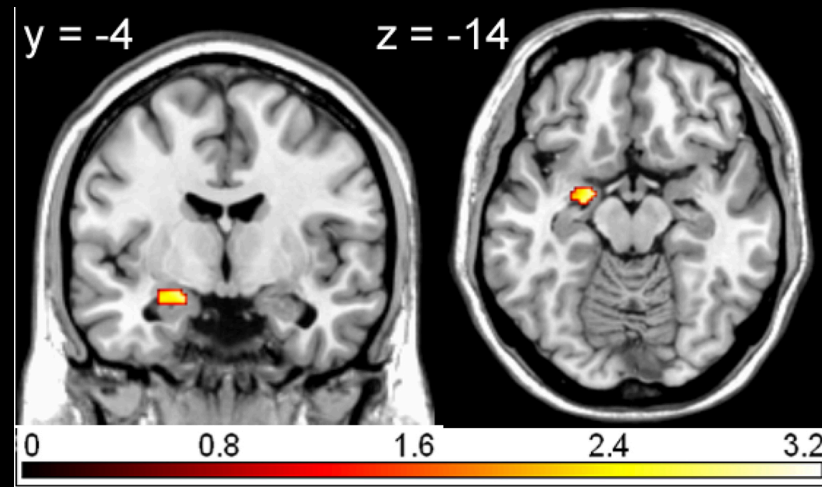


# An Introduction to Neuroscience

Dr. Olav E Krigolson  
krigolson@gmail.com



## Tonight

Parkinson's Disease

Motor Control

Transcranial Magnetic Stimulation

## Other Information

Next week is Attention

krigolsonlab@gmail.com







# Levels of Motor Control

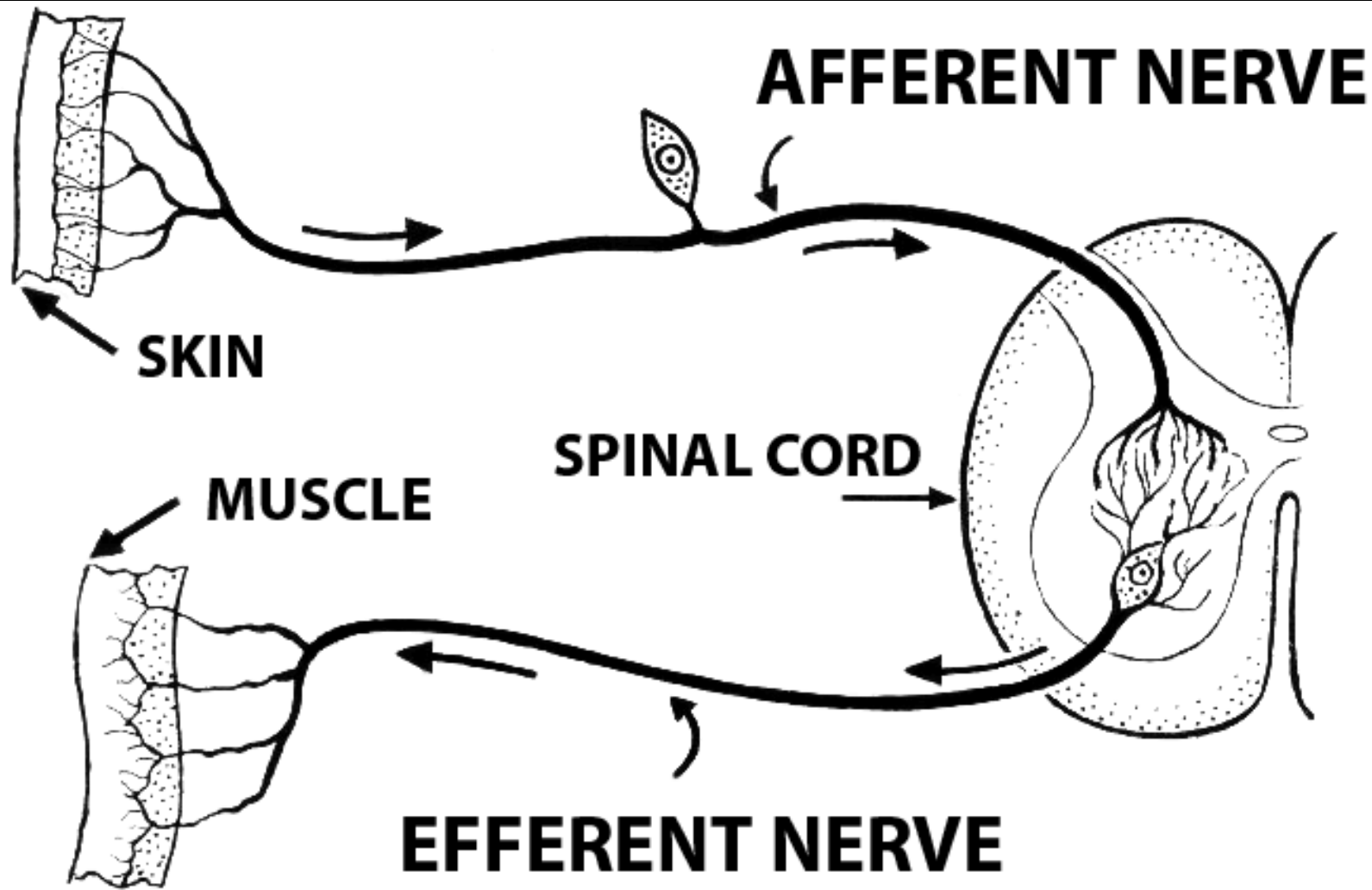
1. Reflexes
2. Postural Control
3. Cyclical Movements
4. Goal Directed Action
5. Motor Control



