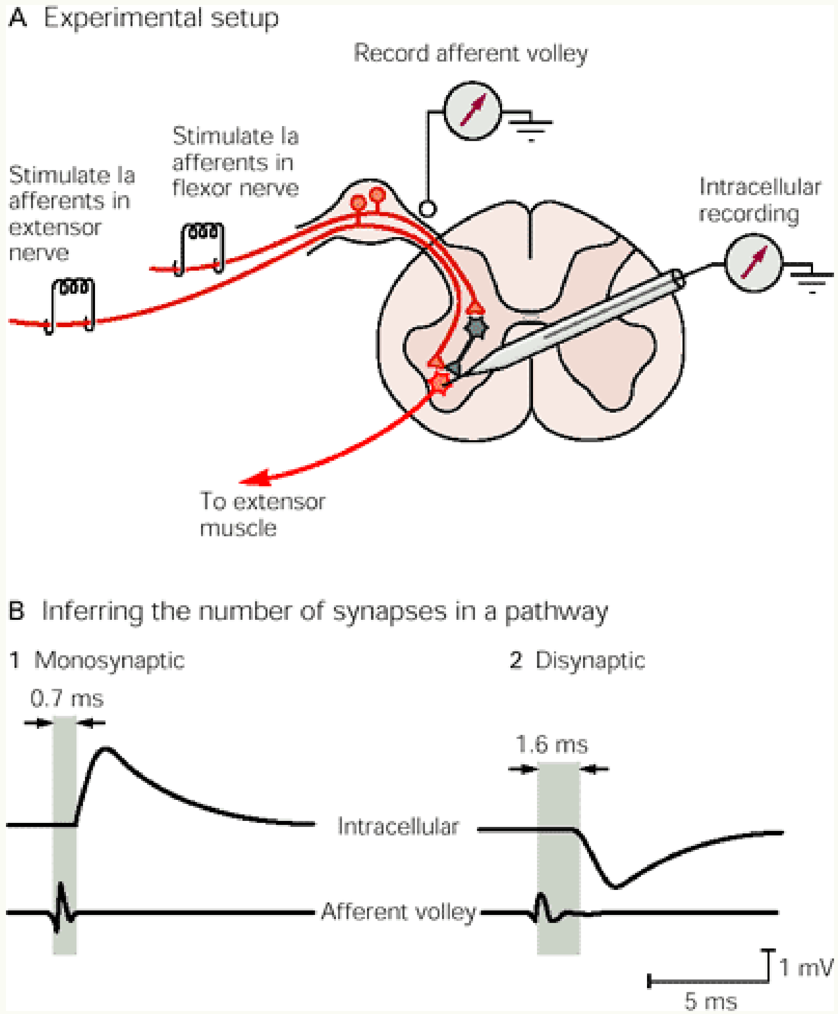
Function: muscle protection

Augmented in decerebrated animals

Stretch Reflex



How Number of Synapses is Measured



Muscle Spindles

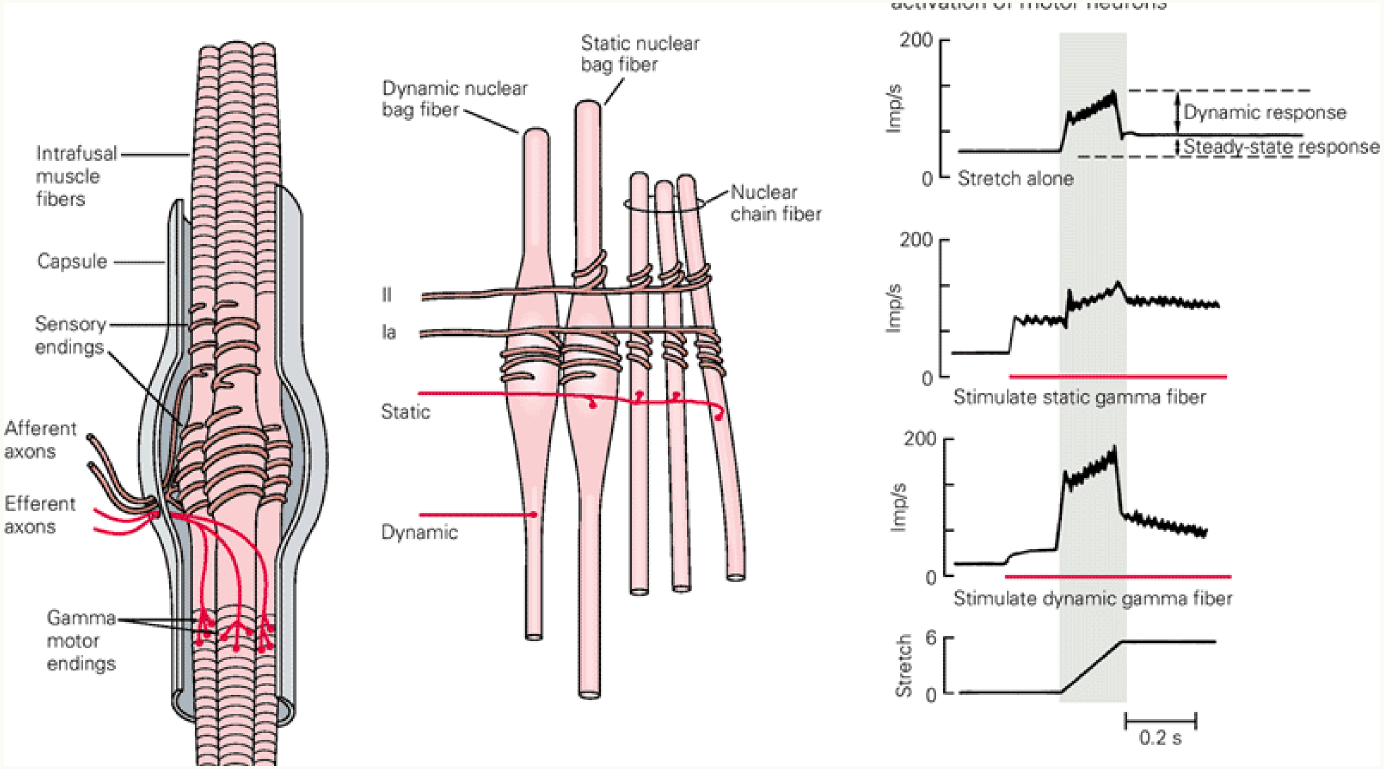
Main function is to signal changes in the length of the muscle

Changes in the length of muscles are closely associated with changes in the angles of the joints -> sense relative positions of the body segments

Each spindle has three main components:

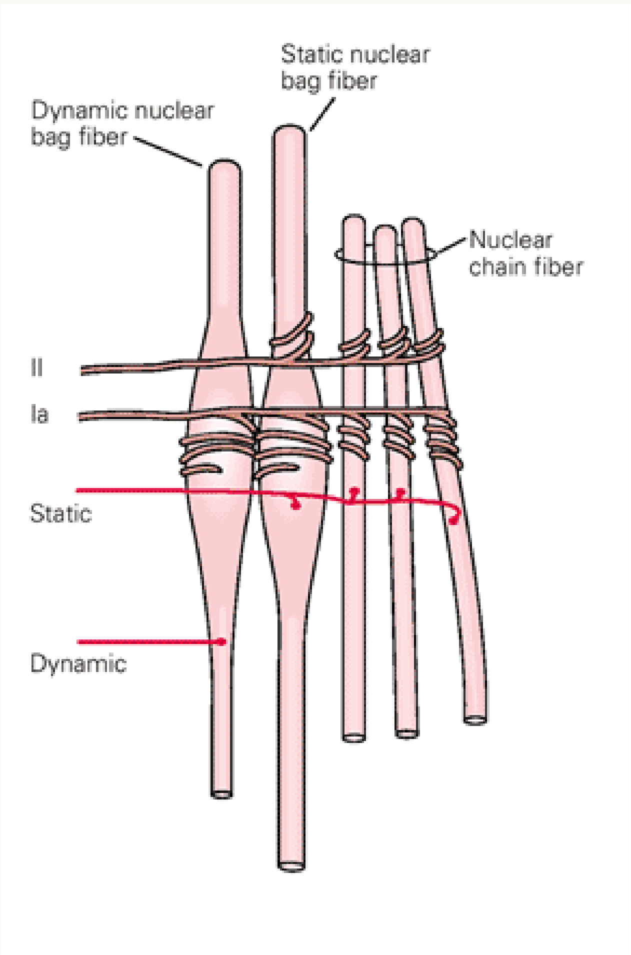
- Specialized intrafusal muscle fibers
- Large-diameter myelinated sensory endings that originate from the central regions
- Small-diameter myelinated motor endings that innervate the polar regions

Intrafusal Fibers



- The central regions are not contractile
- The sensory fiber endings spiral around the central regions and are responsive to stretch of these fibers
- Gamma motor neurons innervate the contractile polar regions
- Contraction of the intrafusal fibers pulls on the central regions from both ends and changes the sensitivity of the sensory fibers

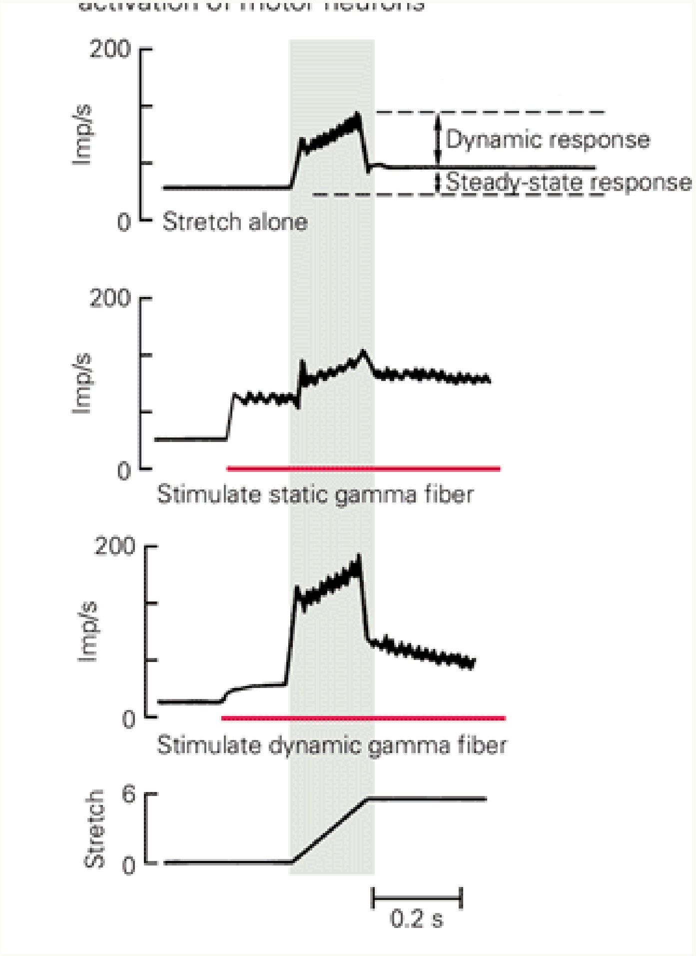
Intrafusal Fibers



- 3 types of intrafusal fibers:
  - dynamic nuclear bag
  - static nuclear bag
  - nuclear chain fibers
- A single Ia sensory fiber innervates all three types of fibers
- A group II sensory fiber innervates nuclear chain fibers and static bag fibers
- Two types of motor neurons:
  - Dynamic gamma motor neurons innervate only dynamic bag fibers
  - Static gamma motor neurons innervate various combinations of chain and static bag fibers

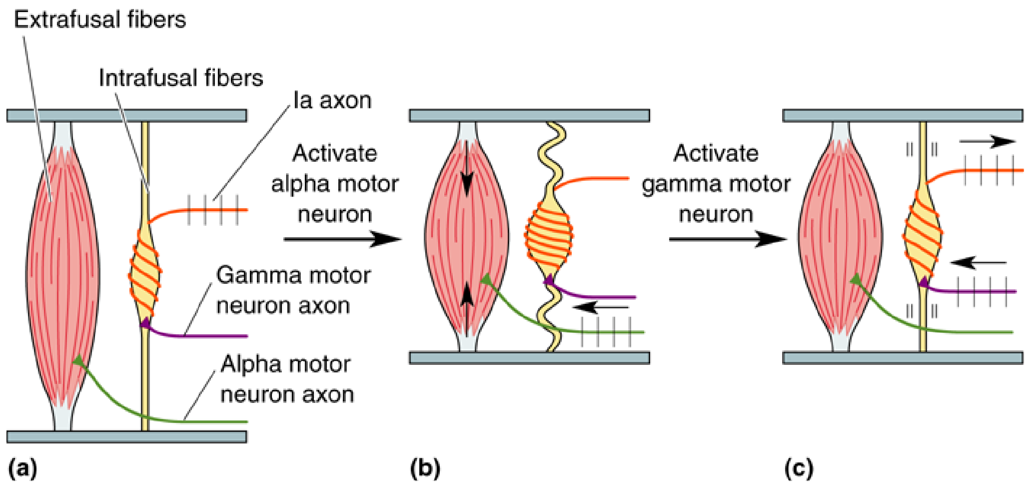
Intrafusal Fibers

- Without gamma stimulation the Ia fiber shows a small dynamic response to muscle stretch and a modest increase in steady-state firing
- Static gamma motor neuron stimulation -> steady-state response of the Ia fiber increases and decrease in the dynamic response
- Dynamic gamma motor neuron stimulation -> dynamic response of the Ia fiber is enhanced and steady-state response reduced



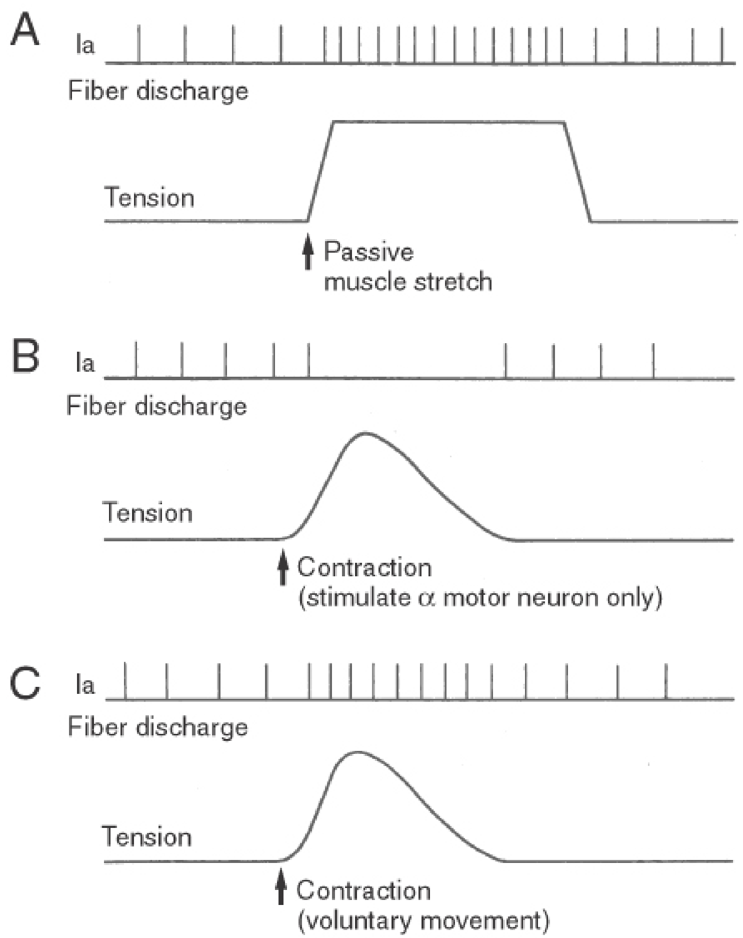
Alpha/Gamma Motor Neuron

- Muscle contractions slackens the spindle -> unable to signal further changes in muscle
- When alpha are stimulated, the firing of the spindle sensory fiber shows a characteristic pause during the contraction
- When gamma and alpha are activated there is no pause -> gamma keeps intrafusal fibers loaded
- Essential role of gamma motor neurons is to enable the spindle to signal length changes over the full range of muscle lengths



Neuroscience: Exploring the Brain, 3rd Ed, Bear, Connors, and Paradiso Copyright © 2007 Lippincott Williams & Wilkins

Gamma's Activity

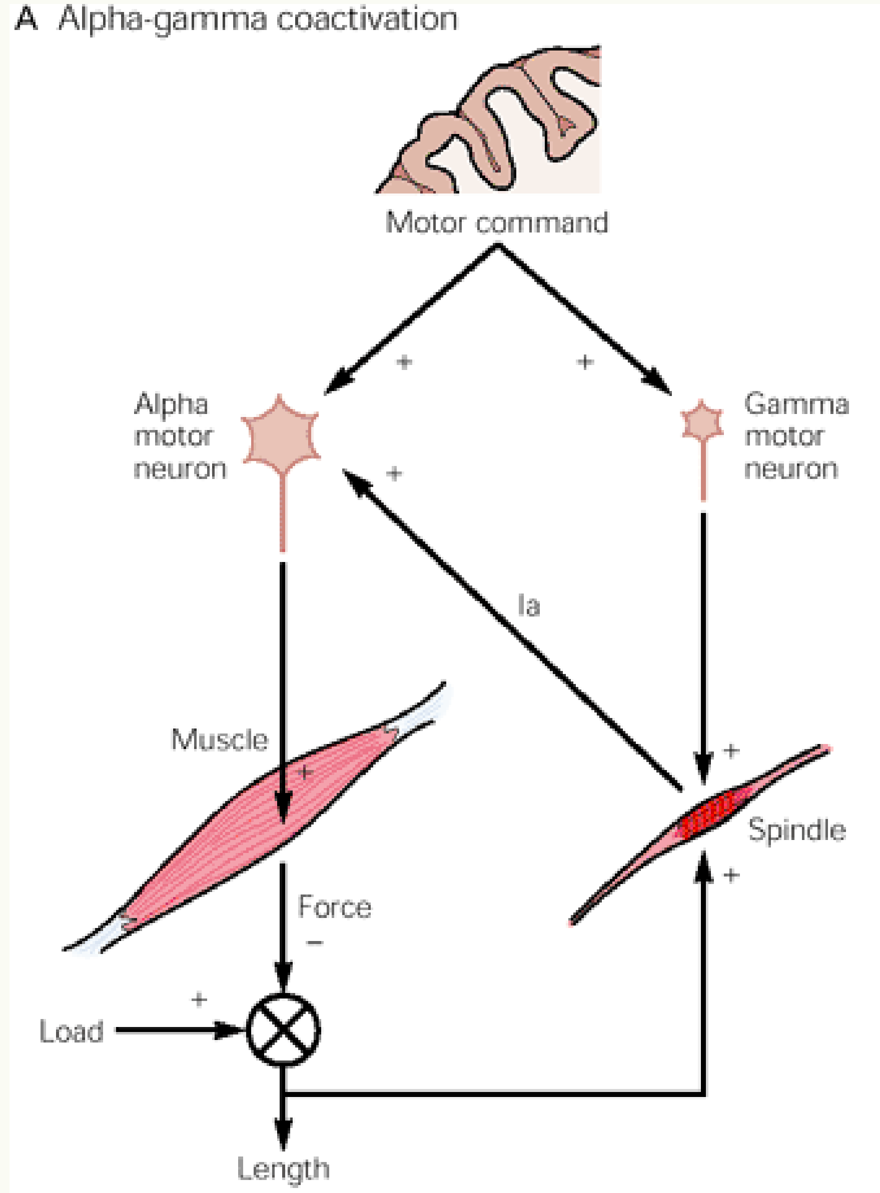


Alpha / Gamma Circuit

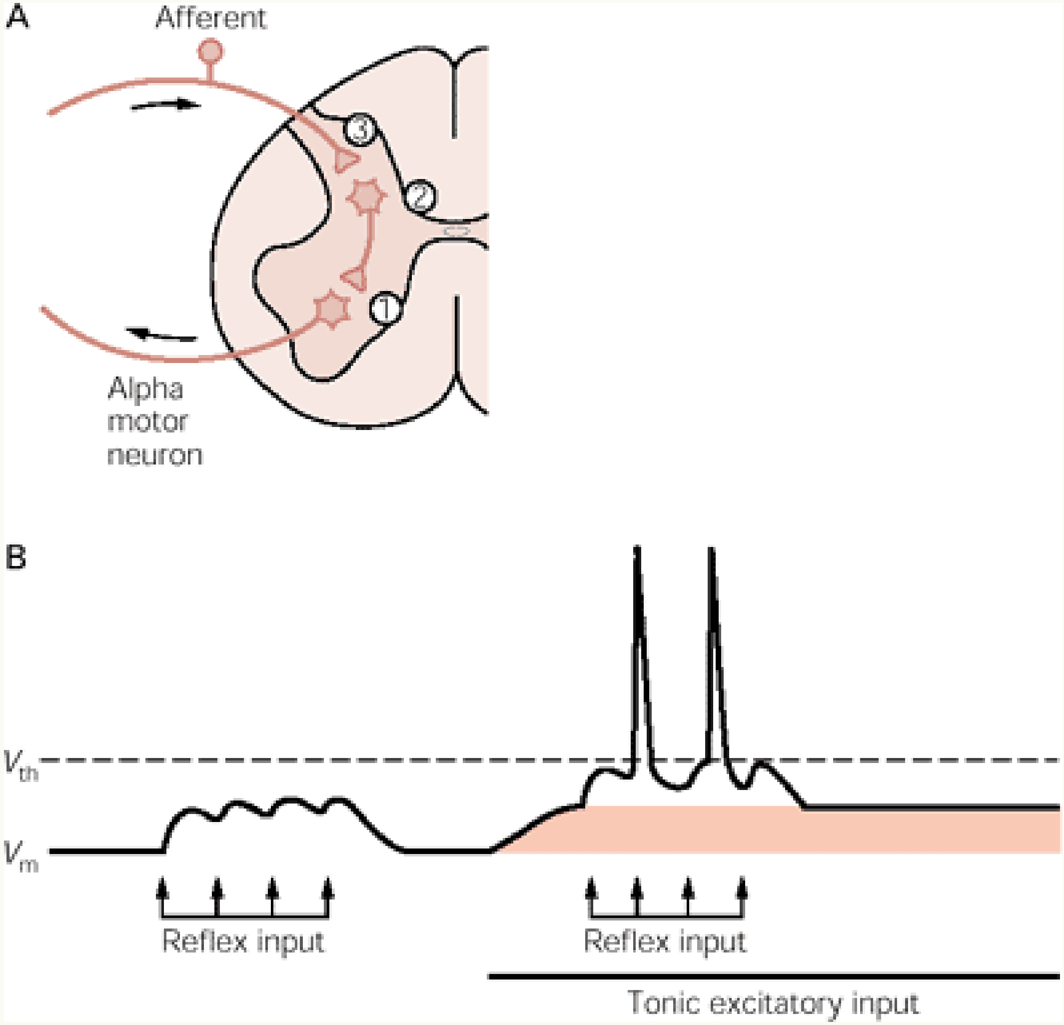
Co-activation of alpha and gamma by a motor command allows feedback from muscle spindles to reinforce the activation of the alpha motor neurons

