MOVEMENT DISORDERS

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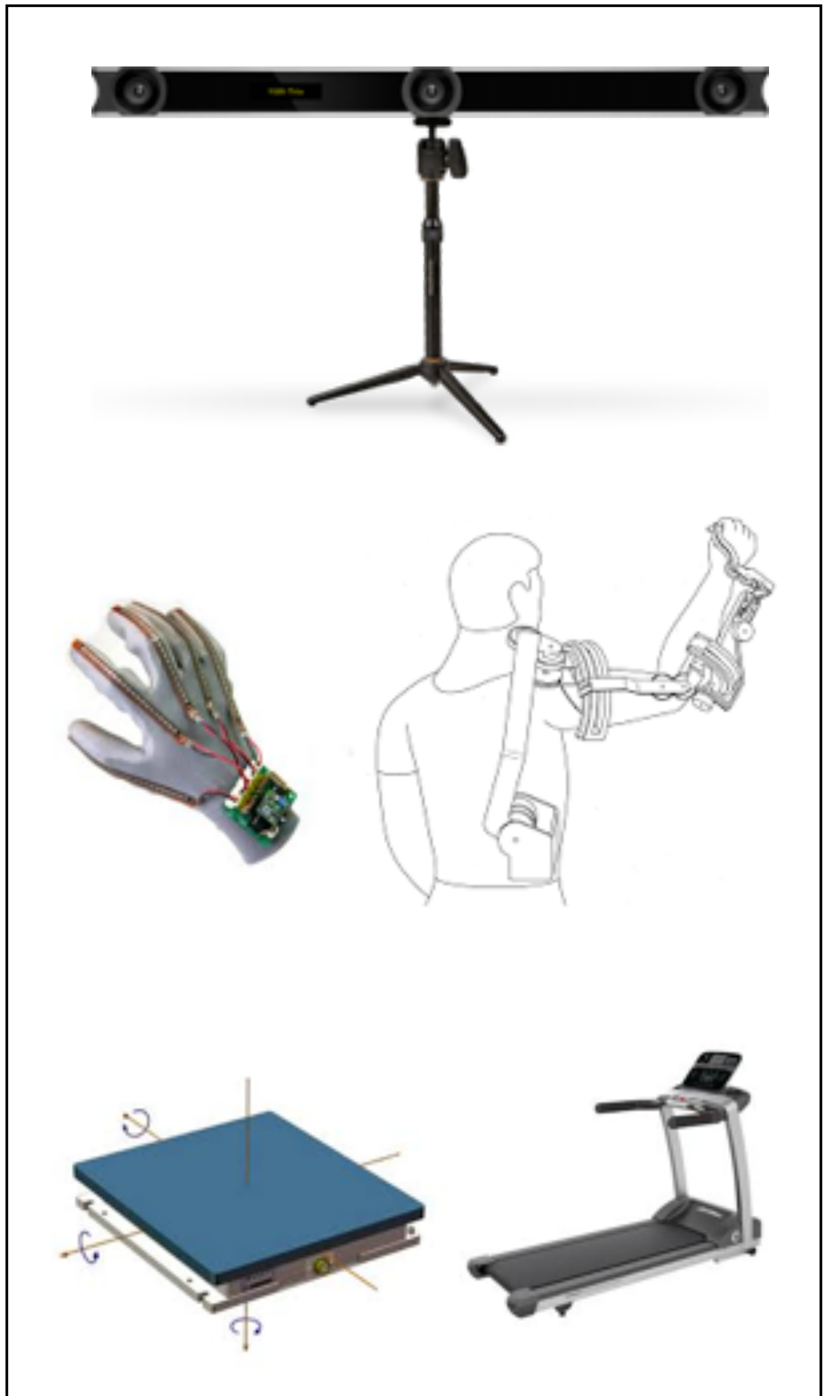
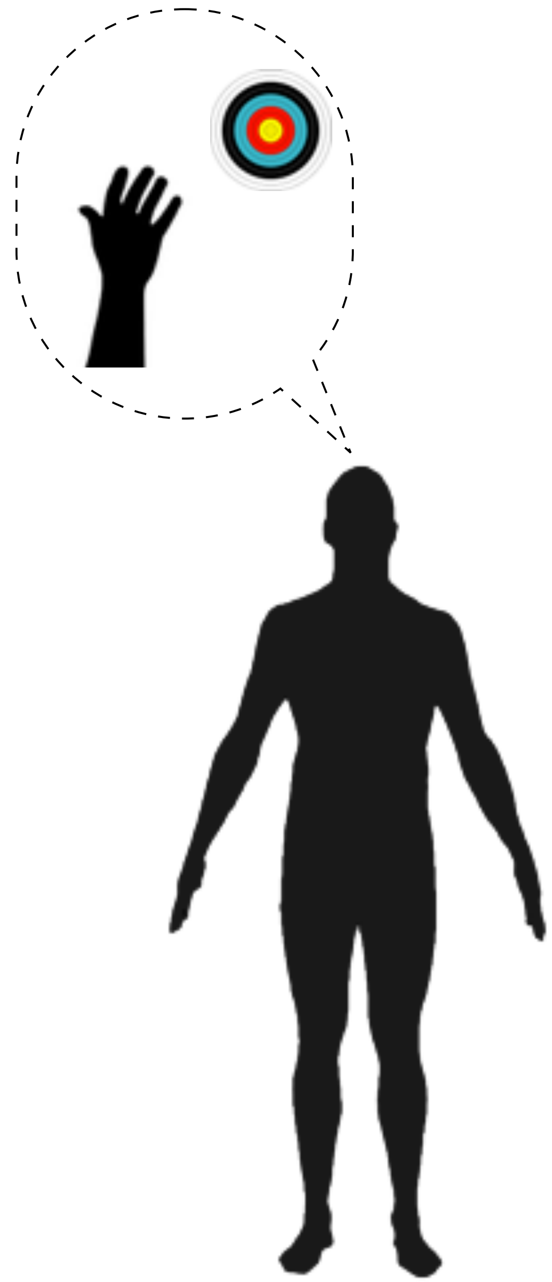
introduction

THE GRAND EXPERIMENT

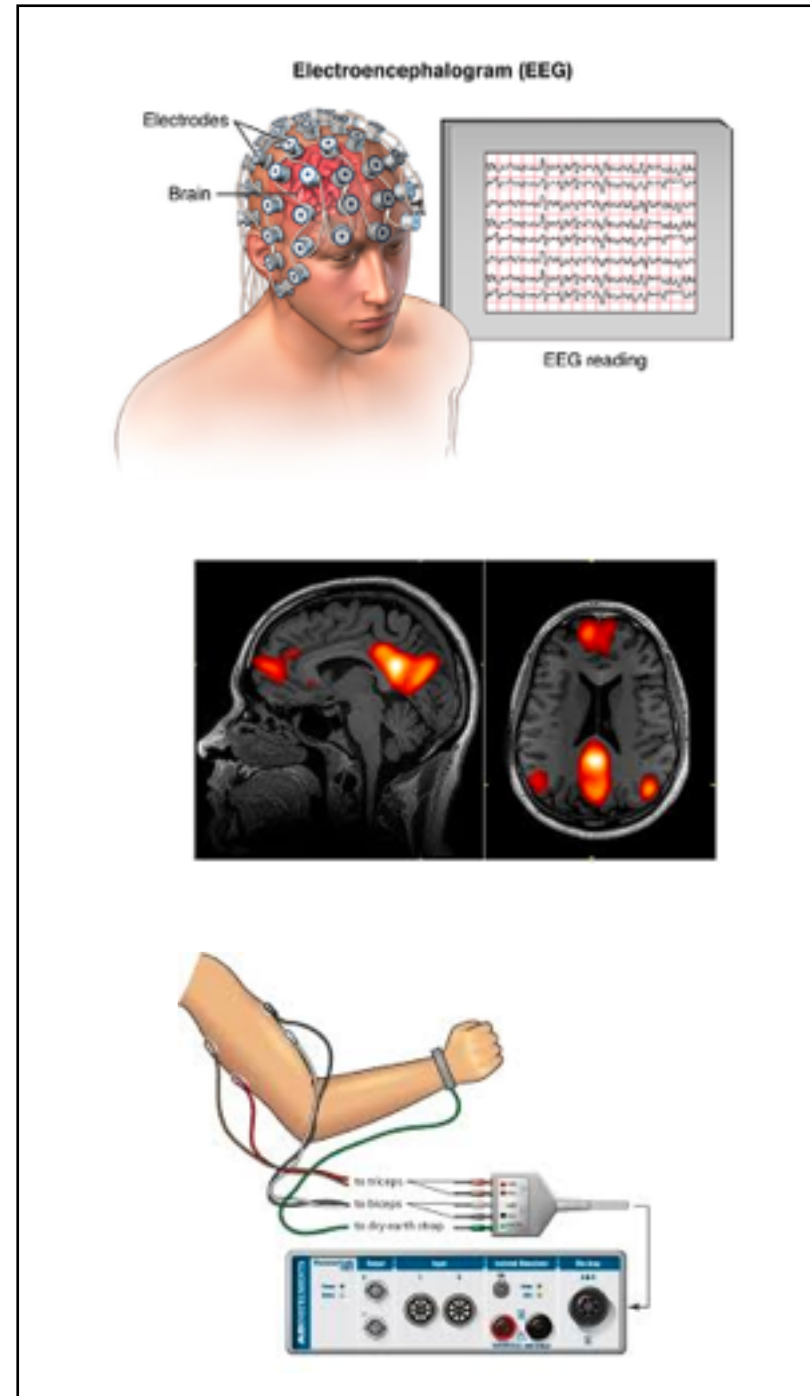
kinematics, dynamics



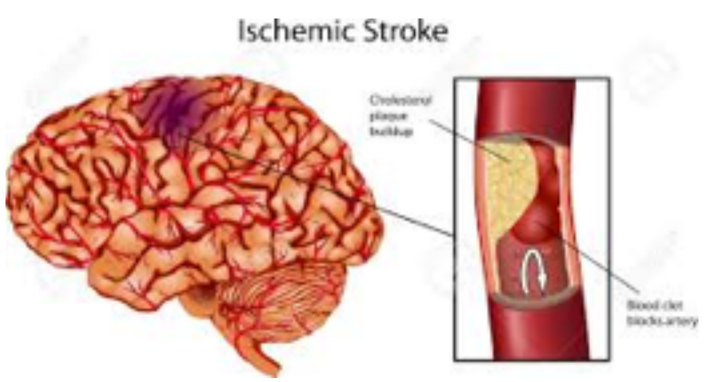


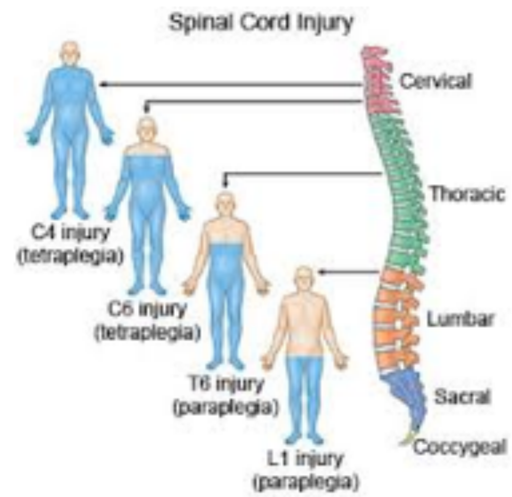
healthy subject
non-invasive
recordings

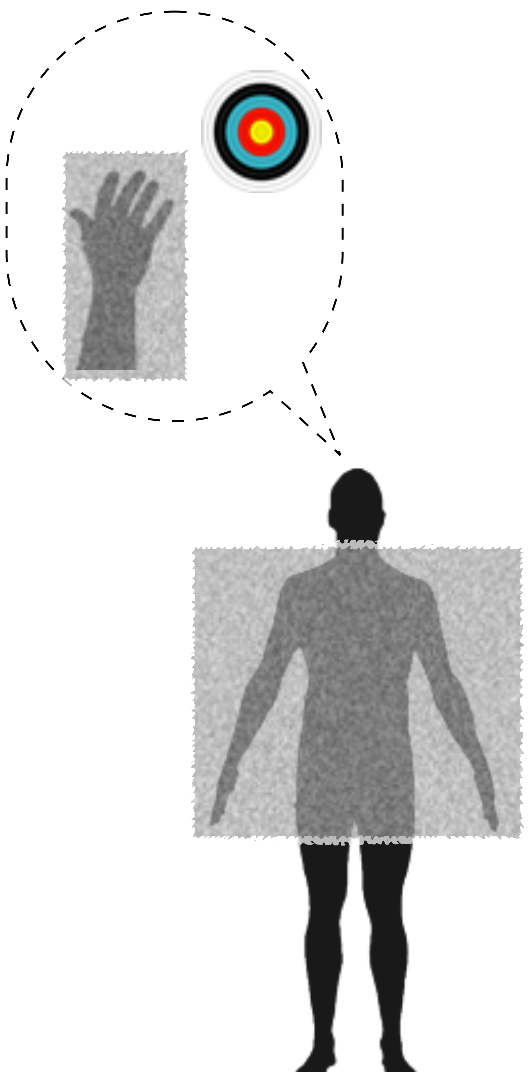
physiological signals

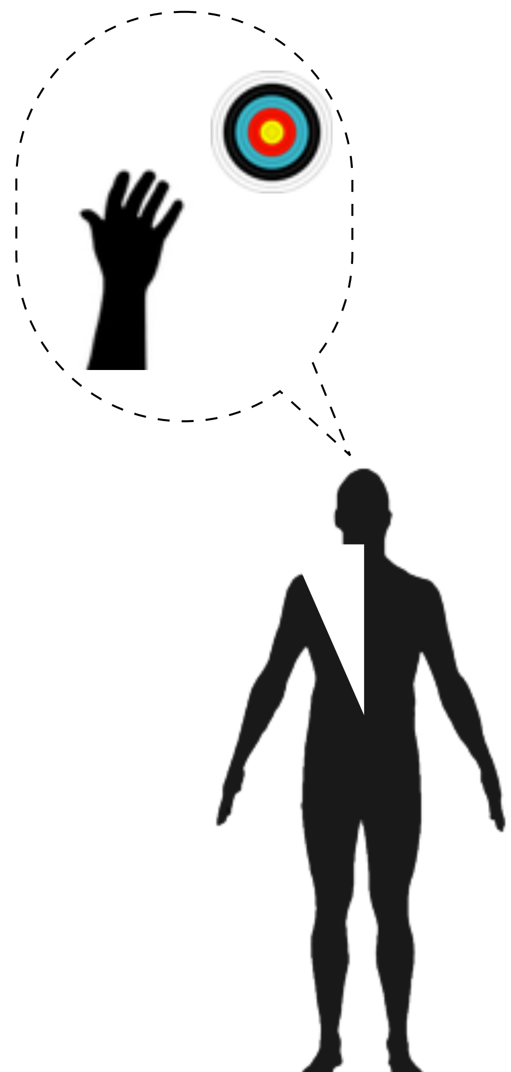


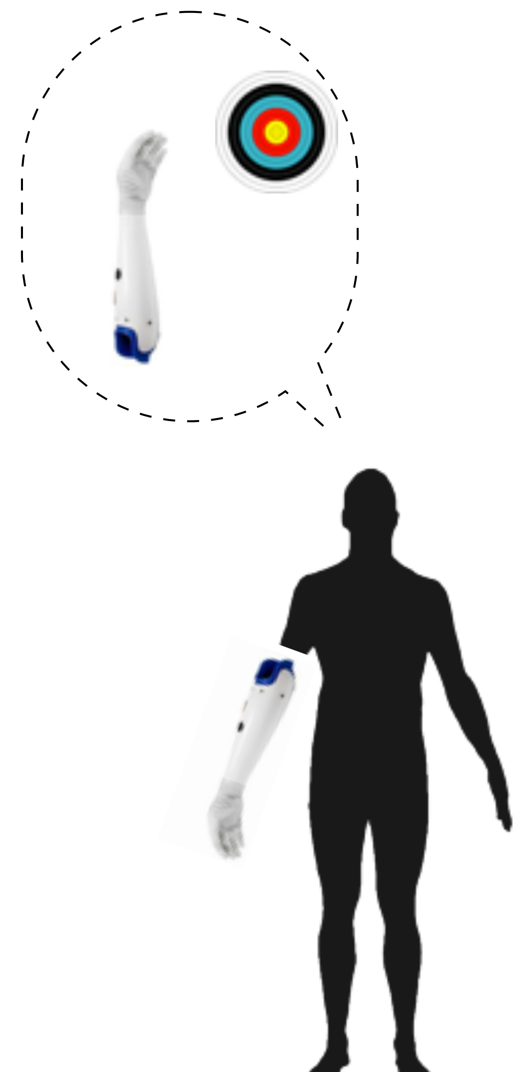
MOVEMENT DISORDERS



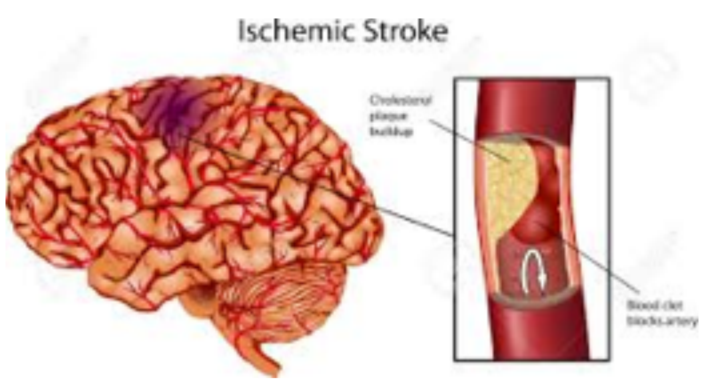


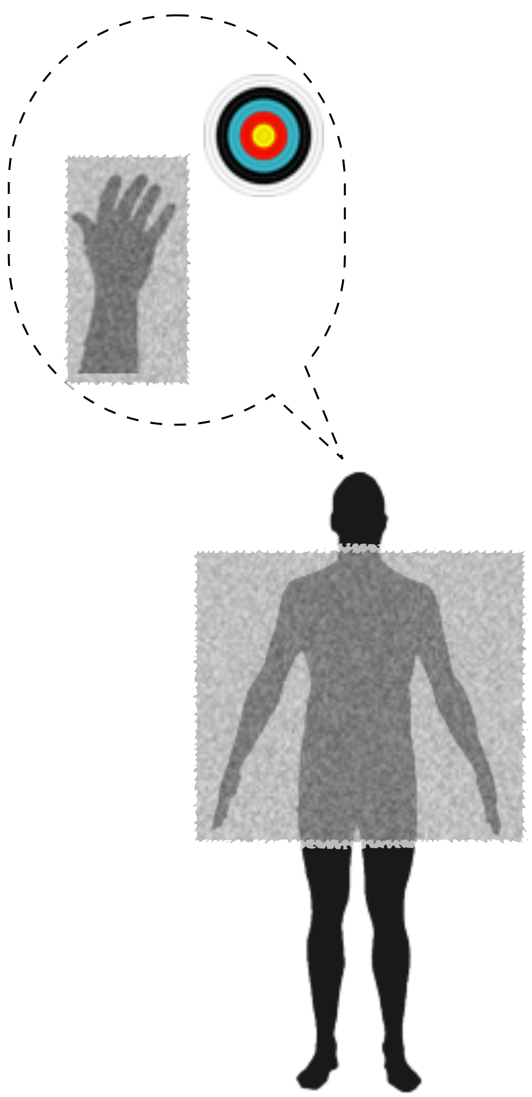






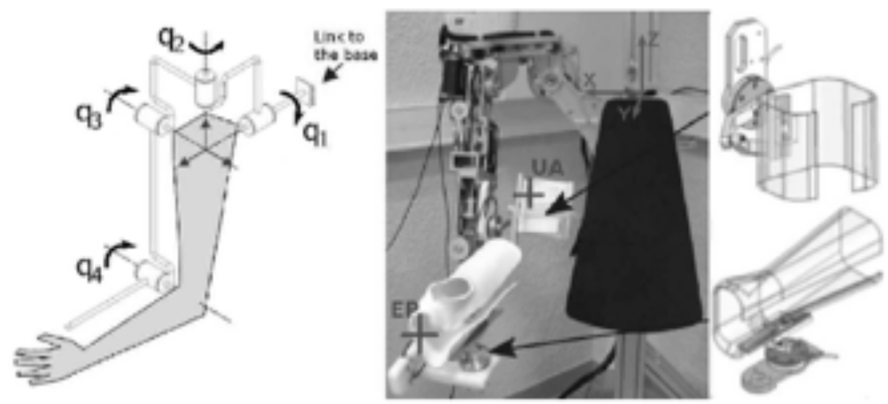
SOLUTIONS





rehabilitation

robot arm
MIT manus

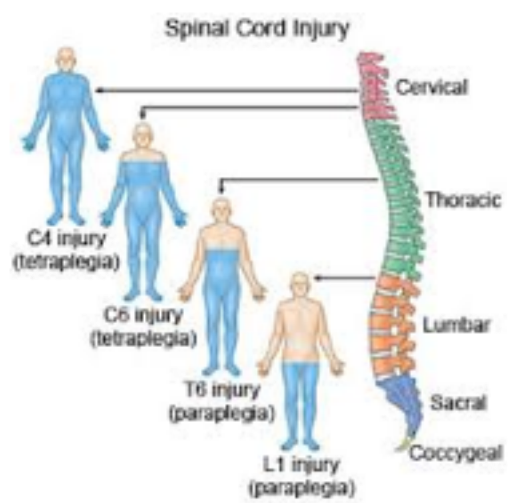


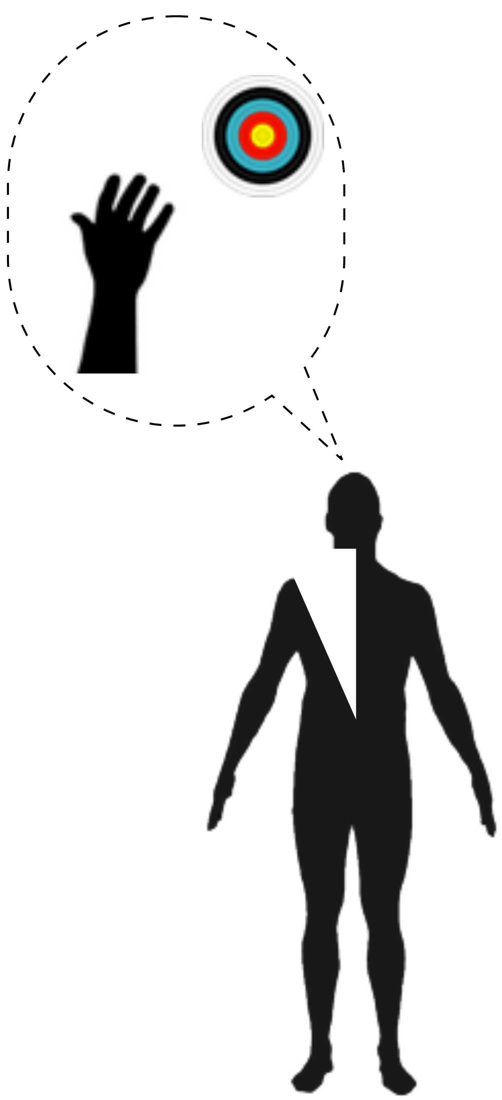
exoskeleton
ABLE (CEA-LIST)

exoskeleton
Armeo Spring

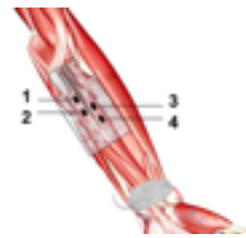
requisite – **understanding normal motor control and the effect of strokes**

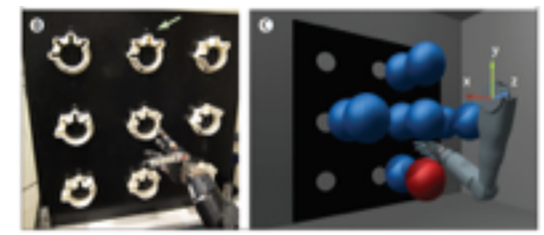
SOLUTIONS





substitution



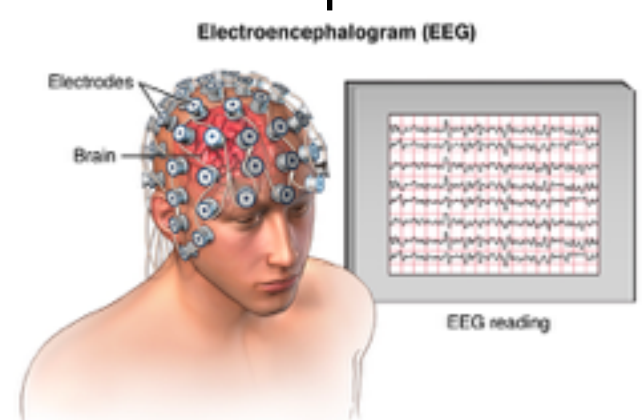


myo-electric control

brain-machine interface

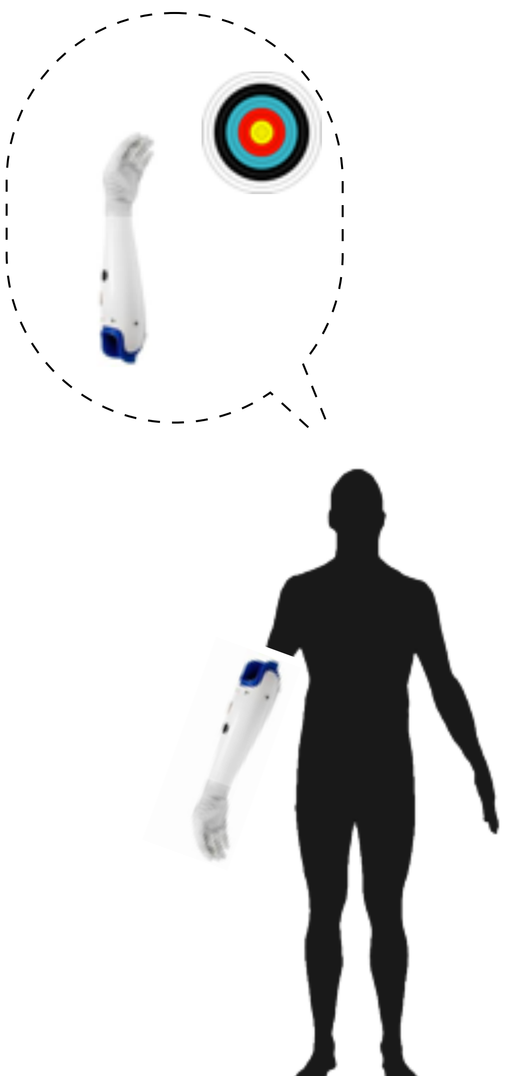
brain-computer interface

decoding?



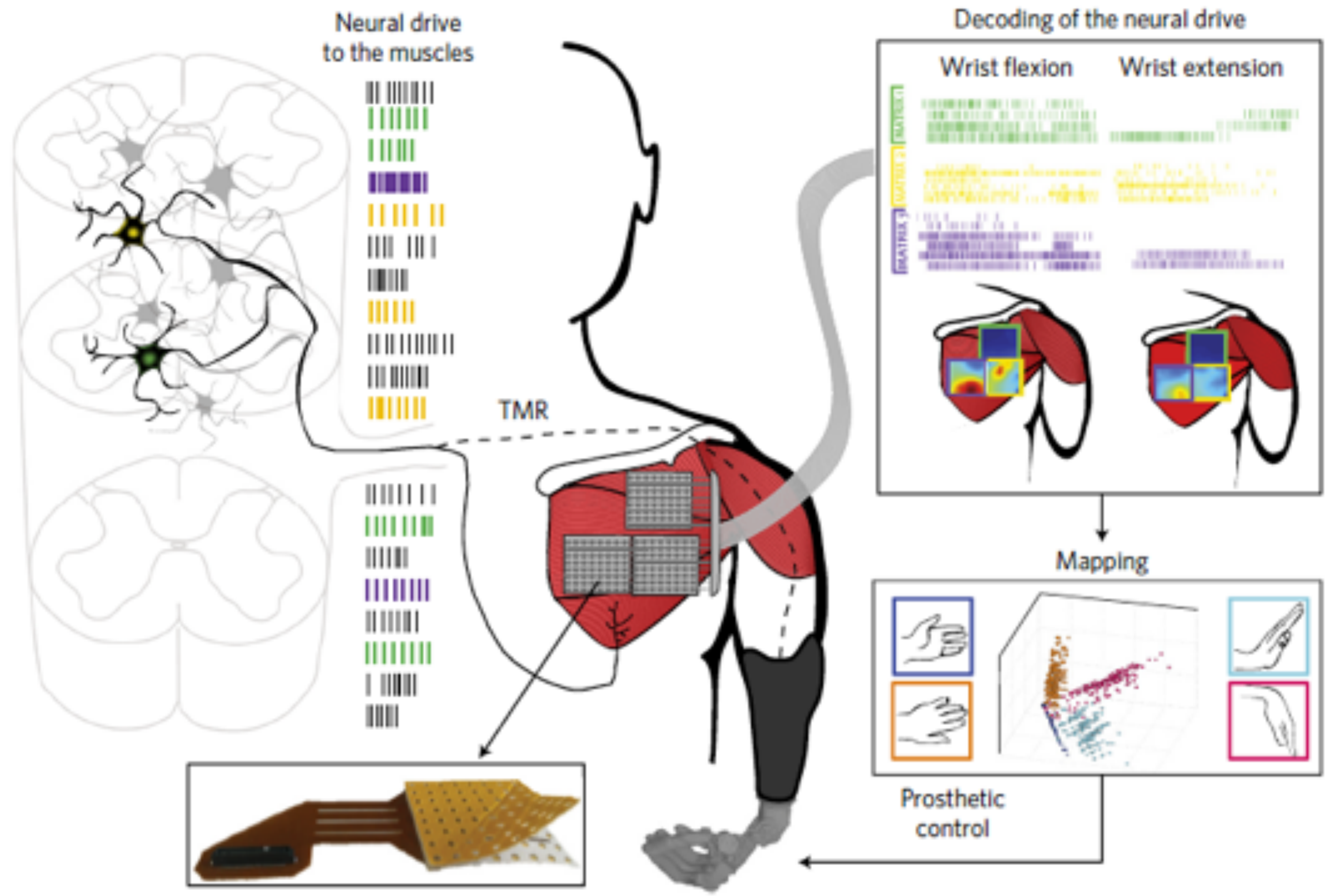
requisite – understanding the ***functional motor anatomy*** **of the brain**
– decoding neural and muscular signals

SOLUTIONS



augmentation

Interfacing spinal motor neurons in humans
(TMR = Target Muscle Reinnervation)



— Farina et al., 2017, *Nat Biomed Eng* 1:0025

requisite – **understanding the *functional motor anatomy* of the brain**
– decoding neural and muscular signals

WHAT ARE MOVEMENT DISORDERS?

Why is a complex system functioning improperly?

— e.g *broken down car* vs *the motor brain*

It could work
— no keys
— no gazoline
— no driver

It works improperly
— no breaks
— no lights
— drunk driver

It does not work
— no engine
— no tires

It could work
— no motivation
— sleep
— coma

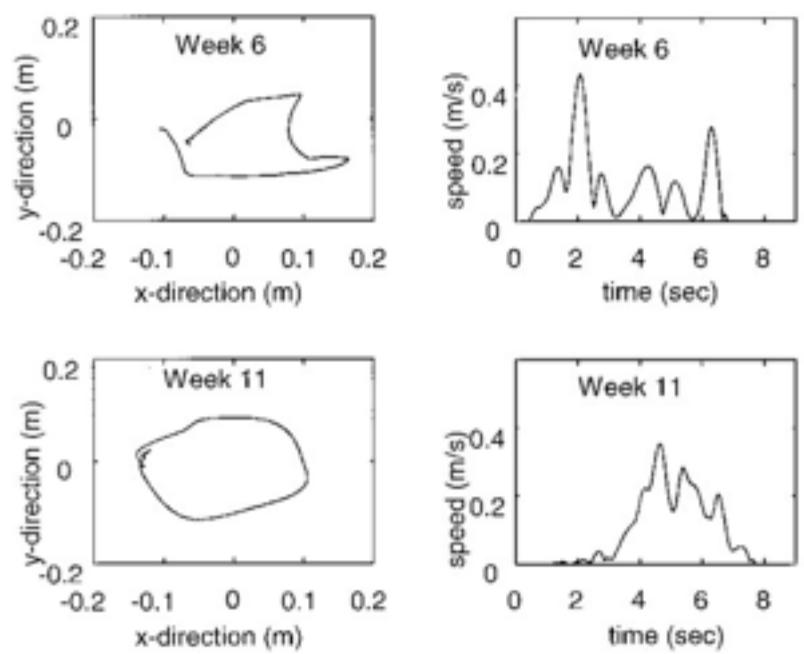
It works improperly
— disease/lesion
— blindness
— drunk driver

It does not work
— no muscle
— paralysis

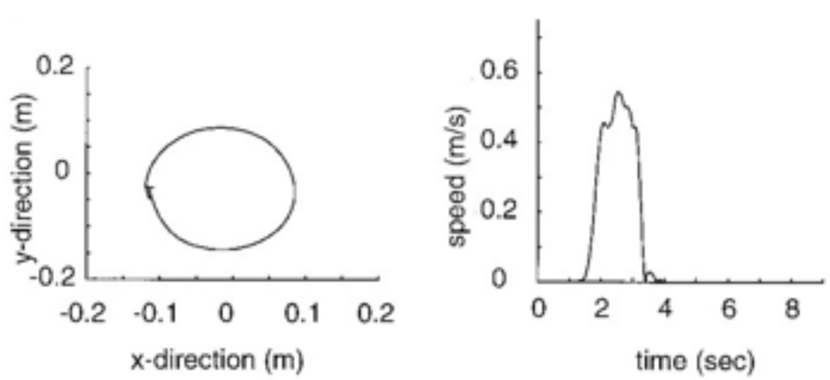
WHAT ARE MOVEMENT DISORDERS?