# Levels of Motor Control

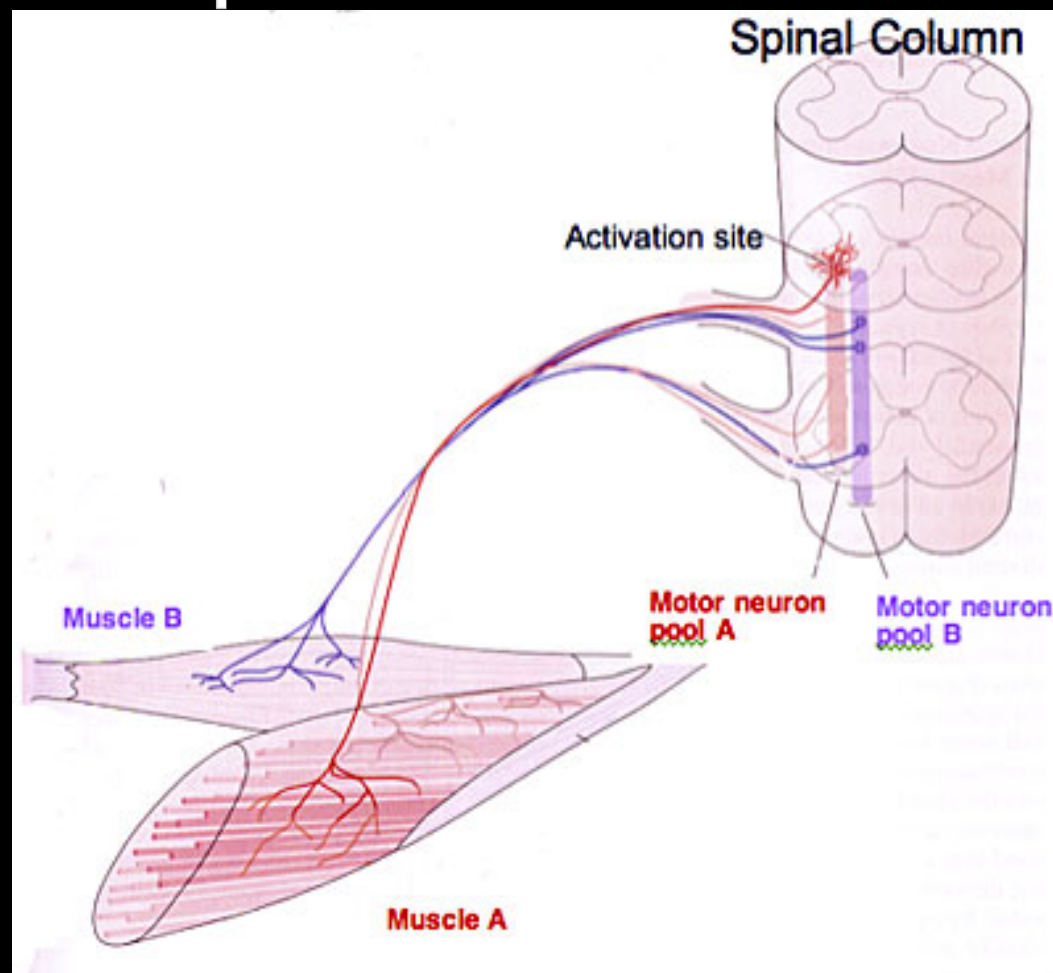
1. Reflexes