- Disturbance alters the muscle length and spindle activity
- Spindle input to alpha compensates for the disturbance

This mechanism permit the CNS to produce a movement of a given distance without having to know the actual load being moved



CNS Modulation of Reflexes



3 possible sites for the modulation of a spinal reflex:

- Alpha motor neurons
- Interneurons in all reflex circuits
- Presynaptic terminals of the afferent fibers

CNS Modulation of Reflexes

The case of Ia interneurons:

One CNS command -> two effects

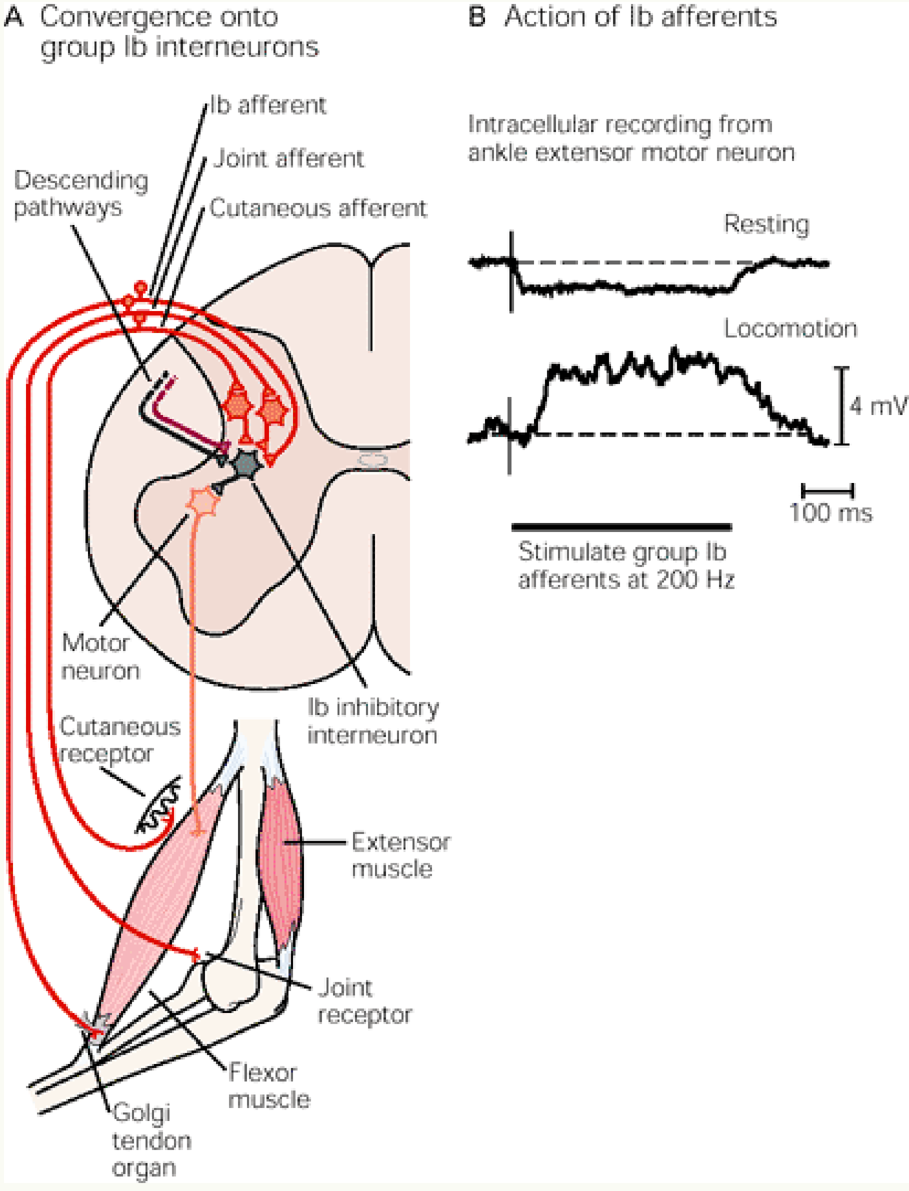
- Agonist contraction (central command)
- Antagonist relaxation (free side effect)

One CNS command -> two effects

- Inhibition of Ia interneuron (central command)
- Cocontraction (free side effect)

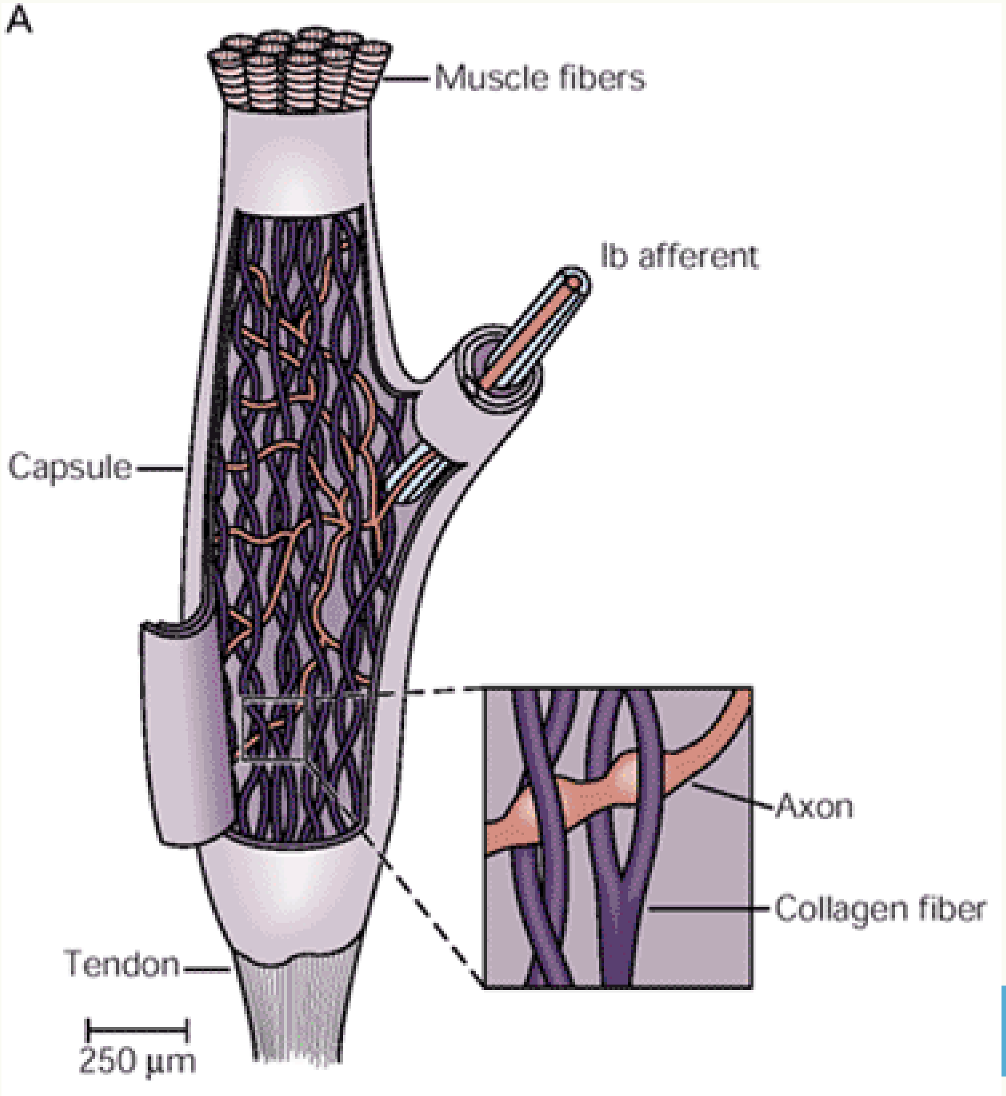
Ib Interneuron

- Extensive convergent input
- Principal input from Golgi tendon organs
- Widespread connections with motor neurons innervating muscles acting at different joints



Golgi Tendon Organ

When the Golgi tendon organ is stretched the afferent axon is compressed by the collagen fibers and its rate of firing increases (Ib)



Golgi Tendon Organs

Golgi tendon organs originally thought to have a protective function, preventing damage to muscle, since it was assumed that they fired only when high tensions were achieved

Signal minute changes in muscle tension, providing precise information about the state of contraction of the muscle

The convergence of afferent input may allow for precise spinal control in skilled activities

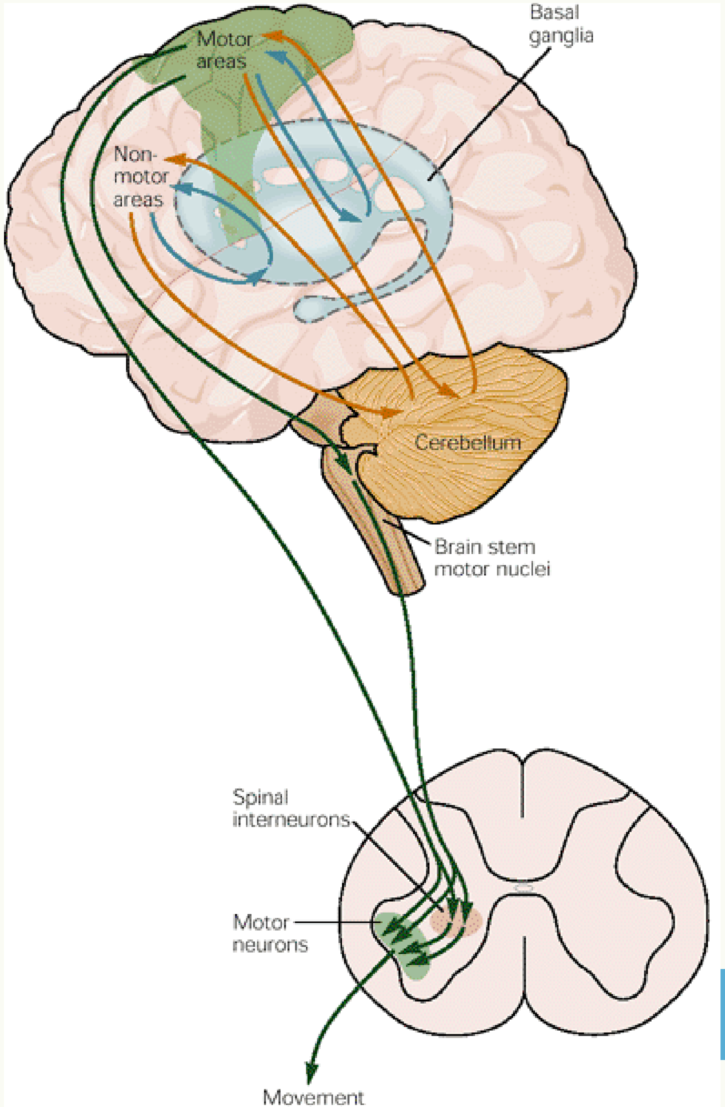
Descending Pathways

Neurophysiology of the Motor System

Descending Paths

Motor areas can influence the spinal level:

- Directly
- Descending systems of the brain stem



Brain Stem Paths

Medial paths

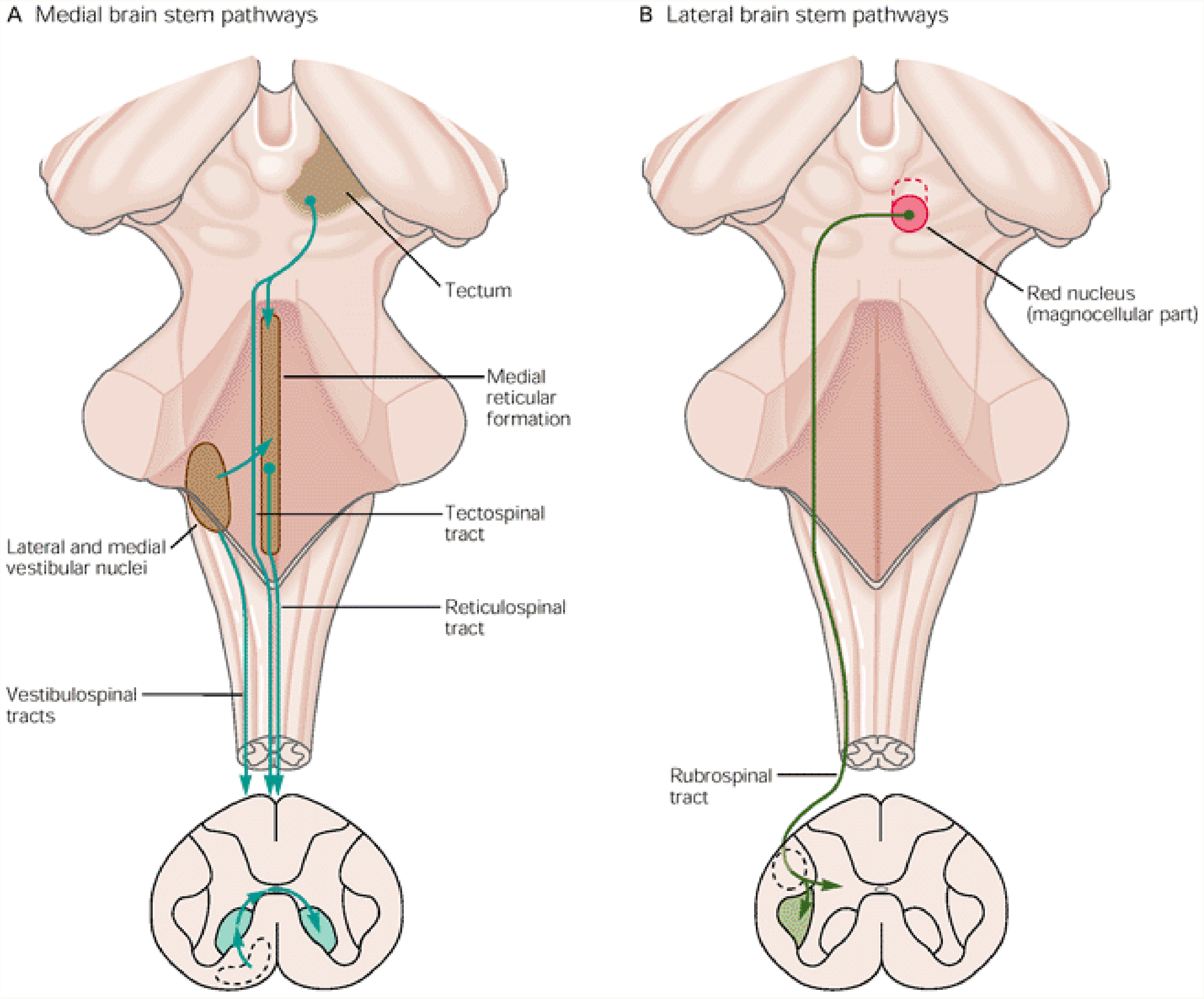
- Postural control
- Philogenetically older
- Descend in the ipsilateral ventral columns of the spinal cord
- Terminate on interneurons and long propriospinal neurons in the ventromedial part
- Influence motor neurons that innervate axial and proximal muscles
- vestibulospinal (medial and lateral), reticulospinal (medial and lateral) and tectospinal tracts

Brain Stem Paths

Lateral paths

- goal-directed limb movements such as reaching and manipulating
- Philogenetically newer
- Descend in the dorsal part of the lateral column of the spinal cord
- Terminate on interneurons in the dorsolateral part
- Influence motor neurons that control distal muscles of the limbs
- Rubrospinal tract

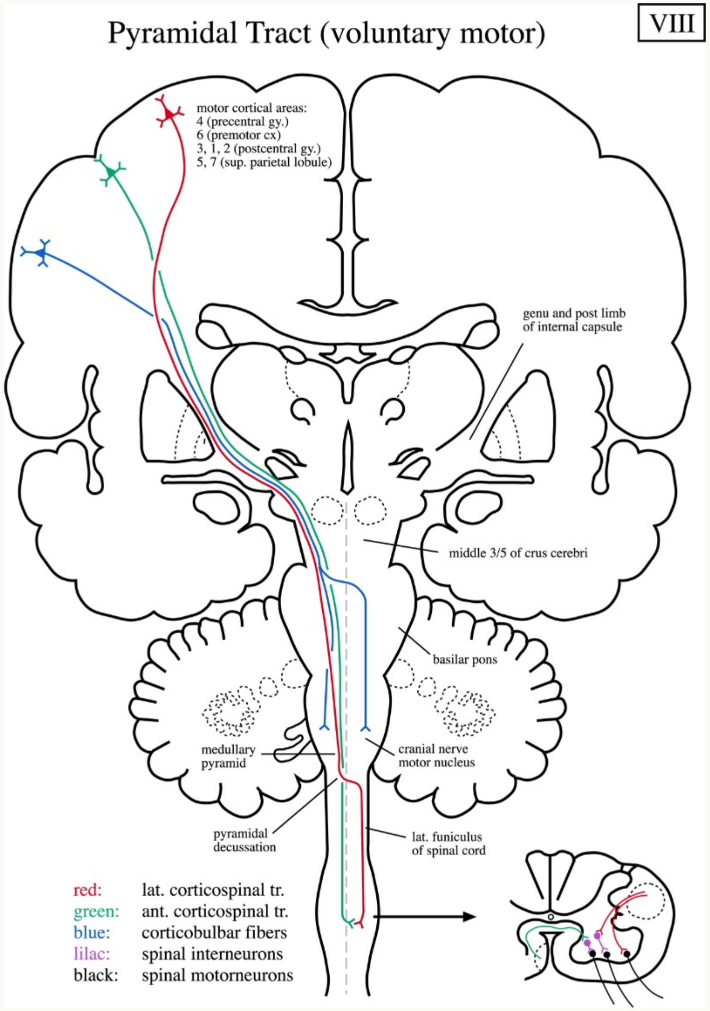
Medial and Lateral Brain Stem Paths



Pyramidal Tracts

- Originates from the cerebral cortex
  - terminate on sensory neurons, interneurons and motor neurons
  - Central control for initiating the skilled motor movements
  - Affects reflexes
  - Phylogenetically new
  - Myelination is not completed until the 2nd year
- Cortico-bulbar tract
  - control the motor nuclei in the brain stem that move facial muscles
- Cortico-spinal tract
  - control the spinal motor neurons that innervate the trunk and limb muscles

Pyramidal Tracts



Pyramidal Tracts

PT fibers leave the cortex, pass in the ipsilateral corona radiata, internal capsule and cerebral peduncle where they are arranged somatotopically

PT fibers terminating at the level of the brainstem are mostly cortico-bulbar fibers

Collaterals of PT fibers also terminate in the basal ganglia, thalamus, red nucleus and reticular formation

75-90% of the PT fibers cross the midline and descend in the lateral funiculus as the **lateral corticospinal tract**

The uncrossed 10-25% descends in the anterior funiculus as the **anterior (ventral) corticospinal tract** (cross the midline at their spinal level of termination)