Directly visible

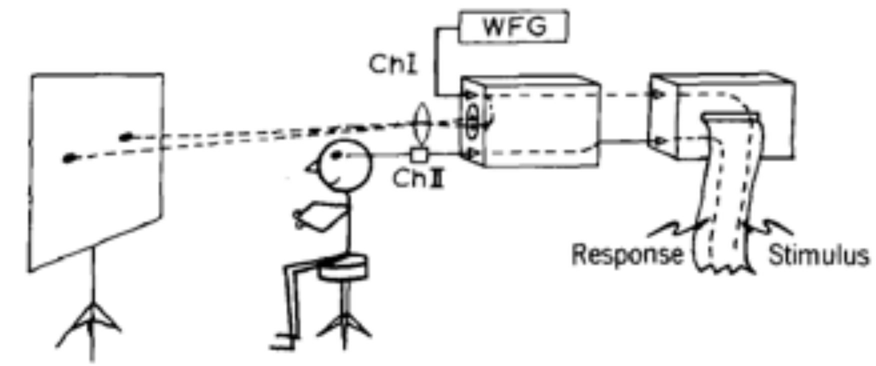
patient with stroke — *draw a circle*



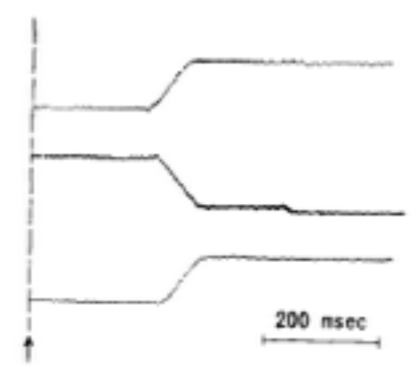
healthy control — *draw a circle*



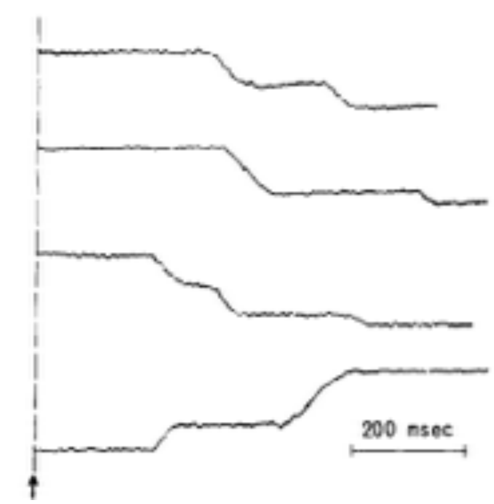
— Krebs et al., 1999, *Proc Natl Acad USA* 96:4645



healthy control — *reflexive saccades*



patient with Parkinson's disease — *reflexive saccades*



— Melvill Jones and DeJong, 1971, *Exp Neurol* 31:17

WHAT ARE MOVEMENT DISORDERS?

Paradoxical kinesia

— **Conditions in which an impaired action recovers**

environment, stimuli, instructions, psychological states

— Snijders and Bloem, 2010, *N Eng J Med* 362:e46

patients who survived the 1917–28 epidemic of encephalitis lethargica

— *Awakenings*, 1990, movie by Penny Marshall, adapted from *Awakenings*, 1973, book by Oliver Sacks

WHAT ARE MOVEMENT DISORDERS?

- **Positive vs negative symptoms**

— symptom whose content is an exaggeration of a function or is a behavior "that normal people do not have" *vs* symptom refering to a deficit or an absence of a function or signal, to a vacuum, to a state of "not having a behavior that normal people have"

- **Akinetic, hypokinetic, hyperkinetic symptoms**

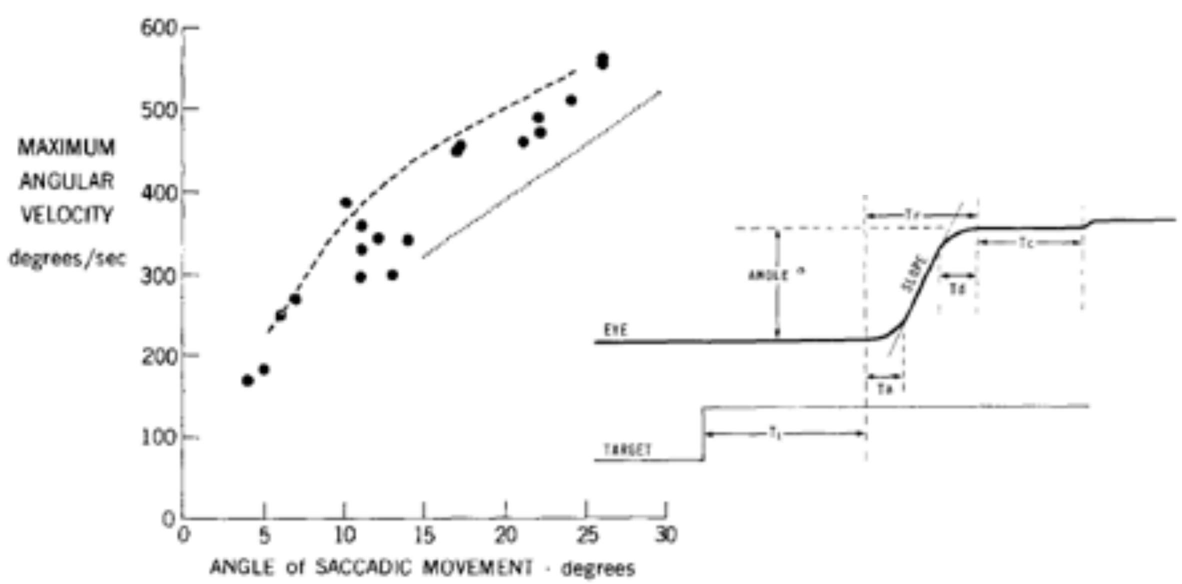
— paucity of movements, mutism
— slowness and reduced amplitude of movements
— abnormal involuntary movements (*chorea*)

— Hughlings Jackson, 1882, *Med Press Circ* 2:411

UNDERSTANDING MOVEMENT DISORDERS

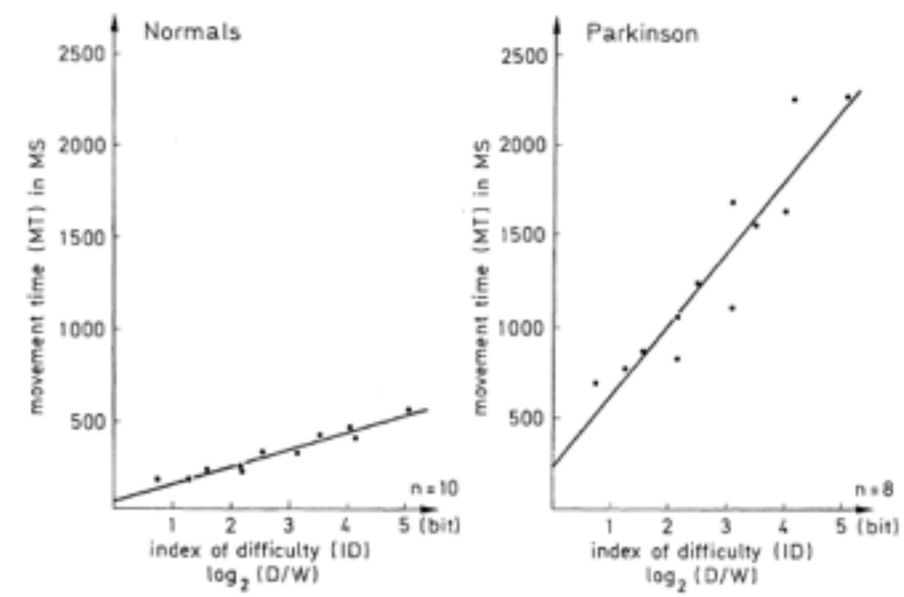
E.g. scaling laws

saccades

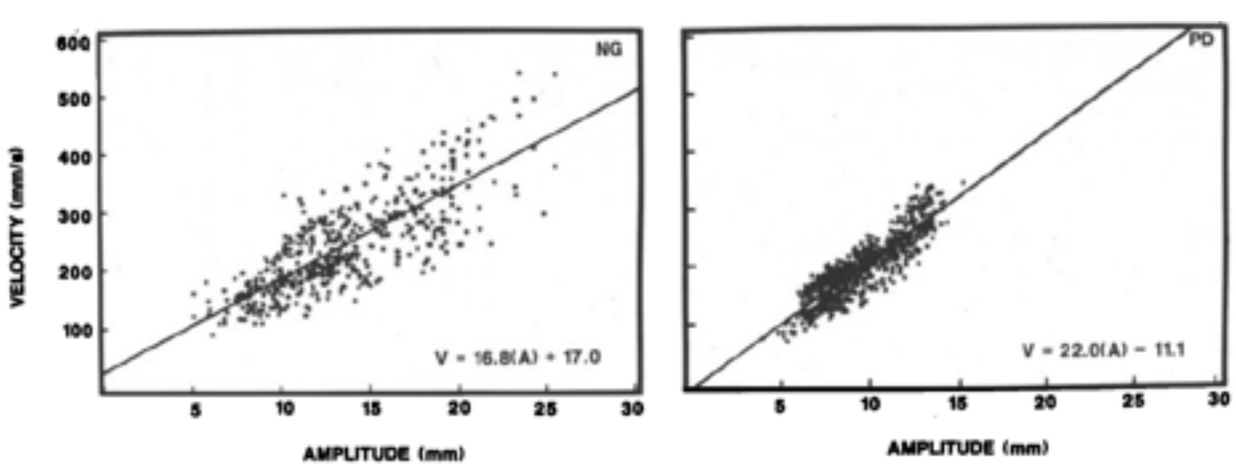


— Melvill Jones and DeJong, 1971, *Exp Neurol* 31:17

arm movements



— Hefter et al., 1988, in *Early Diagnosis and Preventive Therapy in Parkinson's Disease*, Springer



speech task — reduced range and maximum velocity of lower lip movements in PD patients concomitant with preserved speed/amplitude ratios

— Forrest et al., 1989, *J Acoust Soc Am* 85:2608

OUTLINE

1. Functional motor anatomy
spinal cord, motor cortex, cerebellum, basal ganglia

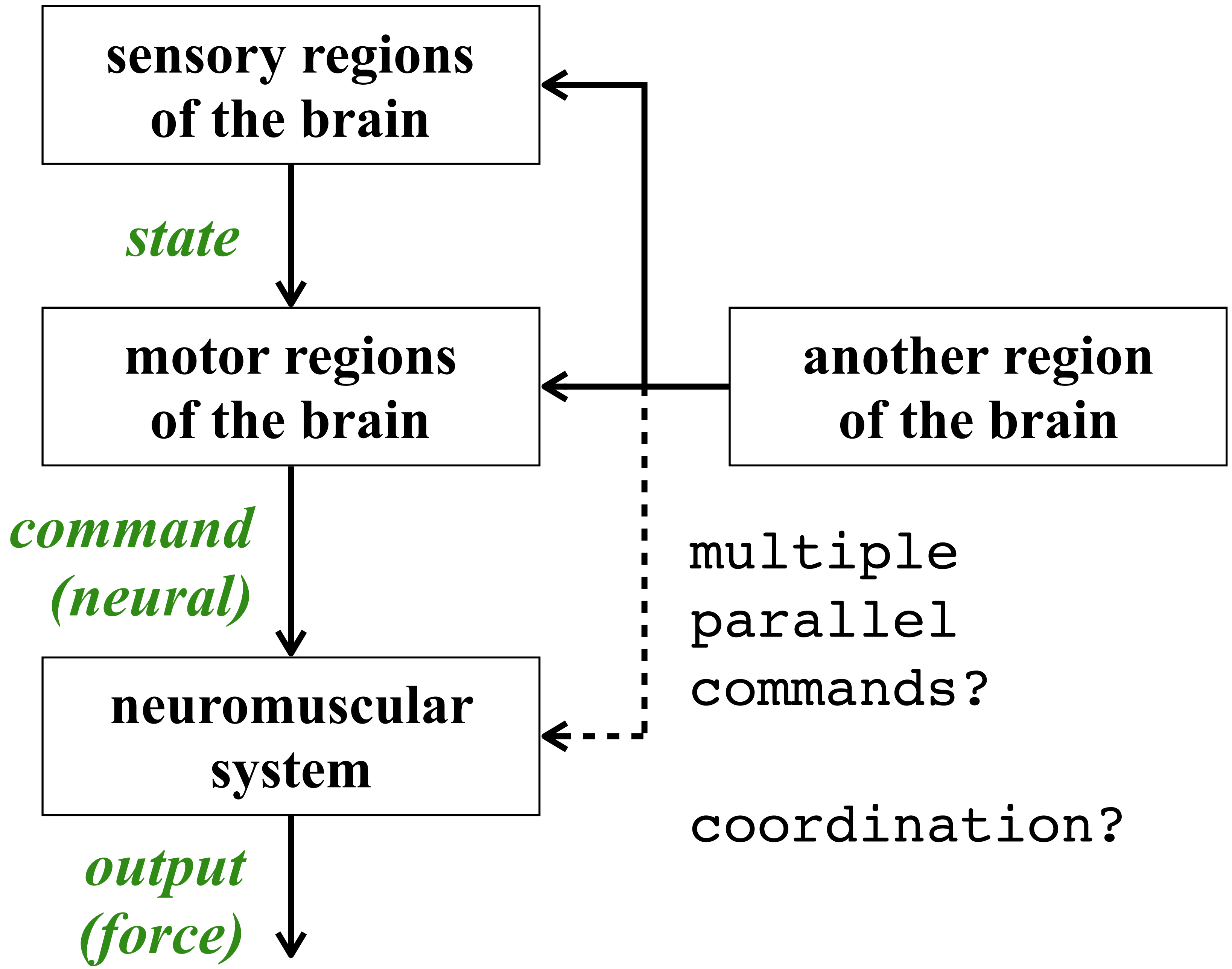
2. Methods & advanced data processing
multidimensional data analysis, time series analysis

I

1. Functional motor anatomy

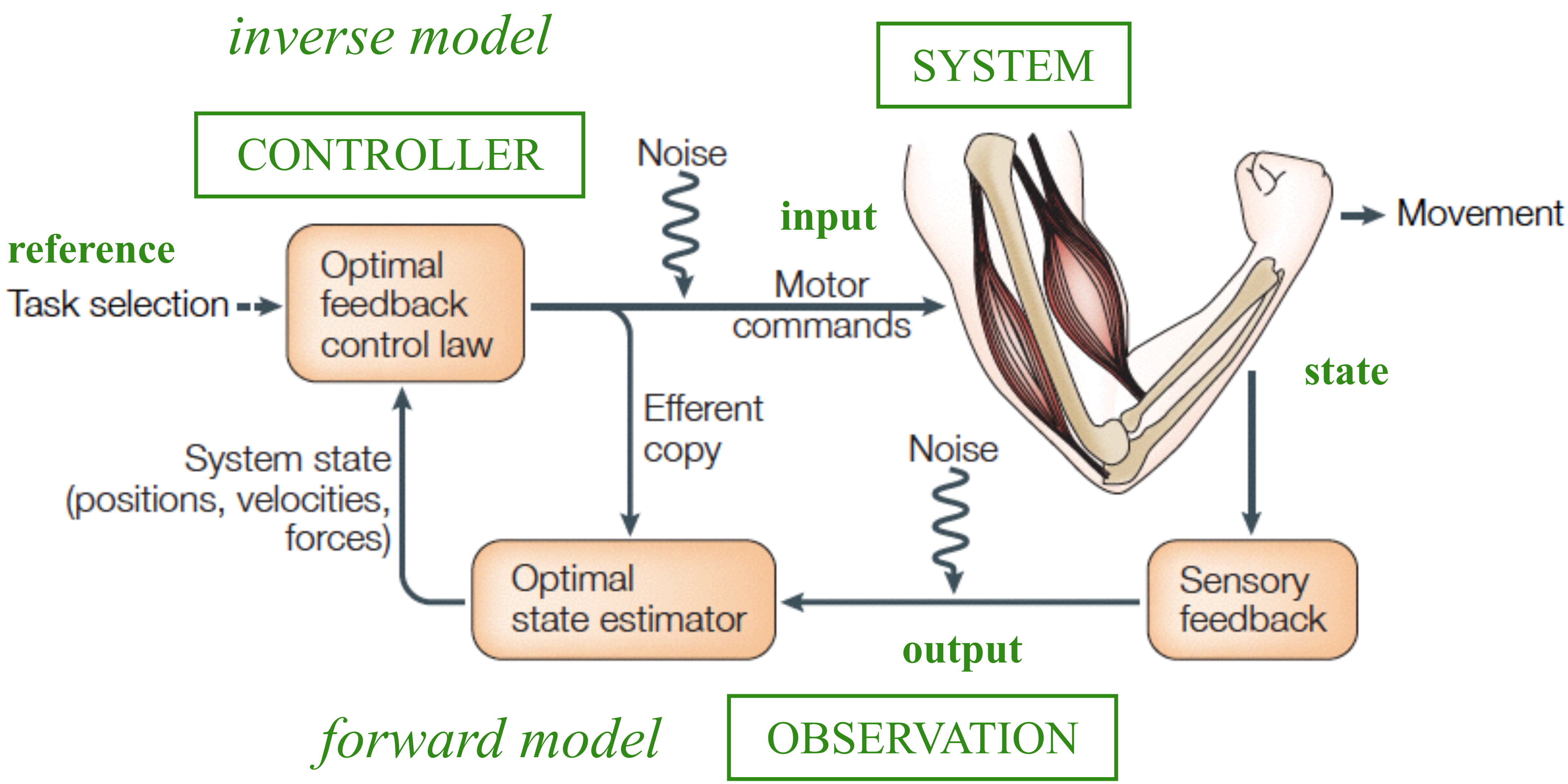
spinal cord, motor cortex, cerebellum, basal ganglia

PROBLEM



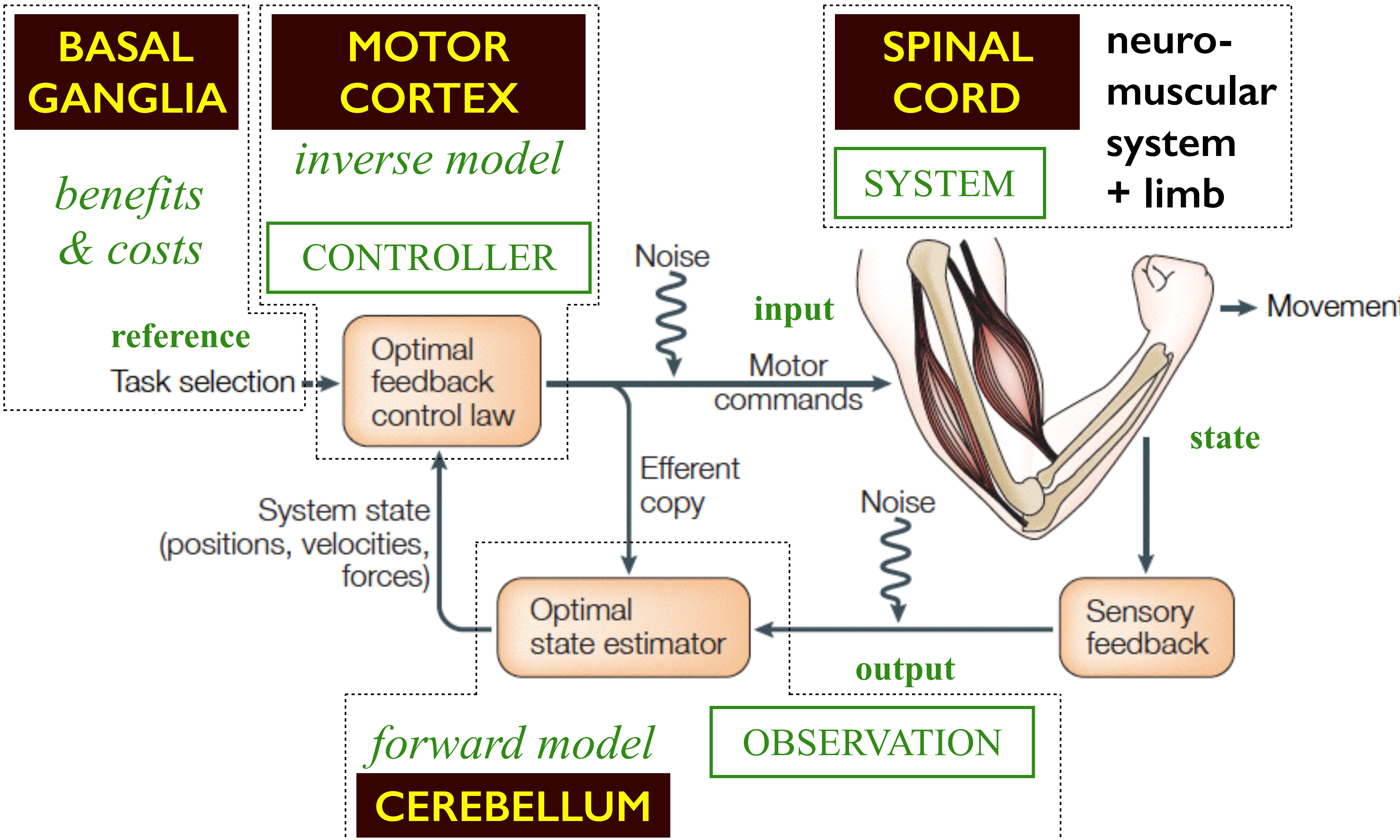
sensory regions of the brain
state
motor regions of the brain
another region of the brain
command (neural)
neuromuscular system
output (force)
multiple parallel commands?
coordination?

COMPUTATIONAL ARCHITECTURE



— Scott, 2004, *Nat Rev Neurosci* 5:534

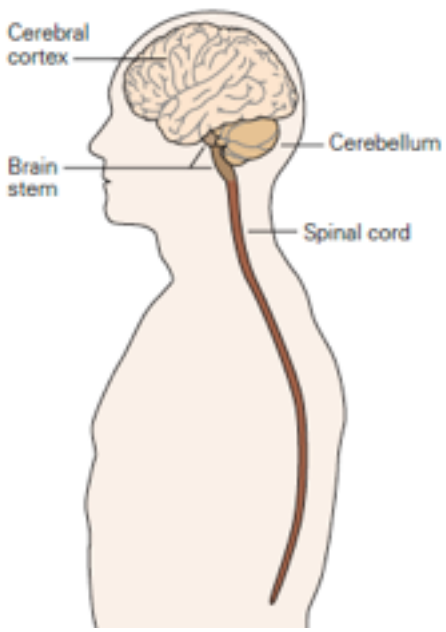
COMPUTATIONAL NEUROANATOMY



— Scott, 2004, *Nat Rev Neurosci* 5:534

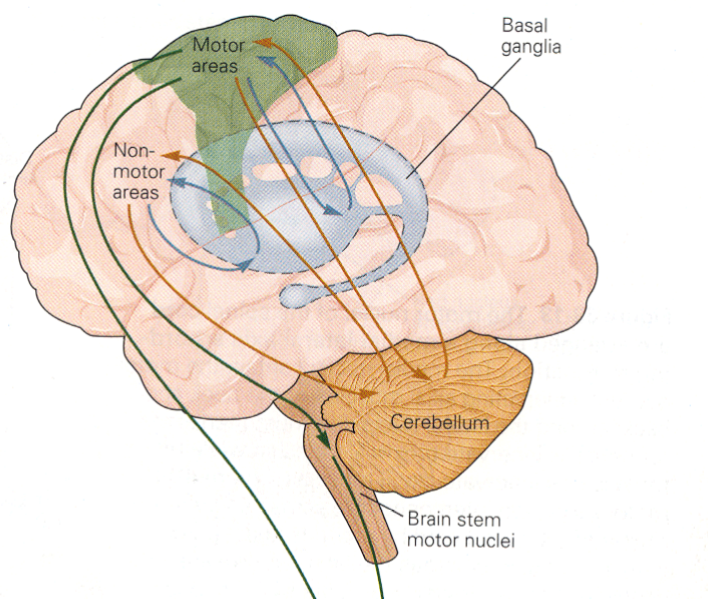
— Shadmehr and Krakauer, 2008, *Exp Brain Res* 185:359

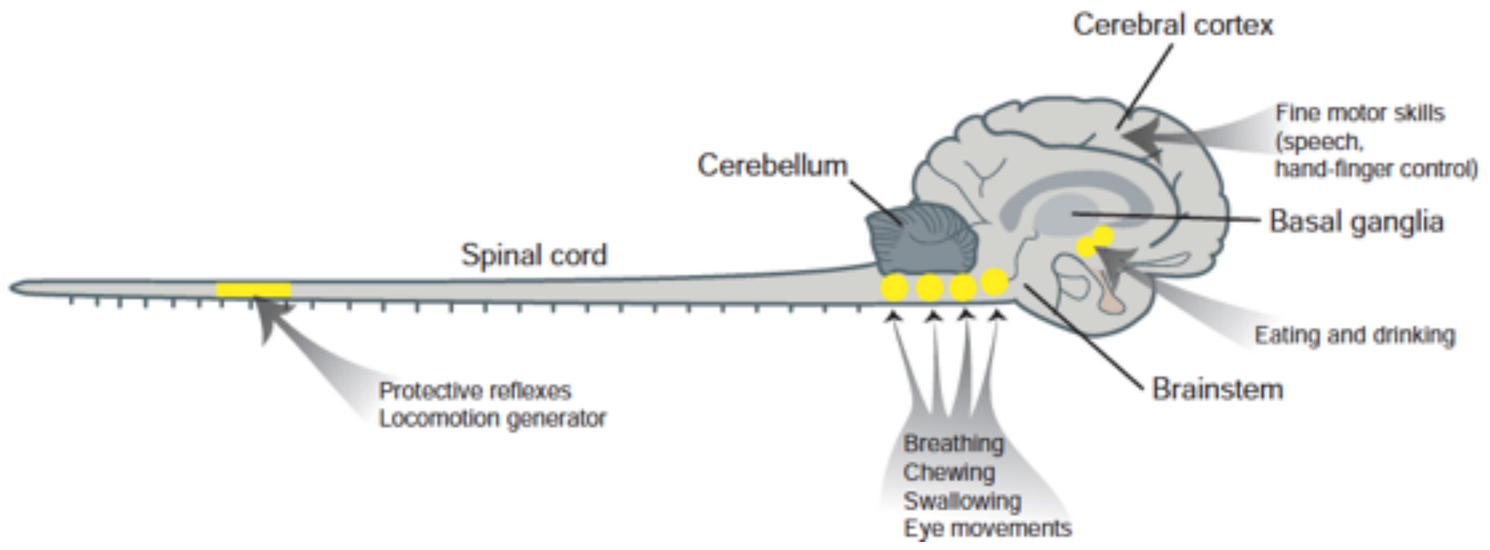
CENTRAL NERVOUS SYSTEM



central nervous system	$86\text{x}10^9$ neurons
cerebellum	$69\text{x}10^9$ neurons
cerebral cortex	$16\text{x}10^9$ neurons
motor cortex	$\sim 10^9$ neurons
basal ganglia	$\sim 10^7$ neurons
spinal cord	$\sim 10^9$ neurons

— Herculano-Houzel, 2009, *Front Hum Neurosci* 3:31





SPINAL CORD

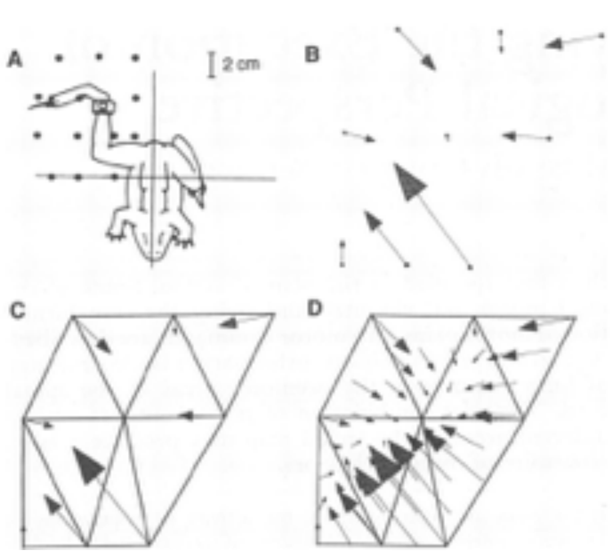
• **Minimal view**
— first relay for somatic sensory information
— last station for motor processing
— monosynaptic reflexes (e.g. *stretch reflex*)
— polysynaptic protective reflexes (e.g. *flexion reflex*, *wiping reflex in the spinal frog*)
— central pattern generator (e.g. *stepping*)

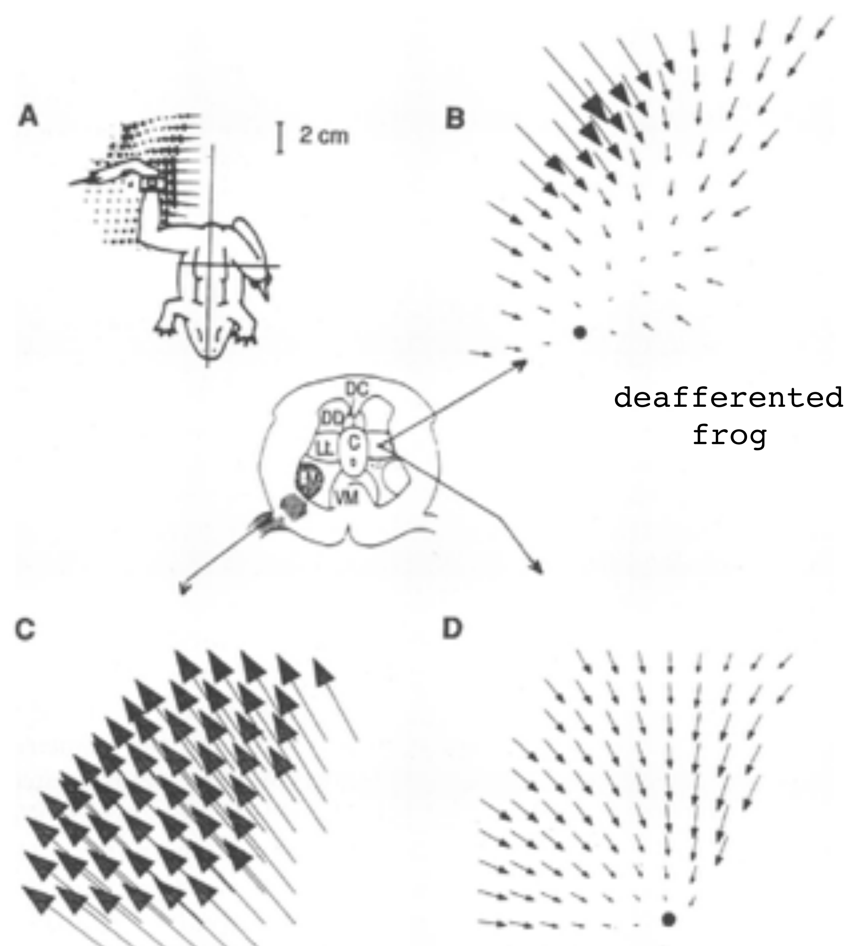
• **More « active » view**
— coordination (e.g. *wiping reflex*)
— transformation of kinematic representations into dynamics (in the framework of the equilibrium point theory)
— postural force fields