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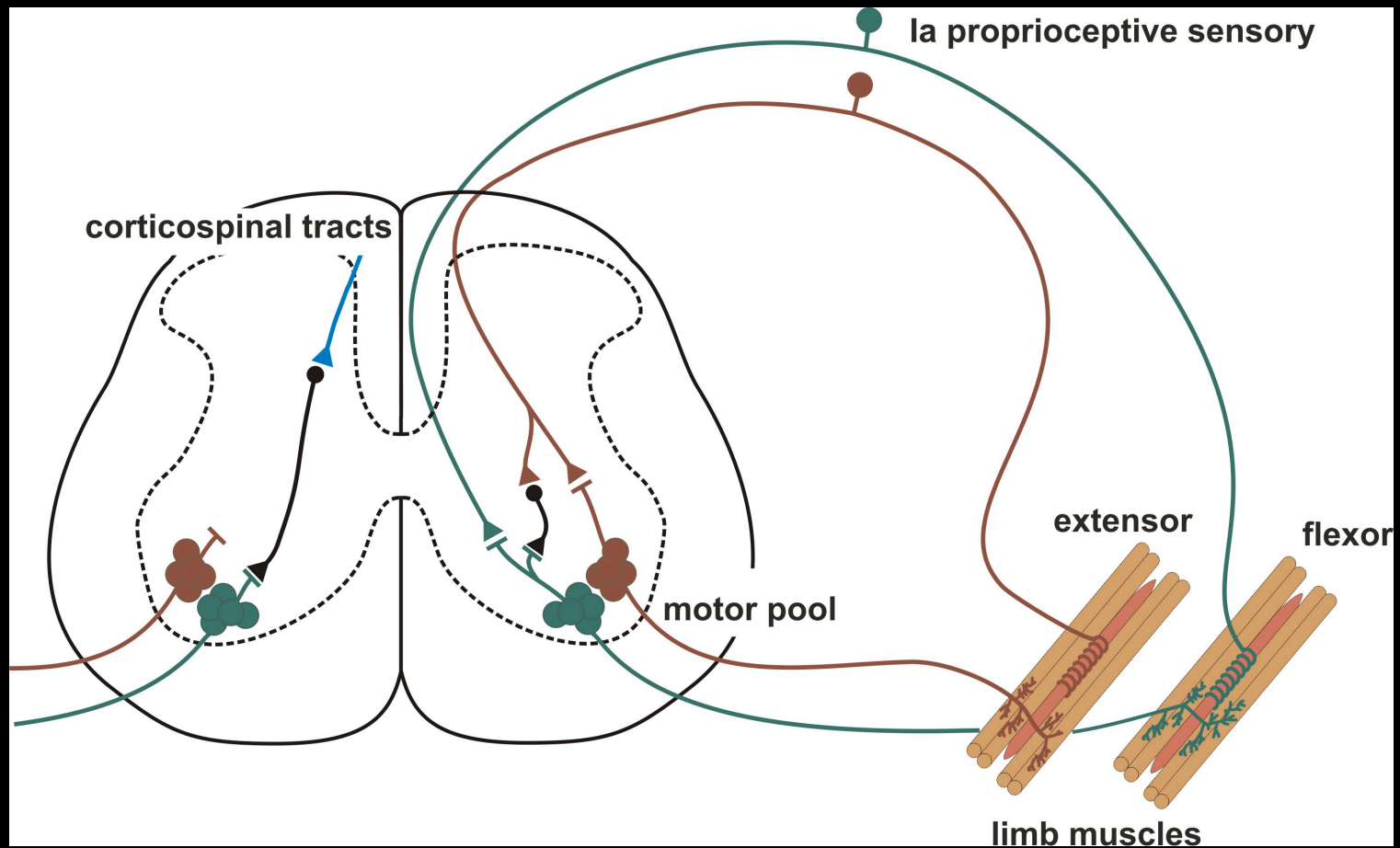