Cortico-Spinal Tract

Pyramidal cells in layer V of cerebral cortex

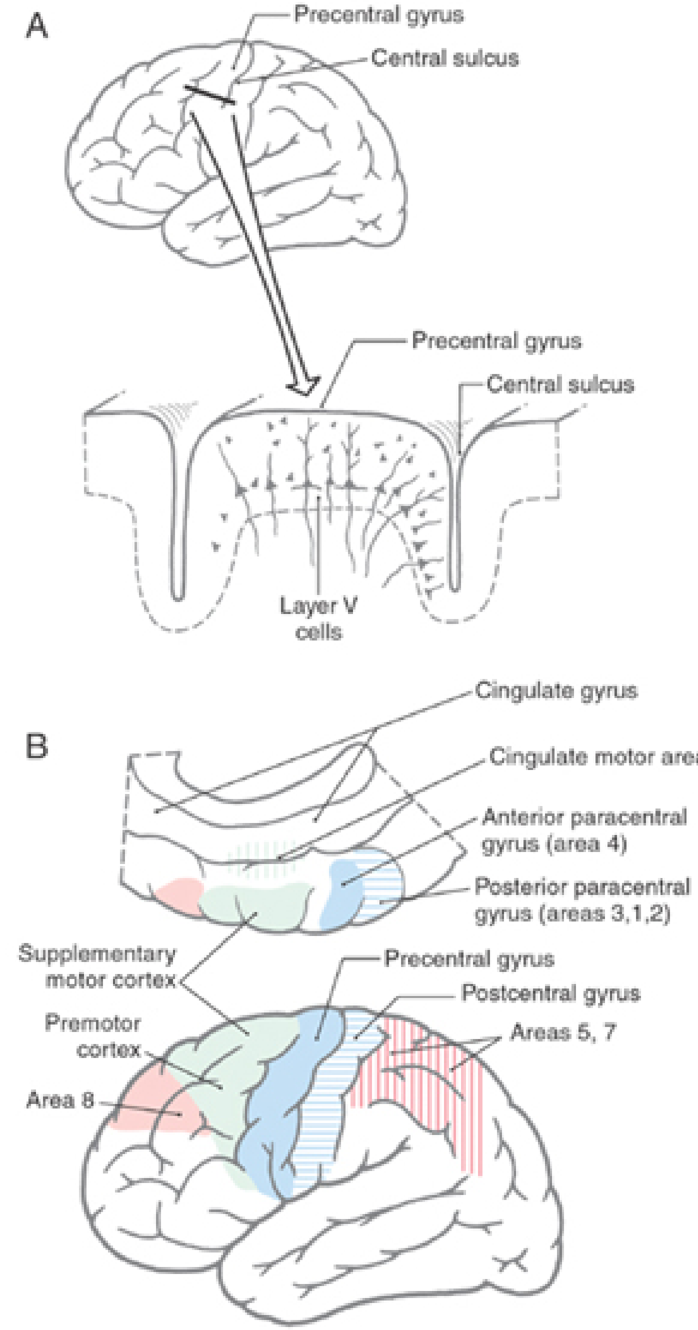
20-24% PT fibers originate from area 4

- 3-4% from giant pyramidal (Betz) cells

30% from areas 3, 1 and 2

30% from area 6

15% from areas 5 and 7



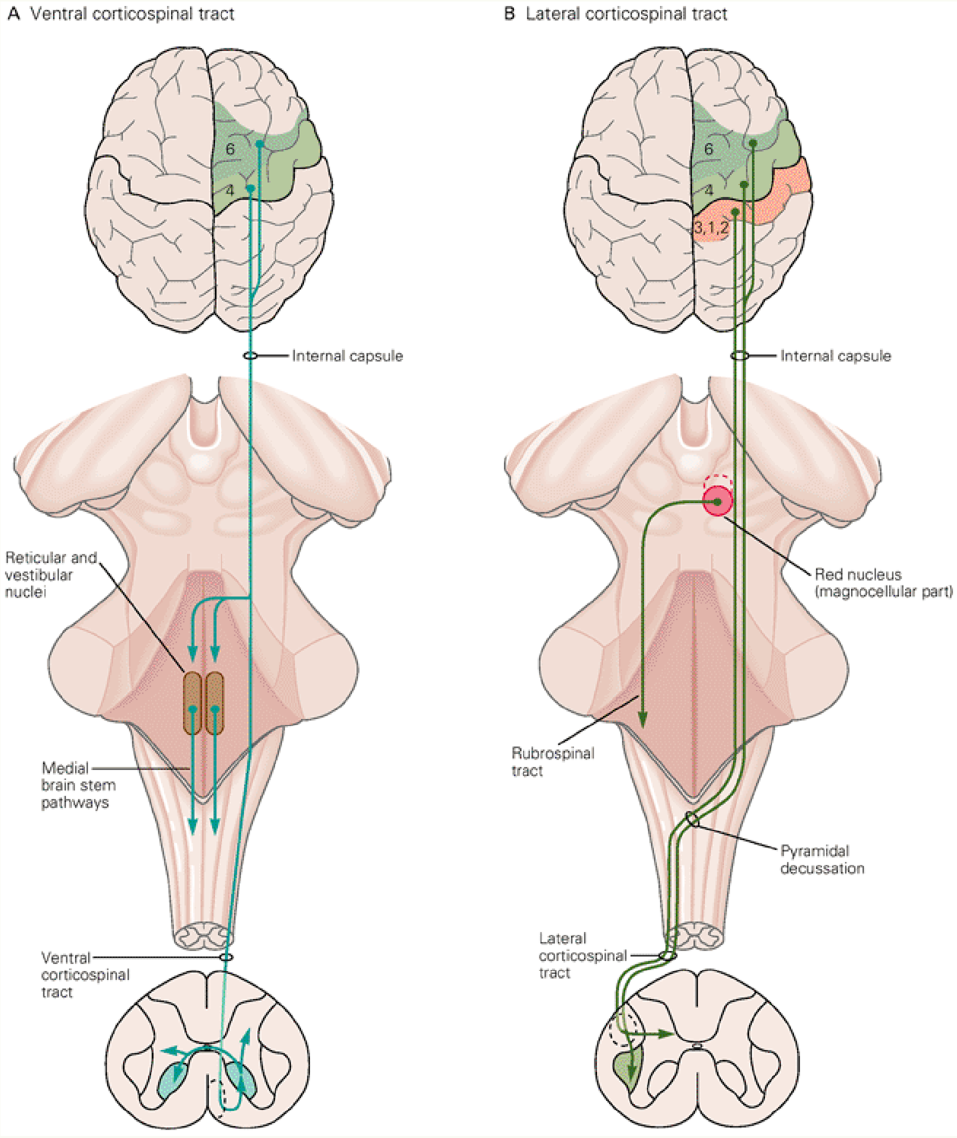
Lateral & Anterior (Ventral) CS Tracts

Ventral CS tract

- Originates from area 6 and 4
- Controls neck and trunk
- Descending fibers terminate bilaterally
- Send collaterals to the medial pathways from the brain stem

Lateral CS tract

- Originates areas 4, 6, 3, 2, 1
- Pyramidal decussation
- Descends in the dorsolateral column
- Fibers from the sensory cortex terminate primarily in dorsal horn and allow the brain to actively modify sensory signals



Cortico-Bulbar Tract

- Monosynaptic connections with motor neurons in:
  - Trigeminal (projections from both hemispheres)
  - Facial (projections from both hemispheres)
  - Hypoglossal nuclei
- Upper part of the face receive axons from both hemispheres
- Lower face receive contralateral fibers
- Damage to uni-lateral cortico-bulbar fibers produces weakness of the muscles of the contralateral lower part of the face
- Movements of the eyes are controlled by a different system

Effect of Lesions

Negative and positive signs

Negative reflect the loss of particular capacities normally controlled by the damaged system

- for example loss of strength

Positive (release phenomena) are abnormal and stereotyped responses that are explained by the withdrawal of tonic inhibition from neuronal circuits mediating a behavior

Lesion to Descending Paths

- Weakness in voluntary movements (a negative sign)
- Increased muscle tone (spasticity)
  - As in decerebrate rigidity, stretch reflexes are abnormally active

Differential Diagnosis – Lower / Upper Neuron Lesion

Both conditions produce weakness by diminishing neural input to muscle with 3 differences

Spasticity

- Diseases affecting the descending pathways give rise to spasticity
- Diseases of motor neurons do not

Athrophy

- Diseases affecting motor neurons directly result in denervation atrophy and reduced muscle volume
- Does not occur with damage to the descending pathway

Body distribution

- Damage to descending systems tends to be distributed more diffusely in limb or face muscles and often affects large groups of muscles, for example the flexors
- Degeneration in local groups of motor neurons tends to affect muscles in a patchy way and may even be limited to single muscles

Cortical Level

Cortical Motor Maps

Primary Motor Cortex

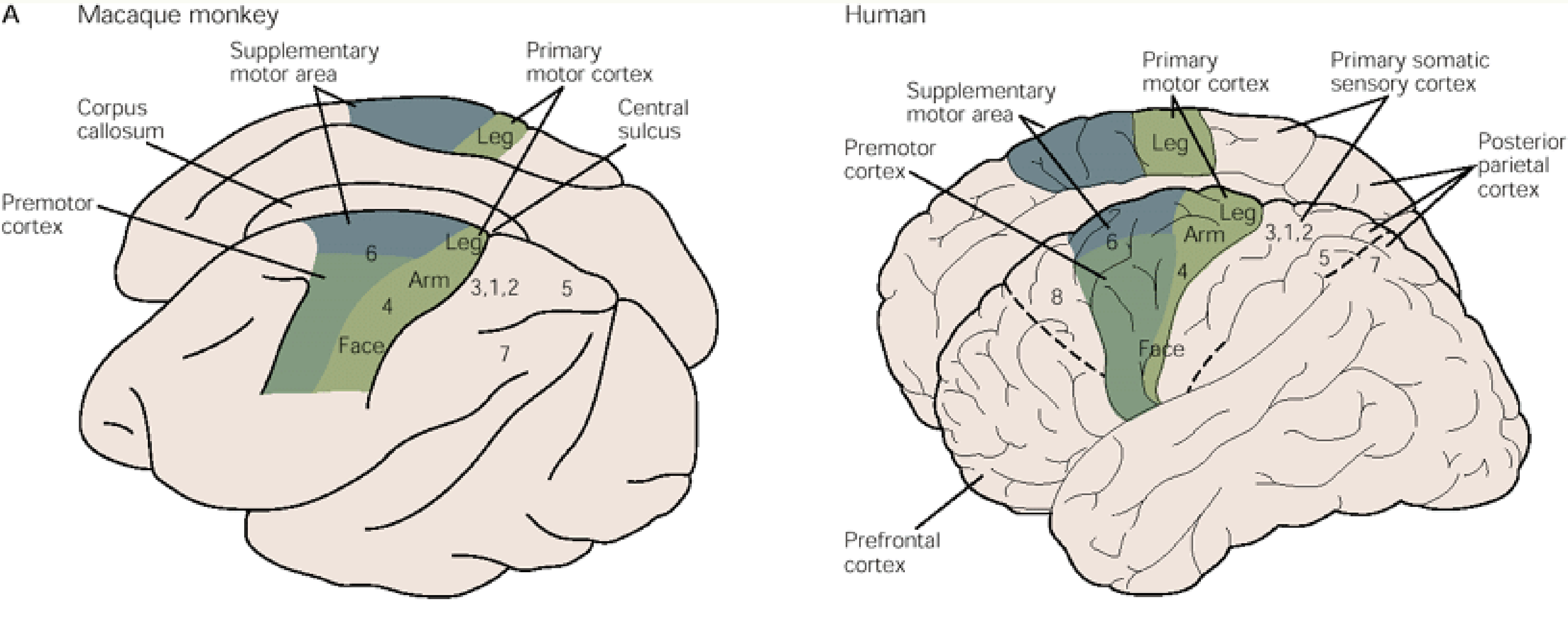
Premotor Cortex

Cortical Motor Maps

Neurophysiology of the Motor System

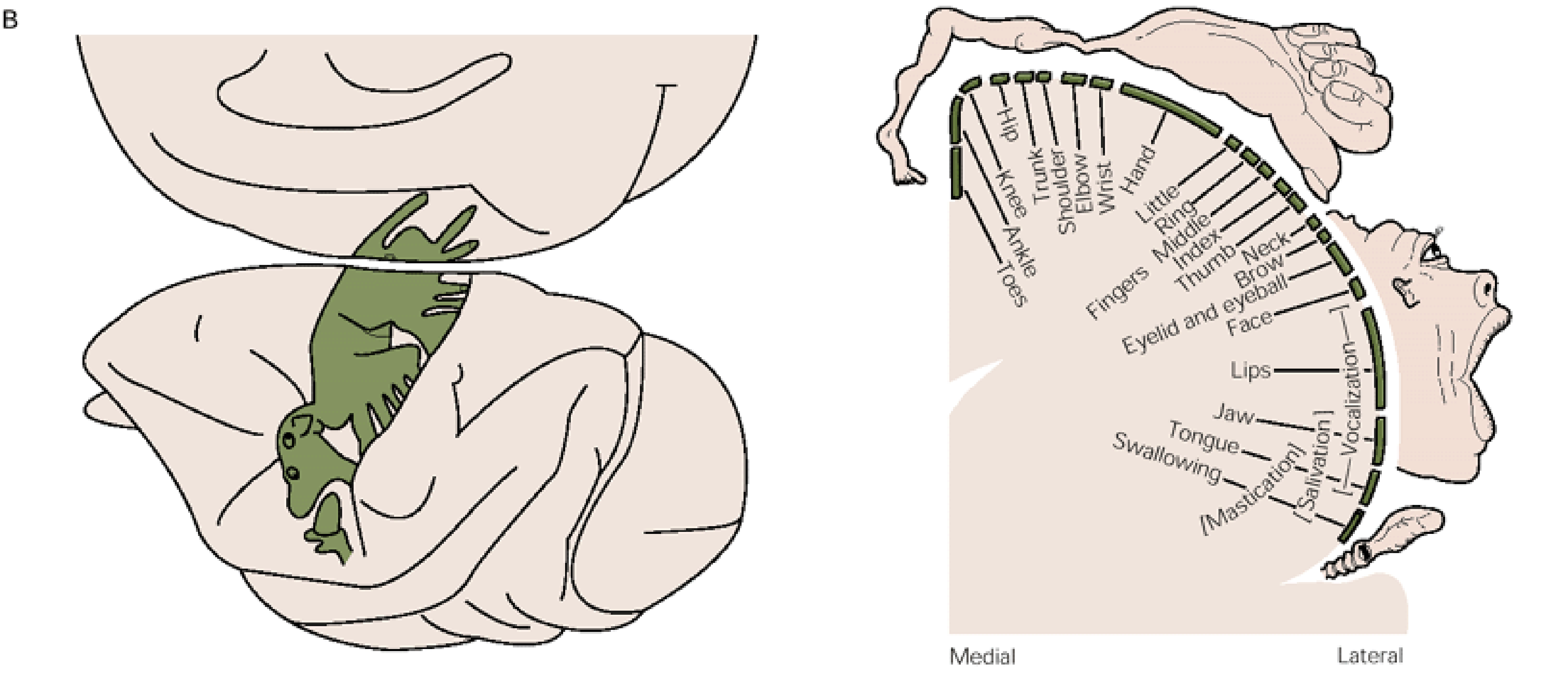
Motor Cortex Somatotopy

Brodmann's cytoarchitectural areas in monkeys and humans



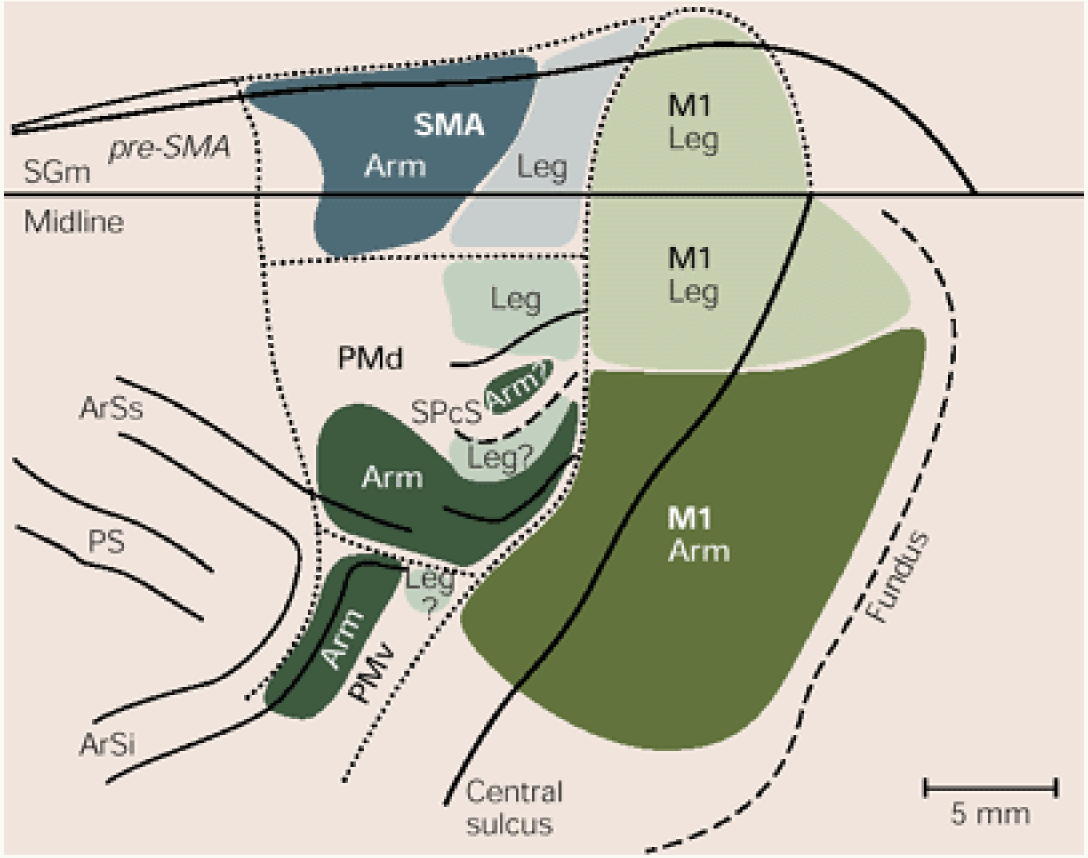
Motor Homunculus

Somatotopic organization of the primary motor cortex in monkeys and humans



Multiple Motor Maps

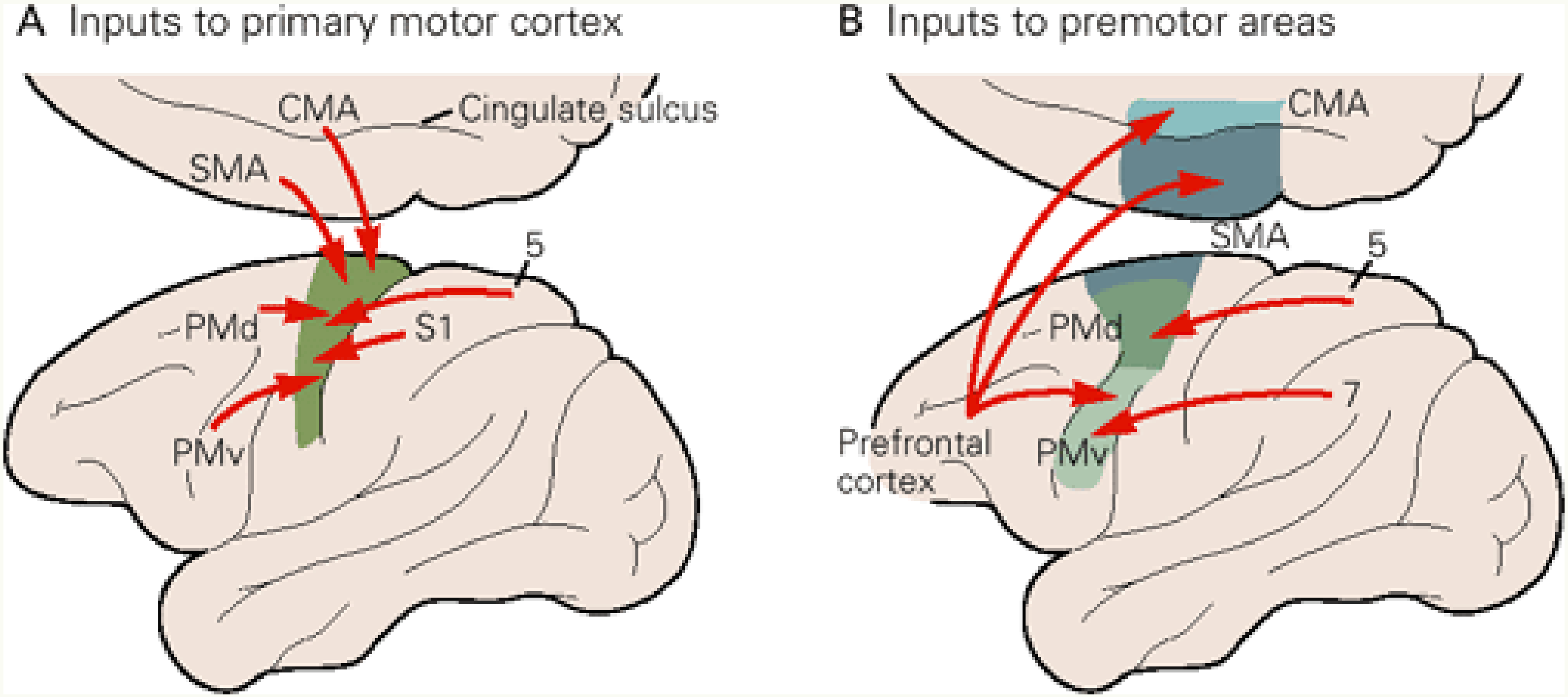
Medial and lateral motor cortex in the monkey



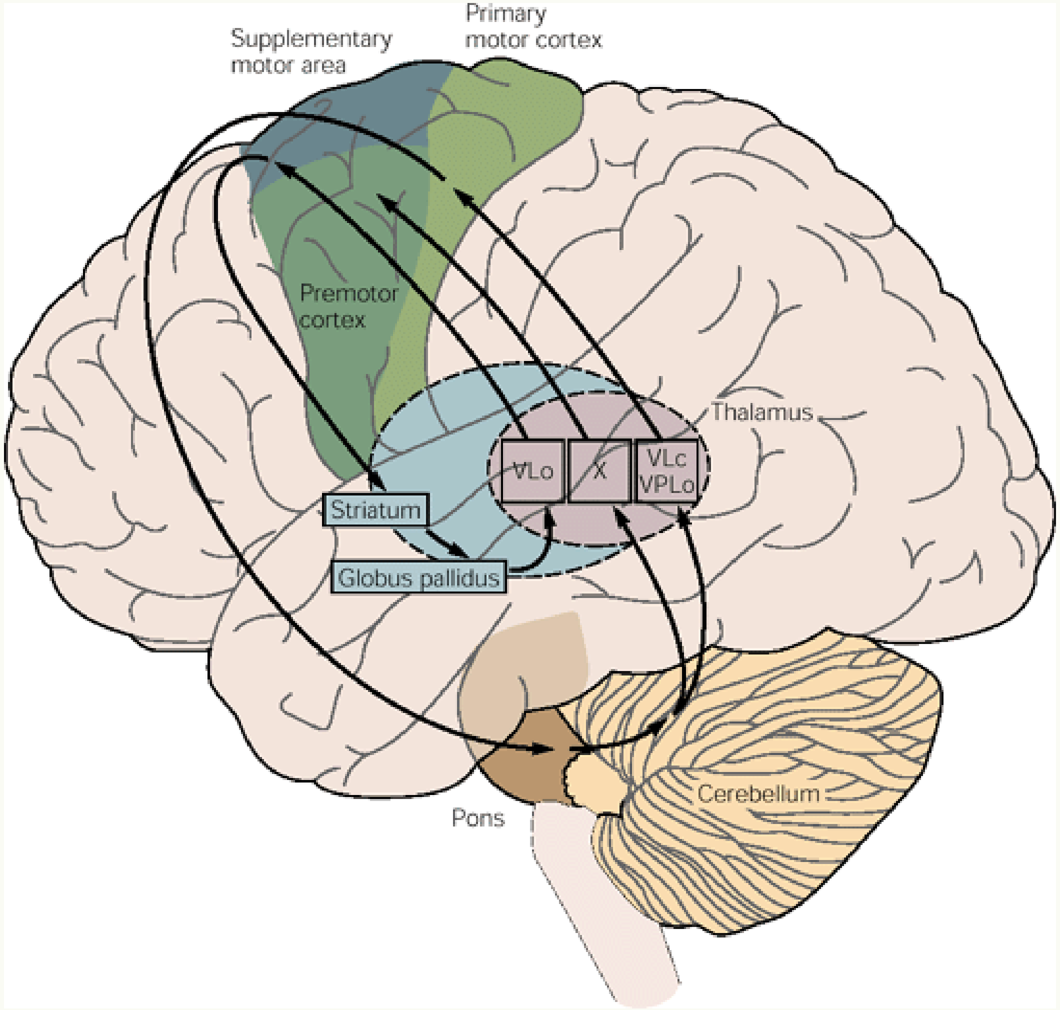
Premotor Areas

- Movements can also be elicited by direct electrical stimulation of the premotor areas (BA 6)
- Intensity of stimulation necessary to produce movement is greater here than in the primary motor cortex
- Brodmann's area 6 lies anterior to the precentral gyrus, on the lateral and medial surfaces of the cortex
- Contain pyramidal (output) neurons in layer V that project to the spinal cord, although the cell bodies are smaller than those in the primary motor cortex
- Four main premotor areas:
  - The two on the lateral convexity are the lateral ventral and lateral dorsal premotor areas
  - The two in the medial wall of the hemisphere are the supplementary motor area and the cingulate motor areas
- Stimulation:
  - M1: evokes simple movements of single joints
  - PMv - PMd: complex movements involving multiple joints and resembling natural coordinated hand shaping or reaching movements
  - SMA: bilateral movements
- Premotor areas project to both the primary motor cortex and the spinal cord

Cortical Connectivity



Subcortical Conectivity



Focal Epileptic Seizures

- Jackson observed that during epileptic seizures convulsions spread of from one body part to the next
  - Different parts of the brain involved in the control of different muscle groups
  - These parts must be arranged in a way to mimic the organization of the body
- Before EEG proposed that seizure activity resulted from paroxysmal increases in local neuronal activity in a limited area of cerebral cortex
- Focal seizures often start in the fingers and spread proximally down the limb
- Clinically this is known as the Jacksonian march

Was That Really the Cortex?