SPINAL CORD

Microstimulation in spinal frogs

position control and equilibrium point mechanisms in the spinal cord

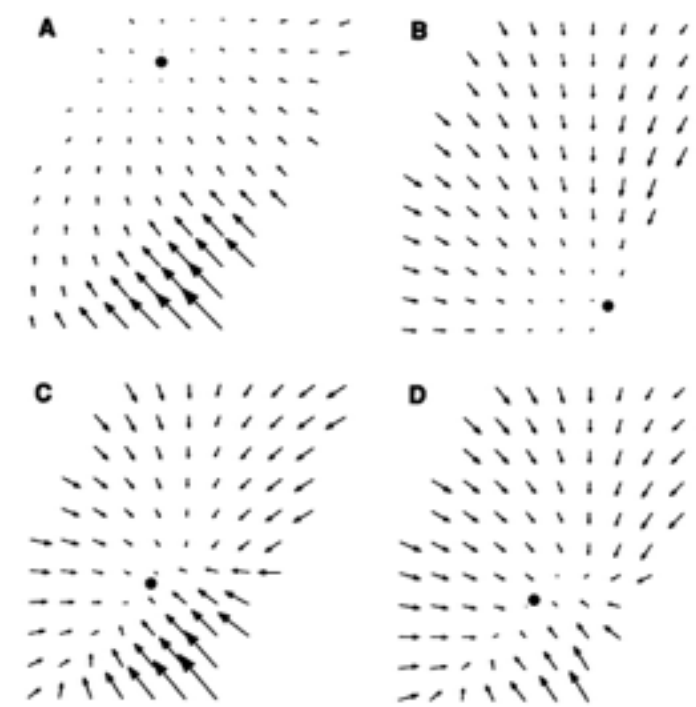




parallel force field
for stimulation of a MN

convergent force fields
derived from activation
of *interneurons*

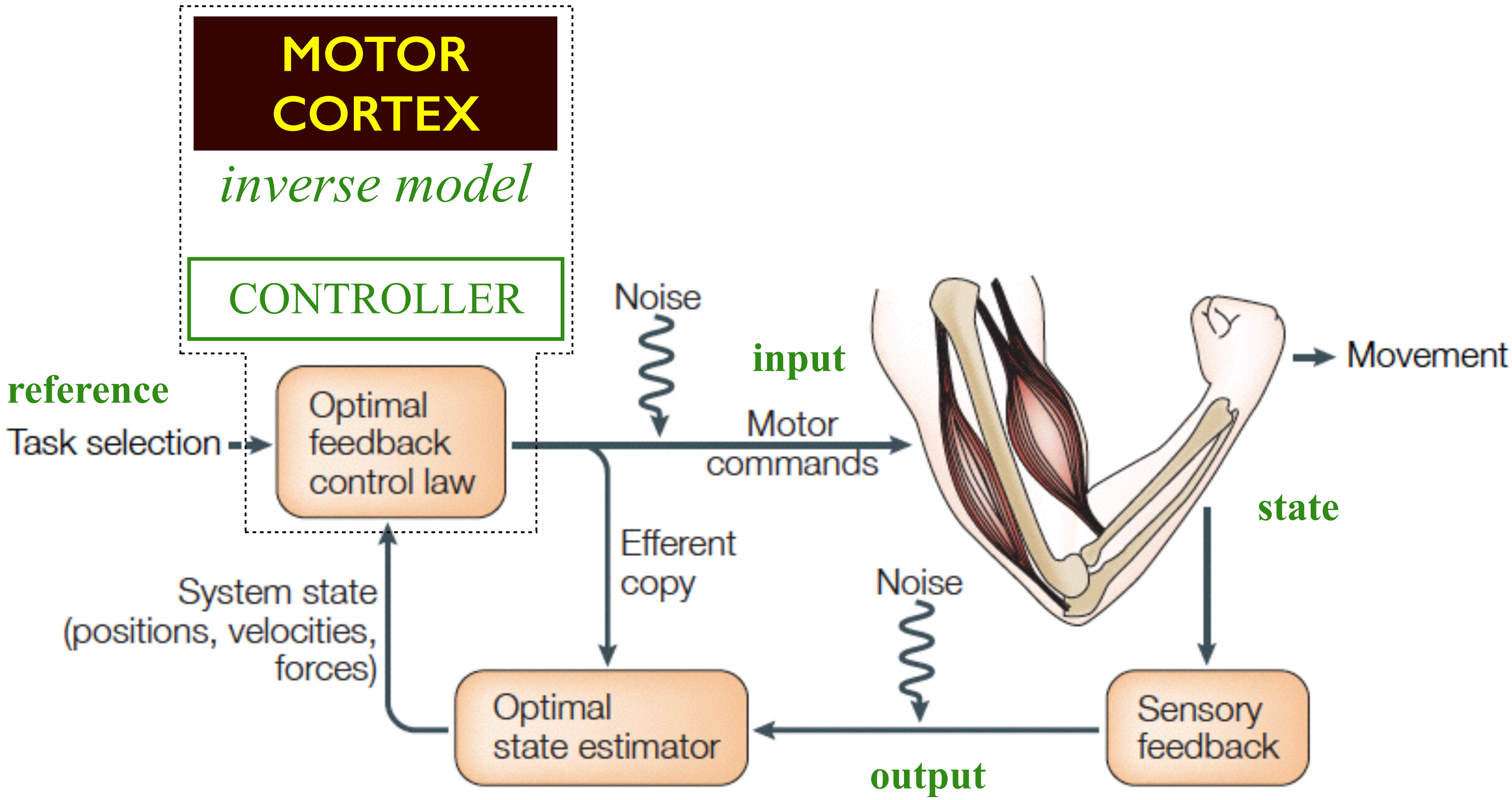
combination of
multiple stimuli



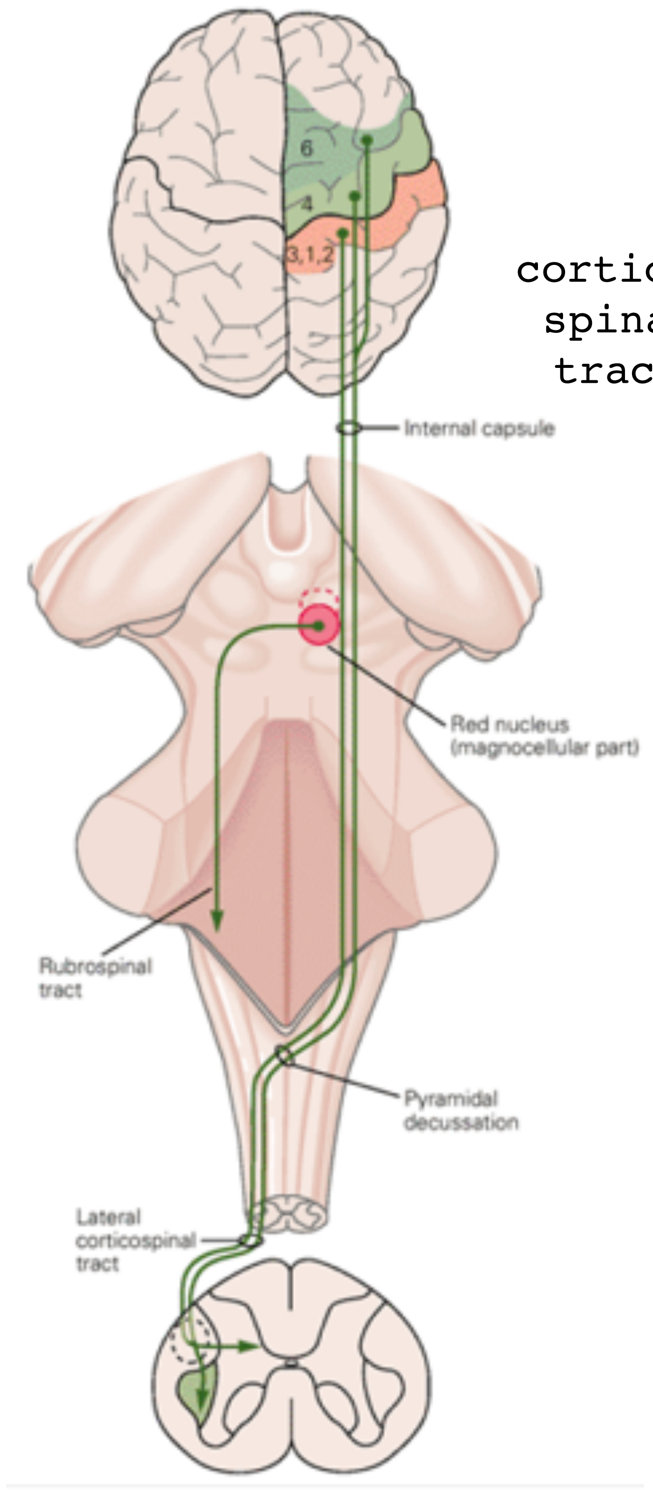
predicted A+B   actual A+B

— Bizzi et al., 1991, *Science* 253:287

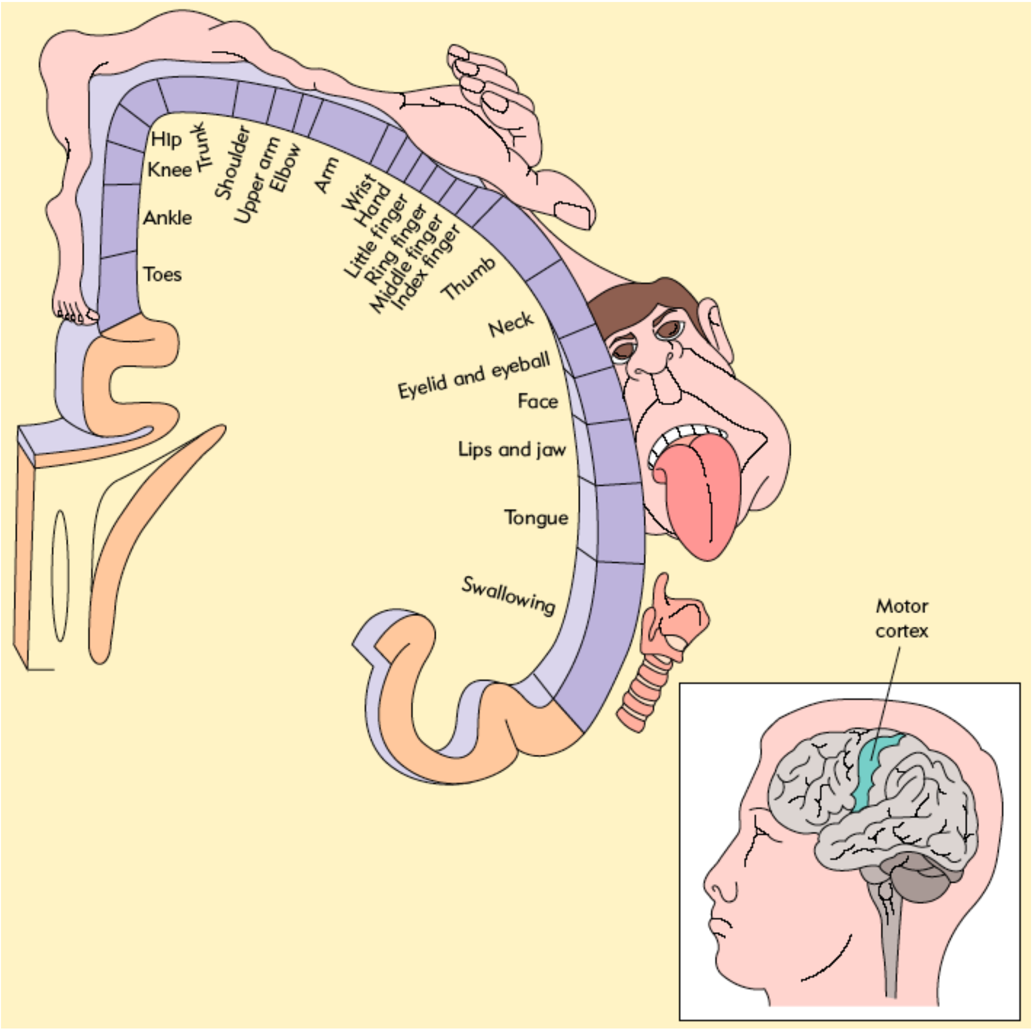
COMPUTATIONAL NEUROANATOMY



MOTOR CORTEX

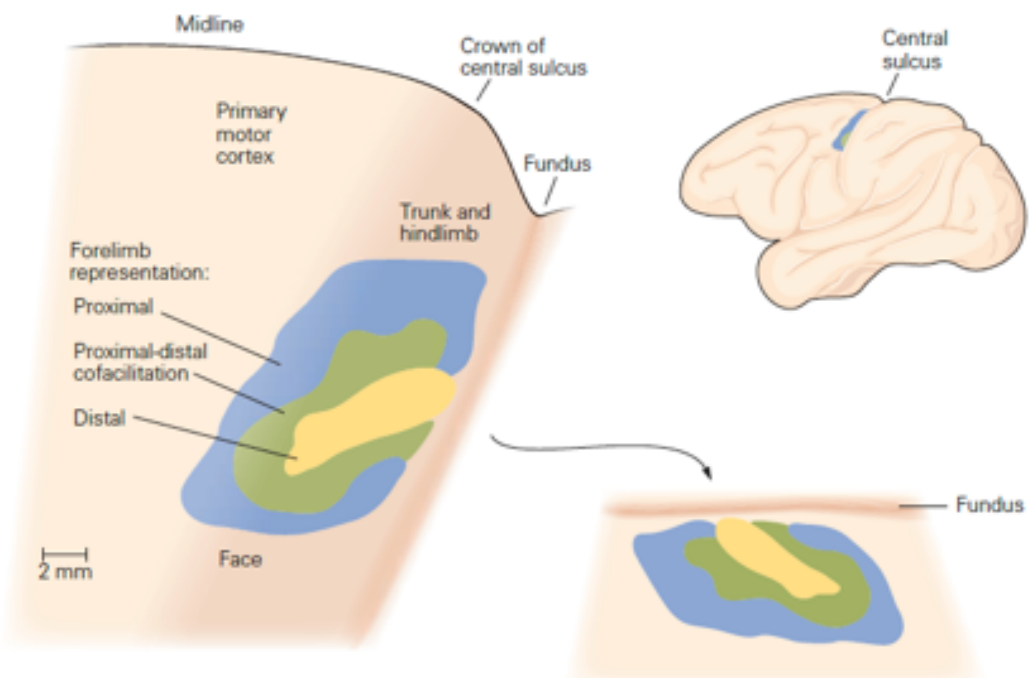


cortico-
spinal
tract

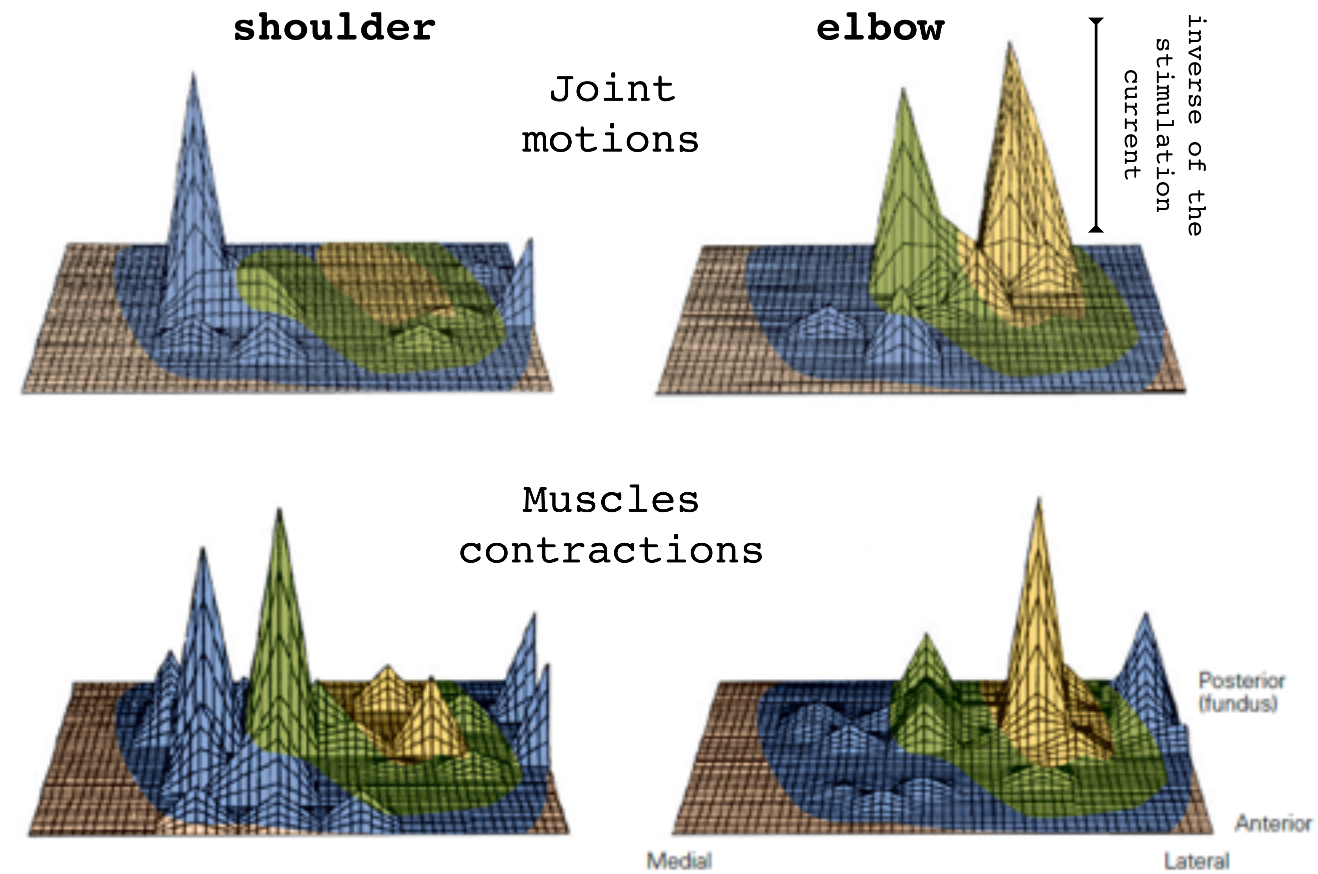


MOTOR CORTEX — PHYSIOLOGY

Intracortical microstimulation



stimulus-triggered averaging
of EMG activity



deltoid

extensor carpi radialis

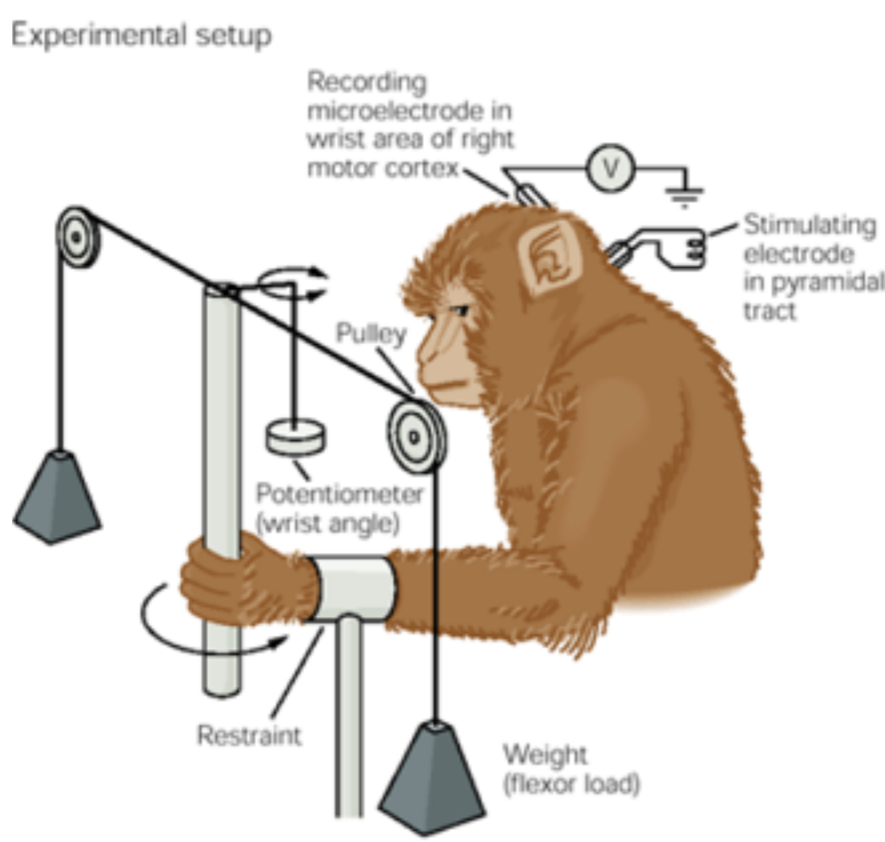
— Park et al., 2001, *J Neurosci* 21:2784

— Humphrey & Tanji, 1991, in *Motor Control: Concepts and Issues*, Wiley

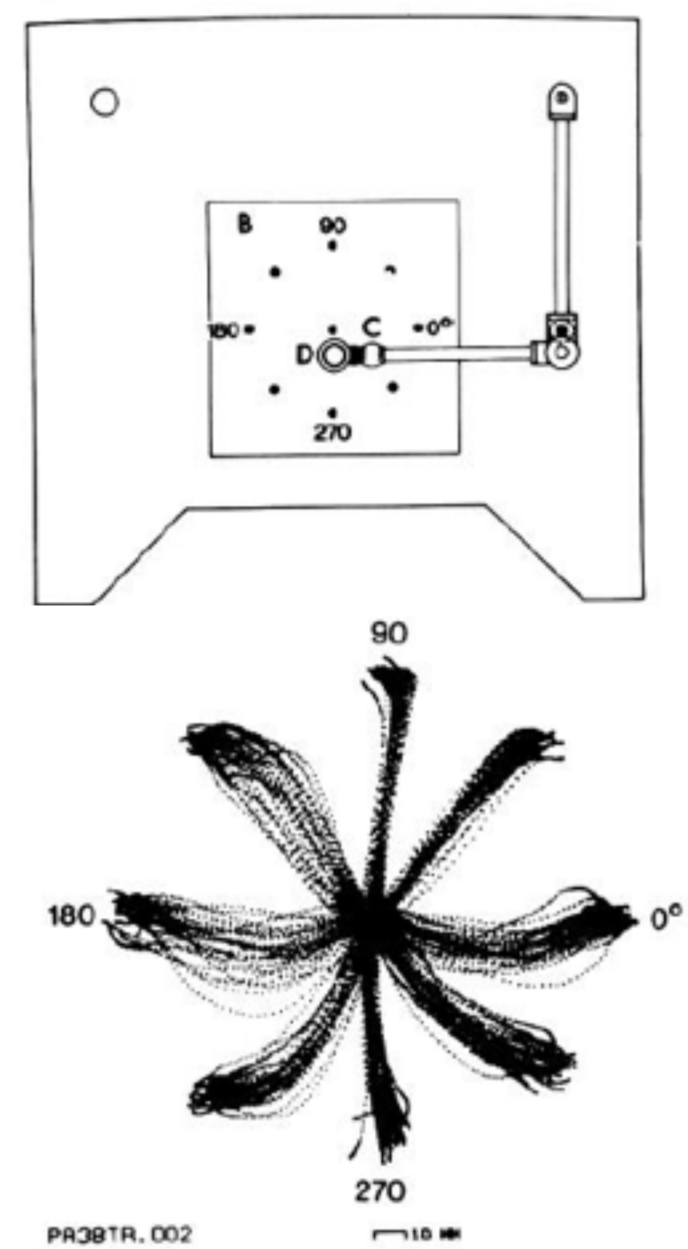
MOTOR CORTEX — PHYSIOLOGY

Reminder

force, movement direction



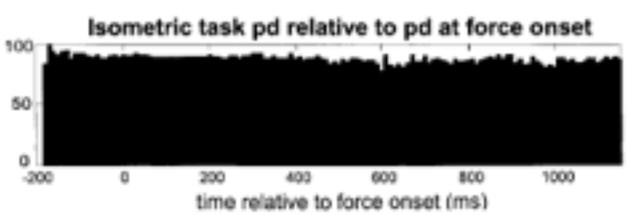
— Evarts, 1968, *J Neurophysiol* 31:14

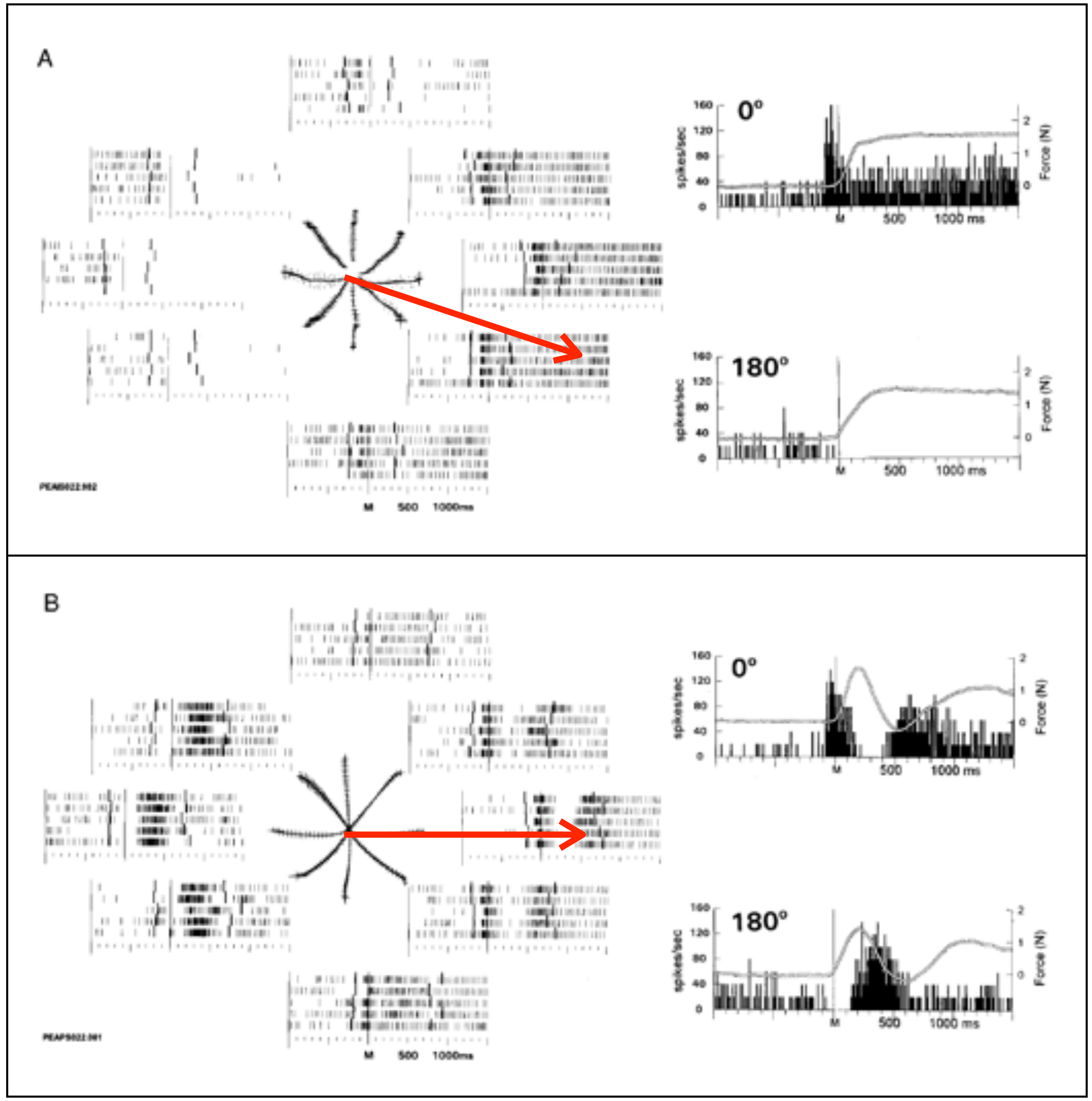


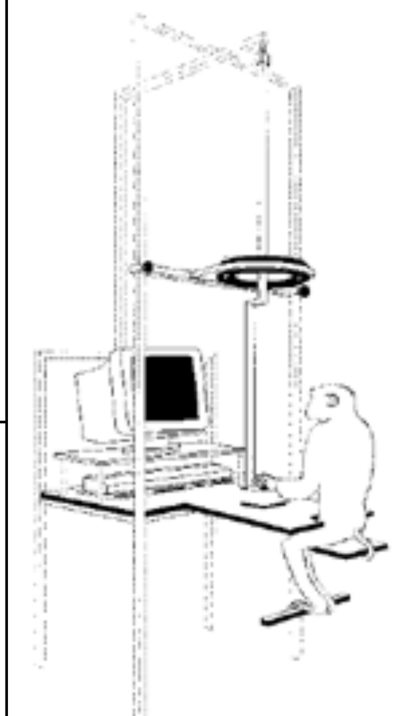
— Georgopoulos et al., 1982, *J Neurosci* 2:1527

MOTOR CORTEX — PHYSIOLOGY

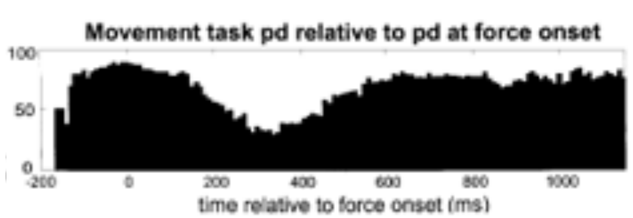
Isometric







Movement

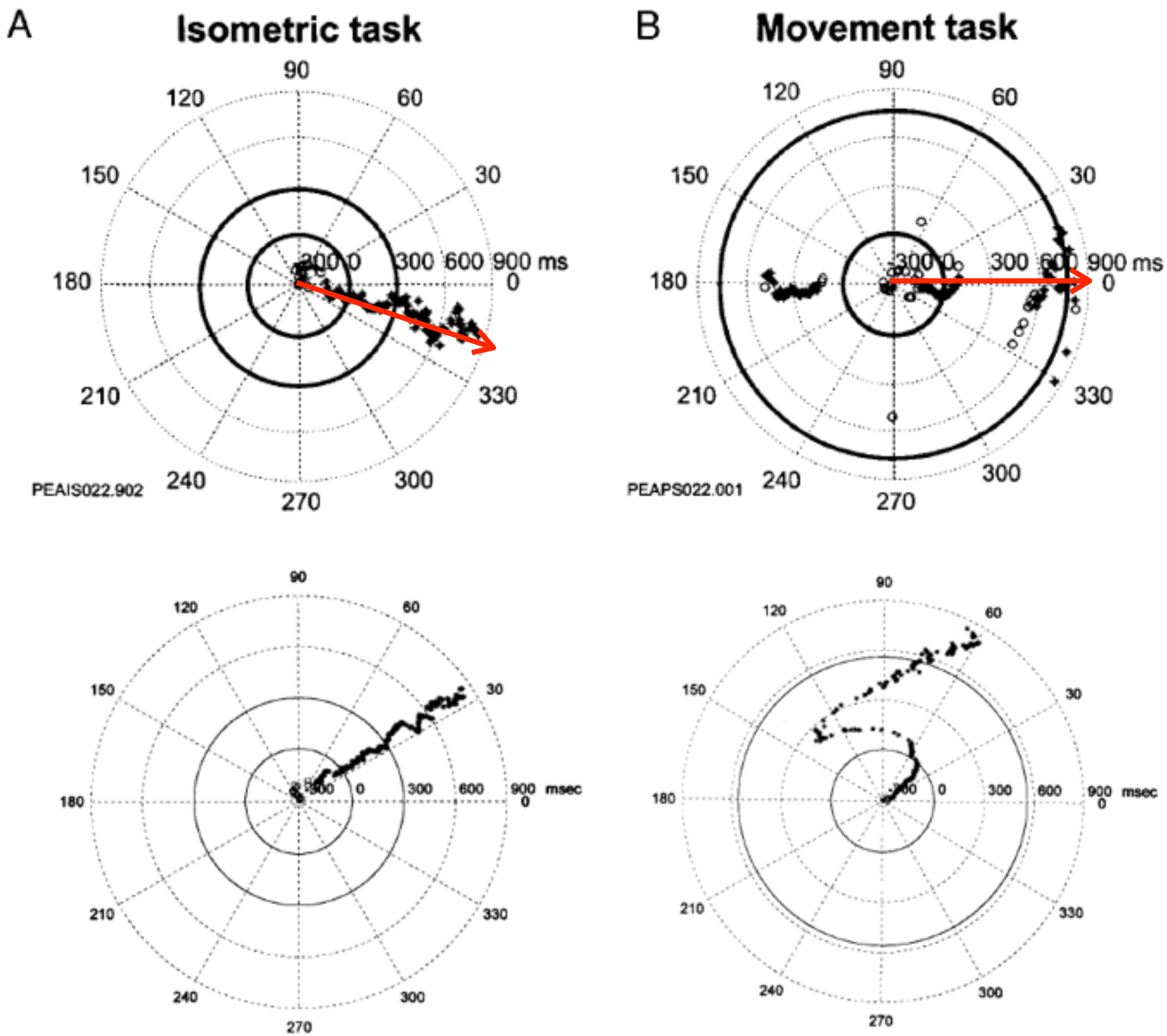


— Sergio & Kalaska, 1998, *J Neurophysiol* 80:1577

MOTOR CORTEX — PHYSIOLOGY

Neuron

Muscle

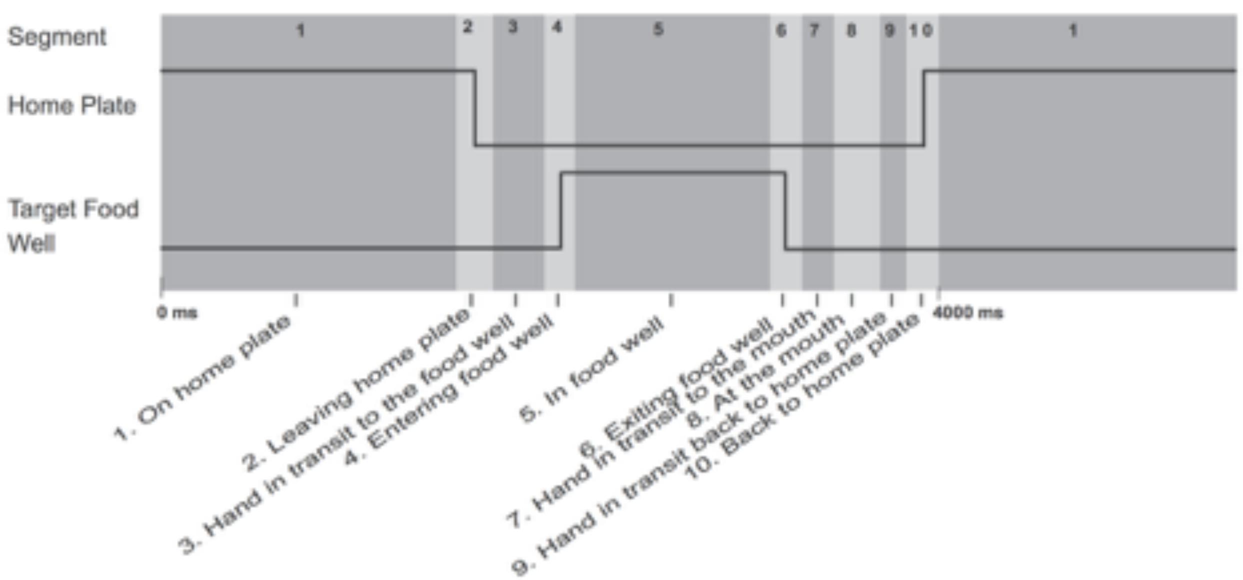


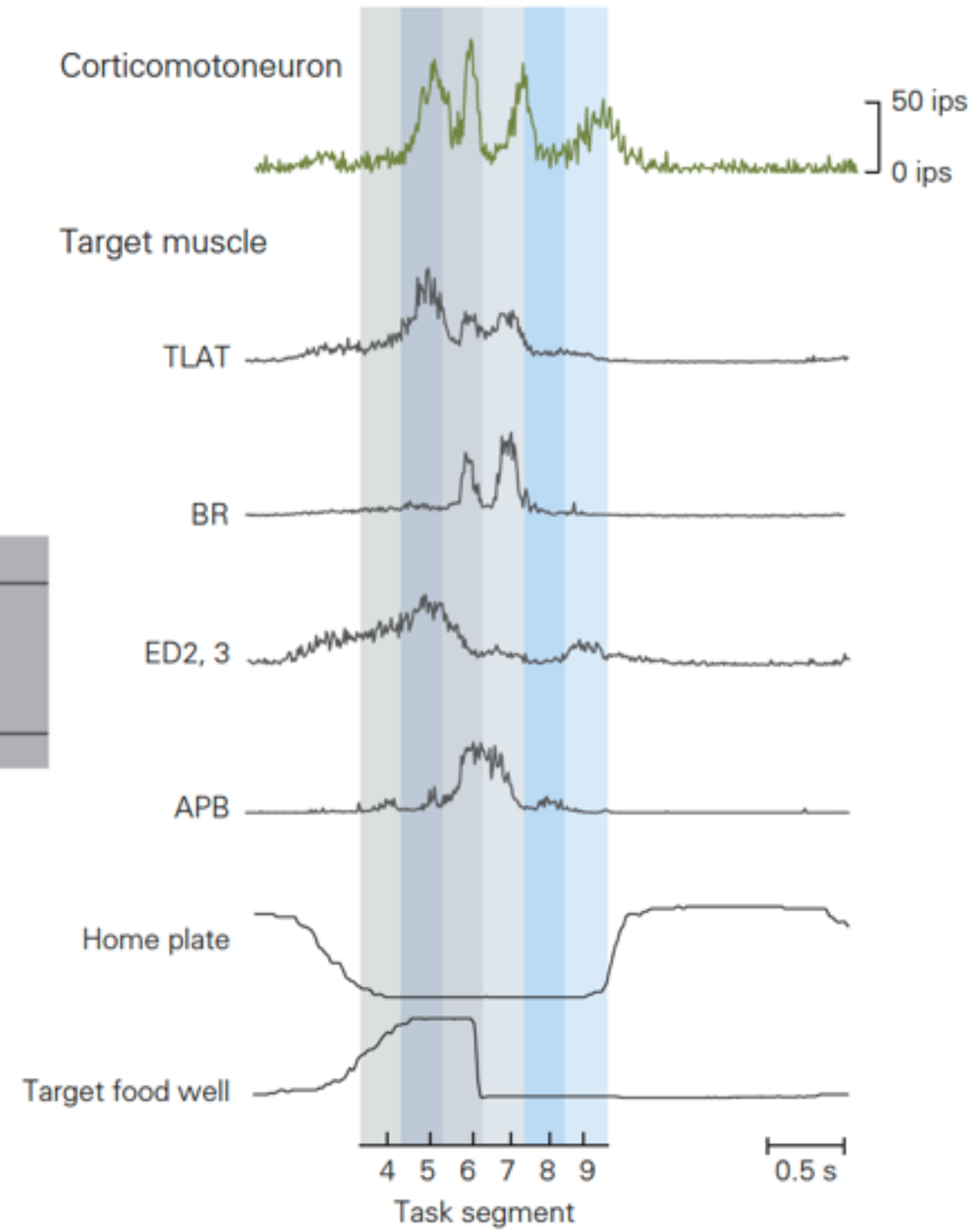
— Sergio & Kalaska, 1998, *J Neurophysiol* 80:1577

MOTOR CORTEX — PHYSIOLOGY

Muscle-like activity

reach-and-grasp movements to retrieve food from a small well

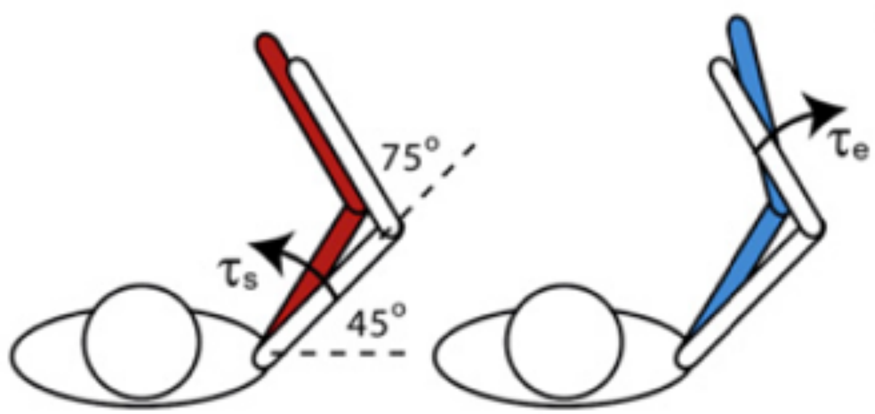




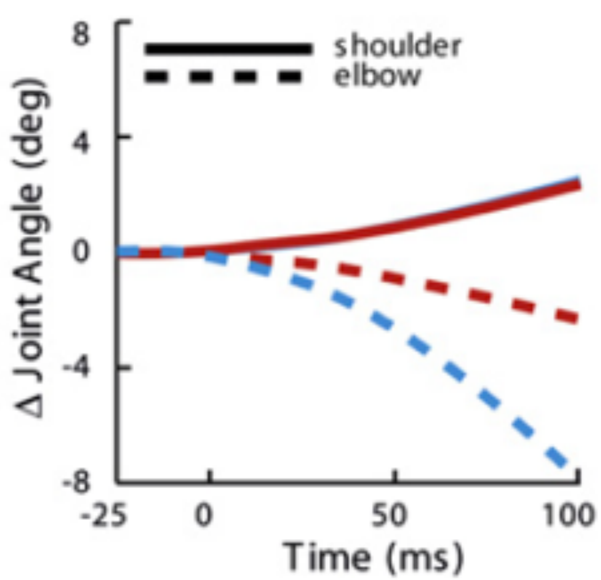
— Griffin et al., 2008, *J Neurophysiol* 99:1169

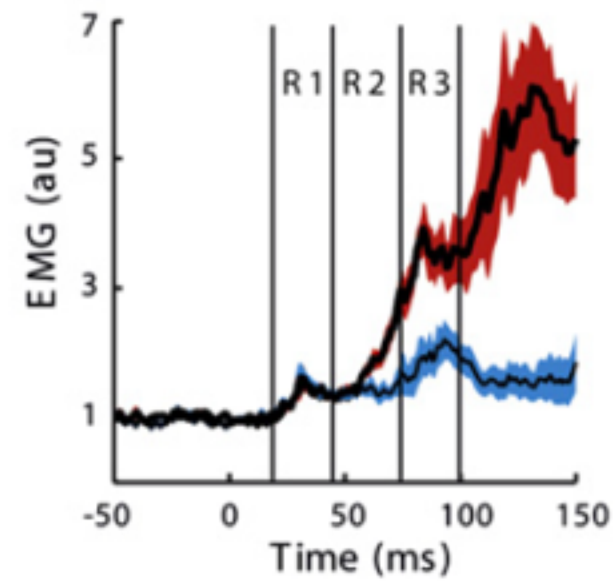
INTERNAL MODEL IN REFLEXES

`single-joint torque perturbations that induce equal shoulder motion but different elbow motion in a postural task`



long-latency activity in the shoulder extensor muscle does not depend only on stretching of the muscle

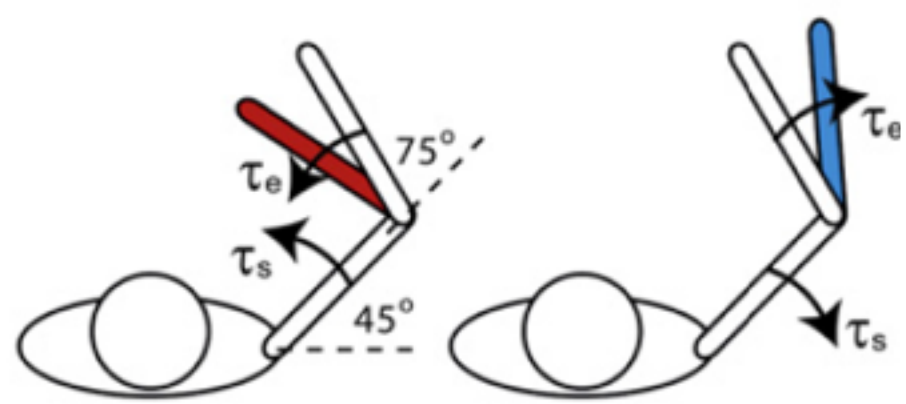




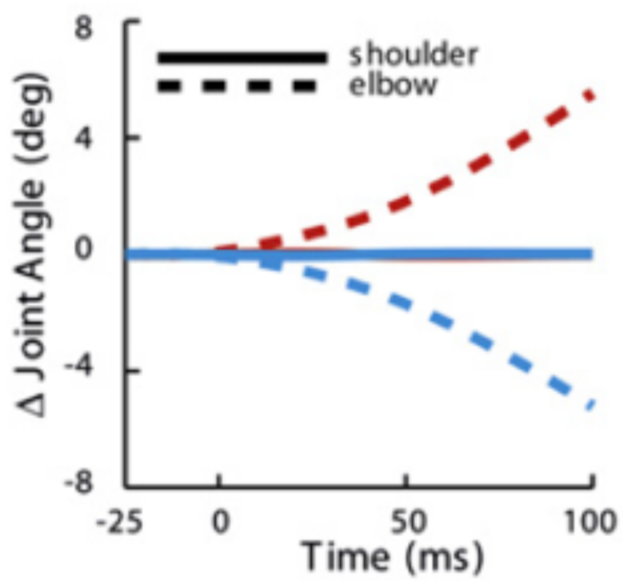
— Kurtzer et al., 2008, *Curr Biol* 18:449

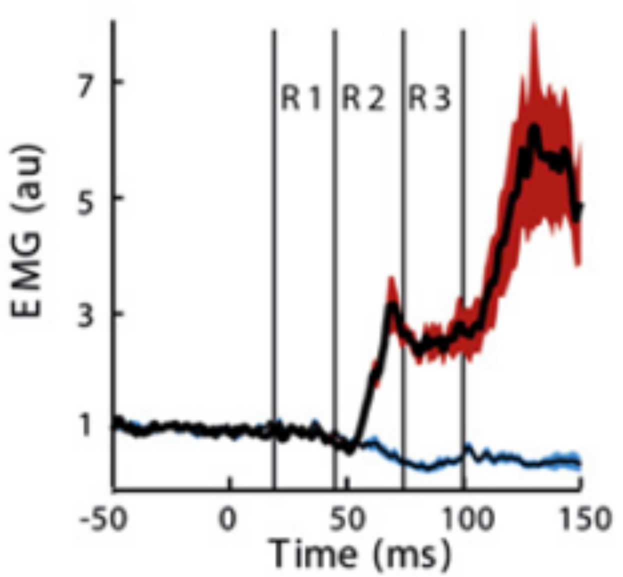
INTERNAL MODEL IN REFLEXES

multi-joint torque perturbations that induce large elbow motion and negligible shoulder motion in a postural task



long-latency activity in the shoulder extensor muscle does not depend only on stretching of the muscle

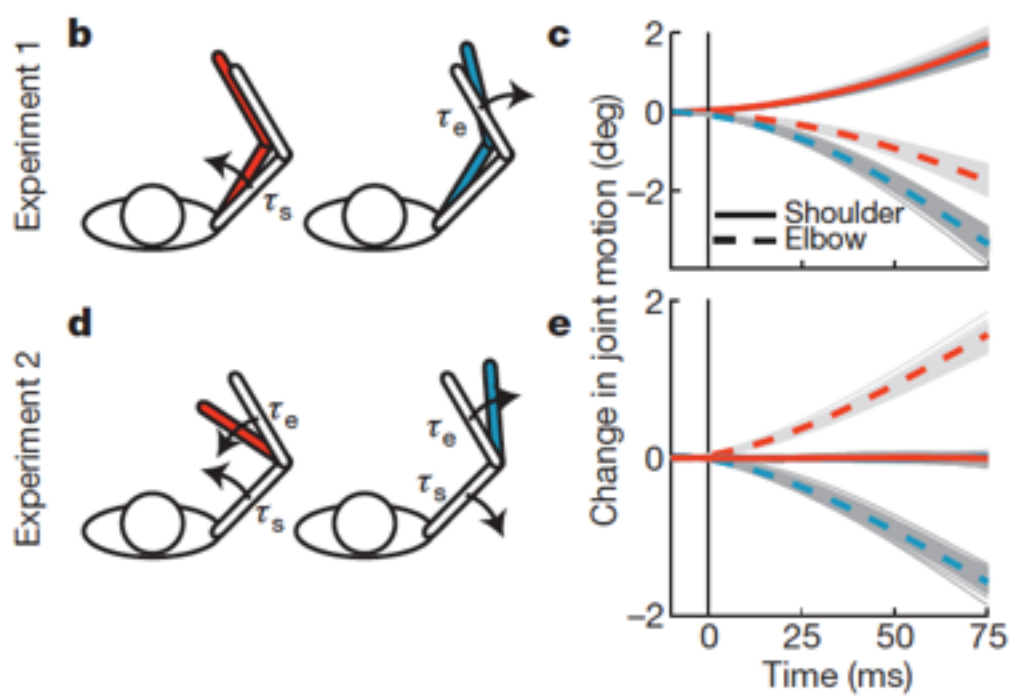


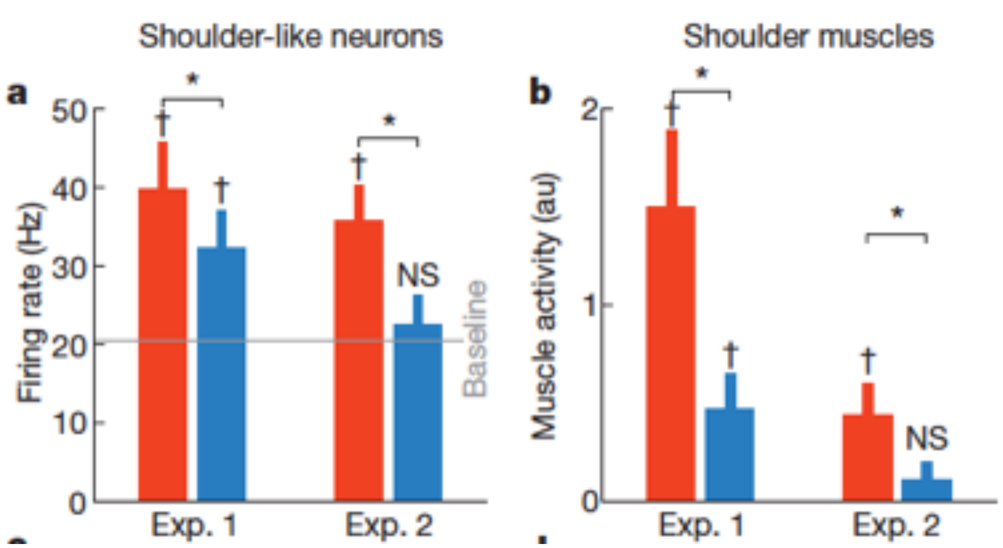


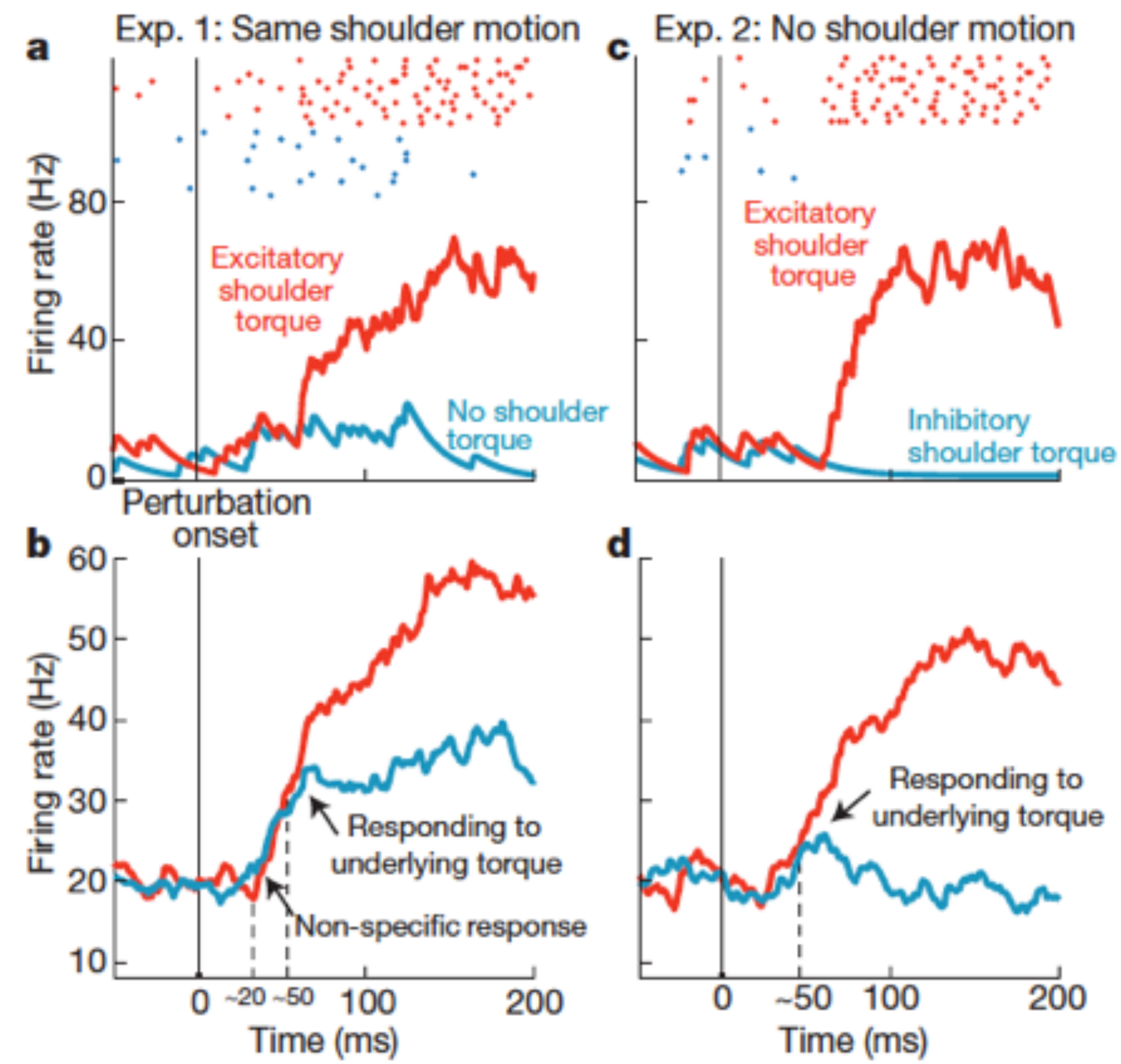
— Kurtzer et al., 2008, *Curr Biol* 18:449

MOTOR CORTEX — INTERNAL MODEL

M1 recordings

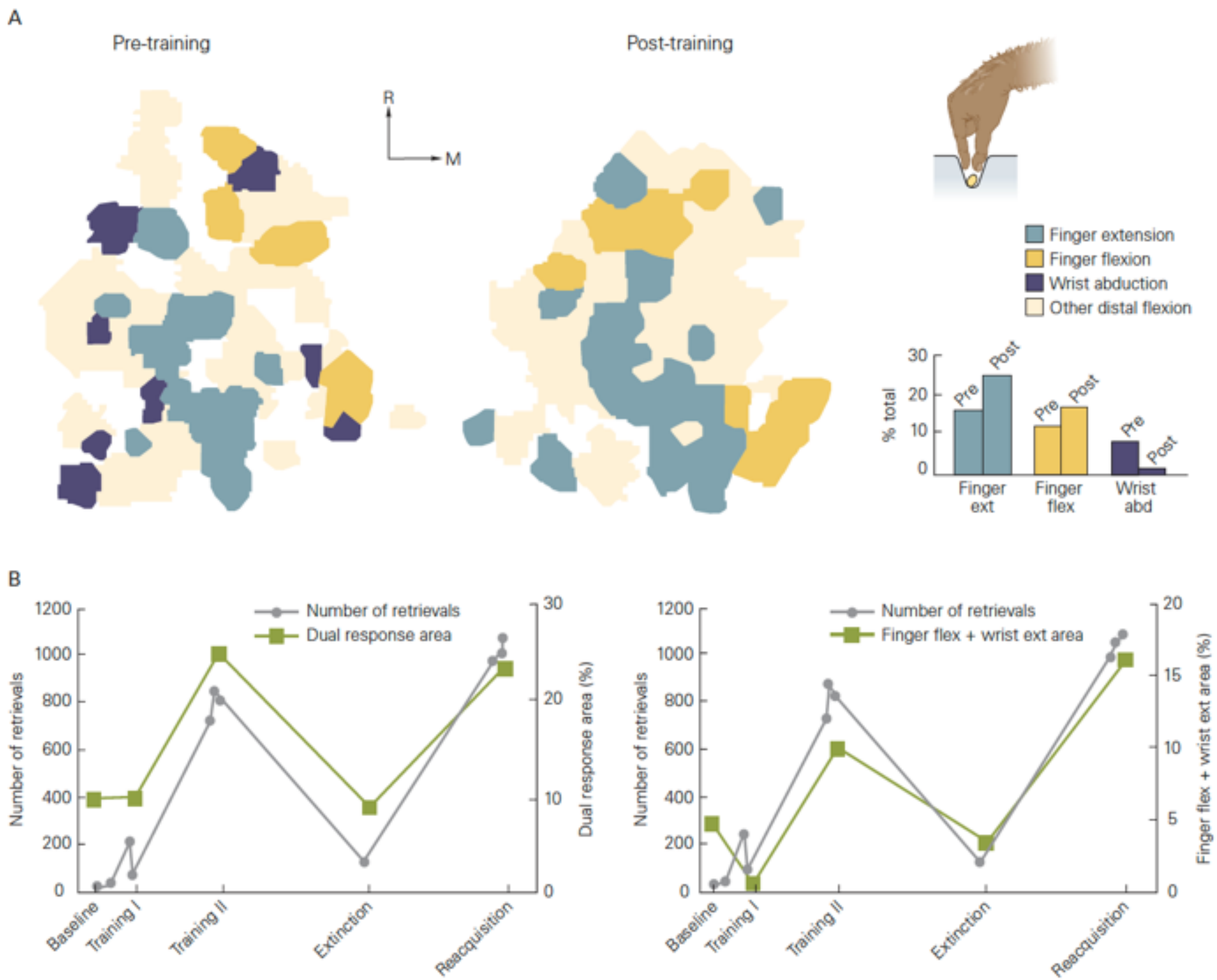






— Pruszynski et al., 2011, *Nature* 478:387

MOTOR CORTEX — PLASTICITY



any combinations of wrist and finger motions

— Nudo et al., 1996, *J Neurosci* 16:785

MOTOR CORTEX — LESIONS

- **Focal lesions**

— from weakness, slowing, discoordination to temporary/permanent paralysis
— effect related to the represented body part, diminished use of this part, distal extremities more affected
— loss of fine motor skills (e.g. independent movements of the fingers, precision grip), clumsiness in most motor functions

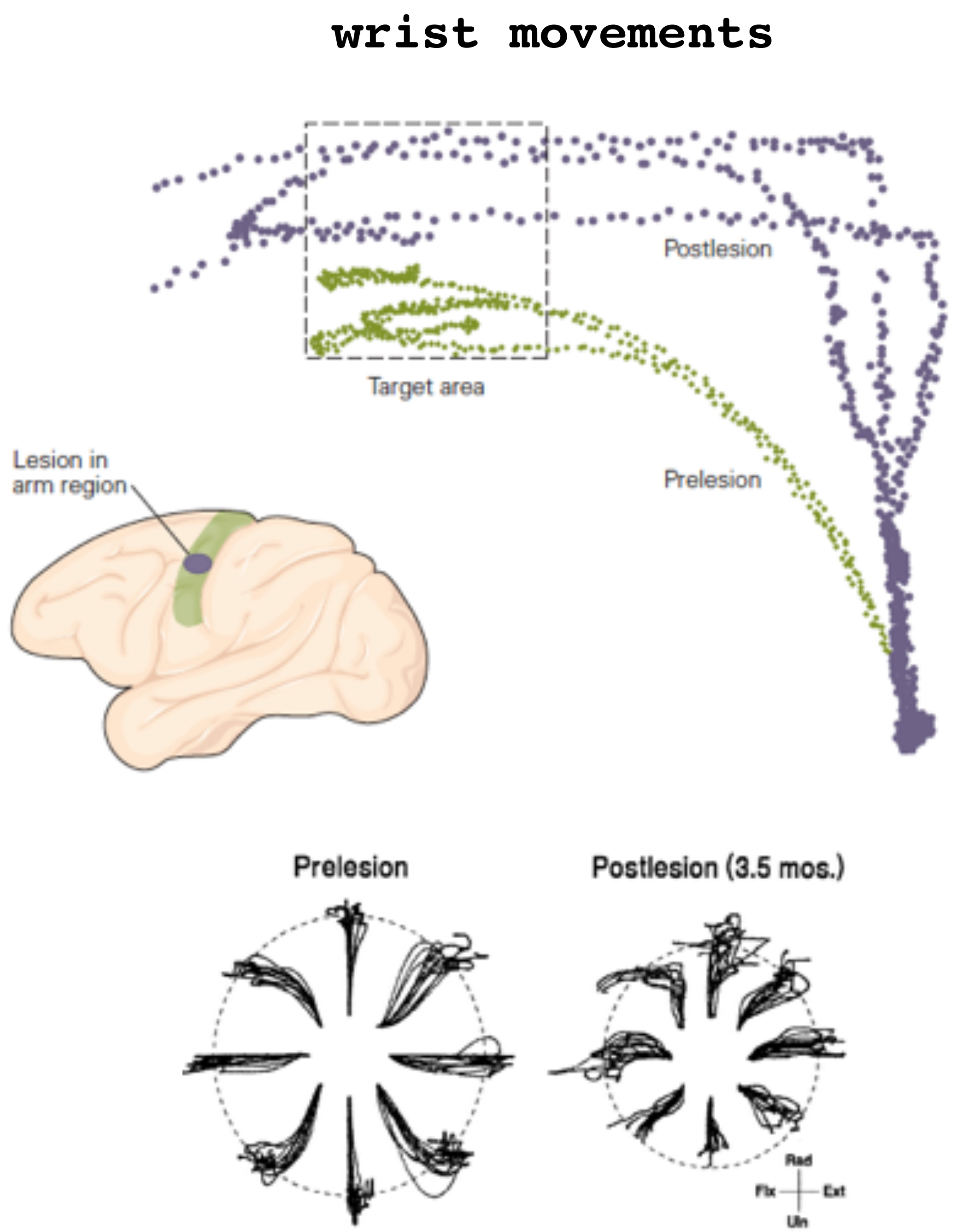
- **Large lesions**

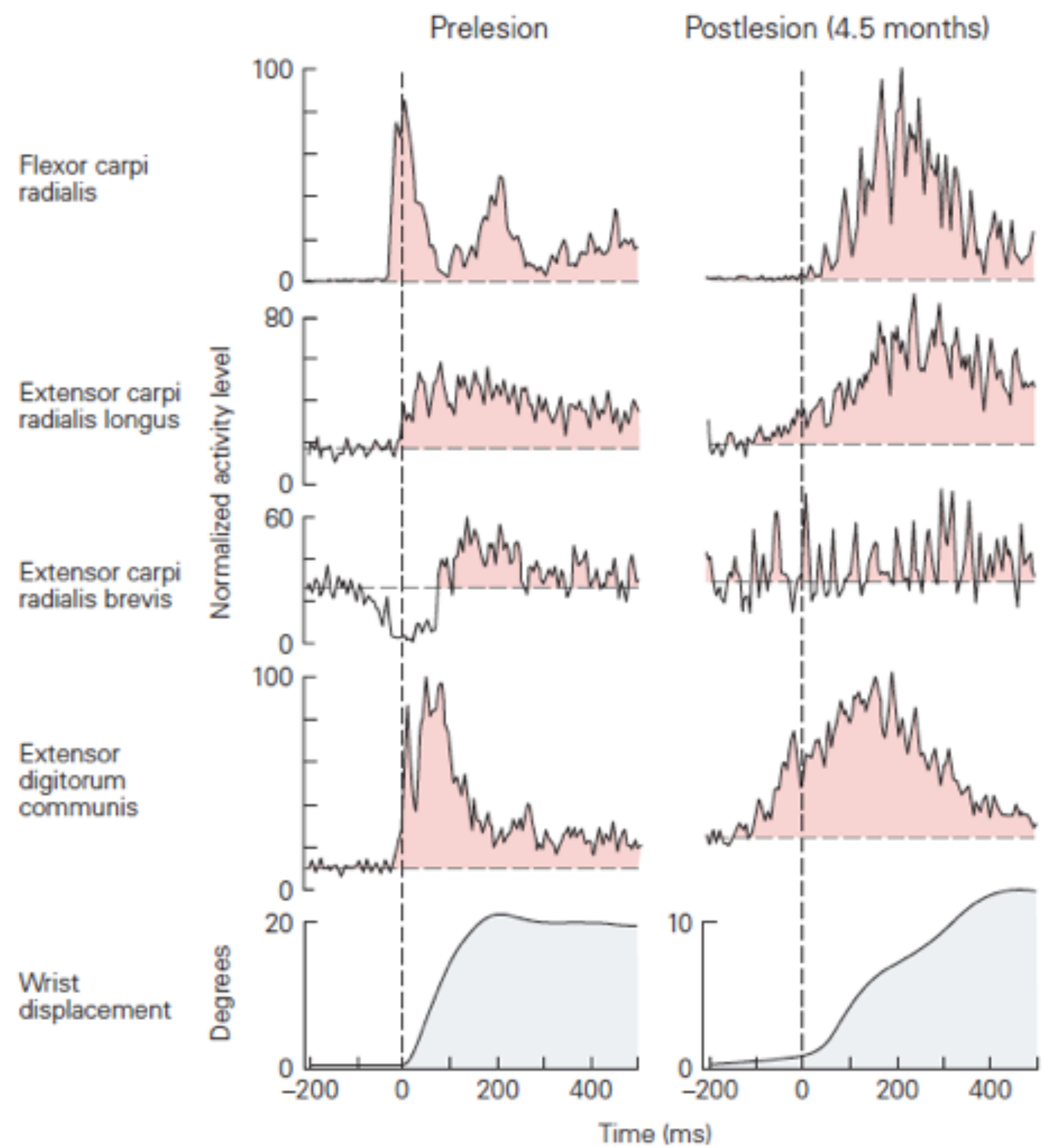
pyramidal syndrom — paralysis, spasticity (increase in muscle tone), increase of deep reflexes, disappearance of superficial reflexes, altered posture