- Before 1870, he appeared unsure whether this somatotopy is found in the corpus striatum, the traditional highest motor structure or in the cortex
- But by 1870, Jackson placed the somatotopically organized structures that are responsible for movement primarily in the convolutions

Jackson's Methods

"Jackson's modus operandi was to come across a clinical phenomenon that caught his interest and seemed to him to hold possibilities for throwing light on human brain function. He next observed the details of this clinical phenomenon with minute care and then reasoned from the data thus collected and from his personally accumulated knowledge of neurophysiology to develop new insights into brain function. He subsequently seems to have sometimes made his insights public before he had carefully studied the existing literature to ascertain what had previously been published on the matter..."

Fritz and Hitzig 1870

Flourens:

- 'signs of will and consciousness of sensations disappear, while nevertheless, by stimuli coming from the outside, quiet engine-like movements could be produced in all parts of the body'.
- 'the cerebral hemispheres were not the seat of the immediate principle of muscular movements but only the seat of volition and sensation'

Fritz and Hitzig:

- '...there is not one fiber in the hemisphere of the brain which goes to voluntary muscles. Not a single observer saw movements of such muscles after stimulation of the central parts.'
- 'A part of the convexity of the hemisphere of the brain of the dog is motor . . . another part is not motor. The motor part, in general, is more in front, the non-motor part more behind. By electrical stimulation of the motor part, one obtains combined muscular contractions of the opposite side of the body.'

Fritsch and Hitzig thus raised three closely related issues:

- The excitability of the hemispheres
- Localization of functions
- Relation of the hemispheres to the immediate principle of muscular movements

Ferrier 1874

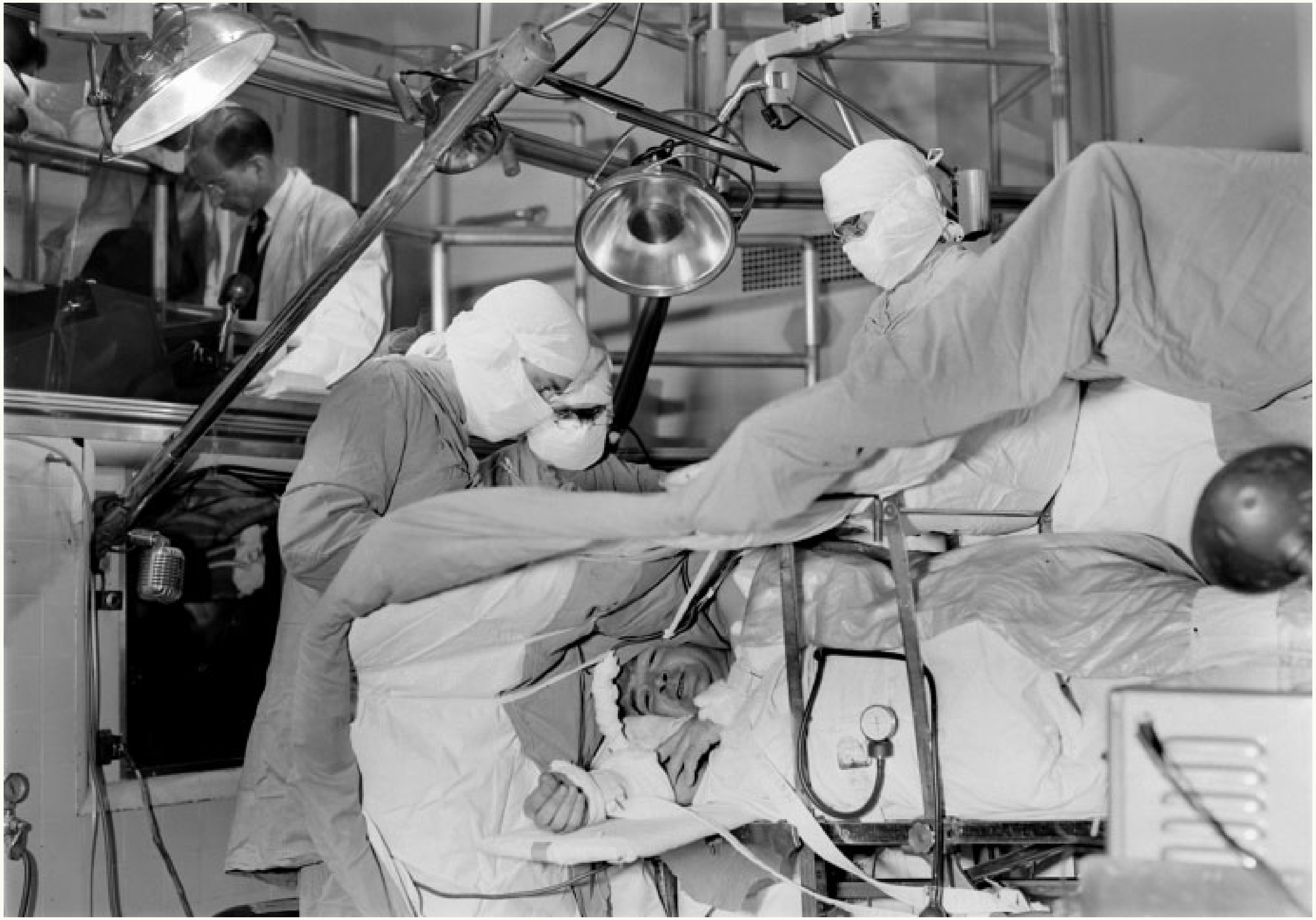
Ferrier replicated Fritz and Hitzig basic findings:

Stimulation of the cortex can produce specific movements and that there is a topographic “motor map” in the cerebral cortex

F&H: brief direct current pulses and obtained localized muscle twitches whereas

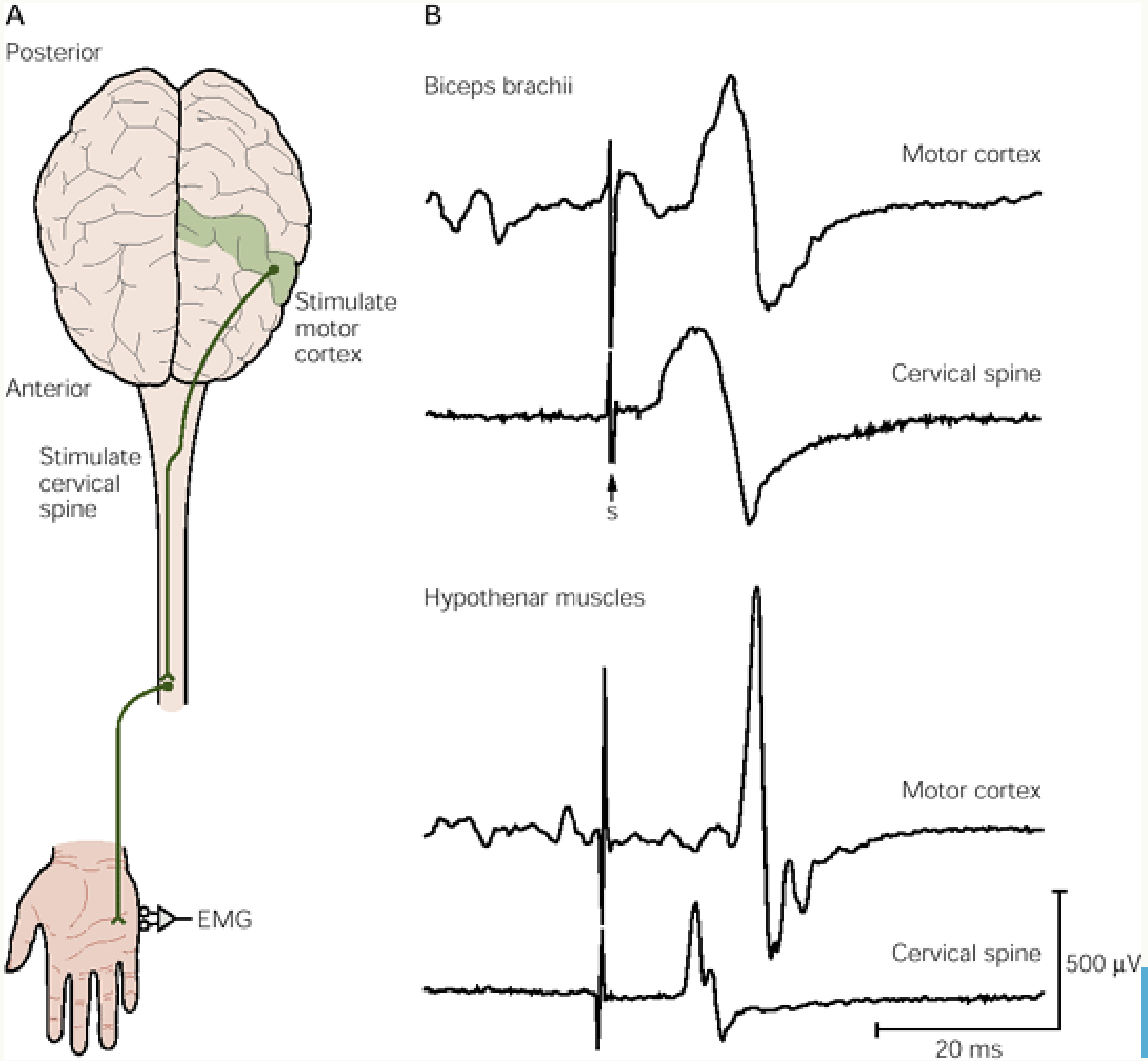
Ferrier: longer duration biphasic stimulation that tended to produce complex integrated movements rather than muscle twitches

Penfield



Cortical (Magnetic) Stimulation

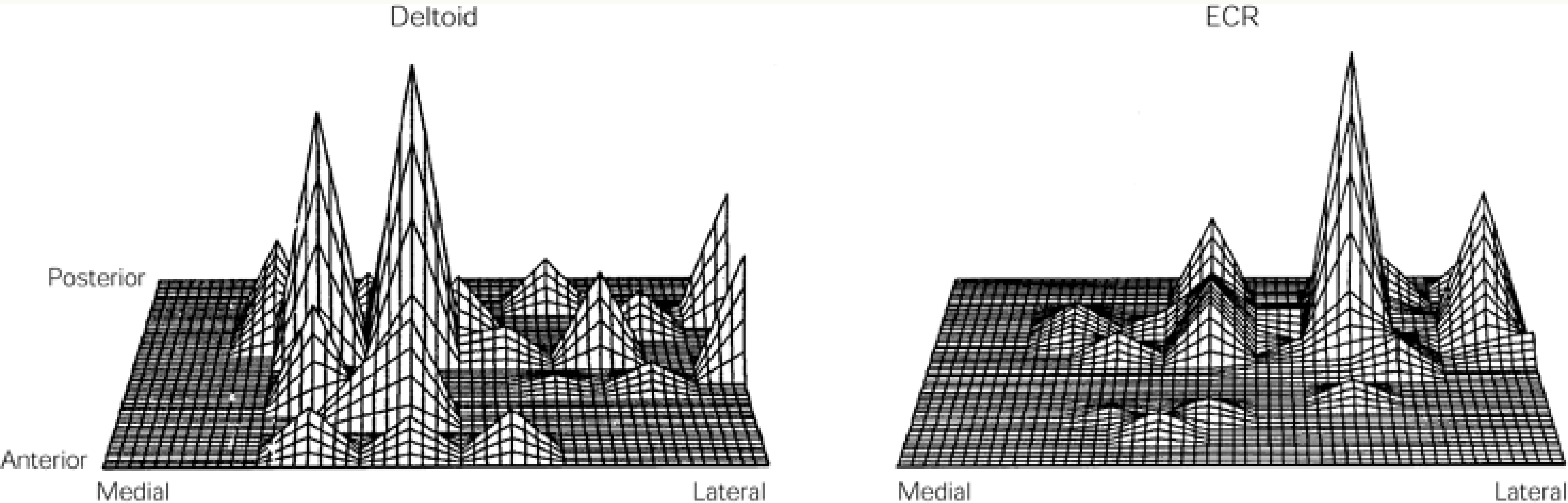
- Magnetic stimulation of the motor cortex or cervical spine produces muscle contraction
- Motor cortex stimulation activates the corticospinal fibers and produces a short-latency electromyographic (EMG) response in contralateral muscles



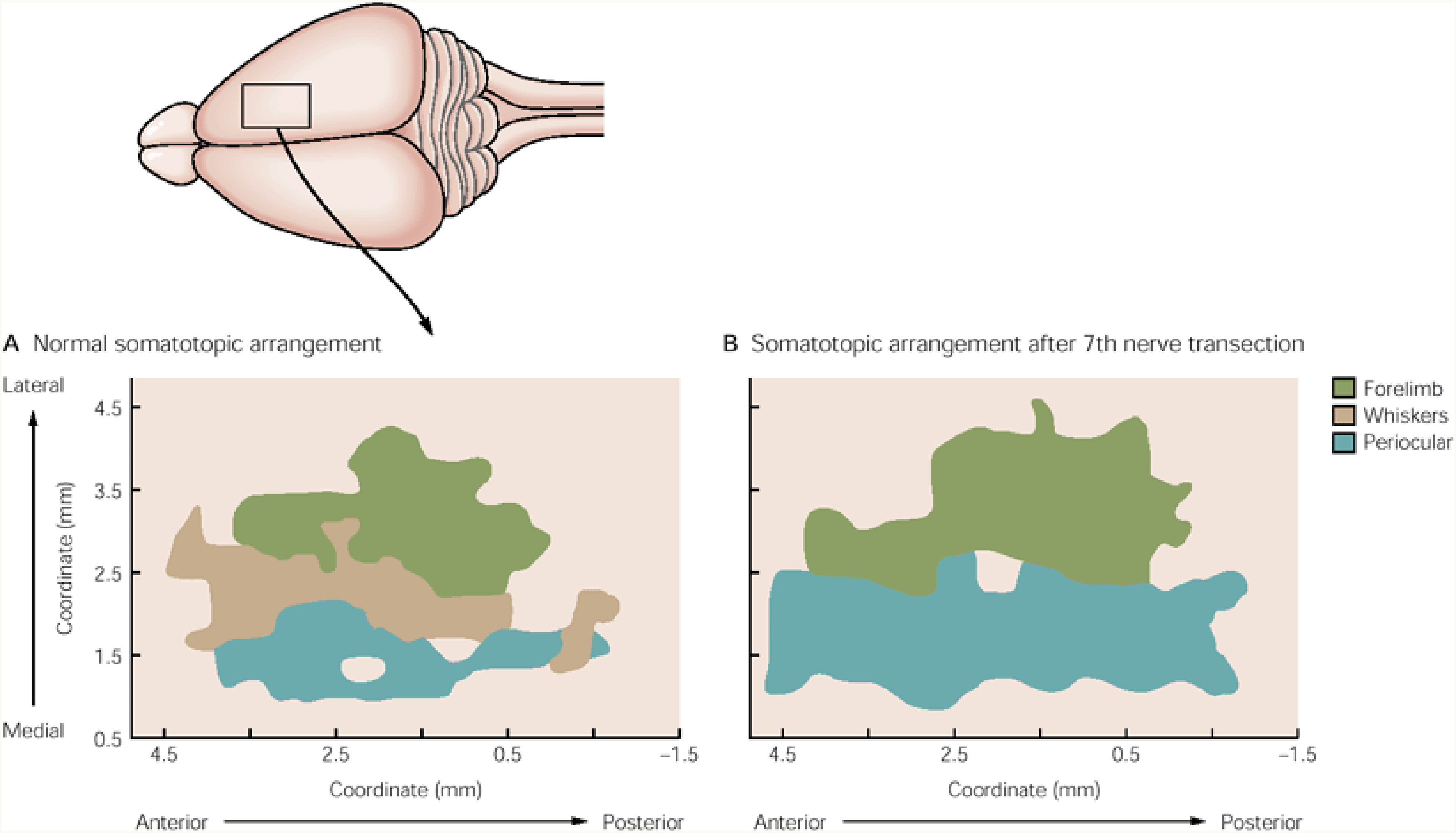
Distributed Coding

- The early mapping experiments led to the simplistic idea that the primary motor cortex acts as a massive switchboard with a switch controlling individual muscles or small groups of adjacent muscles
- Intracortical microstimulation studies indicate that this simple view is incorrect
- Weak stimuli can evoke the contraction of individual muscles, the same muscles are activated from several separate sites
- Most stimuli activate several muscles
- Terminal distributions of individual corticospinal axons diverge to motor neurons innervating more than one muscle
- Concentric organization
  - Sites influencing distal muscles are contained at the center of a wider area containing sites that also influence more proximal muscles, while sites in the peripheral ring around this central area influence proximal muscles alone
  - An implication of this redundancy in muscle representation is that inputs to motor cortex from other cortical areas can combine proximal and distal muscles in different ways in different tasks.