- **Species-specific**

cat, monkey, human

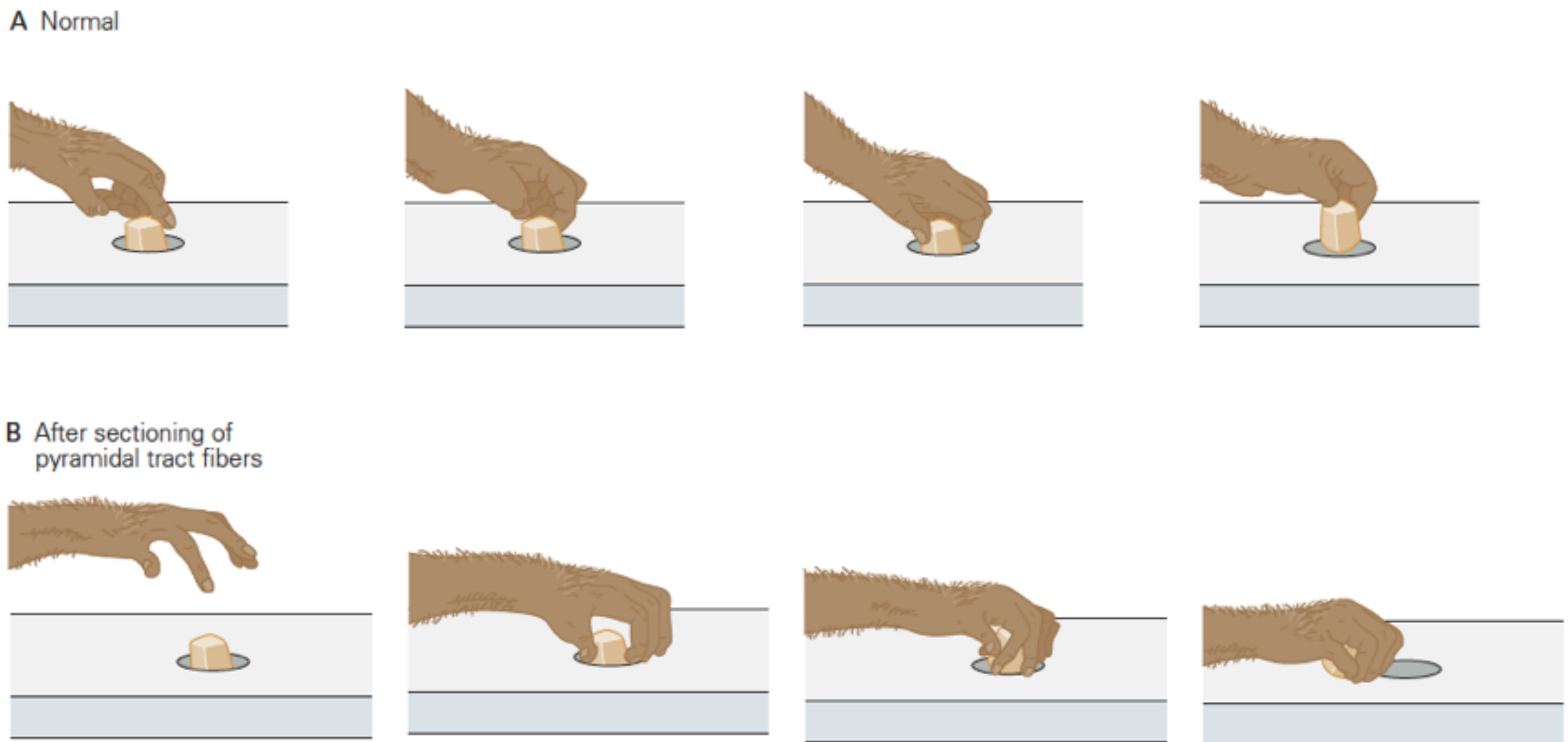
MOTOR CORTEX — LESIONS





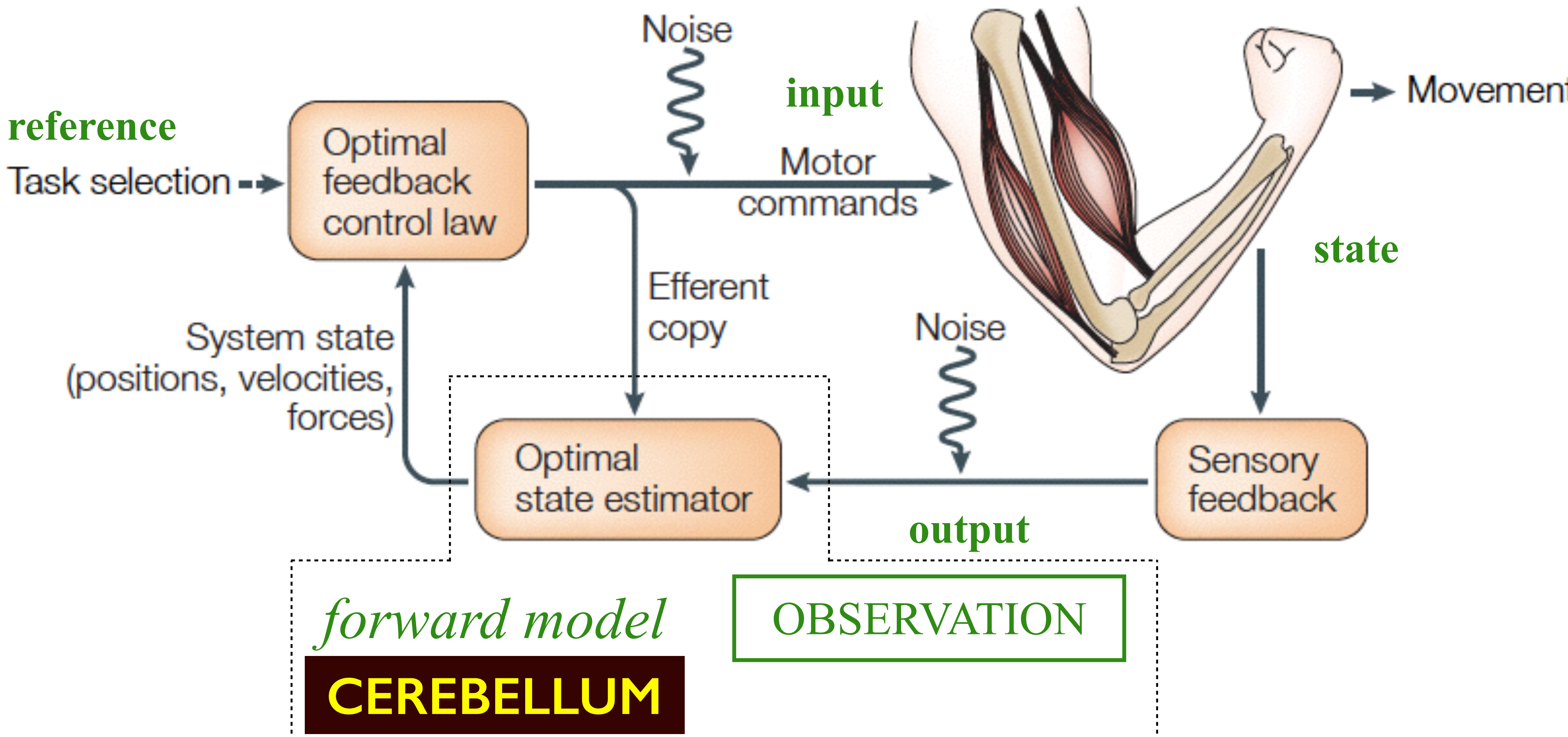
— Hoffman and Strick, 1995, *J Neurophysiol* 73:891

MOTOR CORTEX — LESIONS



— Lawrence and Kuypers, 1968, *Brain* 91:1

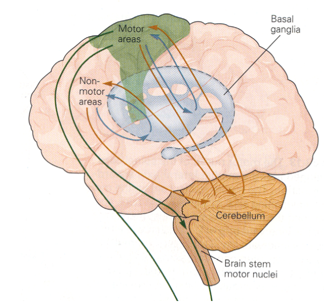
COMPUTATIONAL NEUROANATOMY



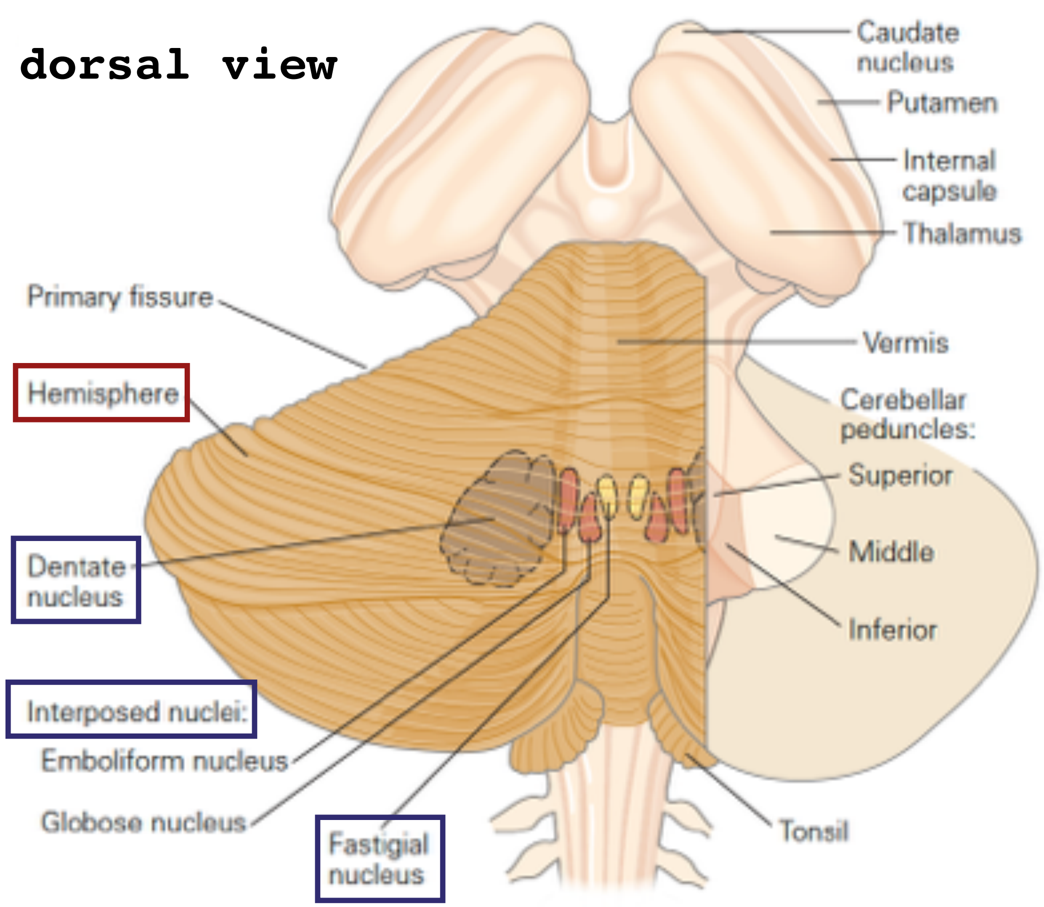
GLOBAL CEREBELLAR ORGANISATION

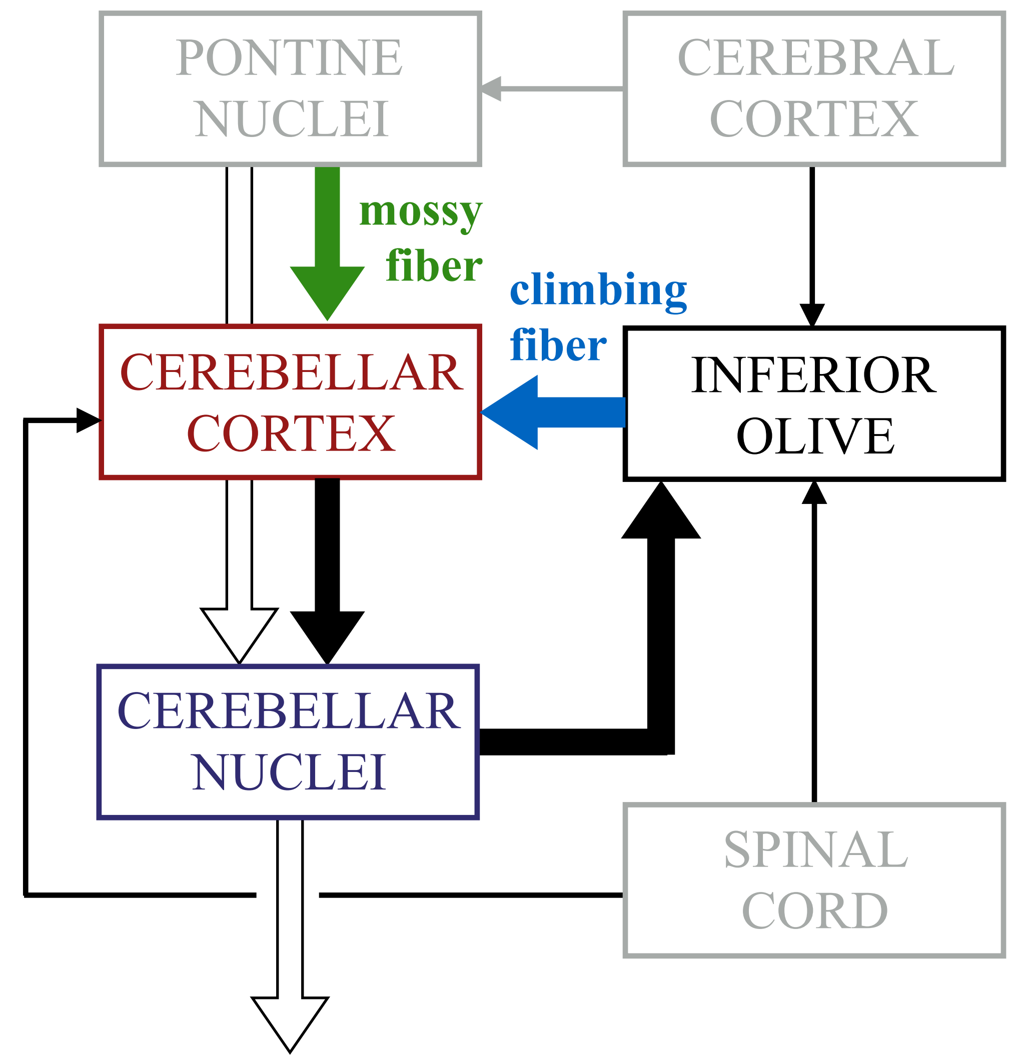
Anatomy

— **cerebellar cortex**, **deep cerebellar nuclei**

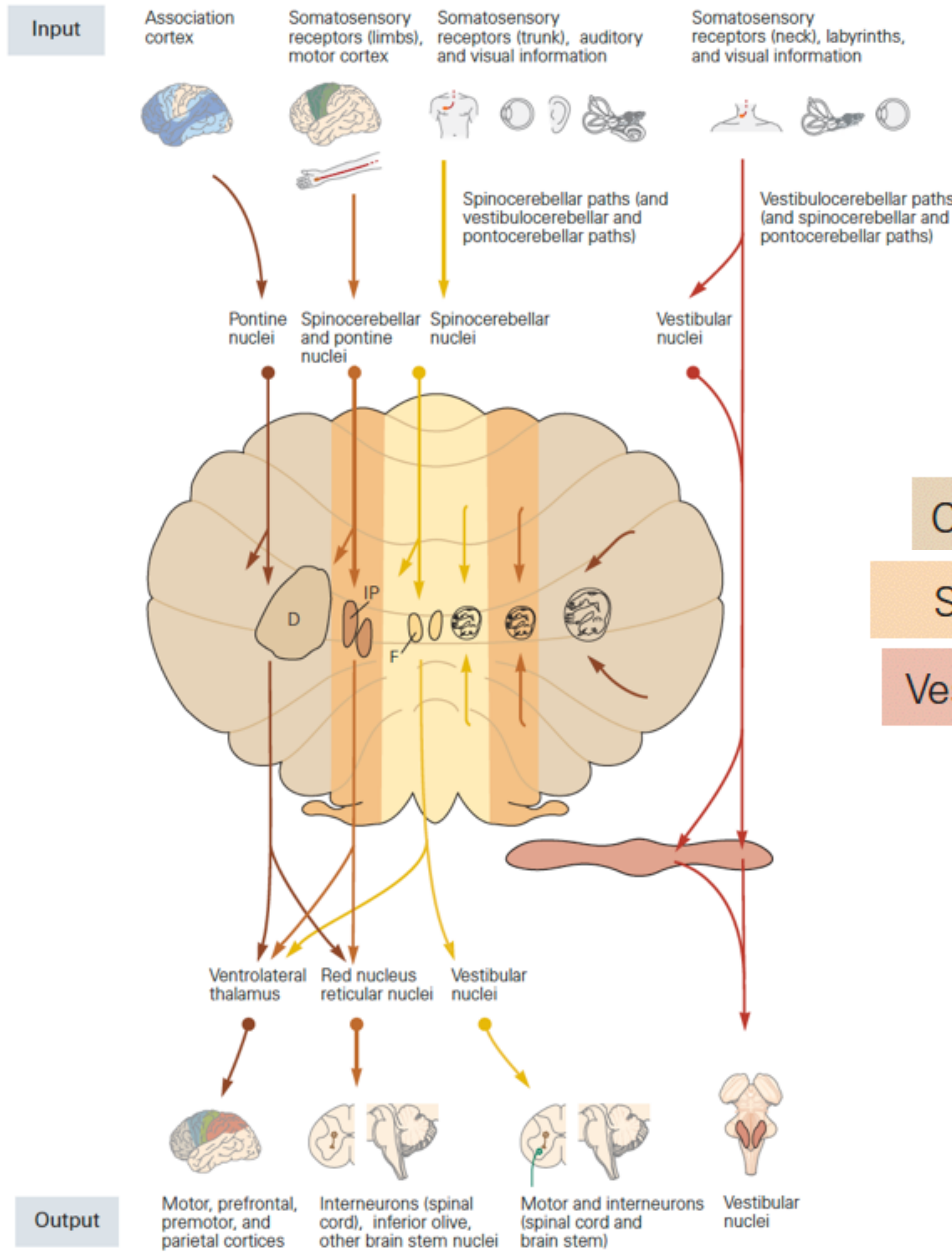


dorsal view





INPUT/OUTPUT ORGANISATION



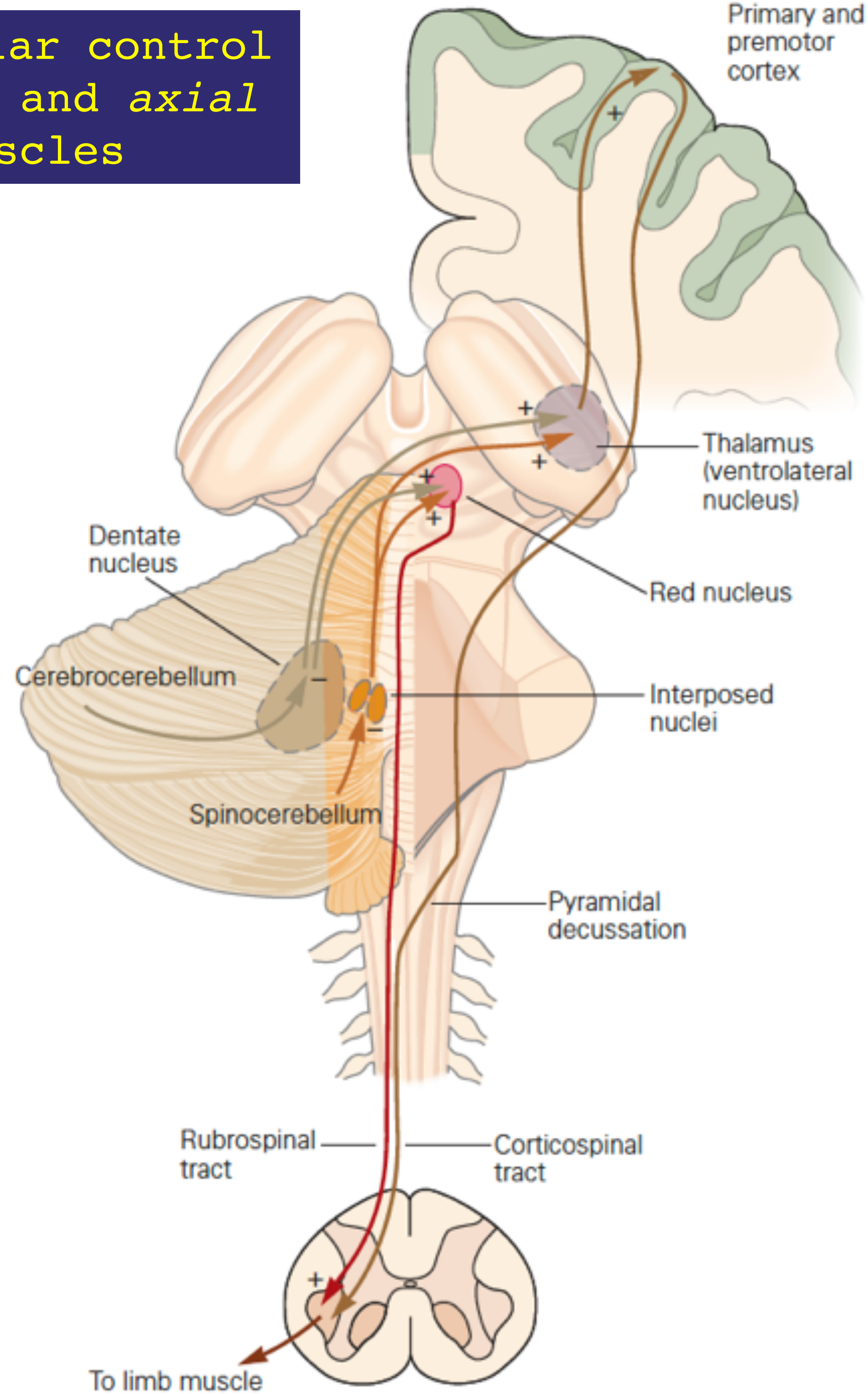
Cerebrocerebellum

Spinocerebellum

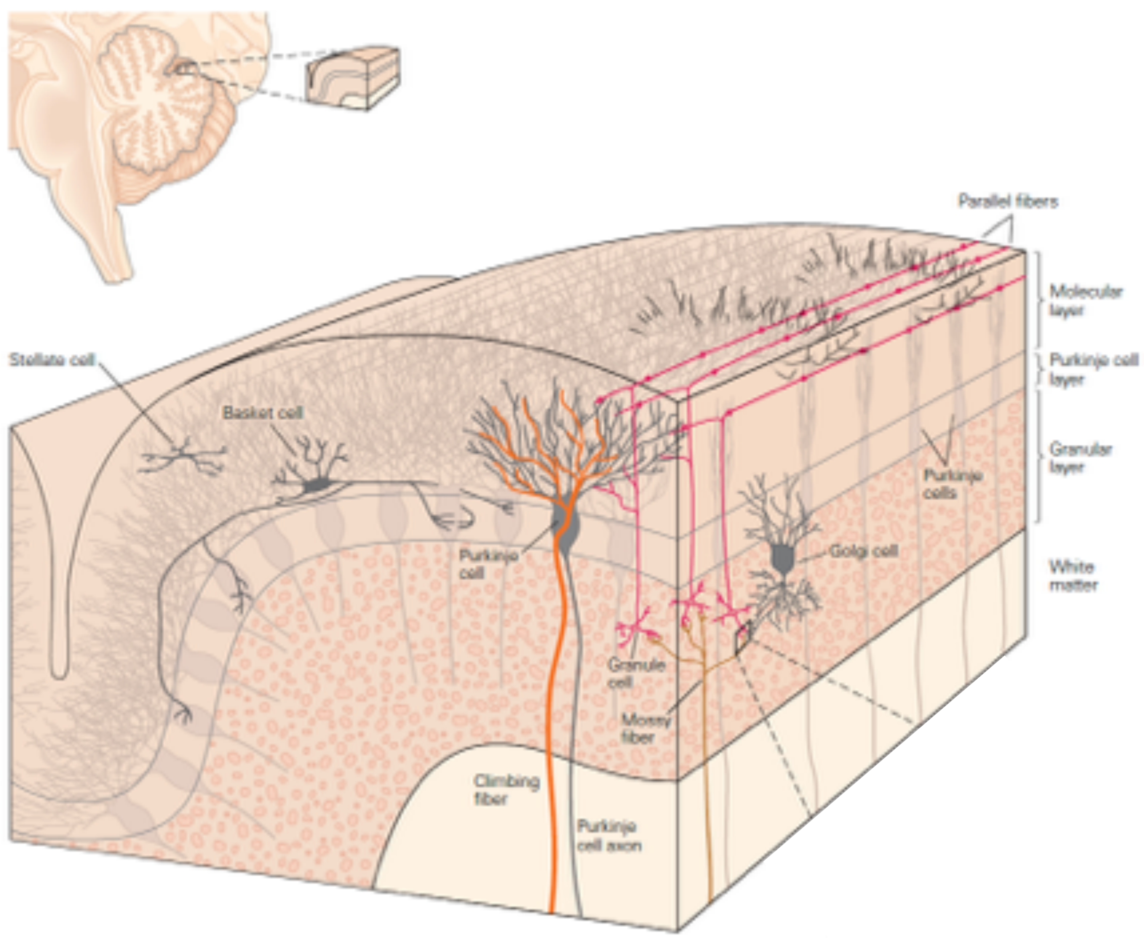
Vestibulocerebellum

OUTPUT ORGANISATION

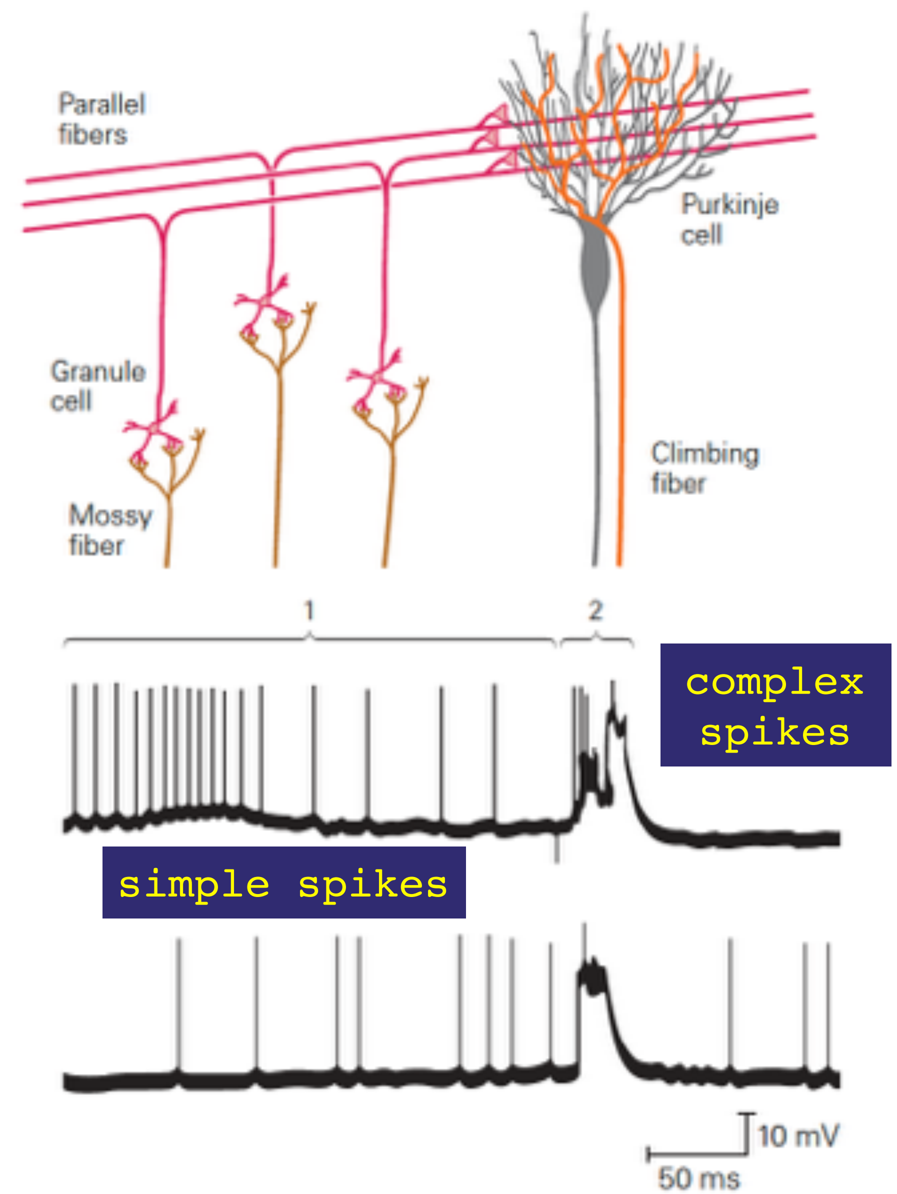
cerebellar control of *limb* and *axial* muscles



LOCAL CEREBELLAR ORGANIZATION

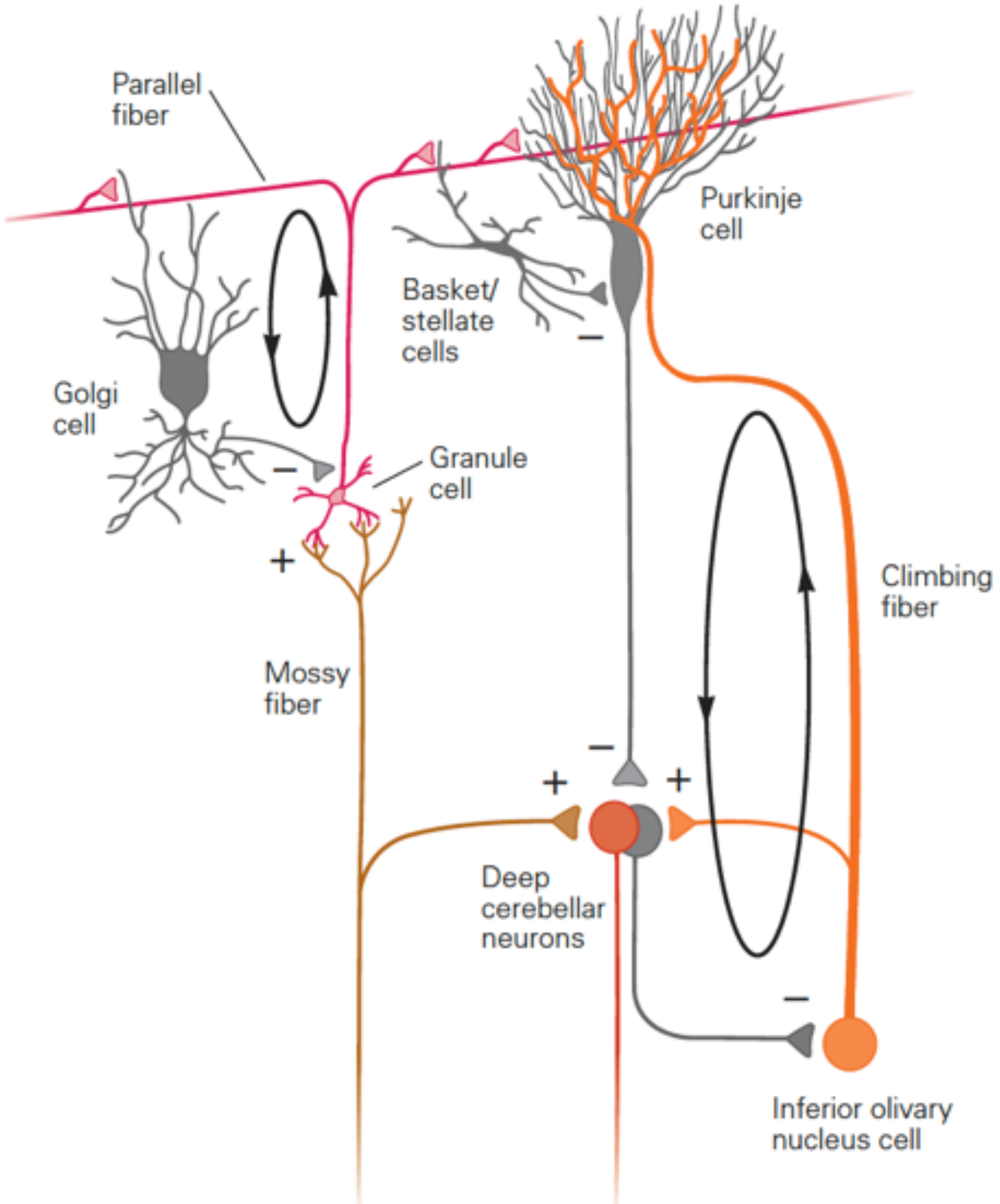


granular layer – **input**
Purkinje cell layer – **output**



connectivity
granule/Purkinje ≈ $0.2\text{-}1 \times 10^6$
climbing fiber/Purkinje = 1
Purkinje/climbing fiber ≈ 1-10

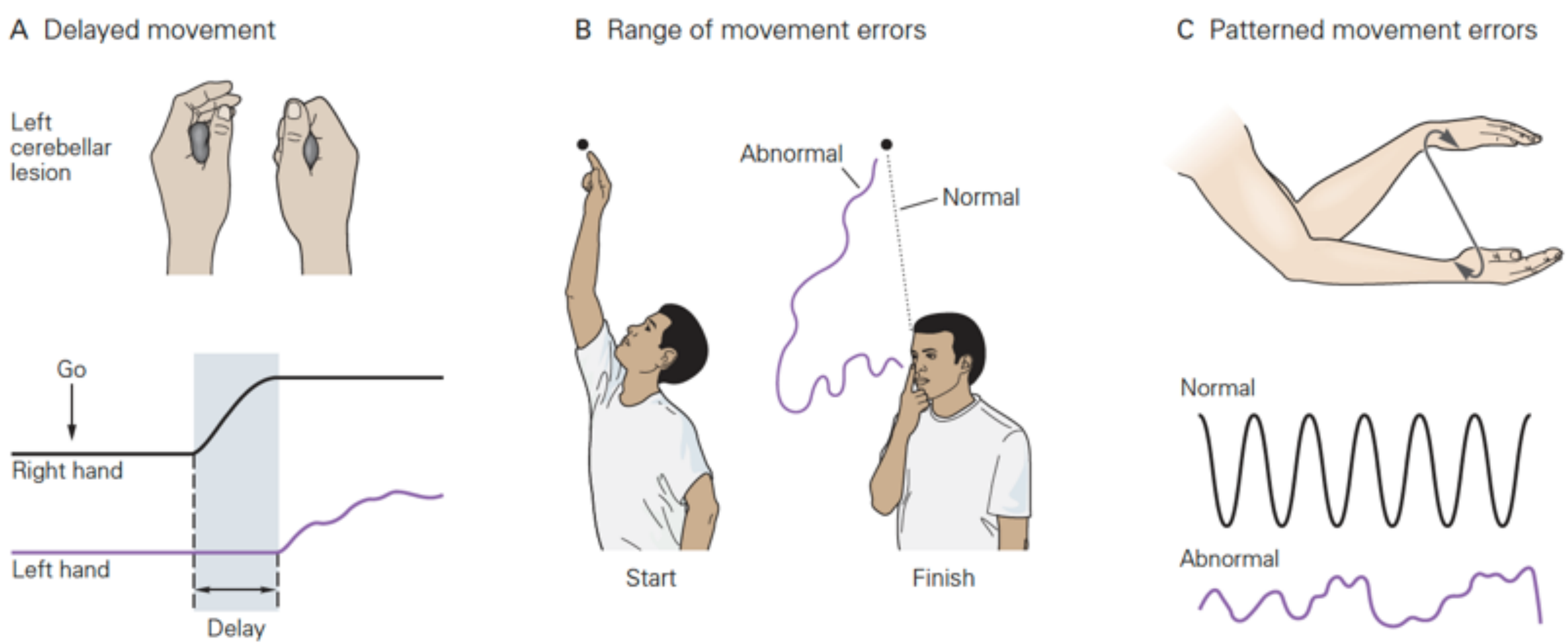
CEREBELLAR MICROCIRCUIT



CEREBELLAR DISEASES

Distinctive symptoms and signs

— **no paralysis**, hypotonia, astasia/abasia (*inability to stand and walk*), ataxia (*abnormal execution of multijoint movements*, e.g. dysmetria, dysdiadochokinesia), tremor (*action* or *intention*, series of erroneous corrections at the end of the movement)



dysmetria

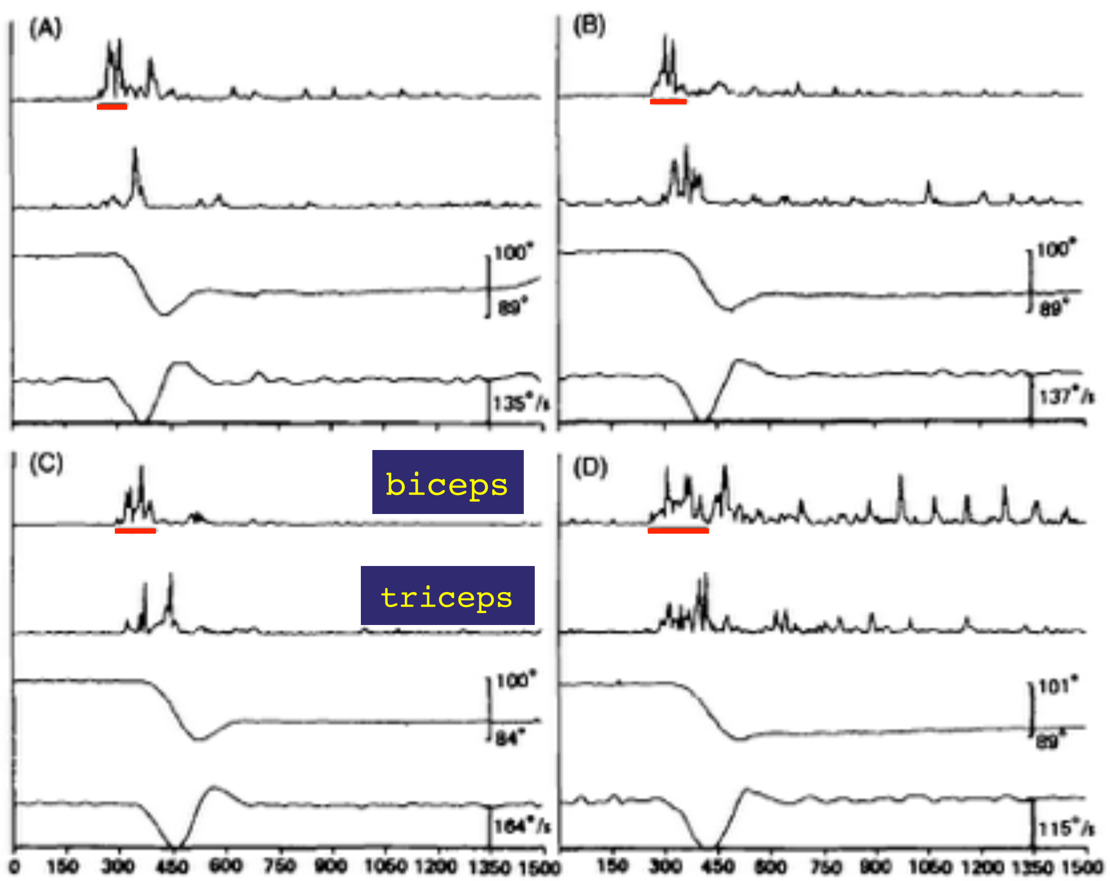
dysdiadochokinesia

CEREBELLAR DEFICITS

Deficits in the control of rapid movements

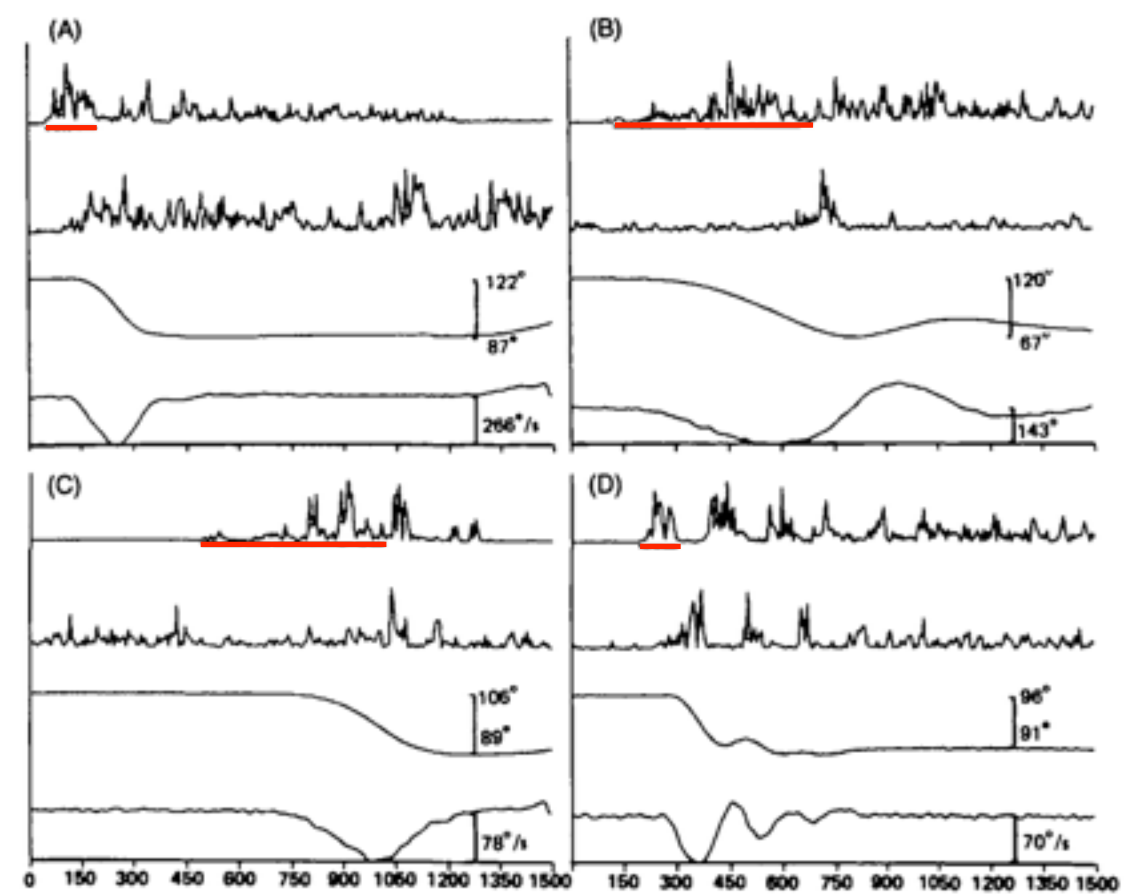
abnormal triphasic EMG — abormal timing

`normal participant – elbow flexion`



`(A) normal triphasic EMG`
`(B-D) different degrees of cocontraction`

`cerebellar patients – elbow flexion`



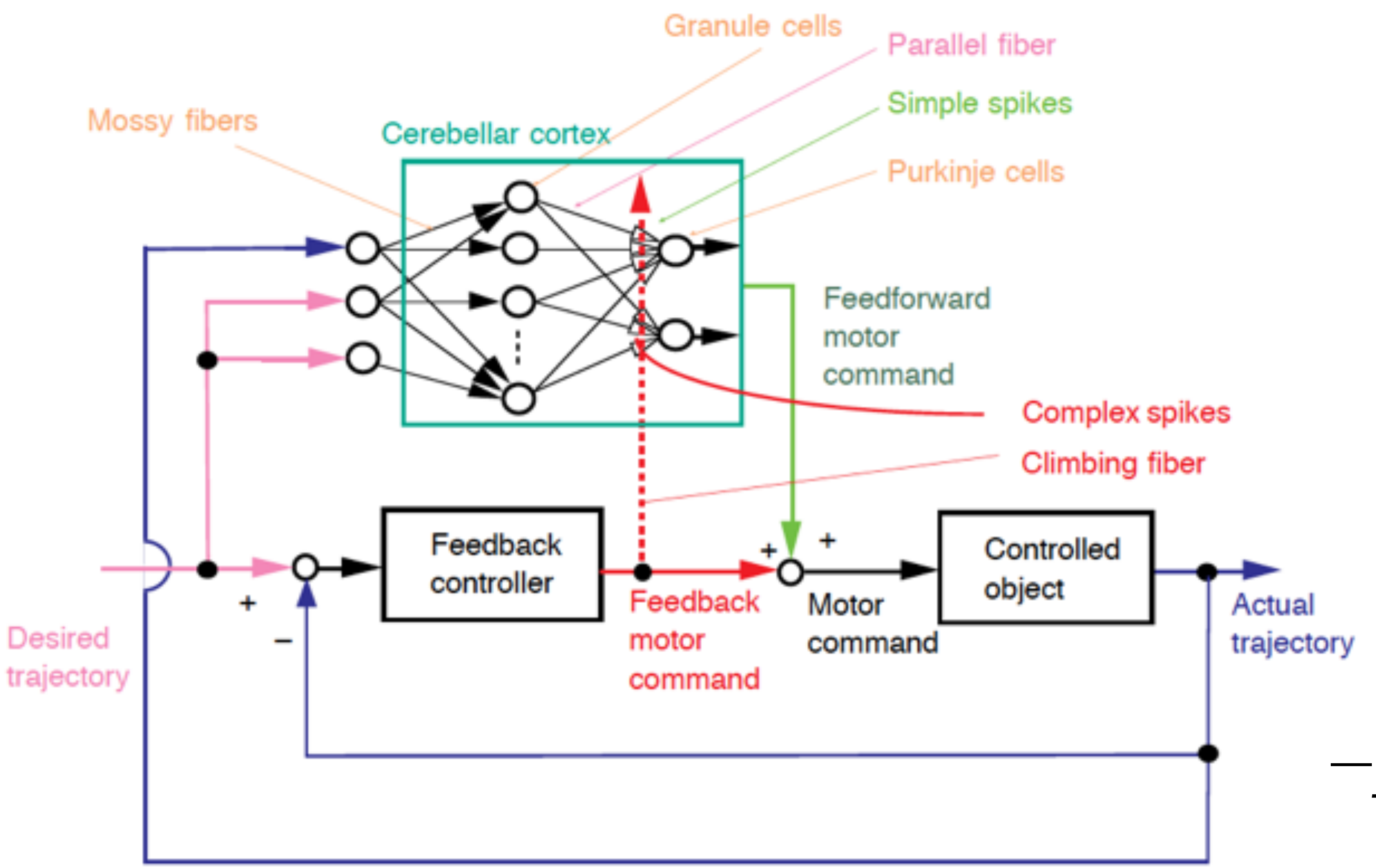
`(A,D) patient with moderate ataxia`
`(B,C) two patients with severe ataxia`

— Hallett et al., 1991, *J Neurol Neurosurg Psychiatry* 54:124

CEREBELLUM — MOTOR THEORY

Storage of inverse models

the cerebellum computes a function that creates or modifies the patterns of muscle activations that underlie coordinated movement



—Wolpert et al., 1998, *Trends Cogn Sci* 2:338

CEREBELLUM — SENSORY THEORY

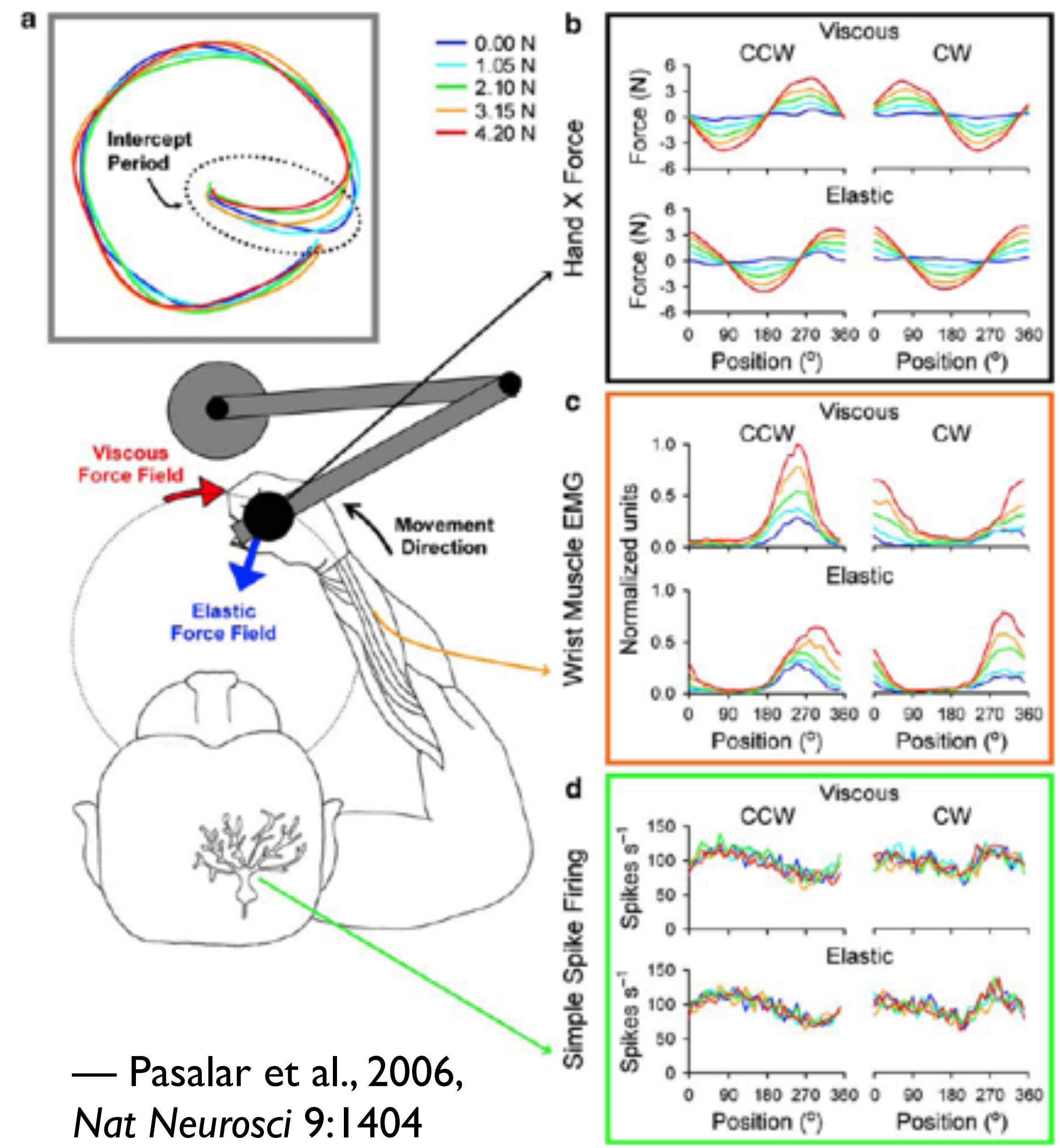
Arguments

— strong parallelism in the phylogeny between the size of the cerebellum and the complexity of sensory systems (Paulin 1993)

— the discharge pattern of Purkinje cells is not modulated by forces applied during movement execution

➤ ***incompatible with a representation of an* internal inverse model**

➤ ***storage of a forward model?***

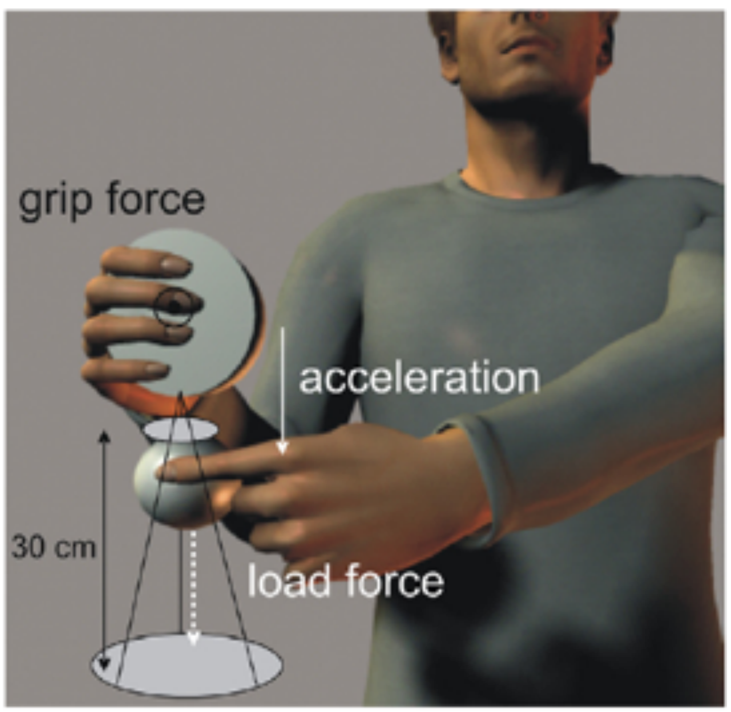


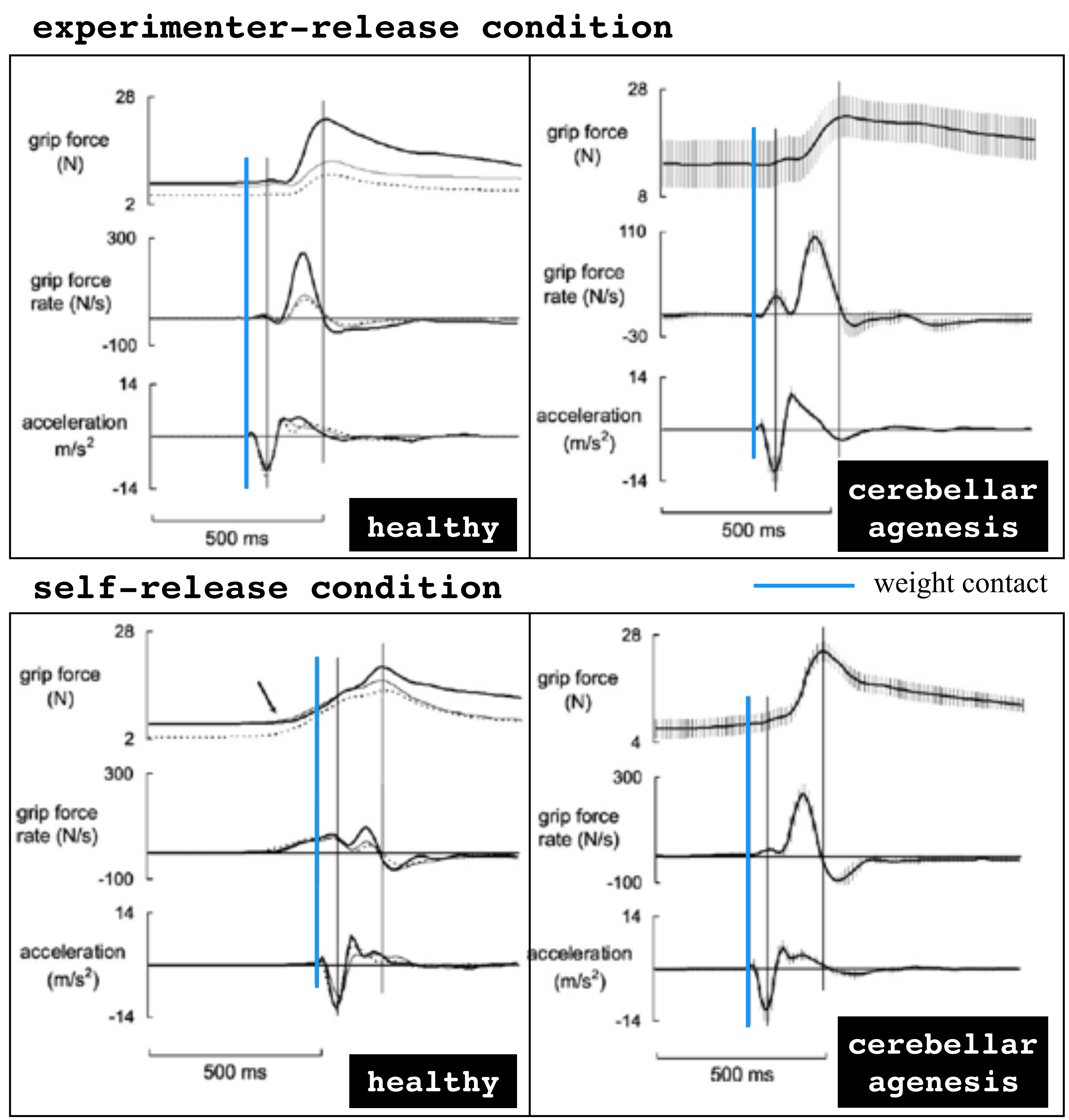
— Pasalar et al., 2006, *Nat Neurosci* 9:1404

— Paulin, 1993, *Brain Behav Evol* 41:39

CEREBELLAR PREDICTION DEFICIT

Predictive grip force control

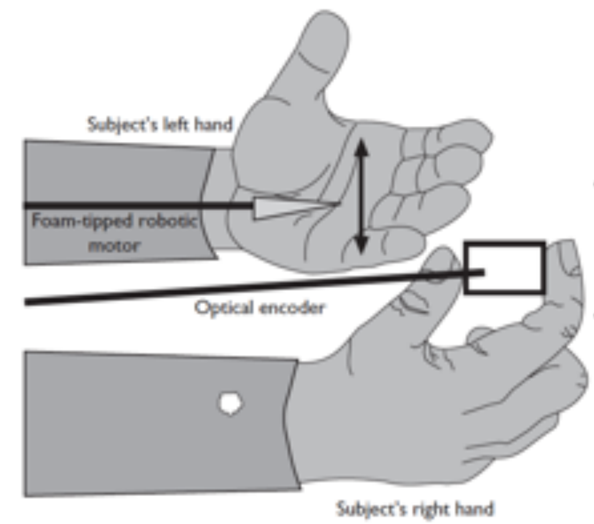


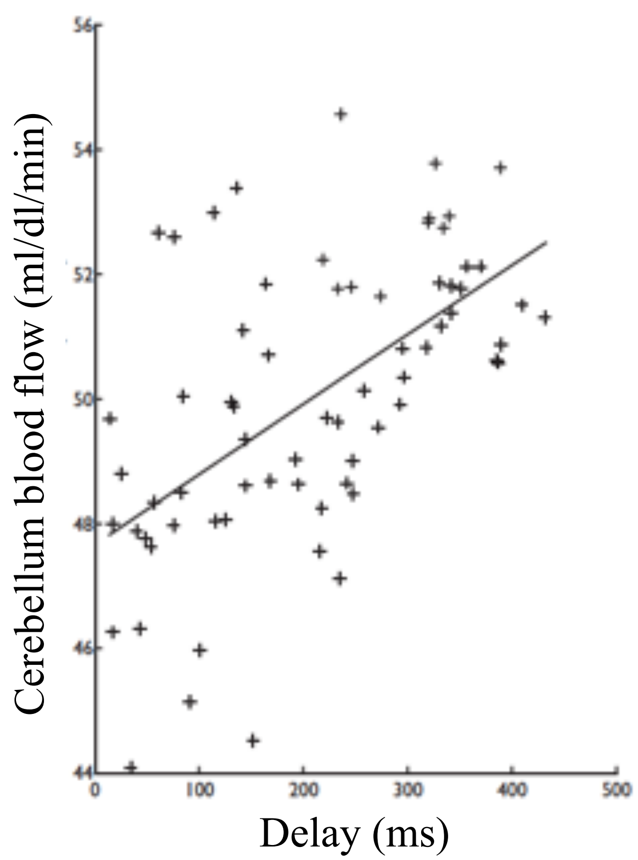


— Nowak et al., 2007, *Neuropsychologia* 45:696

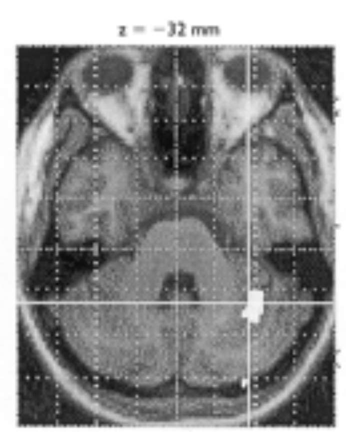
PREDICTING SENSORY CONSEQUENCES

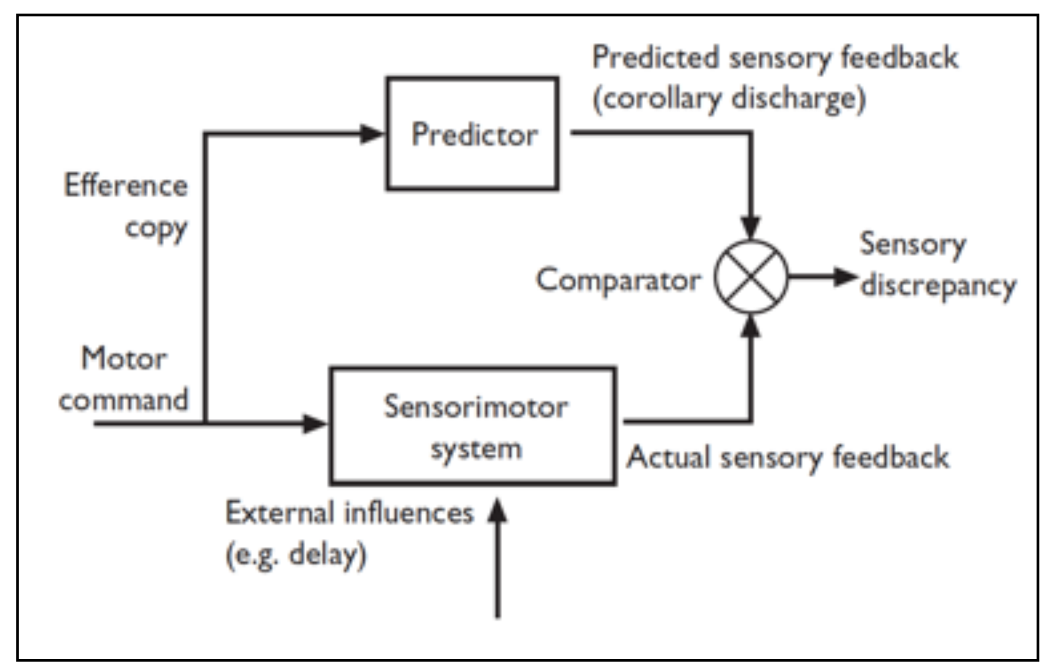
The cerebellum signals
sensory discrepancy between the *predicted* and *actual* sensory consequences of movements





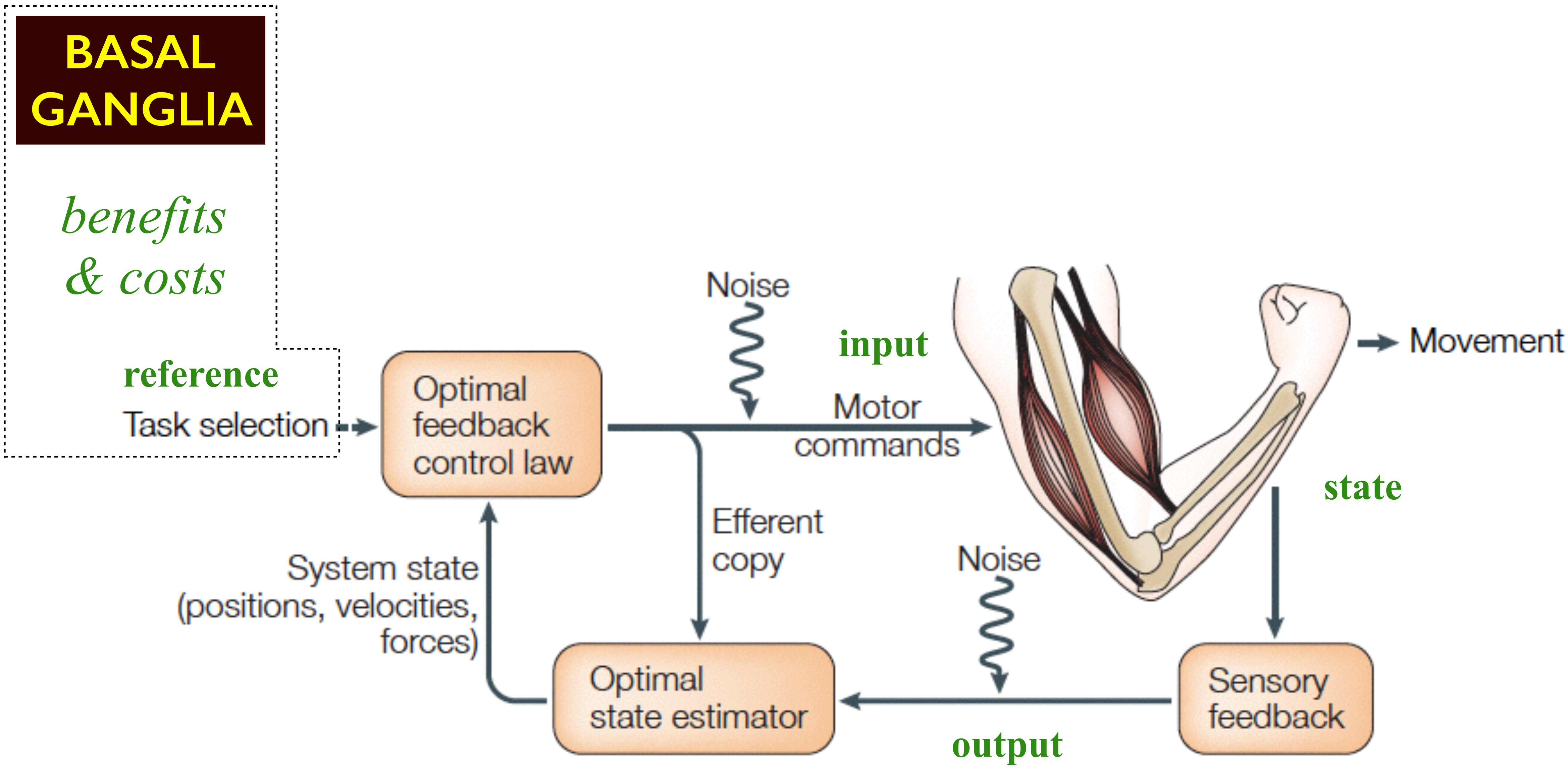
activity in the right lateral cerebellar cortex shows a positive correlation with delay