Distributed Coding



Motor Map Plasticity



Plasticity: Stroke Model

A small cortical artery occluded in squirrel monkeys to destroy a portion of the population of cells in the primary motor cortex controlling the hand and digits

The animals lost the ability to retrieve food pellets from a series of wells

With time, the area of hand representation around the lesion shrank

Plasticity: Stroke Model

Some animals were retrained and others not

Cortical maps of hand and forearm representation were strikingly different in the two groups

Animals with no training:

- Areas of hand and forearm representation were lost
- Neurons outside the lesion did not die but elbow and shoulder areas expanded into the remaining hand area

Animals with trining:

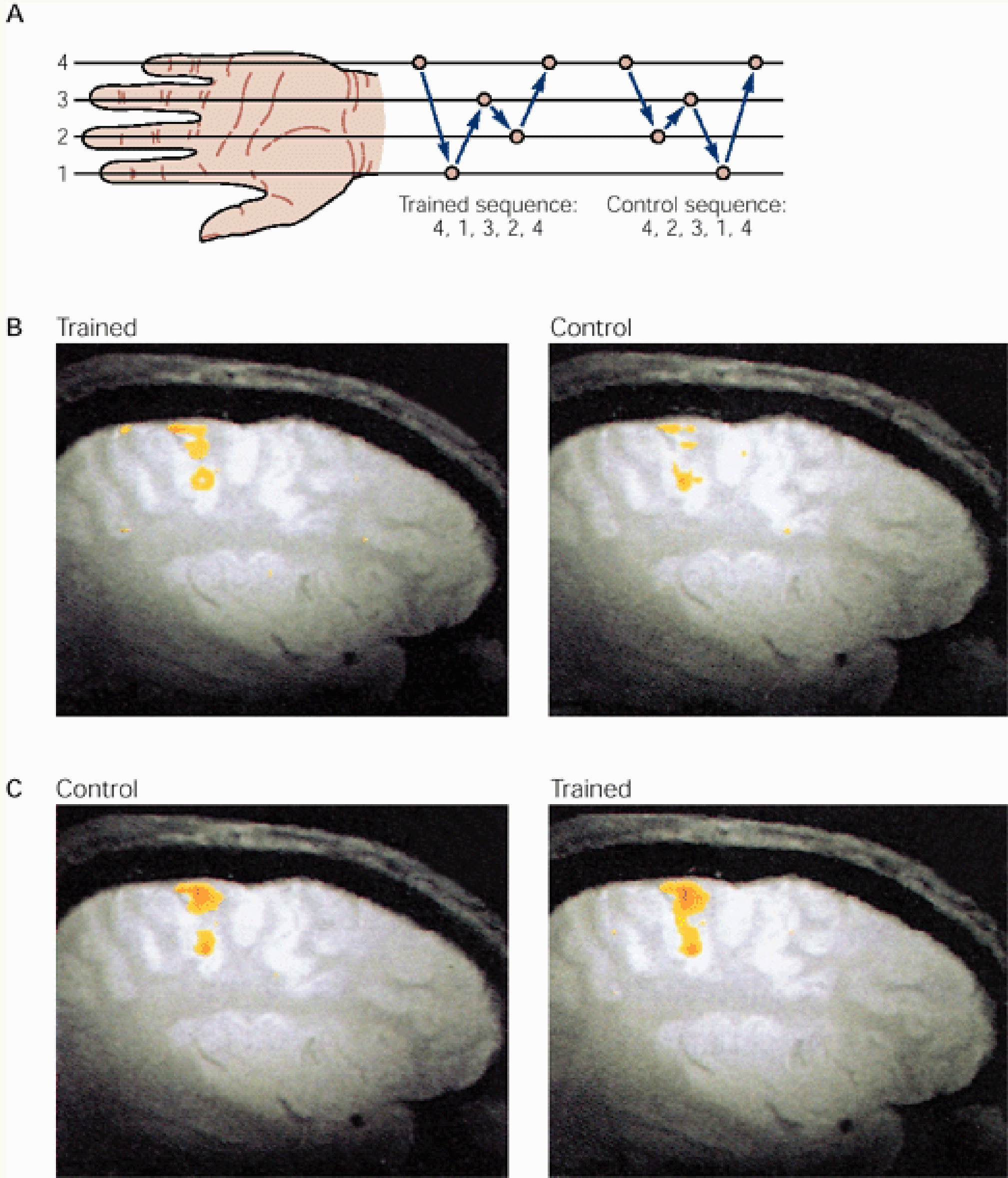
- Undamaged hand cortex controlling expanded into adjacent undamaged cortex
- Animals fully recovered the ability to retrieve pellets after 3 or 4 weeks

Training Induced Plasticity

Human subjects performed two finger-opposition tasks

Both the practiced and the novel sequence were performed at a fixed, slow rate (2Hz).

fMRI scans during the task practiced daily for 3 weeks and a novel sequence



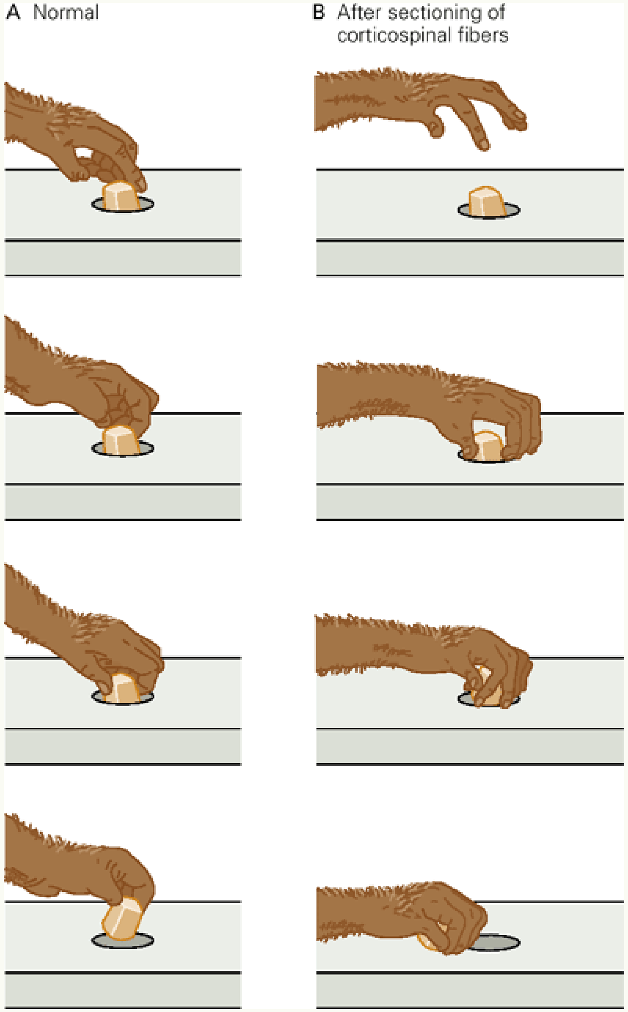
Corticospinal Digit Control

Corticospinal neurons make powerful and direct excitatory connections with alpha motor neurons

This is one of the mechanisms that permit monkeys to perform individual movements of the digits, including the grasping of small objects and to isolate movement of proximal joints

This ability is lost permanently after sectioning the pyramidal tracts in the medulla or after ablating the hand-control area of the motor cortex

Pyramidal Lesion



Pyramidal Lesion

Corticospinal fibers also terminate on interneurons in the spinal cord

These indirect connections with motor neurons regulate a larger number of muscles than do the direct connections and contribute to the organization of multi jointed movements

Sectioning the medullary pyramidal tracts produces contralateral weakness in monkeys

Animals recover after a period of months, leaving only deficits in speed of movement and force

These deficits can be attributed to interruption of the projections from the primary motor cortex because similar deficits arise from lesions in primary motor cortex but not from lesions in premotor areas

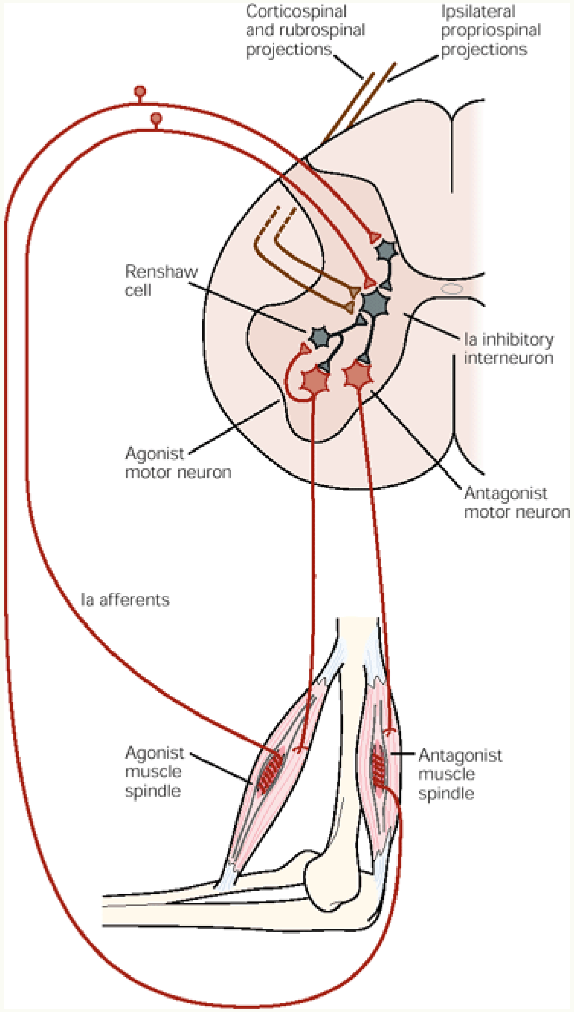
Animals with pyramidal tract lesions climb, jump, and appear generally normal. Their partial recovery is possible because cortical commands have indirect access to spinal motor neurons through the descending systems of the brain stem.

Digits independent control is lost permanently

Cortical Control of Reflexes

- The spinal interneuron receives complex excitatory and inhibitory inputs including direct input from the motor cortex
- Direct cortical connections allow the motor cortex to use reflex circuits as components of complex movements
  - Simplifying the motor cortical program

Ia Interneuron Modulation



Primary motor cortex

Neurophysiology of the Motor System

Single Unit Discharge Properties

Evarts (1968) found that activity in individual neurons in M1 is modulated when monkeys either flex or extend the individual joints

Individual neurons are maximally activated during movement of a particular joint and particular direction of movement

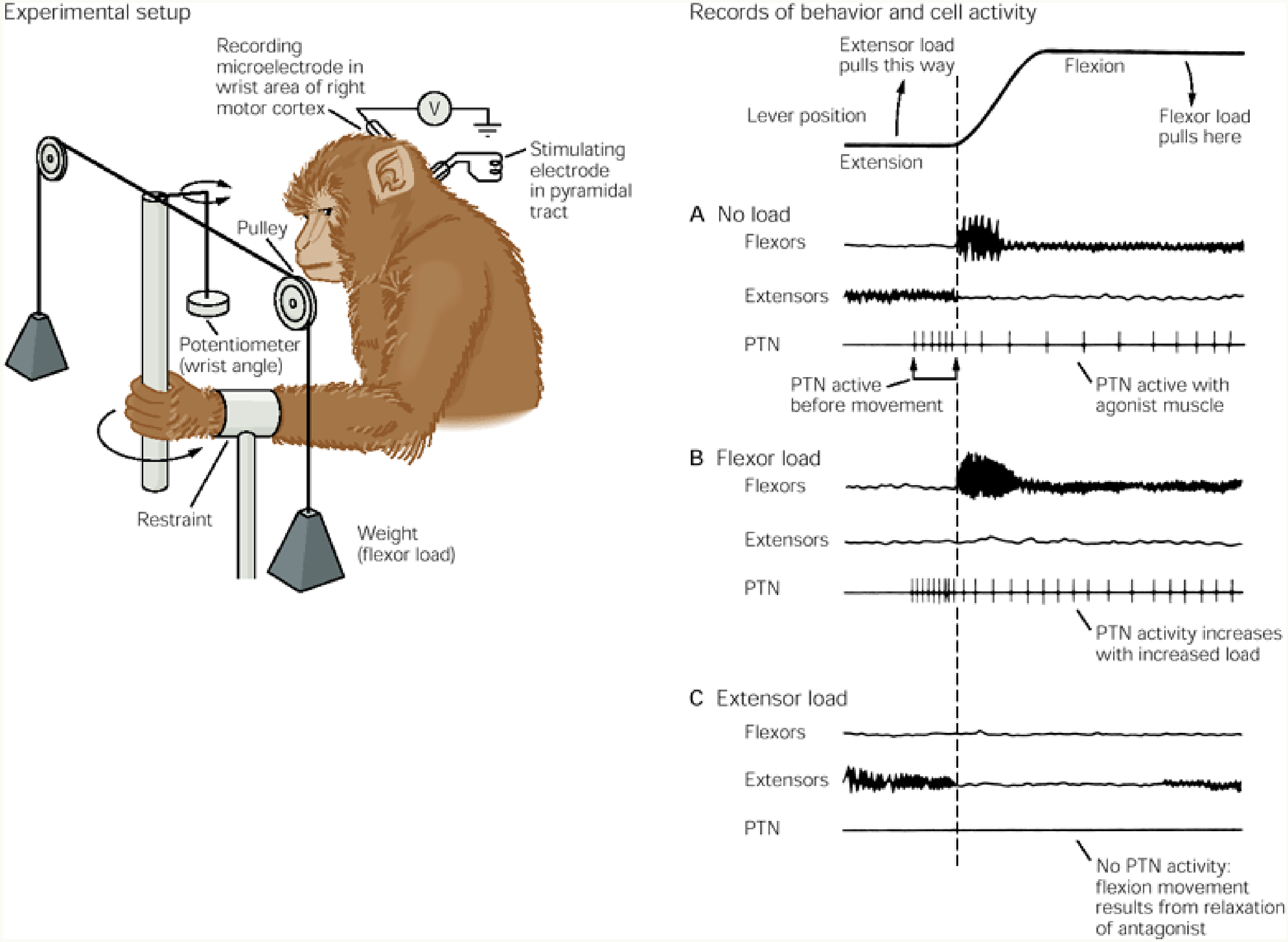
The changes in neuronal activity begin some 100 ms or more before the onset of movement

Single-Joint Control: Force not Position

Firing of neurons varied with the amount of force the animal had to exert not with the amplitude of the hand's displacement

Signal the direction and amplitude of muscle force required to produce a movement rather than the actual displacement of the joint

Evarts, 1968



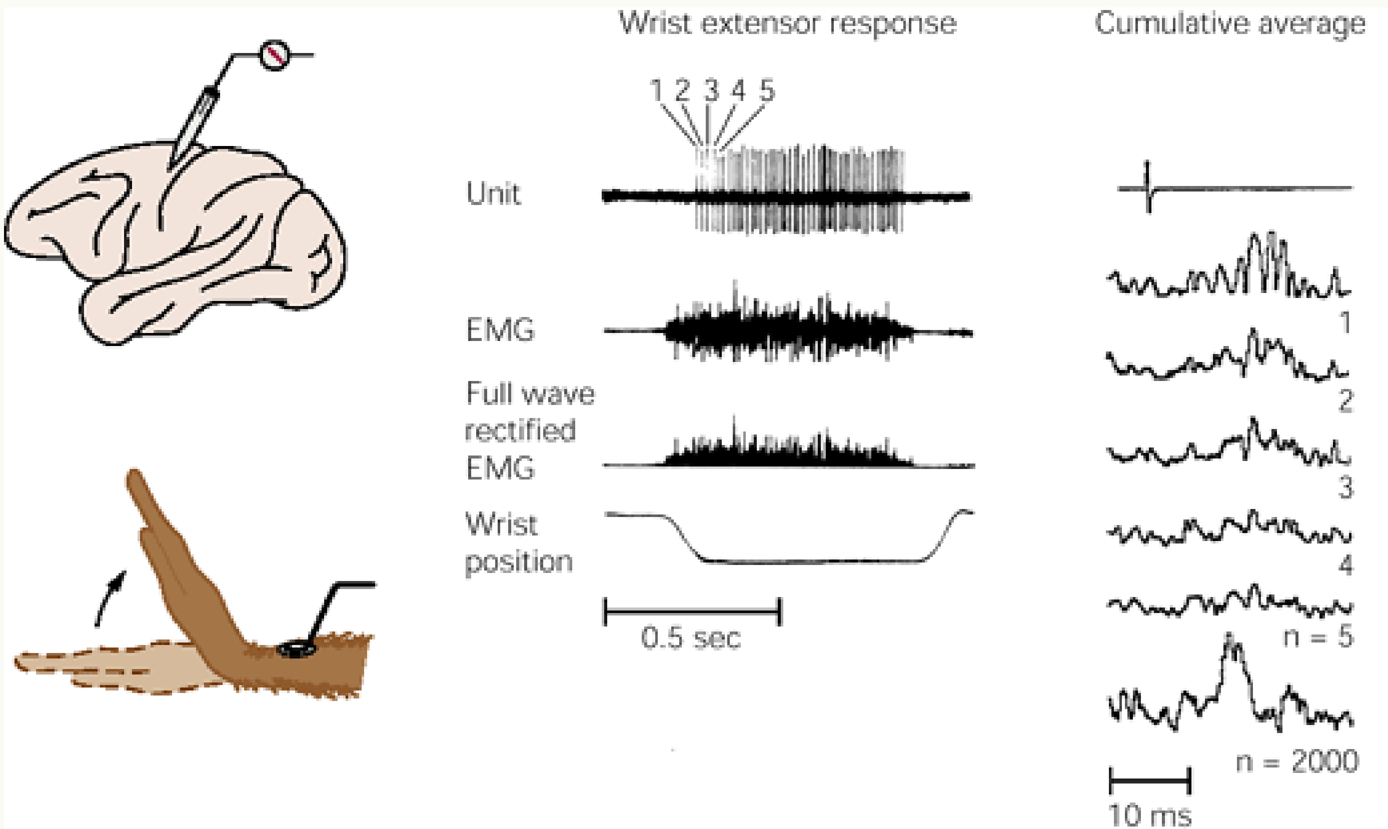
Experimental setup
Recording microelectrode in wrist area of right motor cortex
V
Stimulating electrode in pyramidal tract
Pulley
Potentiometer (wrist angle)
Restraint
Weight (flexor load)
Records of behavior and cell activity
Extensor load pulls this way
Flexion
Lever position
Flexor load pulls here
Extension
A No load
Flexors
Extensors
PTN
PTN active before movement
PTN active with agonist muscle
B Flexor load
Flexors
Extensors
PTN
PTN activity increases with increased load
C Extensor load
Flexors
Extensors
PTN
No PTN activity: flexion movement results from relaxation of antagonist

Evarts, Tanji, 1974

- Baseline discharge changed while the animal waited for a signal to move in a predetermined direction
- This pattern of activity was termed “set related” because it reflected the animal’s preparation to respond to a later stimulus
- These discharges demonstrated that the intent to perform a movement alters the firing pattern of neurons in the primary motor cortex hundreds of milliseconds before the movement takes place

Fetz et al., 1974

Spike-triggered averaging



Fetz, Cheney, 1980

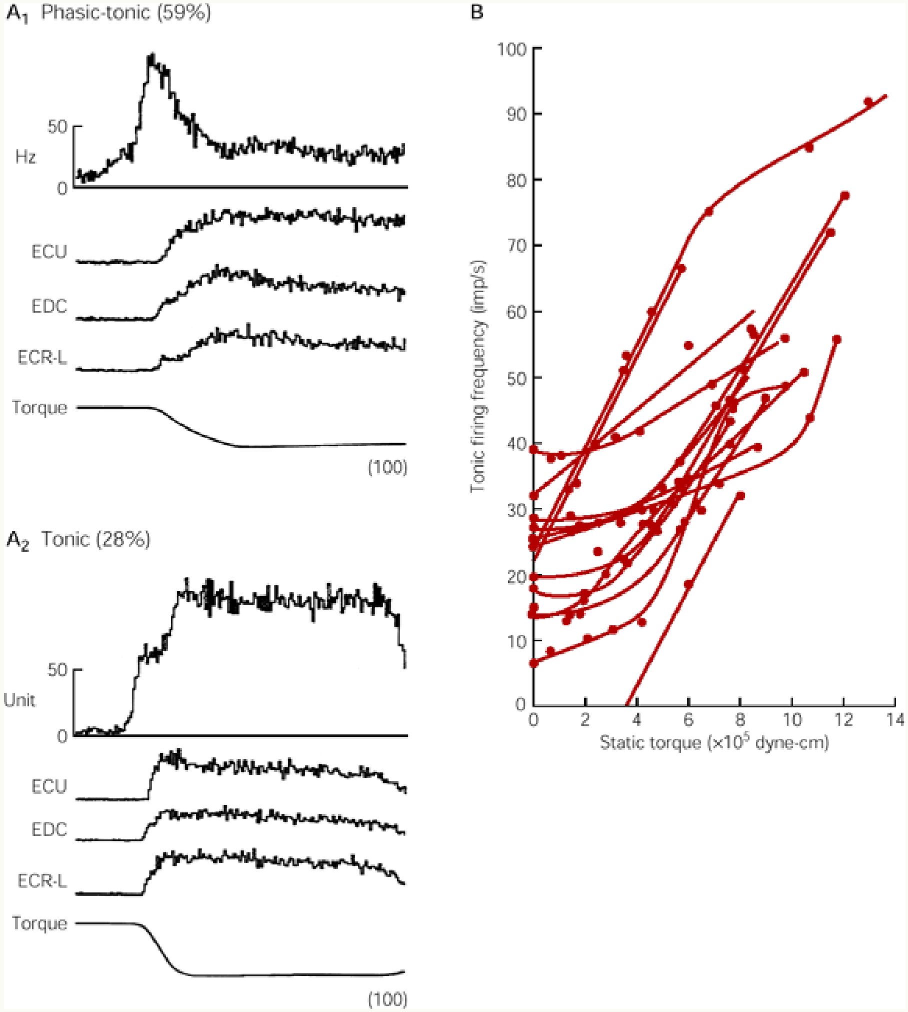
Individual cells project mono-synaptically to more than one motor neuron sometimes to muscles controlling different joints

Muscles are not mapped one-to-one in cortical output neurons

Phasic-tonic and tonic neurons

- Phasic-tonic: firing during the dynamic phase of movement and then a lower tonic rate when a steady torque is reached
- Tonic: follows torque and remains at a high level

Fetz, Cheney, 1980



Multi-Joint Control

M1 cells directly control the specific spatiotemporal patterns of muscle activation or do they encode more global features of the movement such as its direction, extent, or joint angle changes?