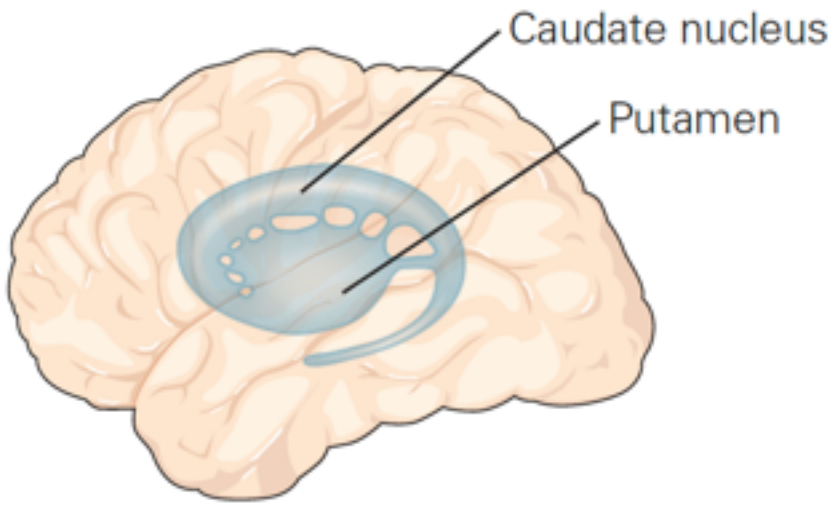
— Blakemore et al., 2001, *NeuroReport* 12:1879

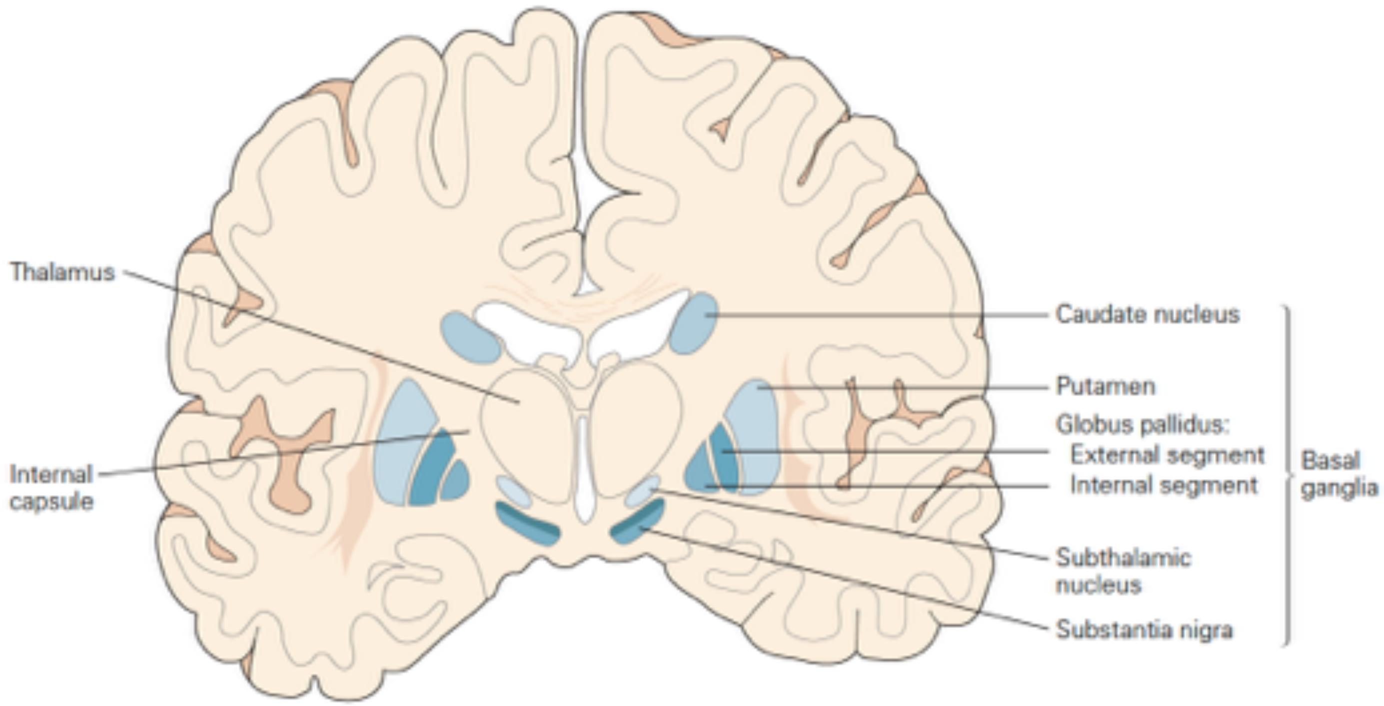
COMPUTATIONAL NEUROANATOMY

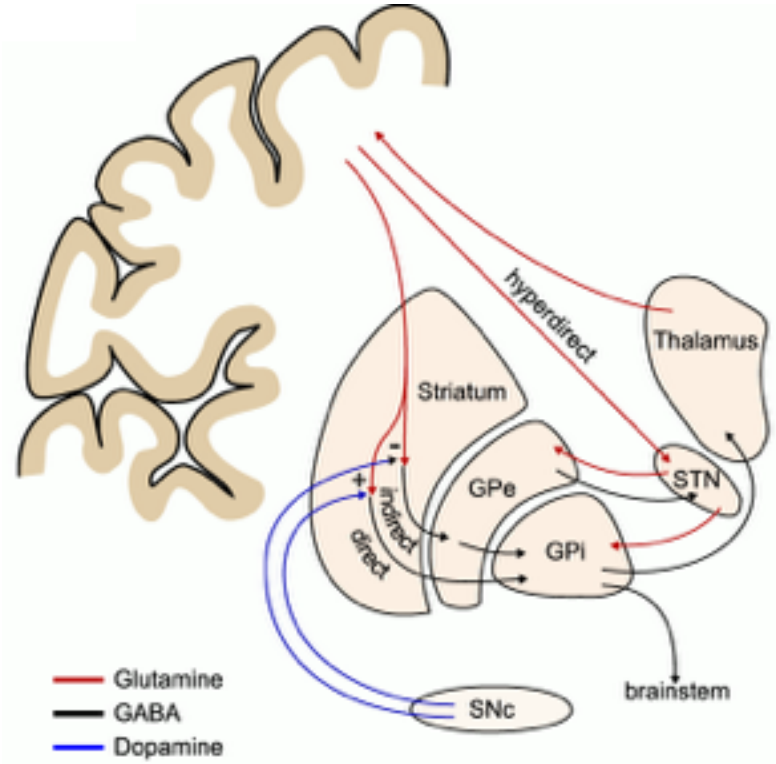


— Scott, 2004, *Nat Rev Neurosci* 5:534
— Shadmehr and Krakauer, 2008, *Exp Brain Res* 185:359

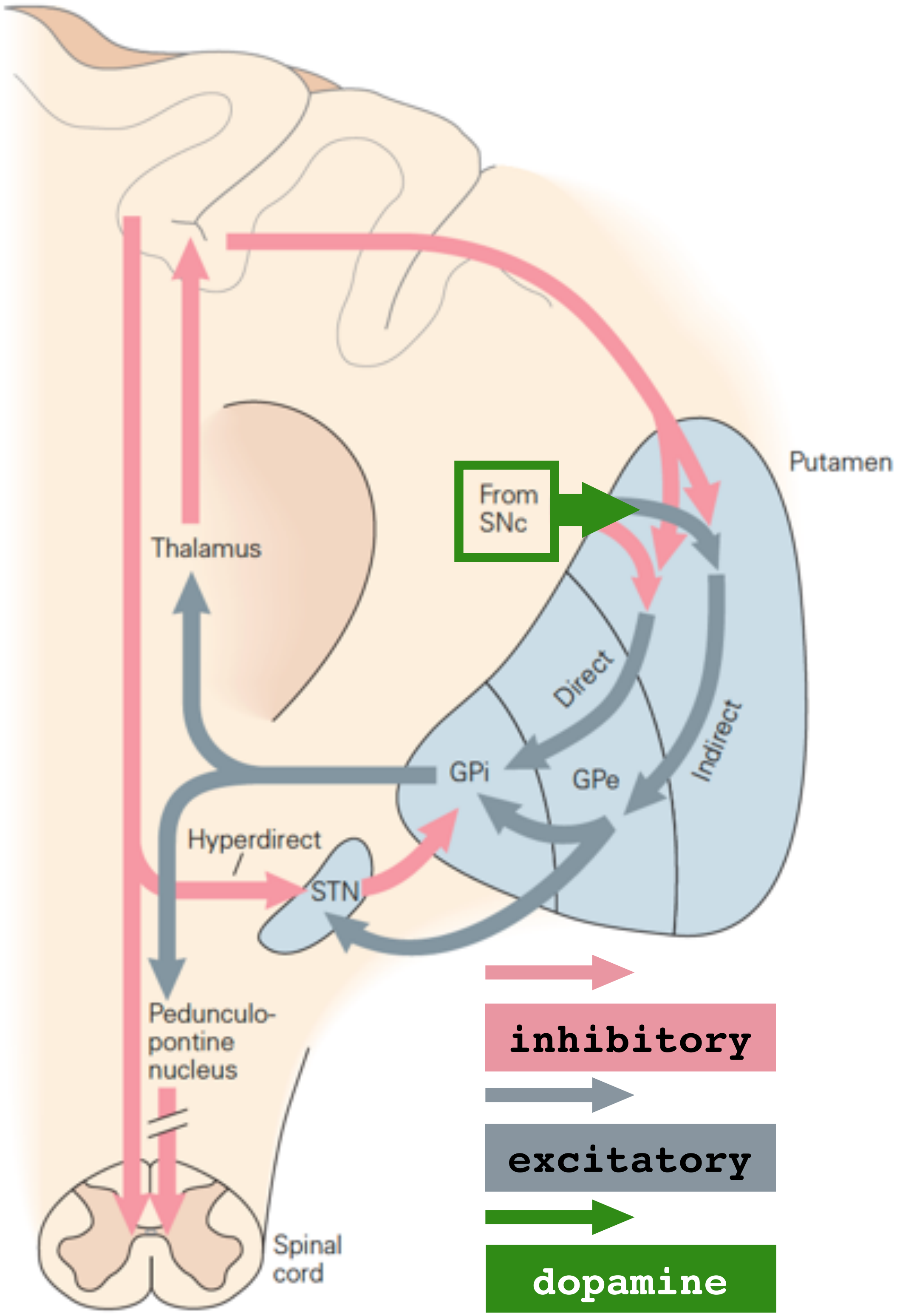
GLOBAL BASAL GANGLIA ORGANISATION

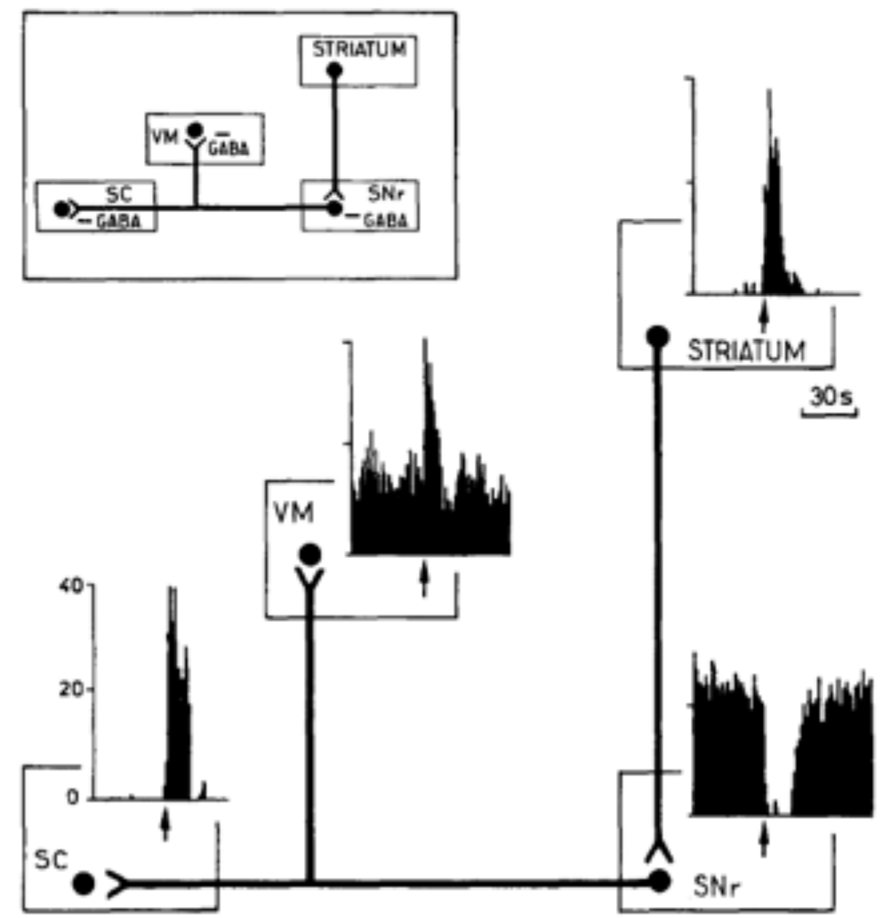






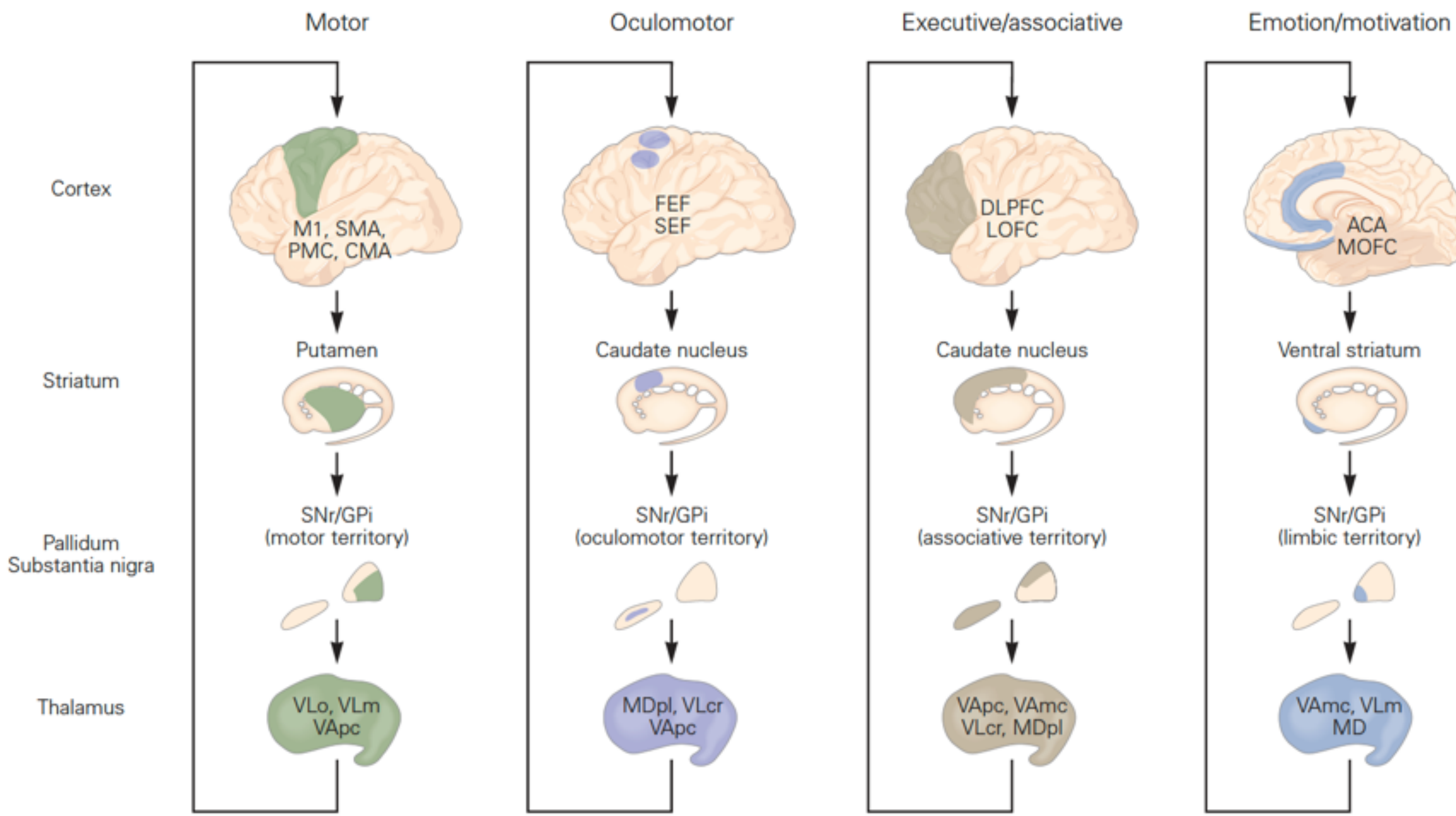
LOCAL BASAL GANGLIA ORGANISATION





— Chevalier & Deniau, 1990,
Trends Neurosci 13:277

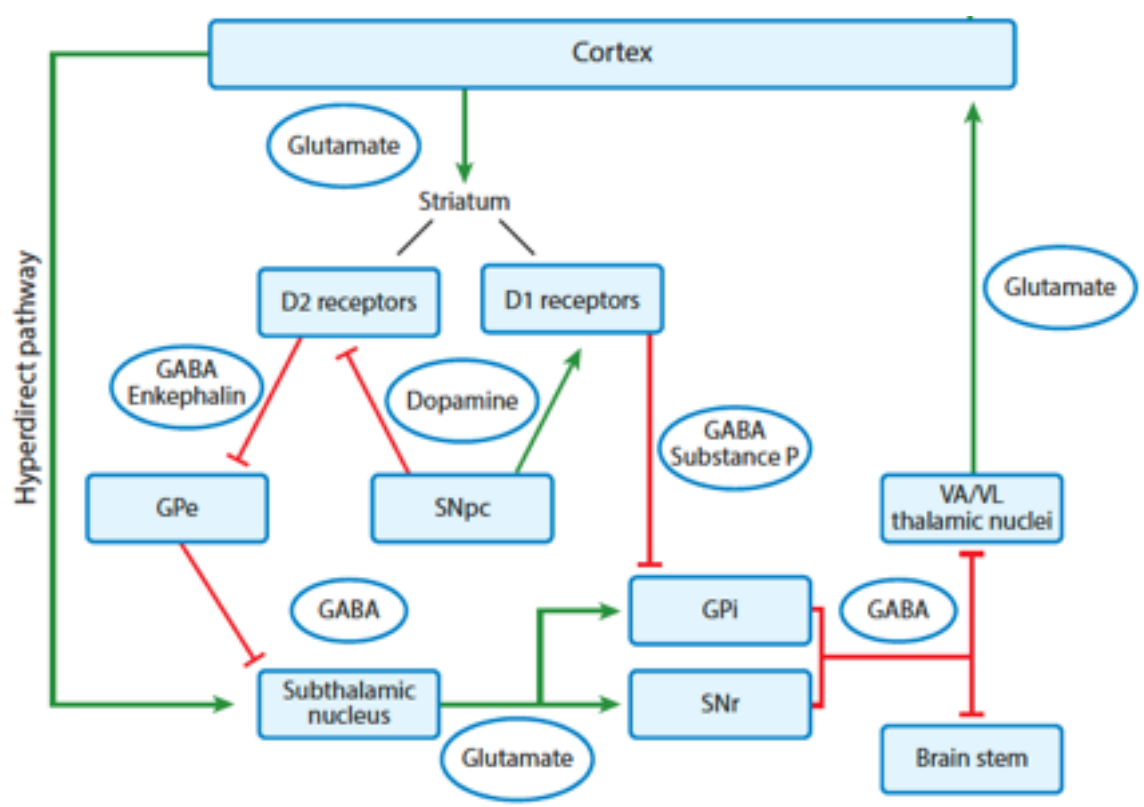
CORTICO-BASAL GANGLIA LOOPS



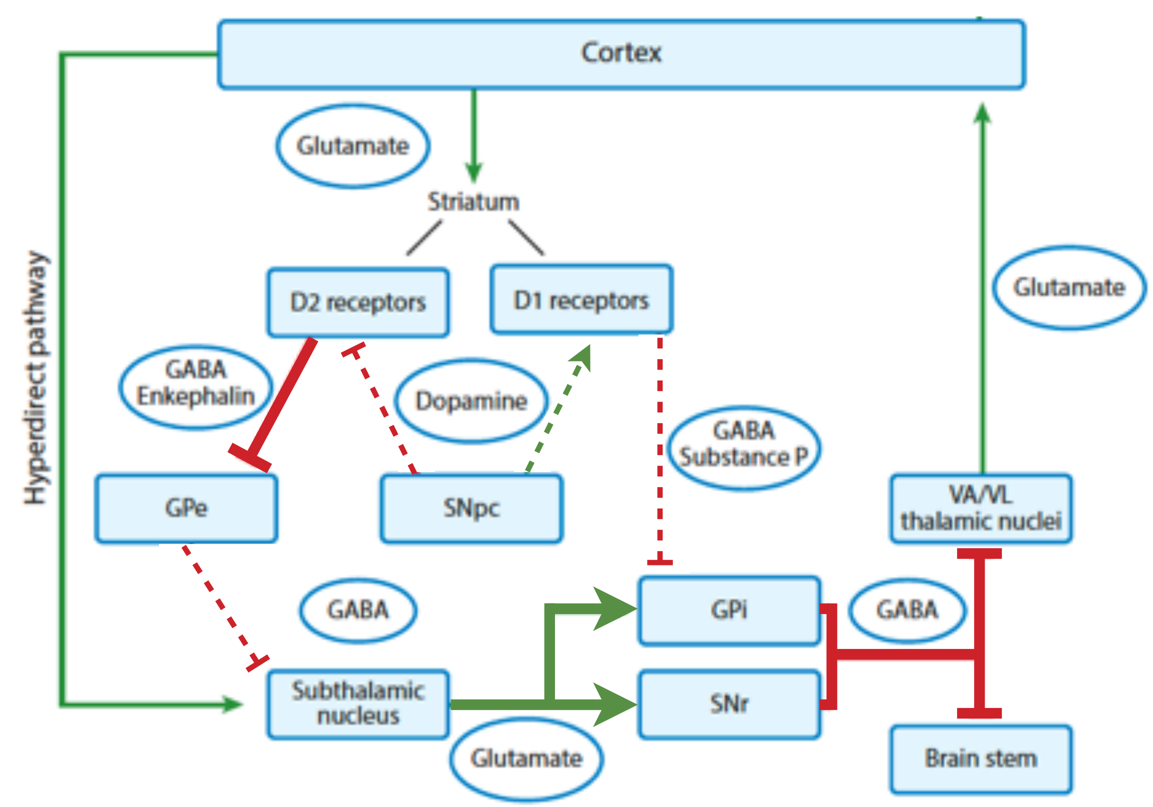
— Alexander et al., 1986, *Annu Rev Neurosci* 9:357

BASAL GANGLIA DYSFUNCTION

normal motor control



hypokinetic motor control



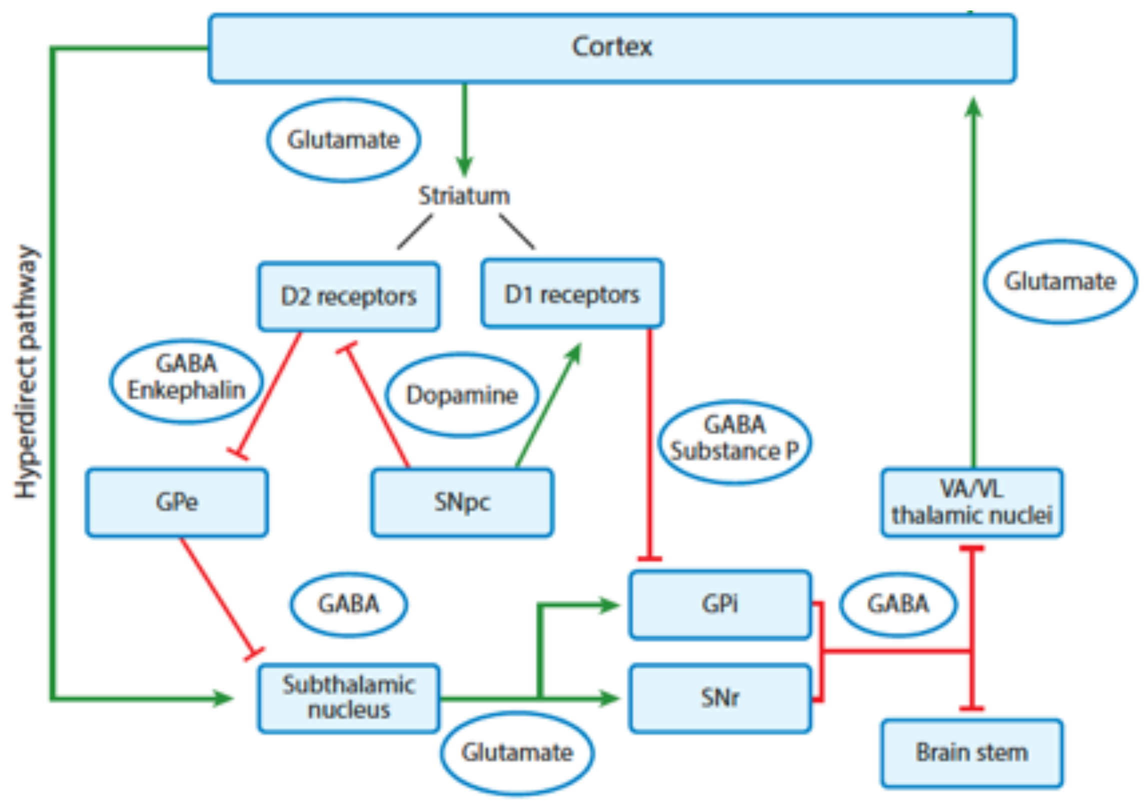
— Lozano et al., 2017,
Annu Rev Neurosci 40:453

inhibitory

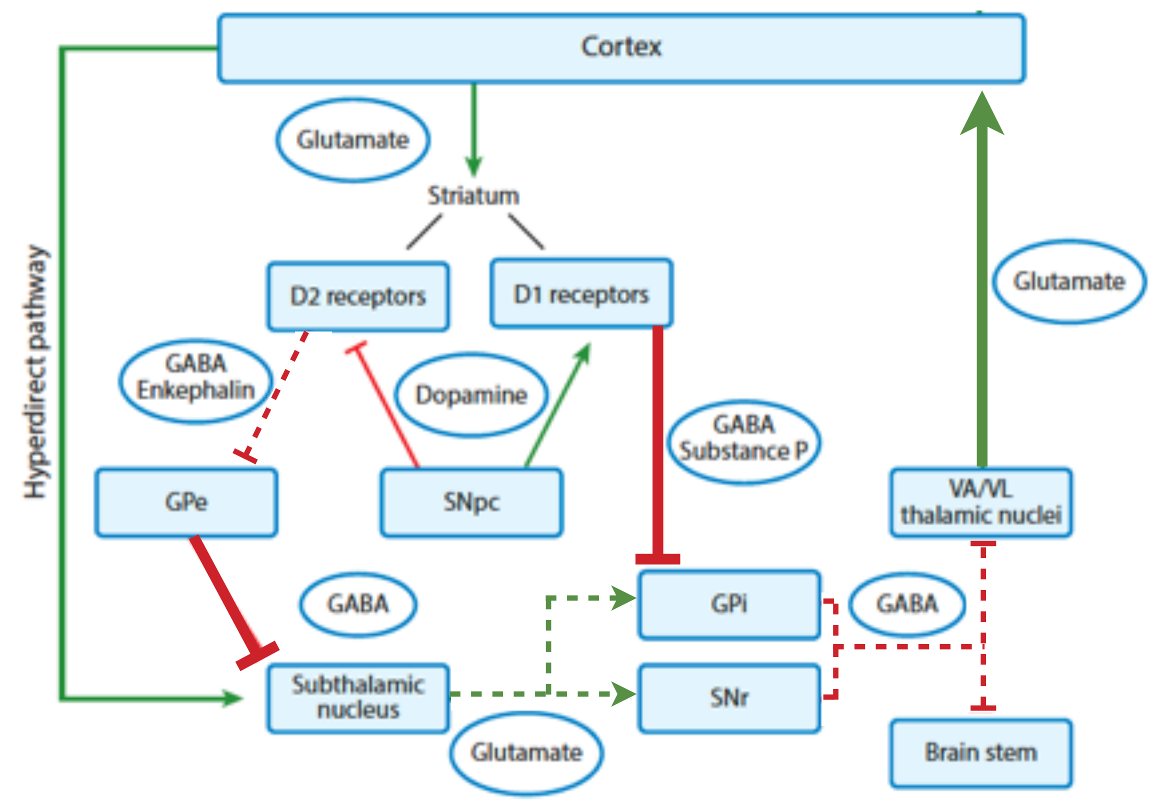
excitatory

BASAL GANGLIA DYSFUNCTION

normal motor control



hyperkinetic motor control



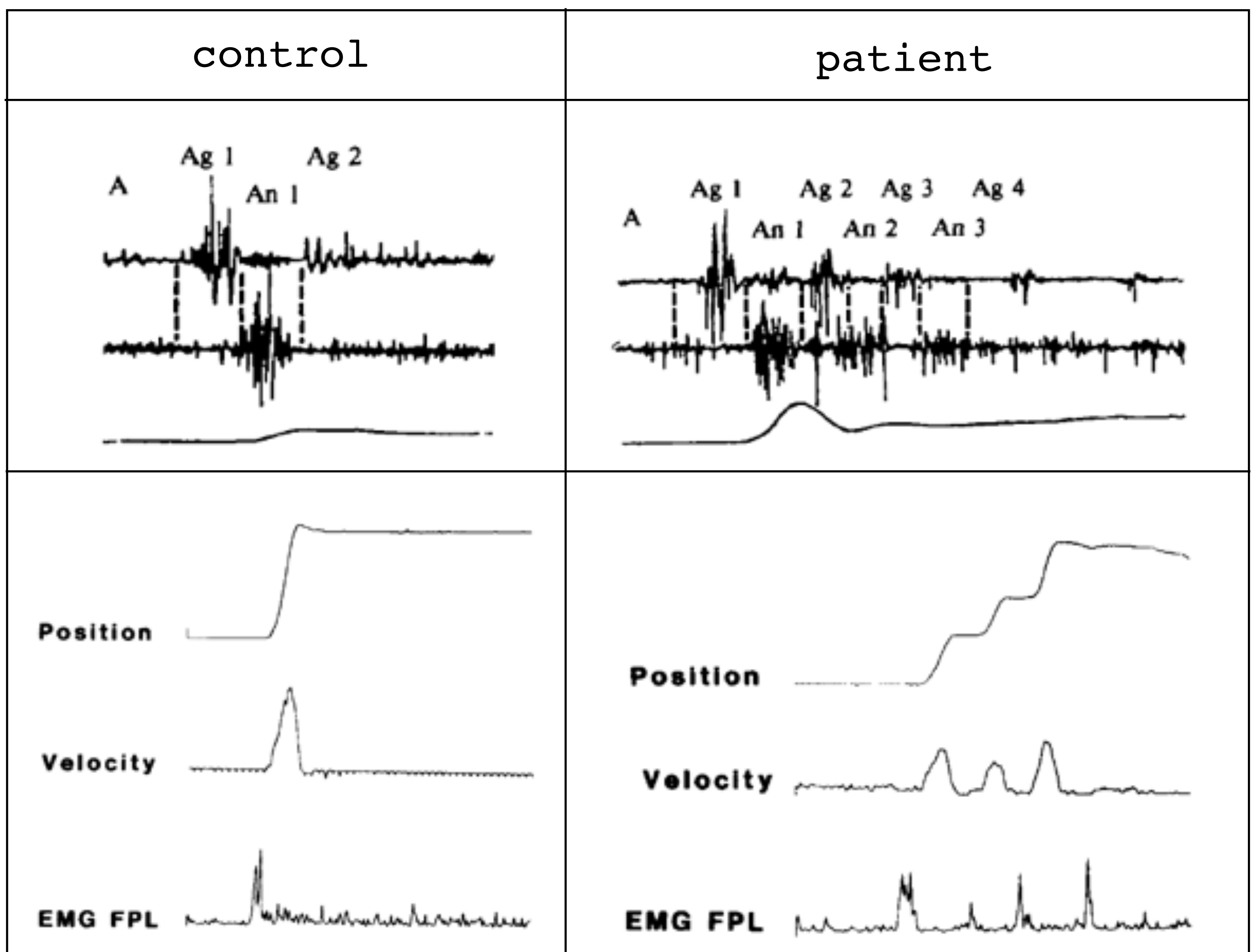
— Lozano et al., 2017,
Annu Rev Neurosci 40:453

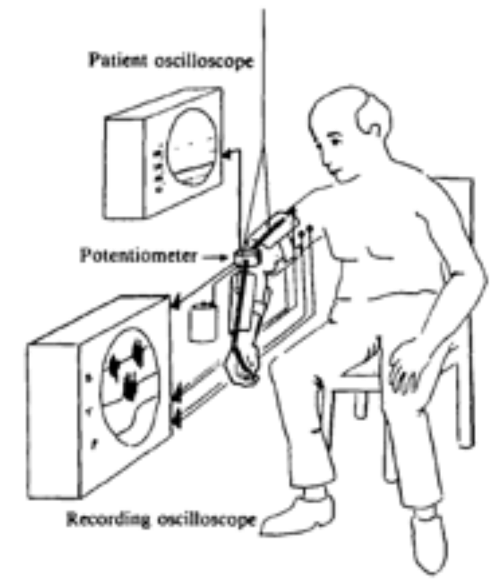
inhibitory

excitatory

BASAL GANGLIA — MOTOR DEFICITS

Movements and EMG are segmented
in patients with Parkinson's disease (PwPD)