Georgopoulos et al., 1982

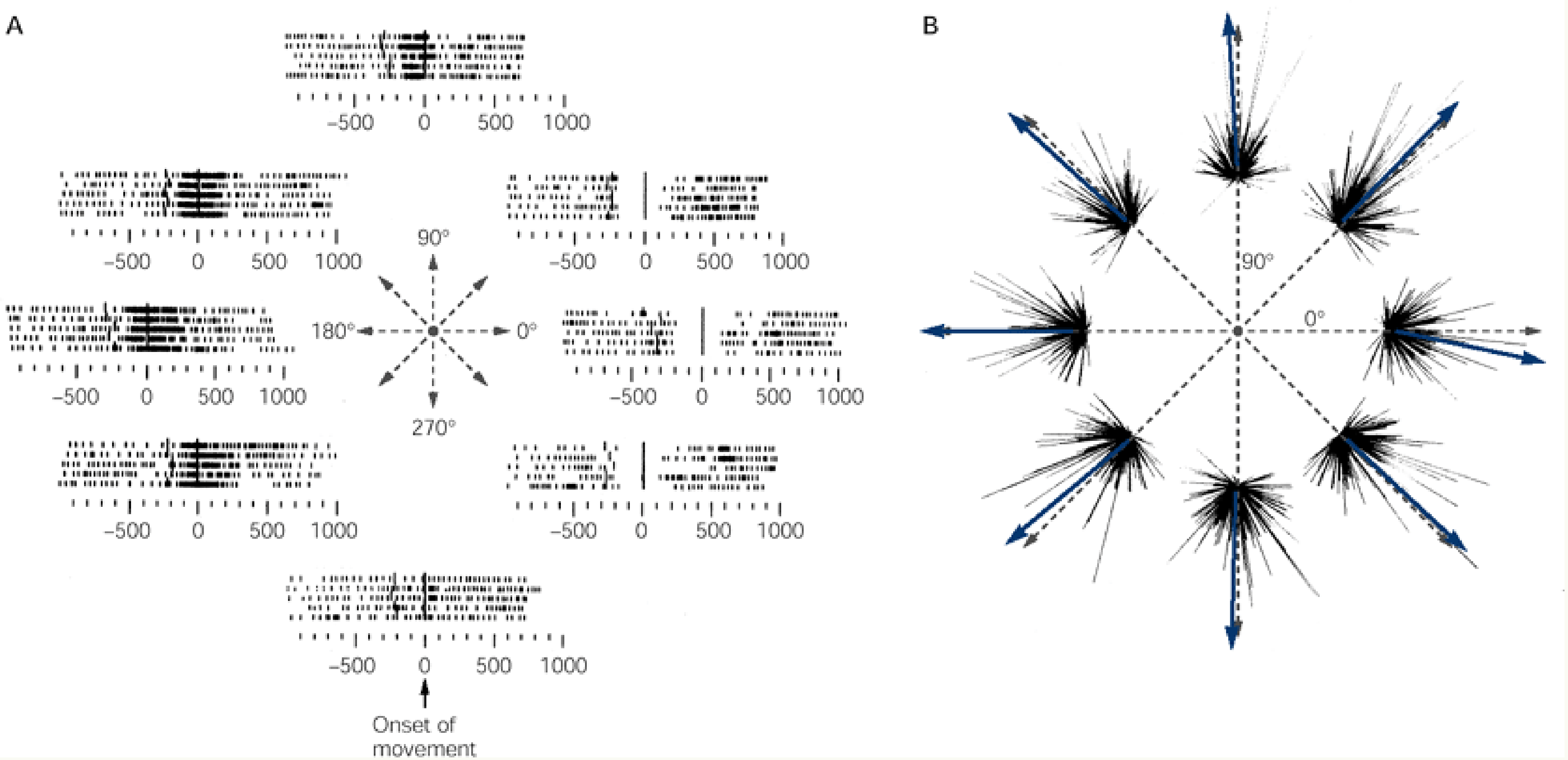
Monkey move a joystick toward visual targets located in different directions and recorded the associated changes in activity in the primary motor cortex

All neurons fired briskly before and during movements in a broad range of directions

Georgopoulos et al., 1982

- Movement in a particular direction is determined not by the action of single neurons but by the net action of a large population of neurons
- The contribution of each neuron to movement in a particular direction be represented as a vector whose length indicates the level of activity during movement in that direction
- Individual cells could then be added vectorially to produce a population vector
- Directions of such computed population vectors closely match the directions of movement

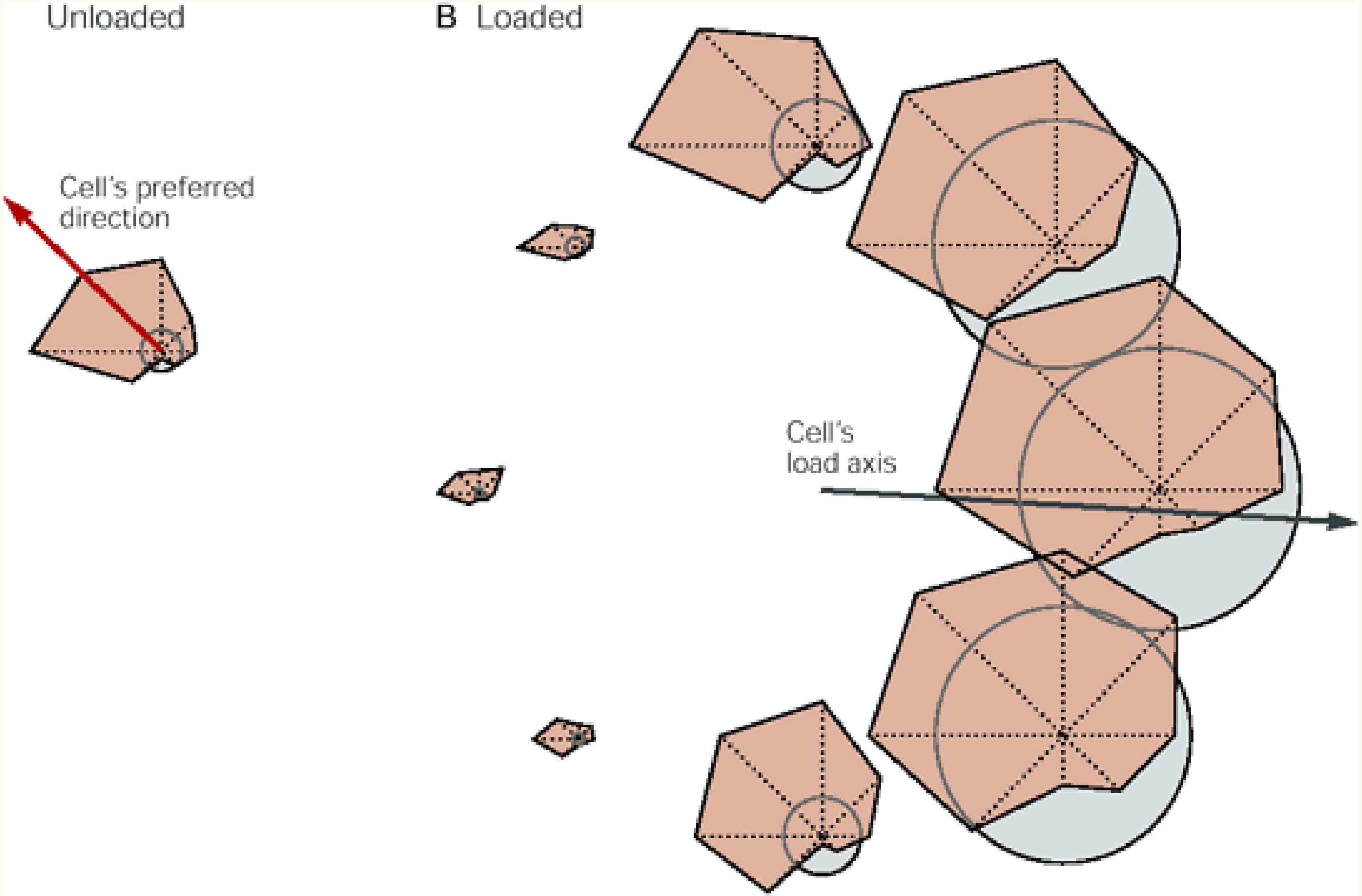
Population Vector



Direction and Force

- The directionally tuned neurons are modulated by the presence of external loads
- The modulation depends on the force required to displace the limb
  - Firing rate increases if a load opposes movement of the arm in the cell's preferred direction
  - Firing rate decreases if the load pulls the arm in the cell's preferred direction
- Activity of neurons in the M1 varies with the direction of forces as well as with movement direction
- This force coding is similar to that for single-joint movements, discussed earlier
- M1 activity signals not only “lower level” movement parameters, such as muscle forces, but also “higher level” parameters related to the trajectory of the hand
- This feature of motor cortex neurons distinguishes them from alpha motor neurons

Direction and Force



A Simplified Analogy…

“Assembly (machine) language”

- Musculoskeletal system control
  - *“Muscle language”*

“High-order computer language”

- Directional motor control
  - *“Movement language”*

After Georgopoulos 1982

Cells with different resting firing patterns

Uniform distribution for the 3D space

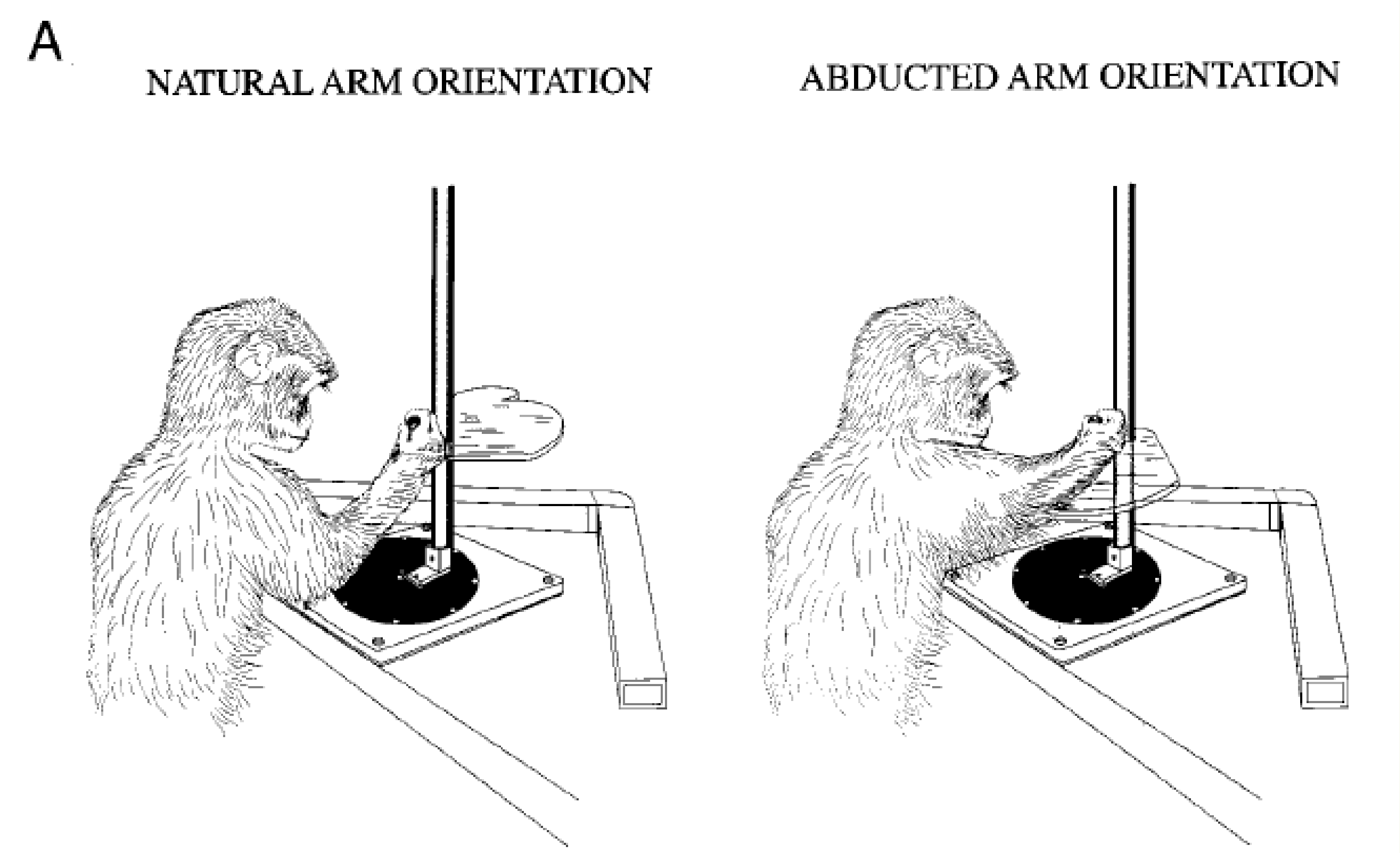
Represented many time

Clustered in columns (excit./inhib.)

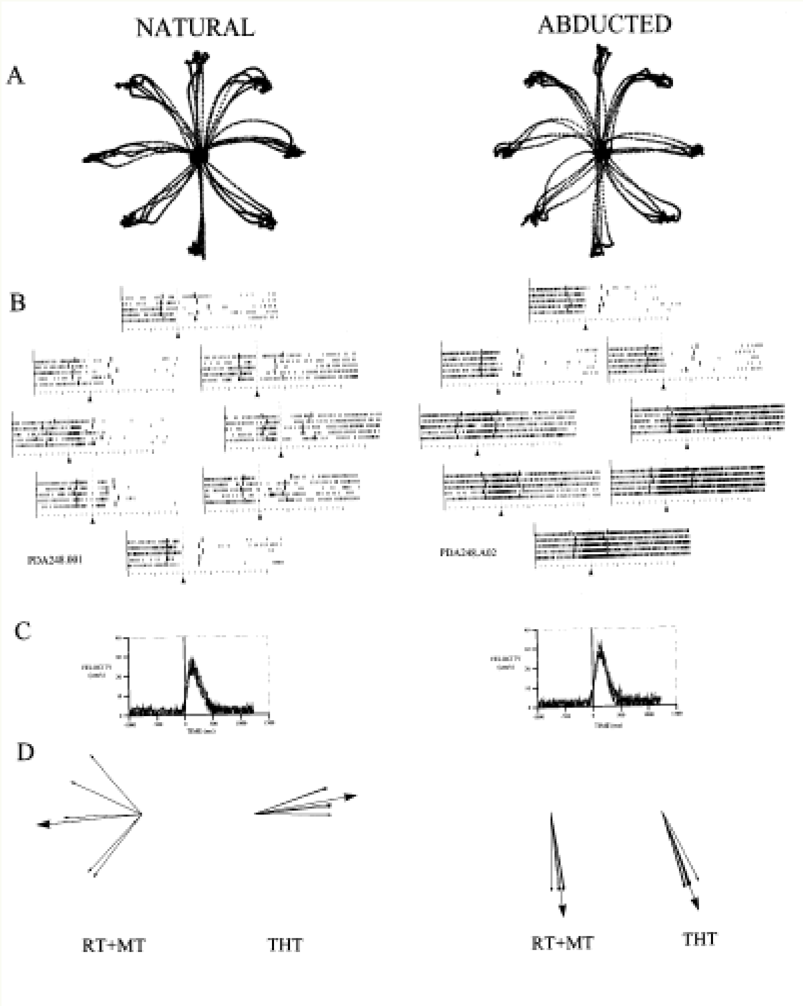
PD is similar for movements of different amplitude

…A V1-like organization

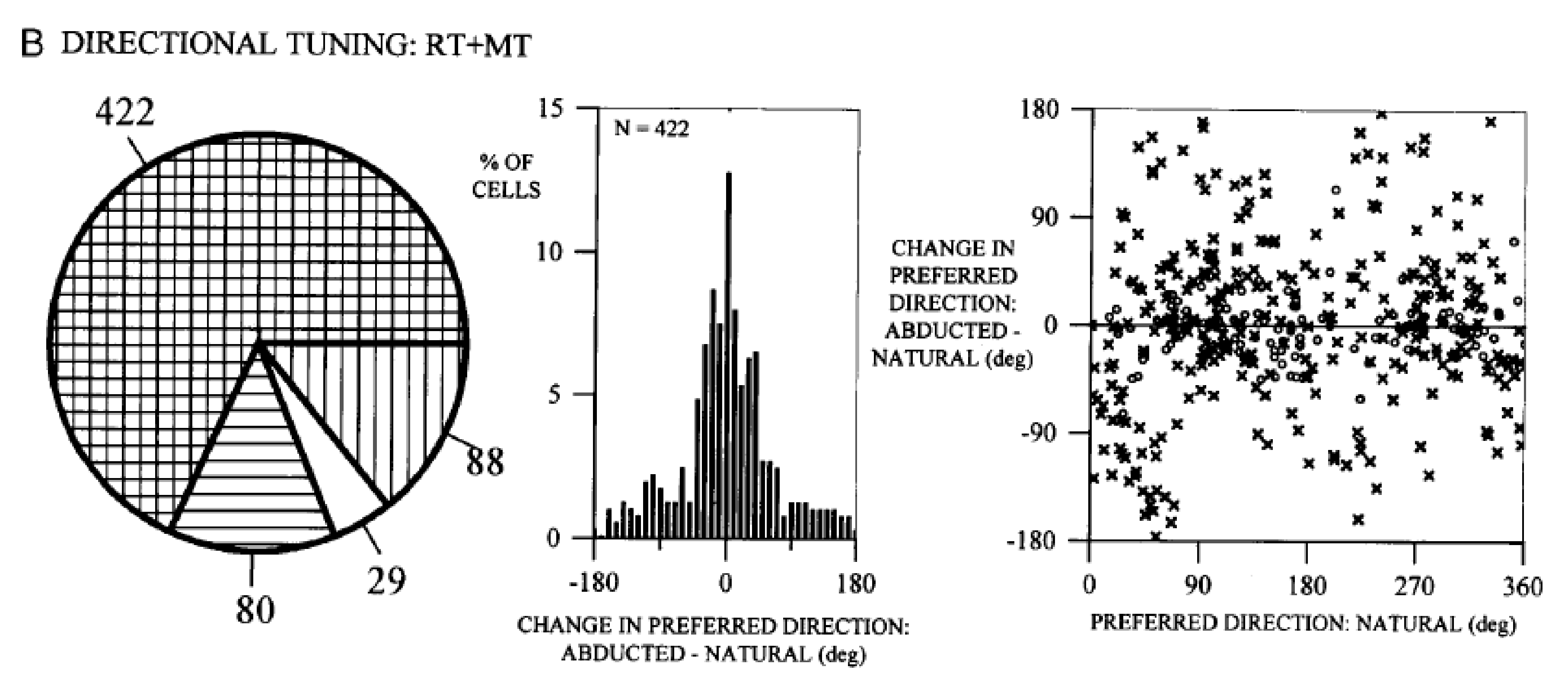
Scott, Kalaska, 1997



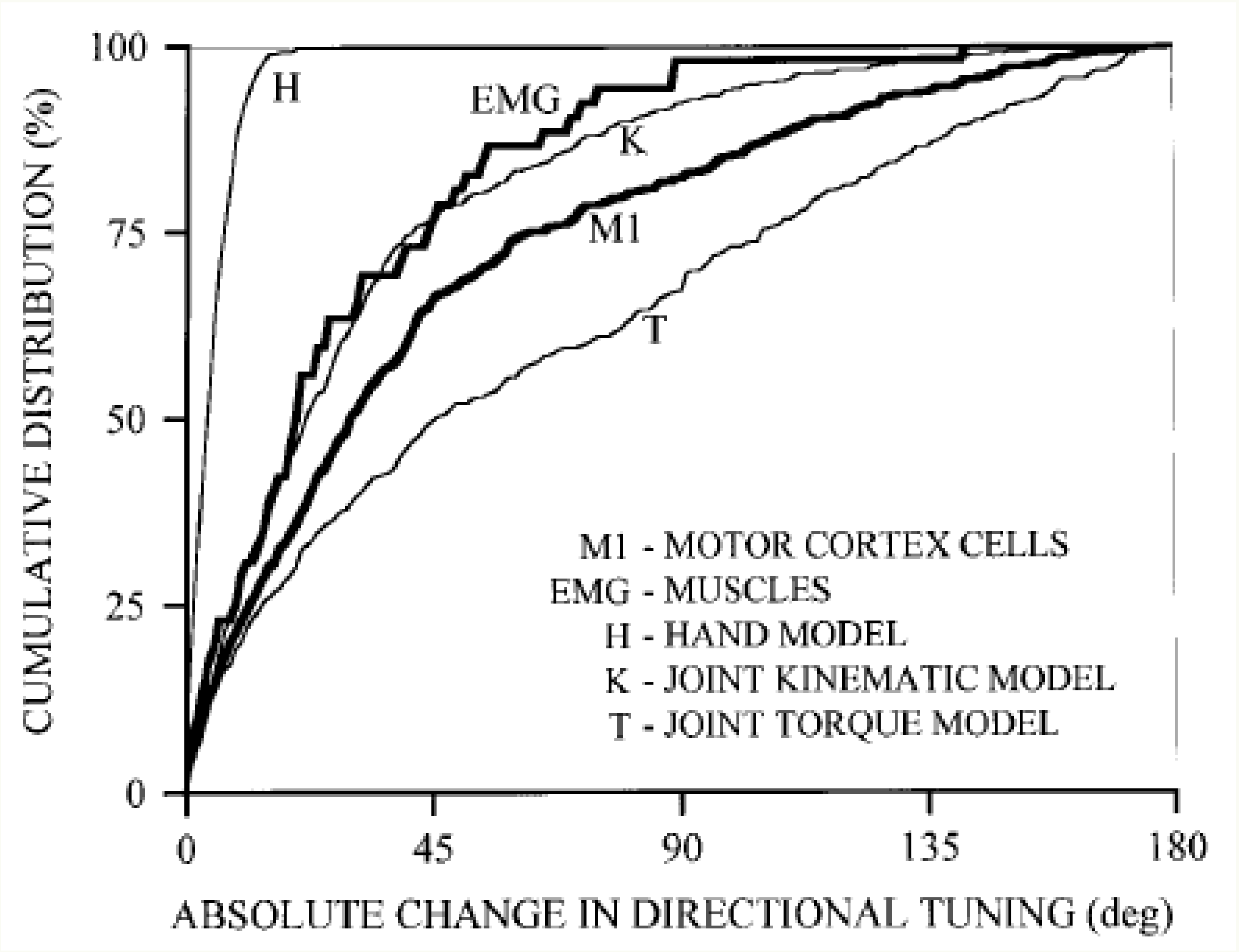
Scott, Kalaska, 1997



Scott, Kalaska, 1997



Scott, Kalaska, 1997



A far more complex Tuning…

Force (Sergio, Hamel-Paquet, Kalaska, 05)

Muscle activity (Holdefer, Miller, 02; Townsend, Paniski, Lemon, 06)

Direction (Georgopoulos et al., 82, 83, 95)

Speed (Moran, Schwartz, 99)

End posture (Aflalo, Graziano, 06, 07)

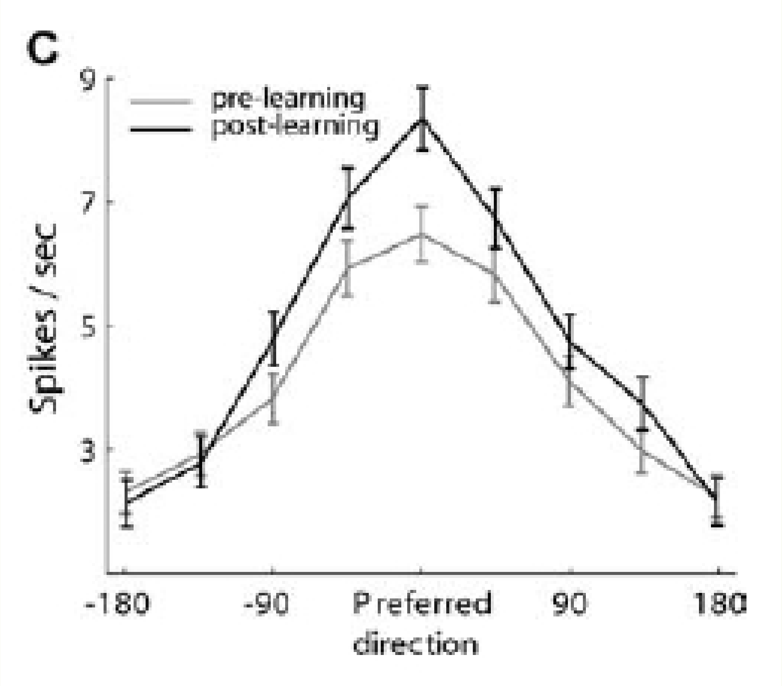
Joint angle (Wu, Hatsopoulos, 06)

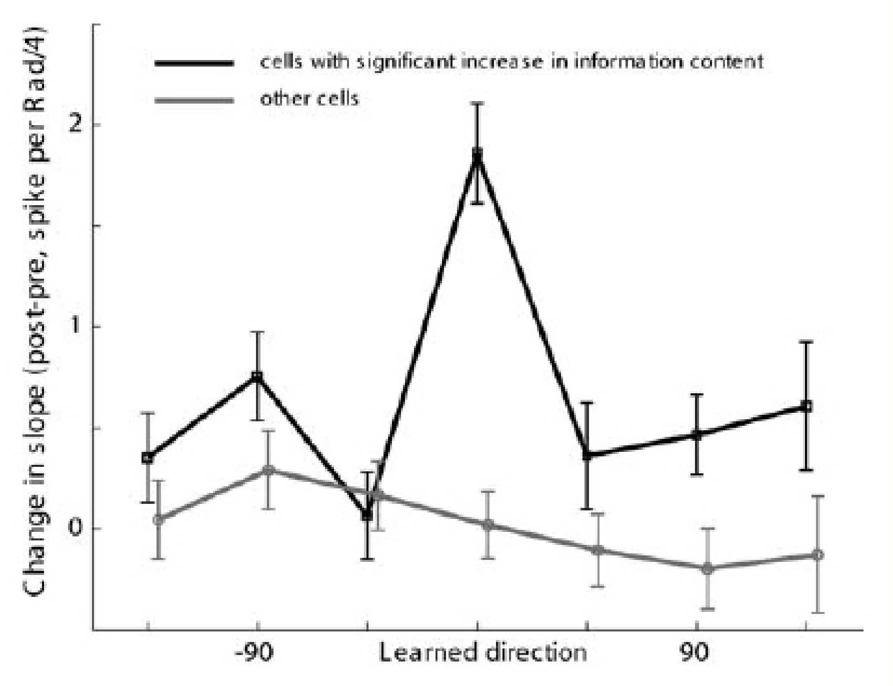
Joint torque (Herter, Kurtzer, Cabel, Haunts, Scott, 07)

Joint angular velocity (Reina, Moran, Schwartz, 01)

Posture (Scott, Kalaska, 95, 97; Caminiti, et al., 90, 91)

Single Cell Tuning and Learning



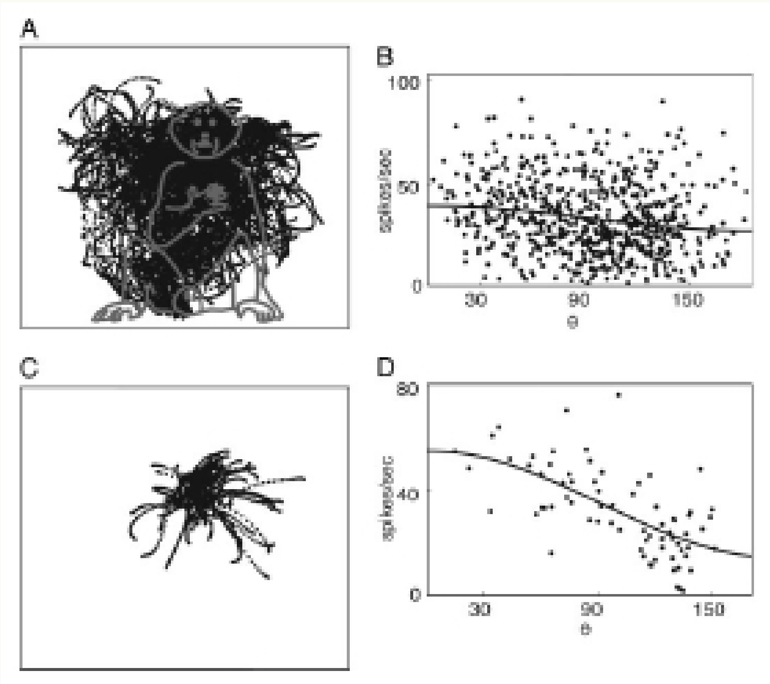


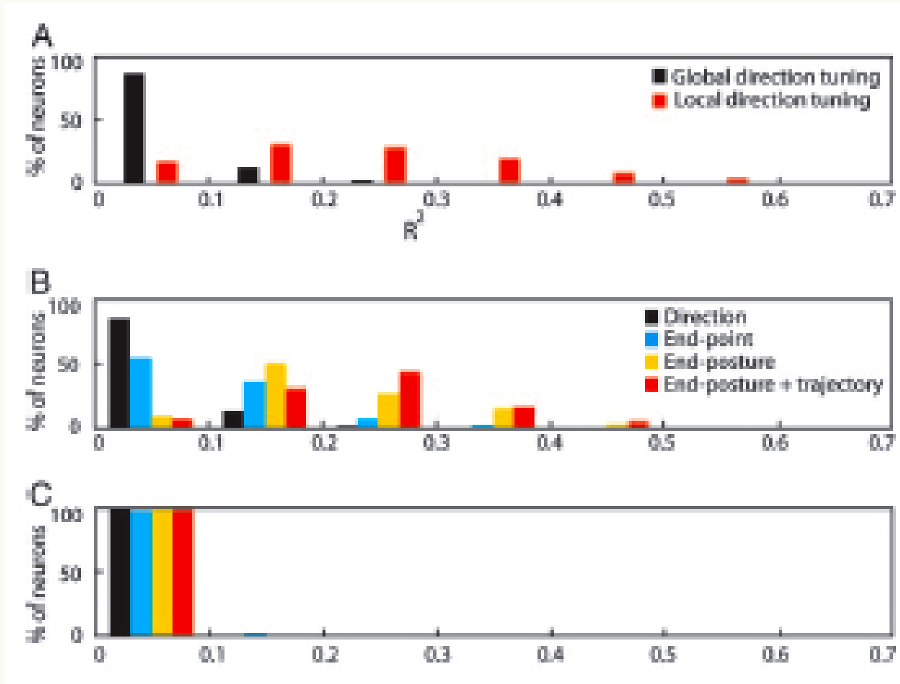
Tuning curve change

- PD slope change induced by learning

Aflalo, Graziano, J Neurosci, 2007

Direction Prior to Learning…

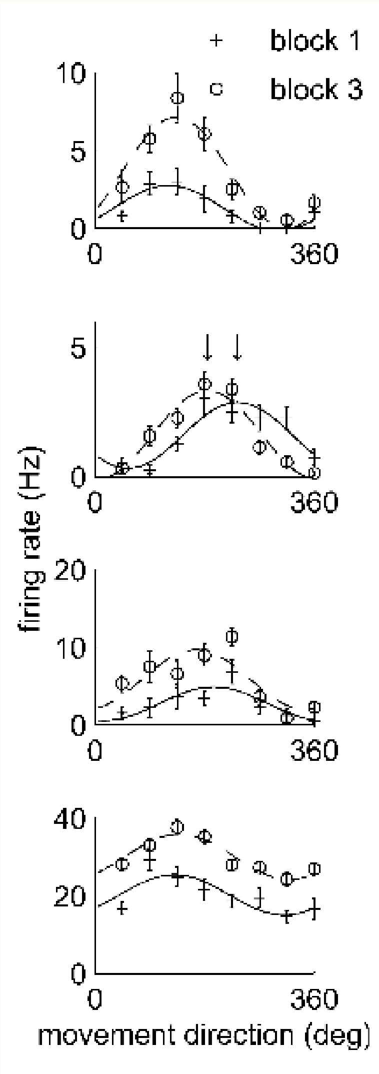




Natural behaviors

- All models explain little variance

Unstable Tuning



Tuning curves:

- Baseline: Slow random drift
- Learning: Systematic shifts

- Unstable neural representation

- Stable Behavior

Summing-up

"...***direction tuning*** may be ***too simple model*** to account for the behavior of motor cortex neurons...maybe [neurons] are hypertuned in a ***complex multidimensional space***...the ***code is a population one*** as first suggested by Georgopoulos but the basis set is ***idiosyncratic and constantly shifting through use***."

Premotor cortex

Neurophysiology of the Motor System

Premotor Vs. Motor Cortex

- Outputs of the premotor areas and the M1 overlap in the spinal cord
- Inputs to the premotor areas are different
- Set-related and preparatory activity predominates
- Damage to premotor areas causes more complex motor impairments than does damage to M1
- Large lesion of the premotor area:
  - If food is presented behind a transparent shield monkey will reach directly for the food and bump into the shield.
  - Unable to incorporate visuospatial information about the shield into the kinematic plan for moving its hand

Premotor Functional Differences

- Movements initiated internally involve primarily the supplementary motor area
- Movements triggered by external sensory events involve primarily the lateral premotor areas
  - Lateral premotor neurons map the often arbitrary relationship between stimulus and response
- Lateral dorsal premotor area is also concerned with delayed action
- Lateral ventral premotor area is concerned with conforming the hand to the shape of objects

M1, SMA and Pre-SMA

Complex movement sequences require more planning than do simple repetitive movements

Imagining complex movements might require the same amount of planning as real movements

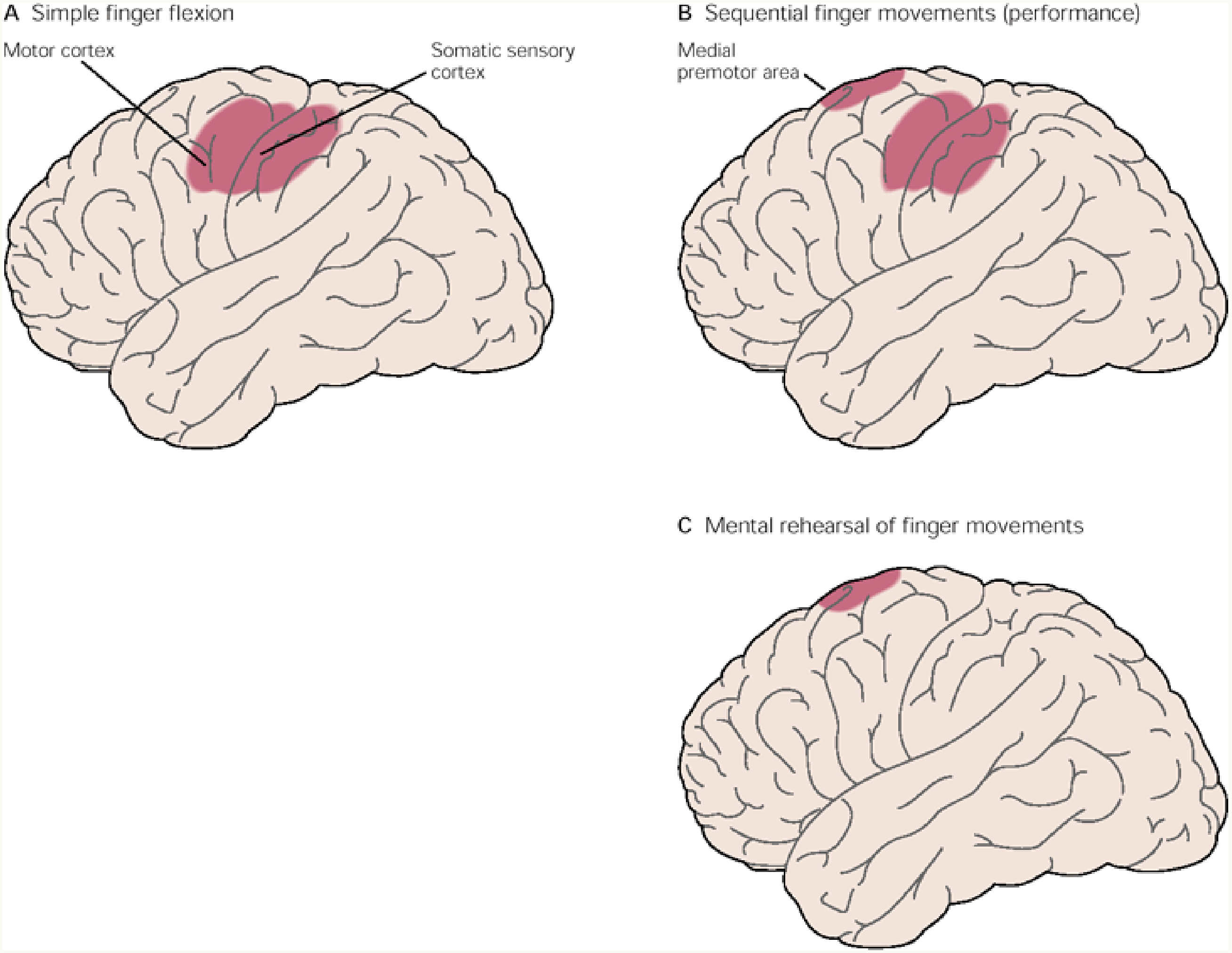
During forceful repetitive finger flexions against a spring increases activity in the contralateral hand M1

A complex sequence of finger movements increases activity in the SMA

When the complex sequence was simply imagined, PreSMA was activated

PreSMA is the main input to SMA

M1, SMA and Pre-SMA



SMA and Sequence Memory

Instructed-delay task

- The monkeys in this experiment were instructed to touch three panels in a specific sequence

Three panels were lit up in a sequence that the monkeys had to follow

In the other variation the monkeys were instructed to perform a previously memorized sequence

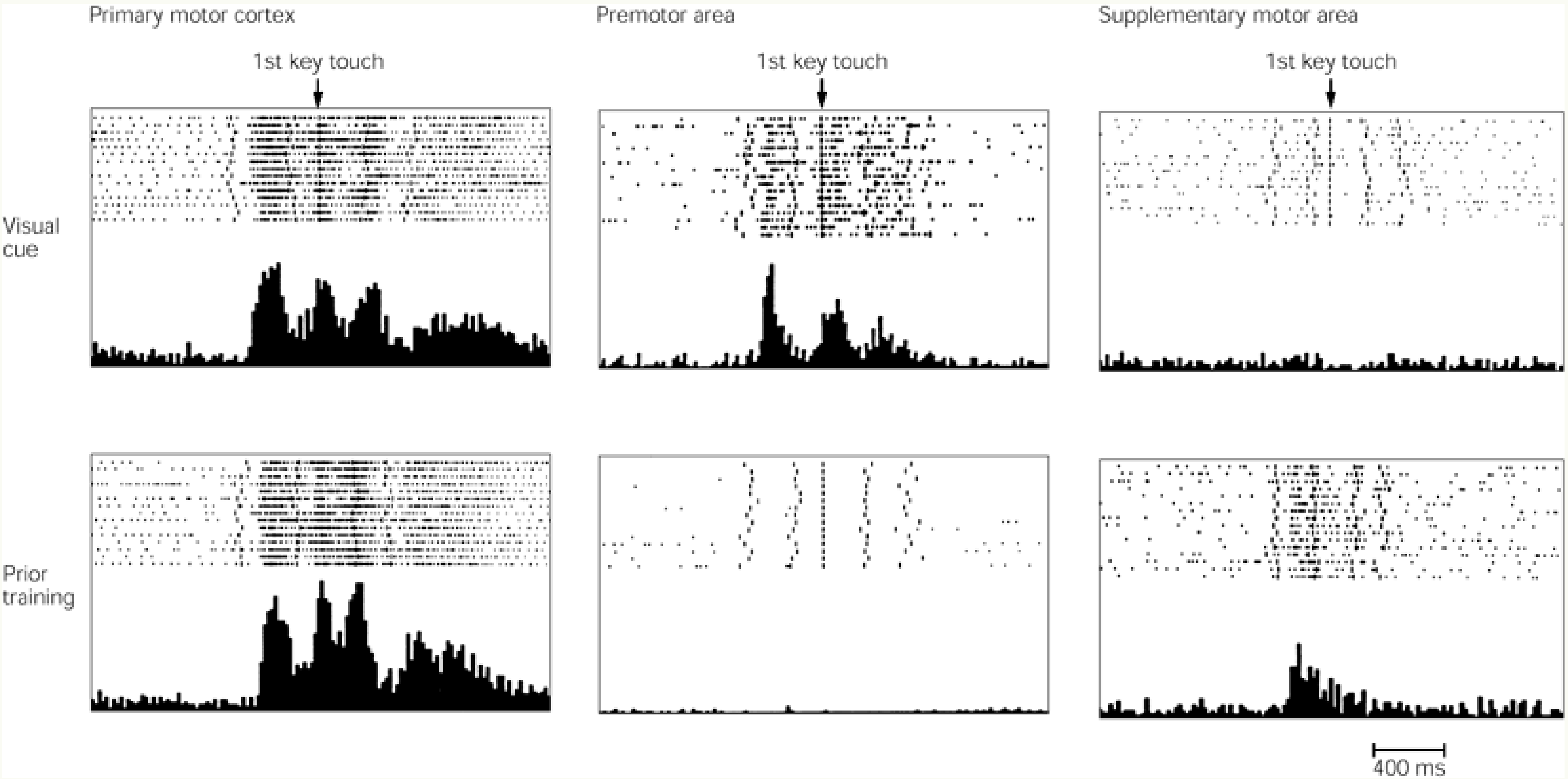
Neurons in the primary motor cortex discharged before and during

SMA neurons fired only before and during performance of a memorized sequence

Movement-related discharge of some SMA neurons is specific to a particular sequence of movements and do not fire with other combinations of the same movements

SMA involved in preparing movement sequences from memory in the absence of visual cues

SMA and Sequence Memory



Complex Motor Learning: SMA to M1

After learning the neural control of task performance can shift from SMA to M1

Monkeys, premovement activity SMA during a key-pressing task disappeared after 12 months of overtraining

Experimental lesion in the right M1 caused weakness, compromising the task

After 21 days monkeys recovered the same skill

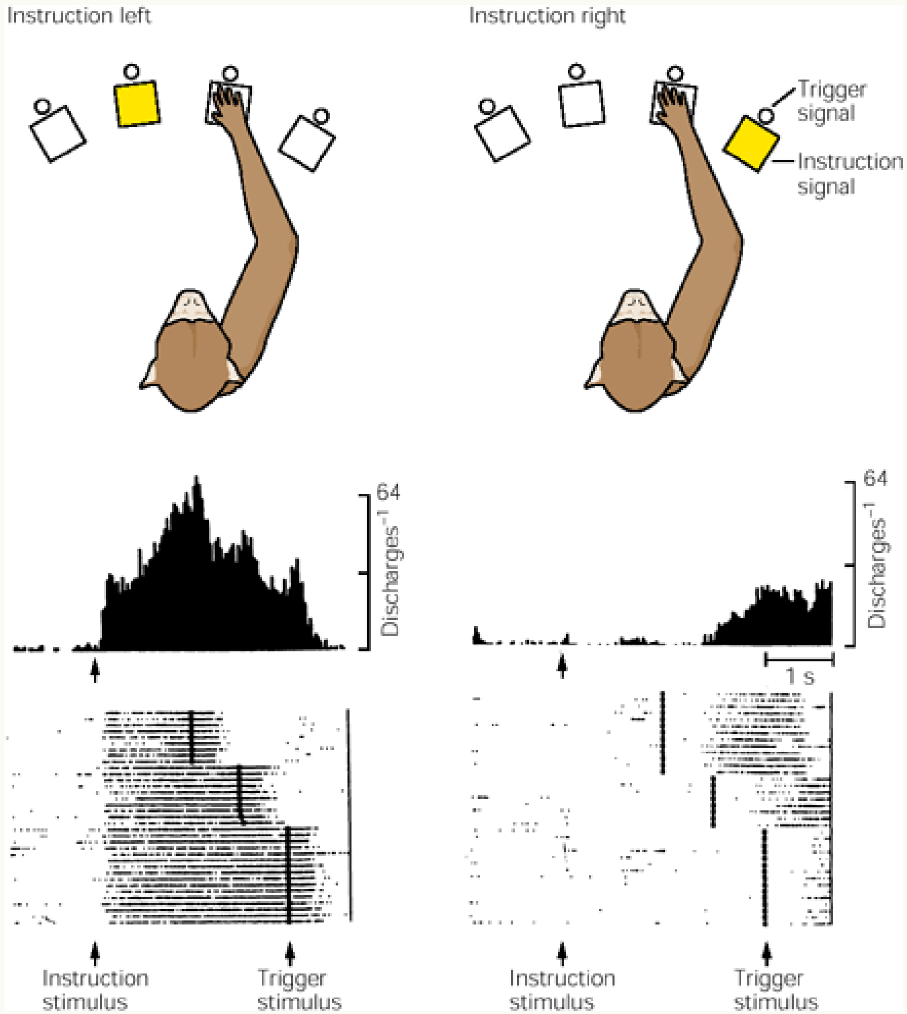
Recordings from SMA showed that neurons were again very active before movement