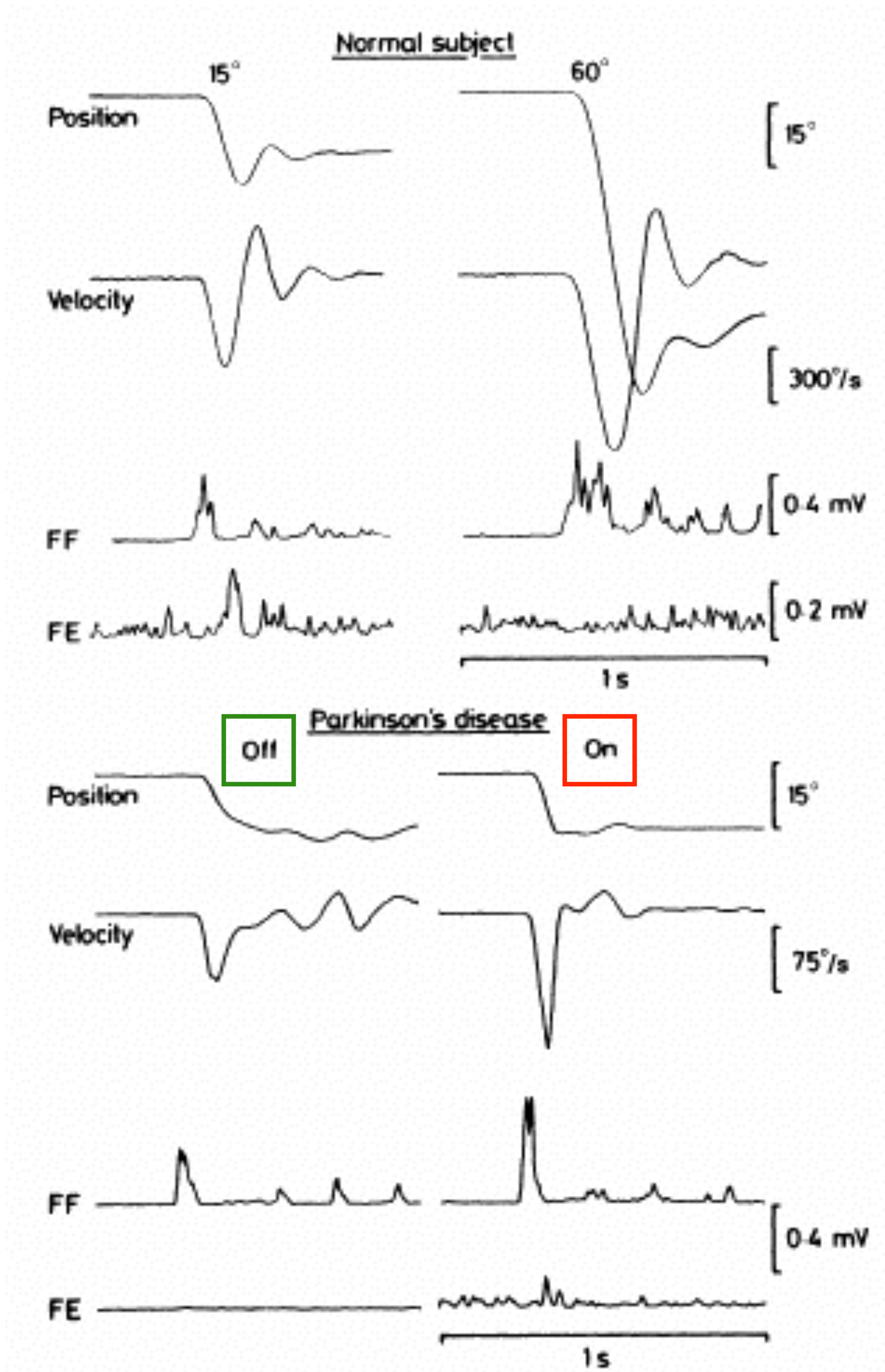
elbow flexion movements

— Hallett & Khoshbin, 1980, *Brain* 103:301

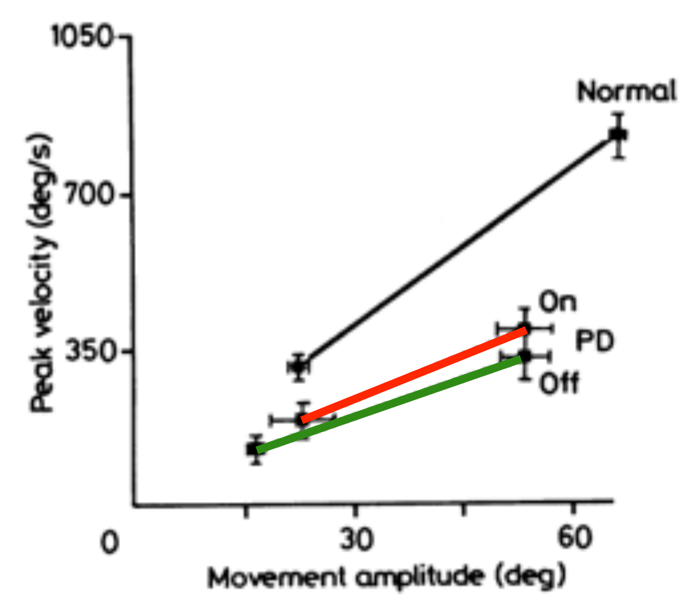
thumb movements

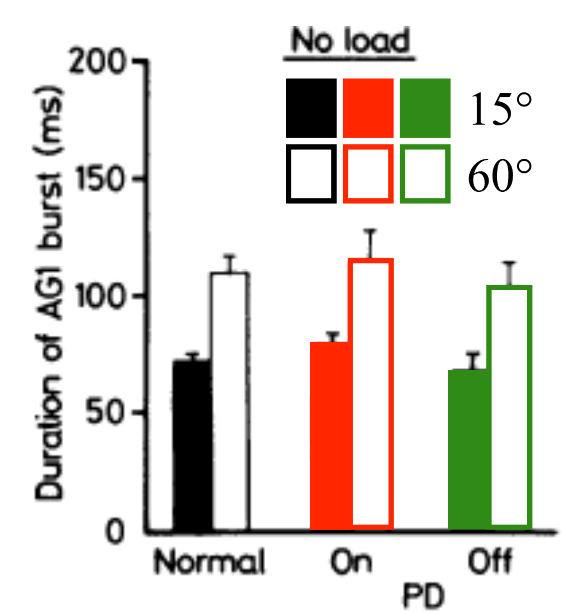
— Berardelli et al., 1984, *Neurosci Lett* 47:47

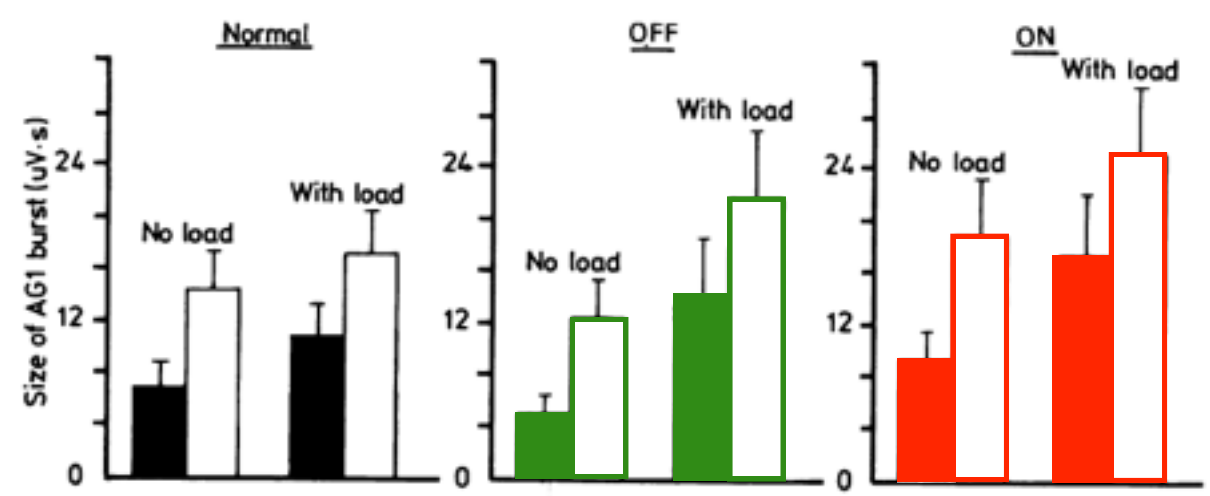
BASAL GANGLIA — MOTOR DEFICITS



rapid wrist flexion in PwPD







normal timing
reduced amplitude

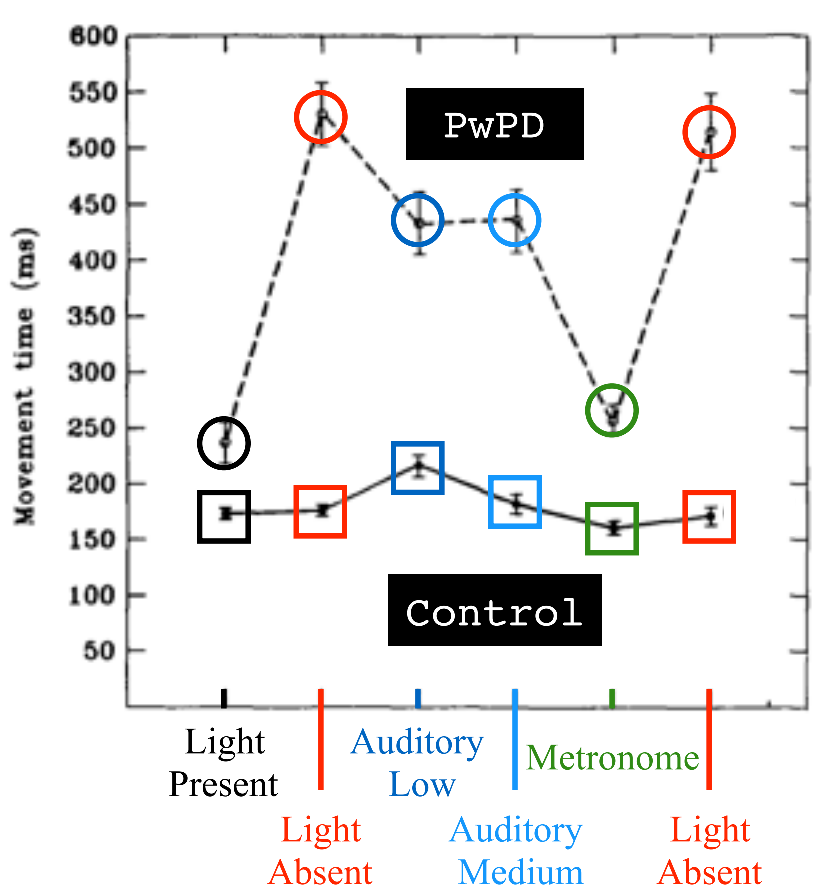
— Berardelli et al., 1986, *J Neurol Neurosurg Psychiatr* 49:1273

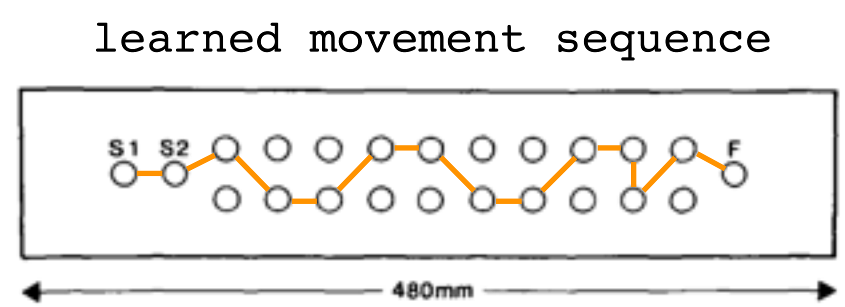
BASAL GANGLIA — MOTOR DEFICITS

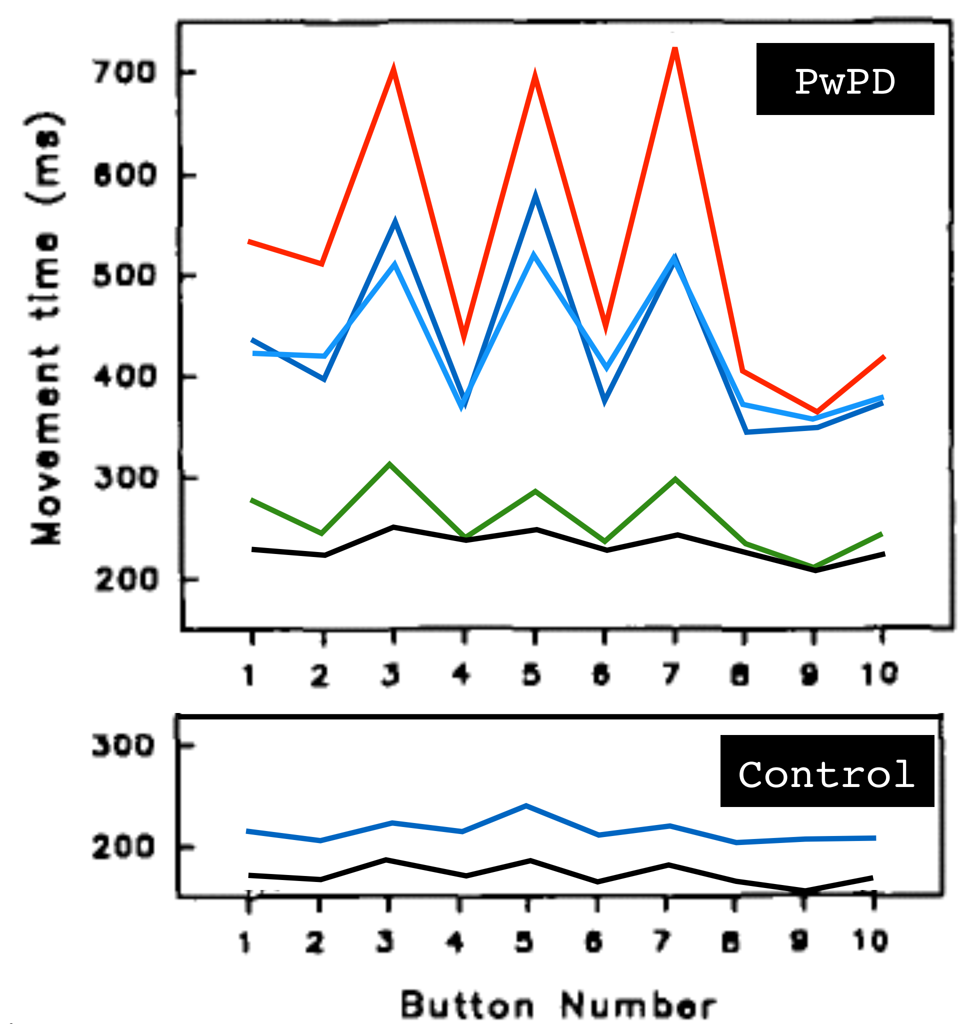
Context-dependent deficits

nature of sensory guidance in PwPD

cue conditions	**all buttons on** **all buttons off** **buttons off, sound at release** **buttons off, sound at press** **metronome**

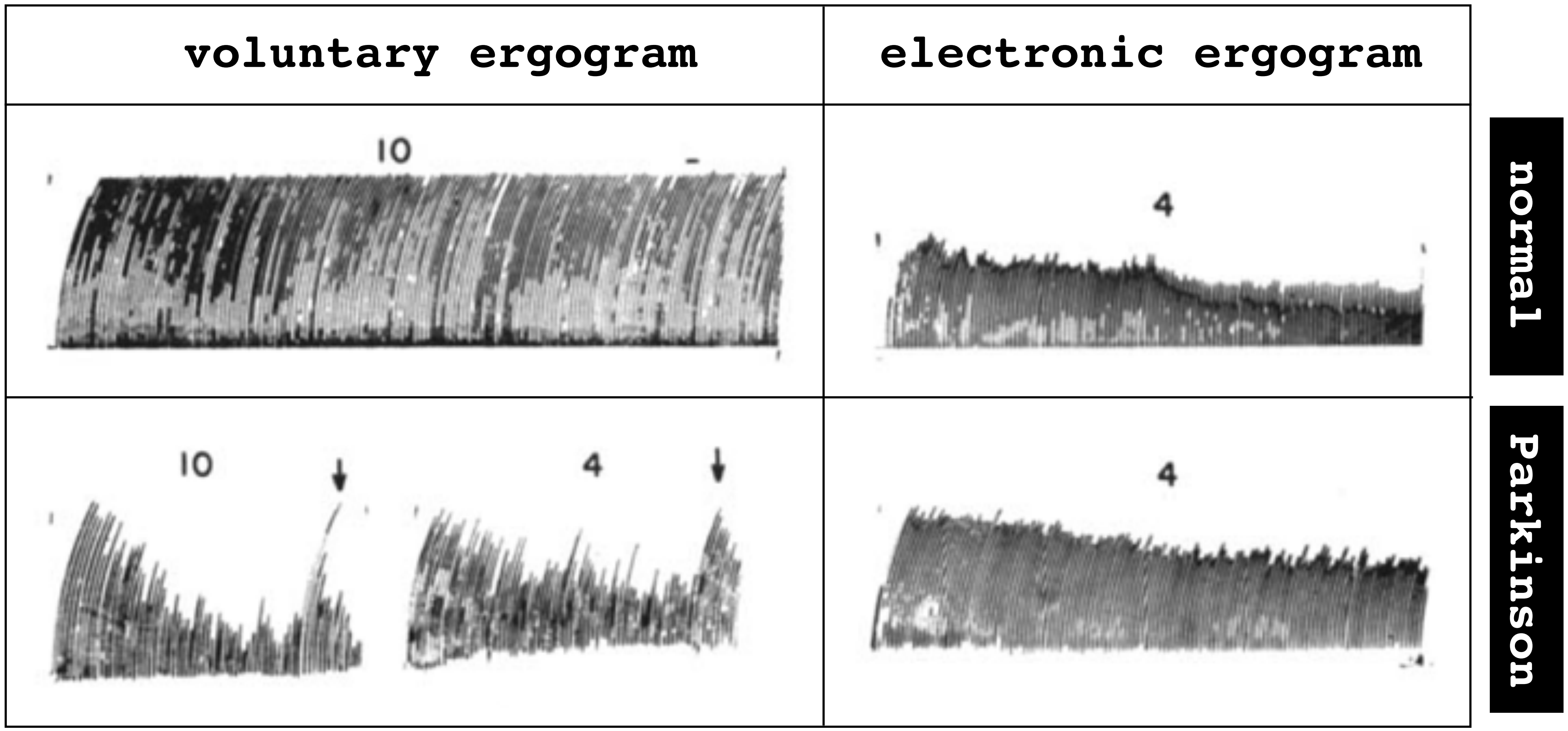


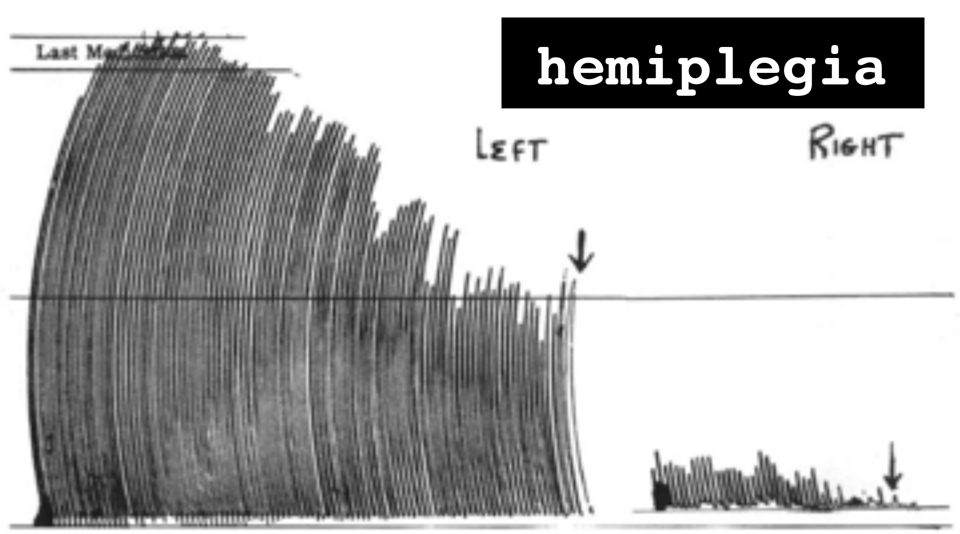




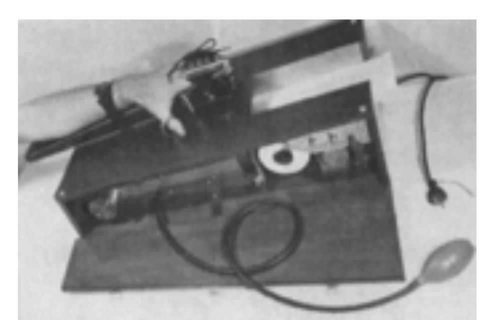
— Georgiou et al., 1993, *Brain* 116:1575

PARKINSON'S DISEASE AND MOTIVATION



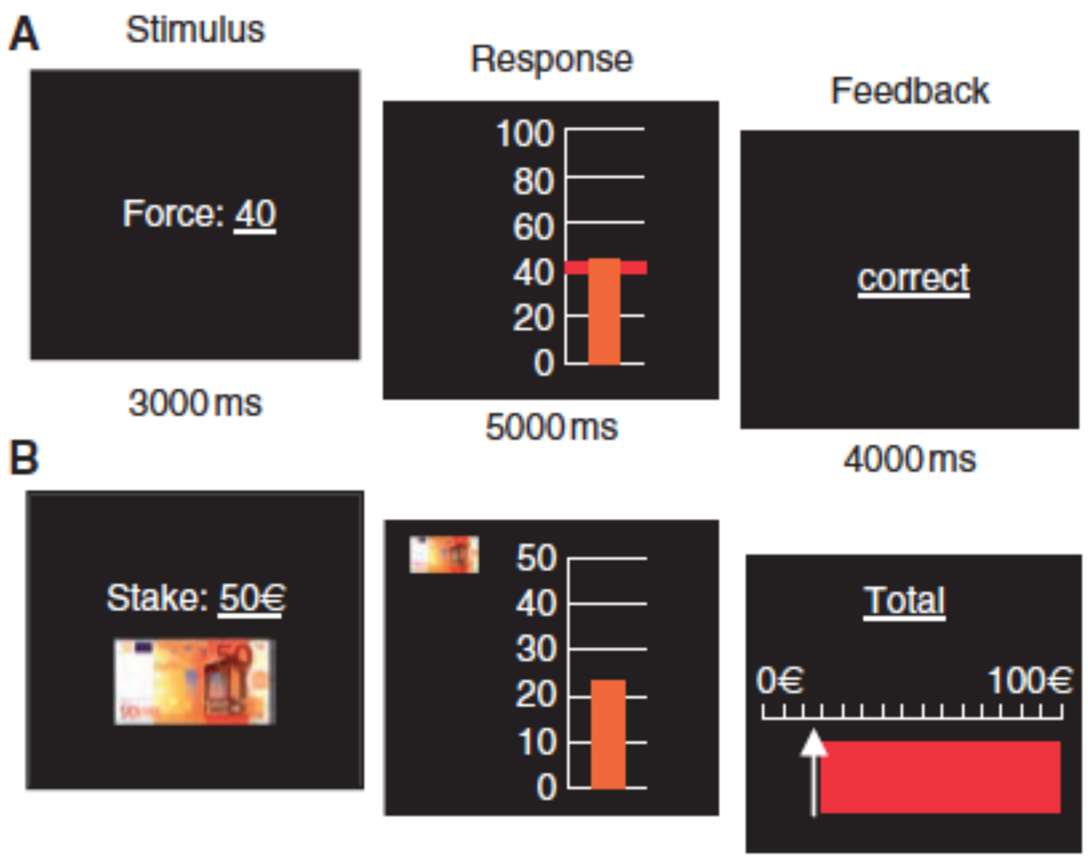


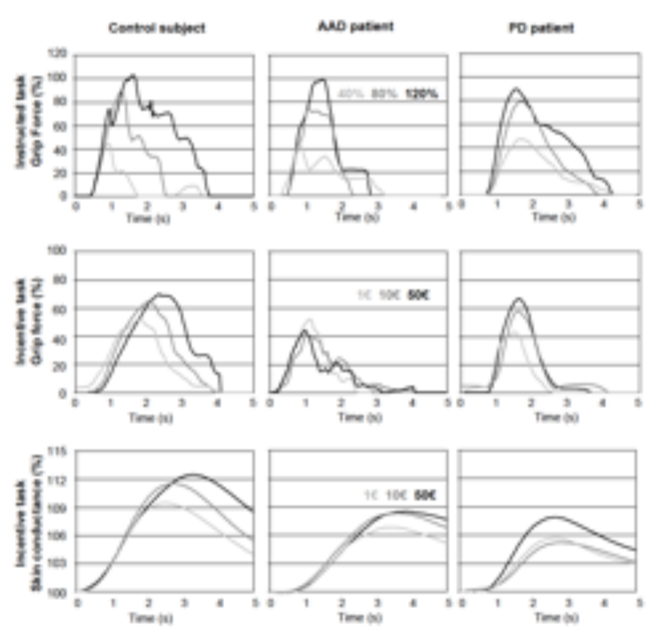
→ increased motivation
urge to make a
vigorous squeeze

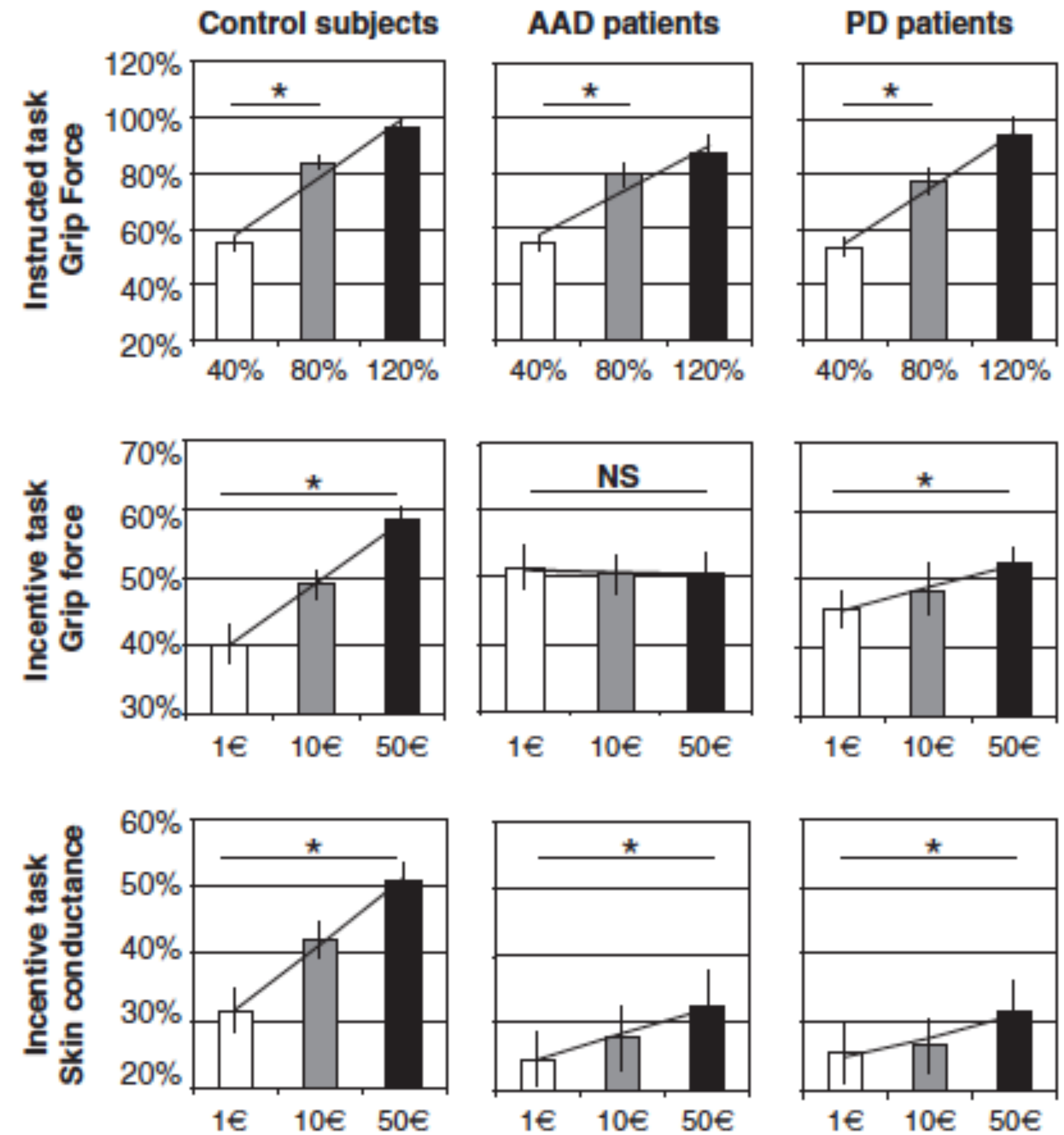


— Schwab et al., 1959, *Neurology* 9:65

PARKINSON'S DISEASE AND MOTIVATION

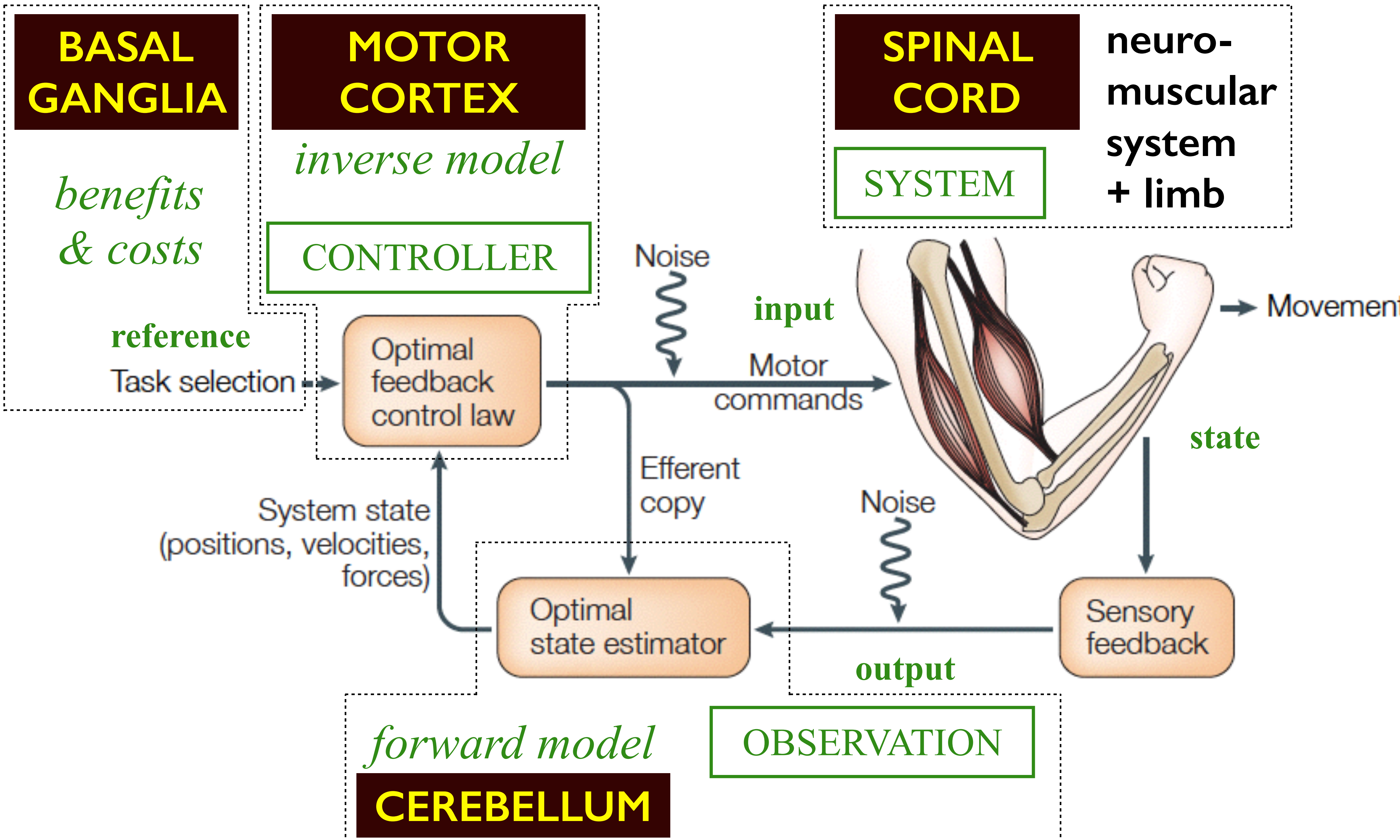






— Schmidt et al., 2008, *Brain* 131:1303

COMPUTATIONAL NEUROANATOMY



— Scott, 2004, *Nat Rev Neurosci* 5:534

— Shadmehr and Krakauer, 2008, *Exp Brain Res* 185:359