Lateral Premotor Cortex

Represents how visual or other sensory stimuli are to be used to direct the movement

Set-related activity in the premotor area persists during the entire interval between an anticipatory cue and the signal to move

Set-Related Activity



Dorsal Premotor Cortex

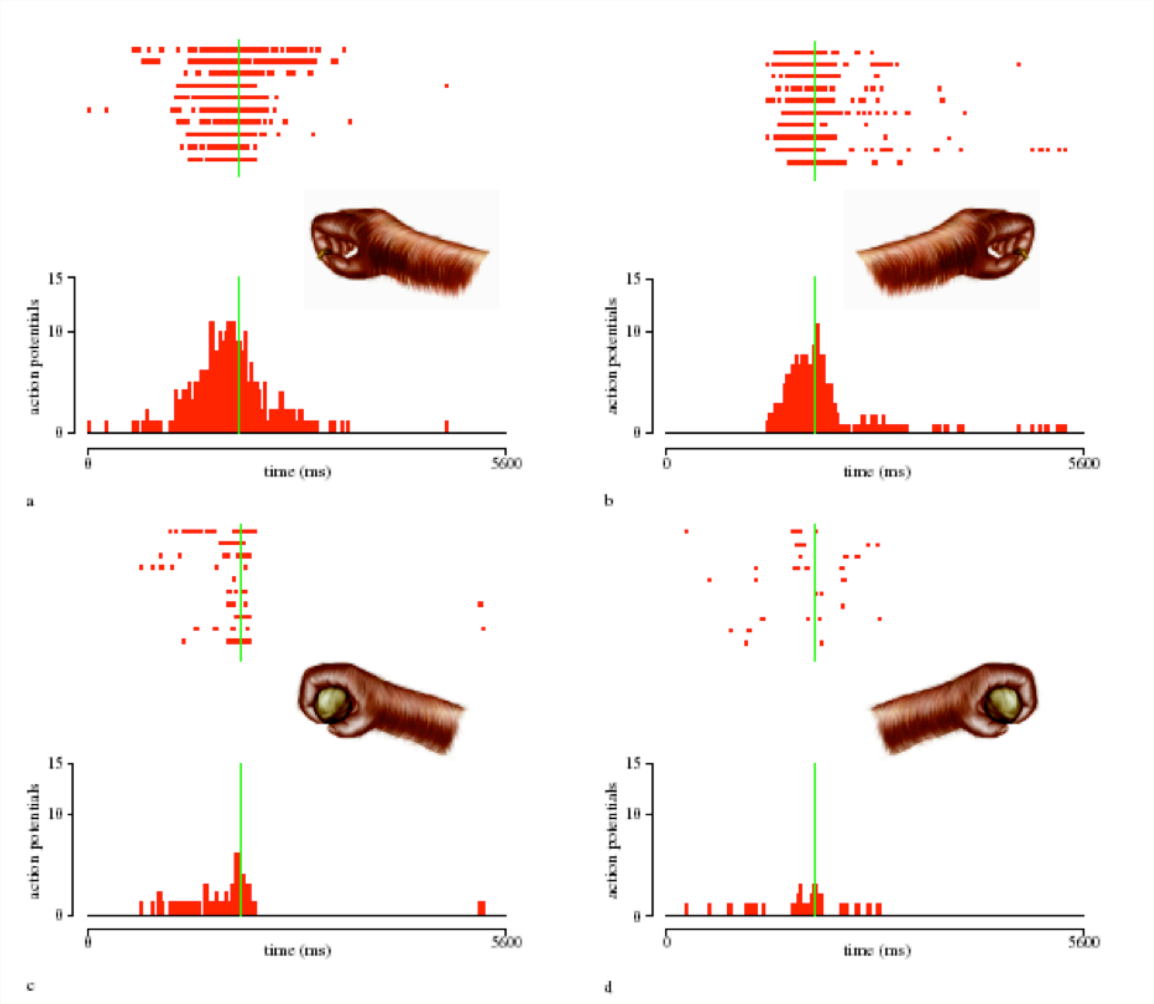
PMd is involved in learning to associate a particular sensory event with a specific movement (associative learning)

Monkeys were taught to associate pulling or pushing a joystick with a particular background light (red or blue)

PMd was then removed from both hemispheres and the animals were retrained two weeks

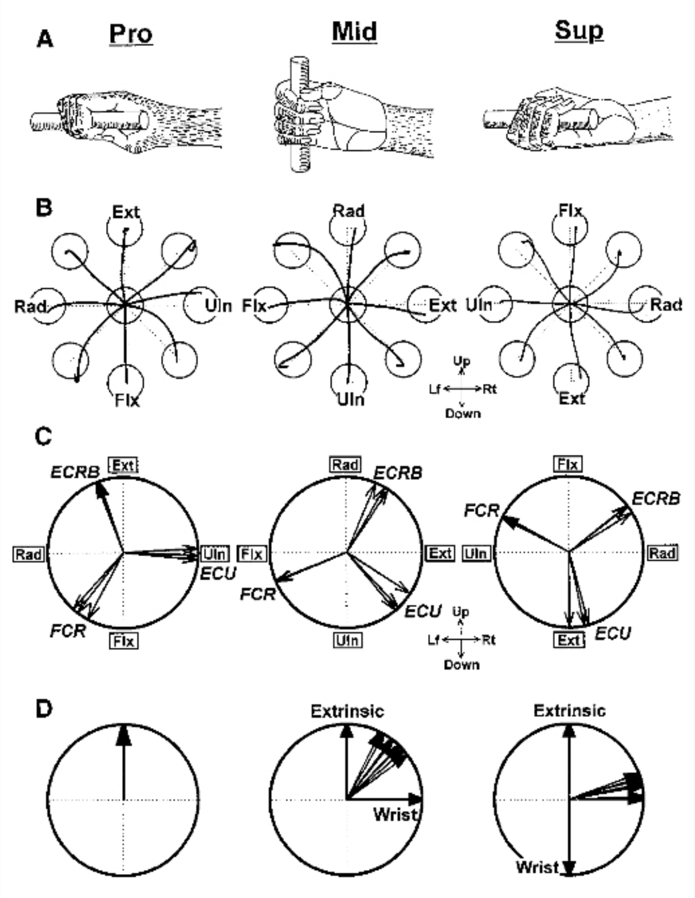
Although the monkeys were able to execute the required movements without impairment, none was able to relearn the association between the background color and whether to push or pull

Ventral Premotor Cortex



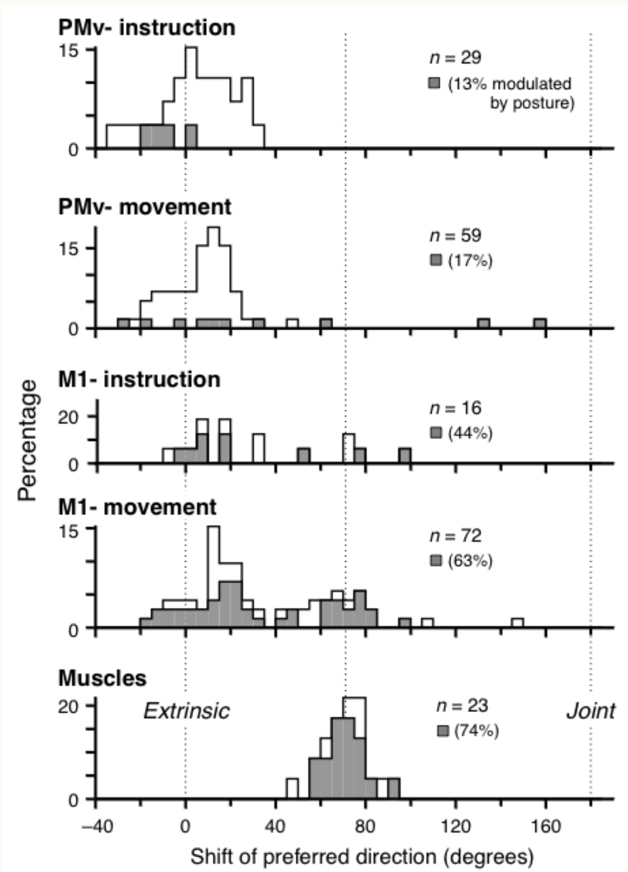
Extrinsic, or Intrinsic Space in M1?

- 3 major variables of wrist movement:
  - Muscle activity
  - Direction of movement at the wrist joint
  - Direction of movement in space
- 28/88 muscle-like properties
- 44/88 tuned to direction
  - Modulated by posture



Kakei, Hoffman, Strick, Nat Neurosci, 2001

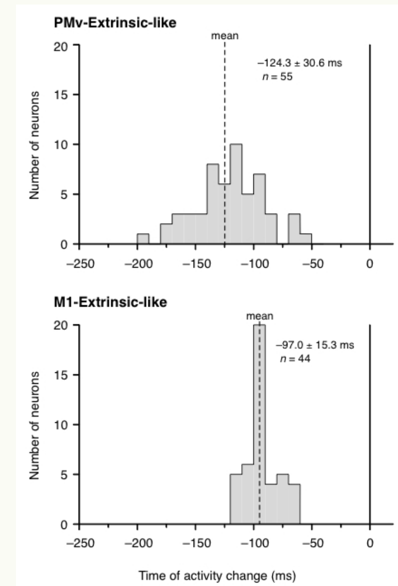
Extrinsic, or Intrinsic Space in PMv?



61/65 Extrinsic (94%)

No modulation with posture

Earlier activity



- Goal of movement regardless of how it is accomplished

Schwartz, Moran, Reina, Science, 2004

M1-PMv Relation

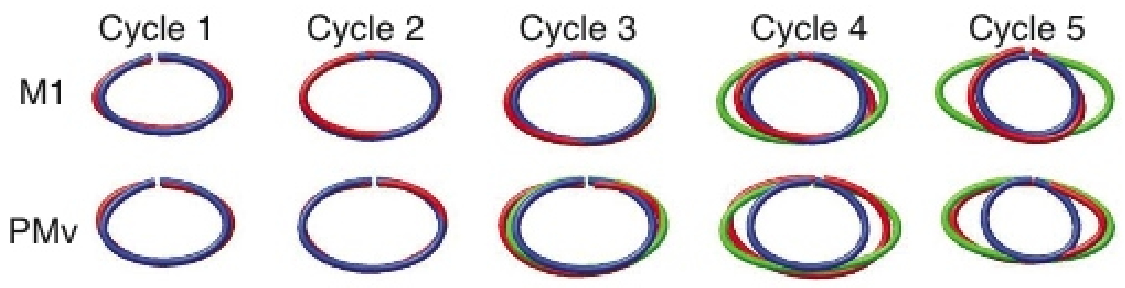


Fig. 3. Illusion task trajectories. Top row is five cycles from M1 units. Bottom row is from the PMv. The hand trajectory is blue, cursor trajectory is green, and neural trajectory is red. Each displayed trajectory is the mean across five repetitions.

“Neural trajectory” (Red) followed:

Hand-traj (Blue) in M1

Cursor-traj (Green) in PMv

Sensorimotor Translation in Parieto-Premotor Circuits

Goal-directed movements require transformation of sensory representations of the environment into muscle-control signals

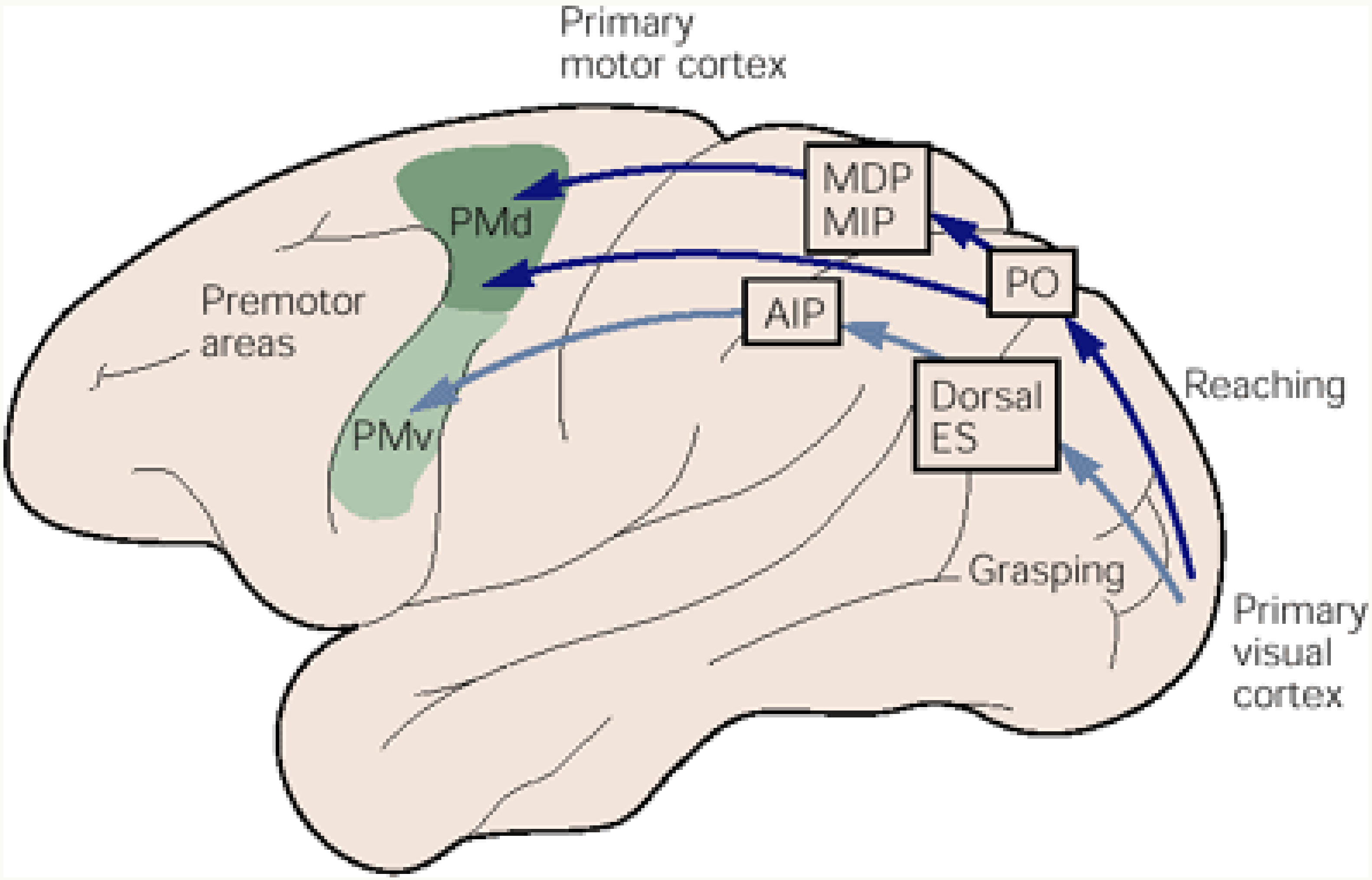
Reaching requires that visual information about target location and the position of the upper limb be used to specify critical features of the upcoming arm movement

- The parameters for reaching movement, notably direction and extent, depend on the location of the target relative to the body, shoulder, or hand

Grasping is governed mainly by the shape and dimensions of the object.

- Grasping involves first a separation of the fingers sufficient to enclose the object and then closure as the object is gripped between the pads

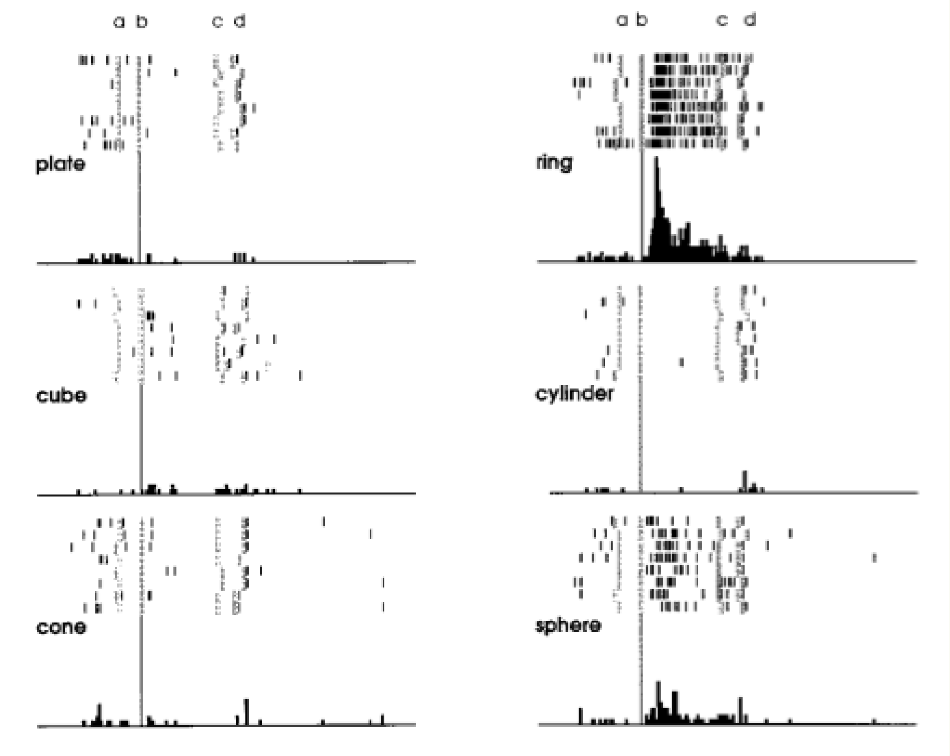
Parieto-Premotor Circuits



Canonical Neurons in PMv

Murata et al., 1997

Visual discharge of canonical neurons shows that there is a close link between the most common 3D stimuli and the actions necessary to interact with them

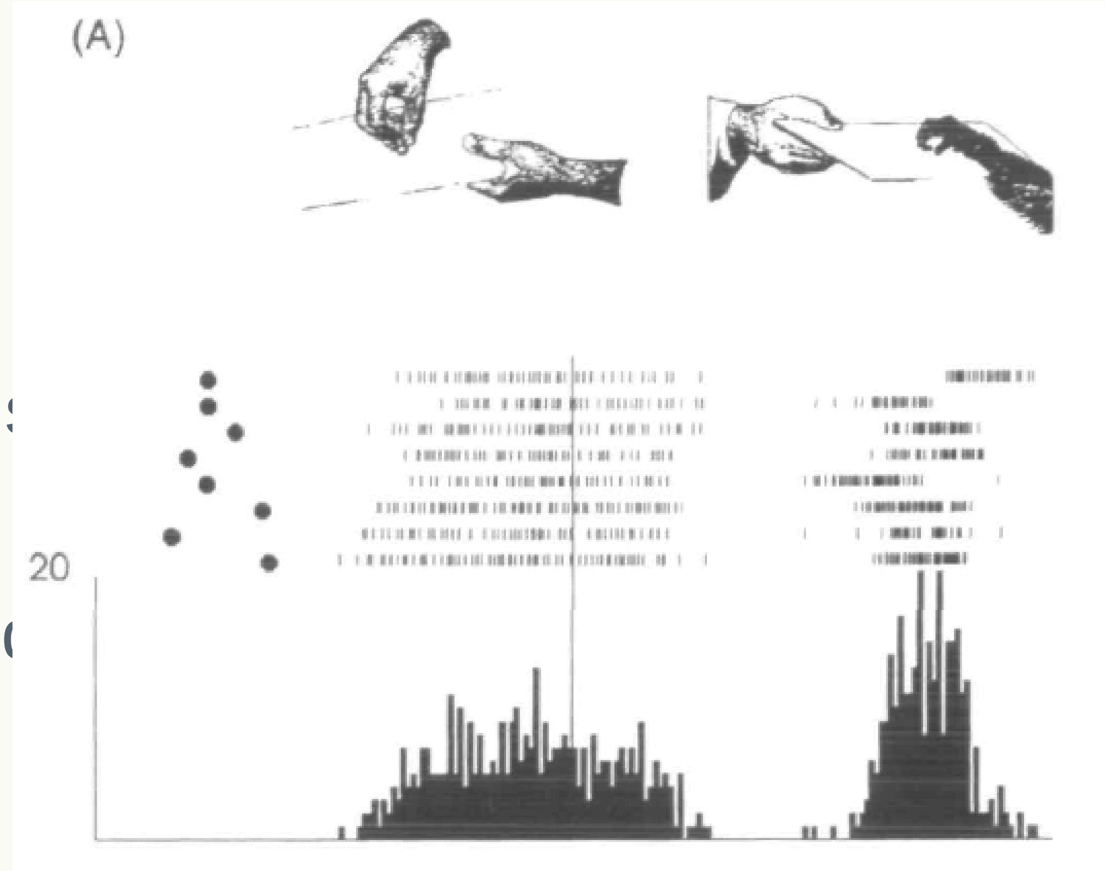


Mirror Neurons in PMv

di Pellegrino et al., 1992

Gallese et al., 1996

Visual discharge of mirror neurons shows that there is a close link between own goal directed action and similar action observation



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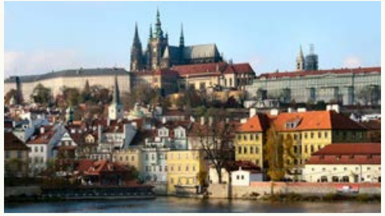

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