# Alpha Motor Neuron





# 1a Sensory Neuron





## Definition of the Reflex

*"A simple reflex is probably a purely abstract conception, because all parts of the nervous system are connected together & no part of it is probably ever capable of reaction without affecting & being affected by various other parts, & it is a system certainly never absolutely at rest. But the simple reflex is a convenient, if not a probable, fiction. Reflexes are of various degrees of complexity, & it is helpful in analysing complex reflexes to separate from them reflex components which we may consider apart & therefore treat as though they were simple reflexes."*

– Sir Charles S. Sherrington, "Integrative Action of the Nervous System" (1906)



# Reflexes

**Muscle Reflex: Contraction induced by external stimulus**

**Once thought to be immutable**

**Now concept of reflex modulation predominates**

- **Nature of a reflex depends on the context**
- **(e.g., sitting versus standing)**



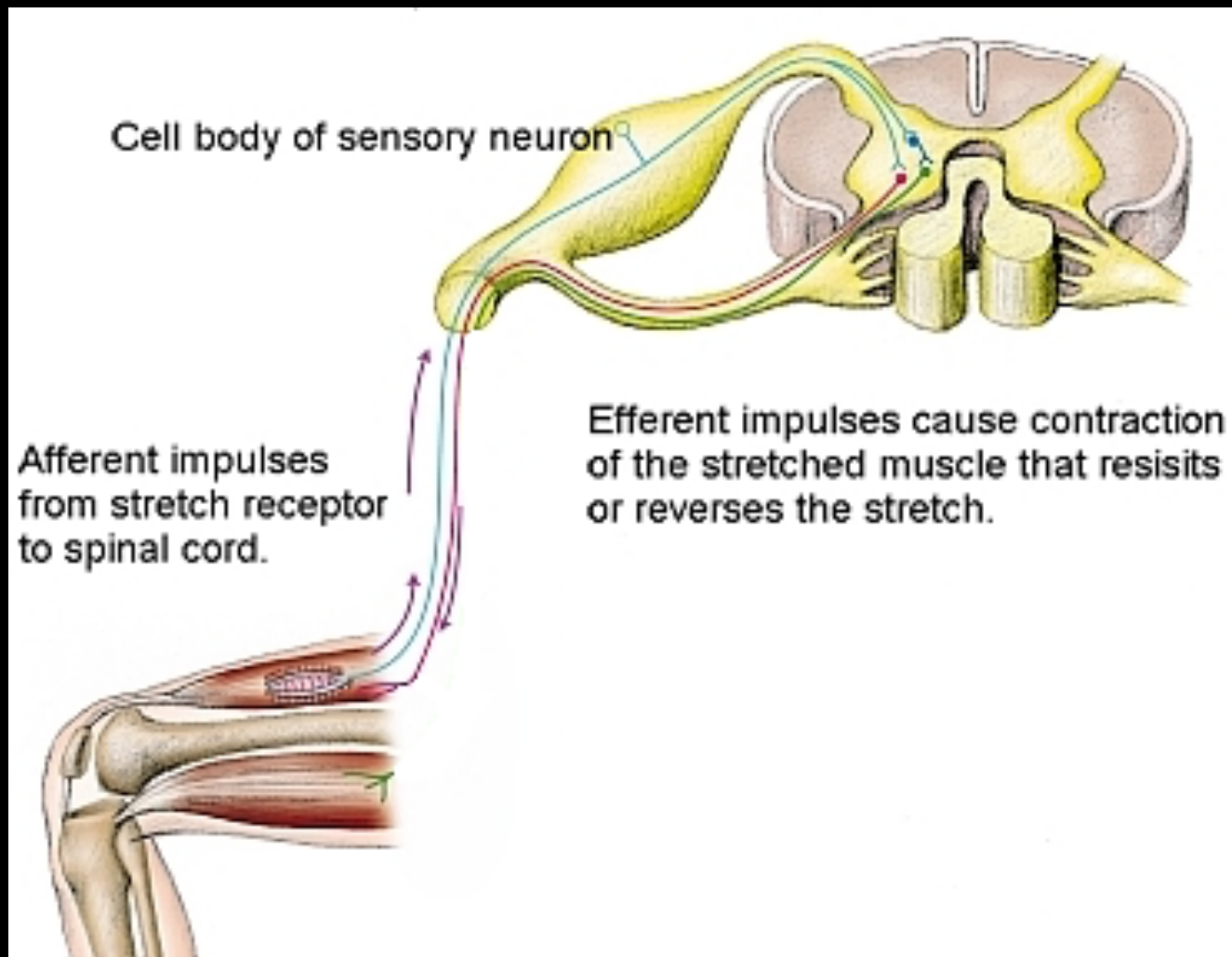
# **Why Do We Care About Reflexes?**

**They underlie and support all posture  
and movement!**

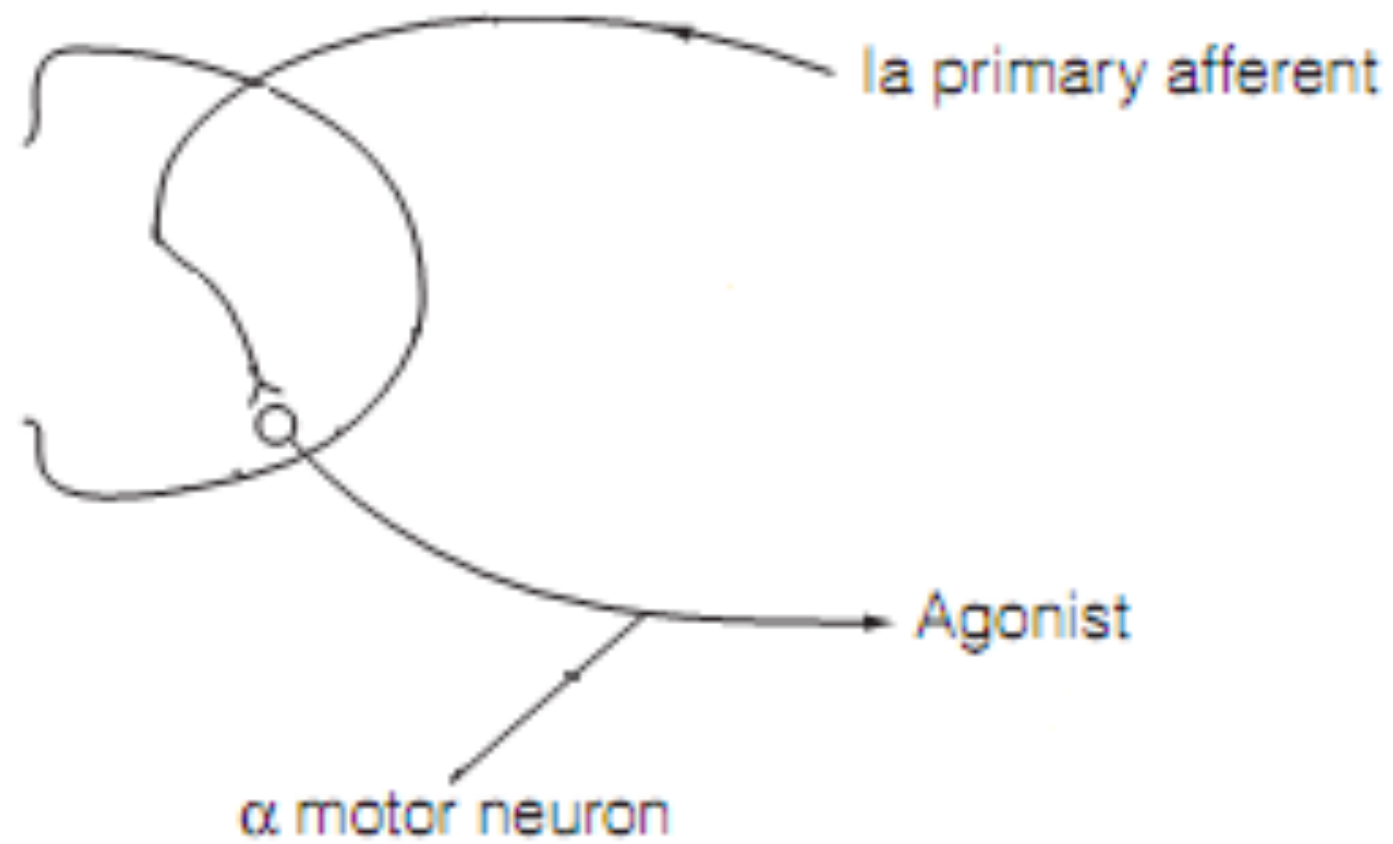


## **The Simple (?) Monosynaptic Stretch Reflex**



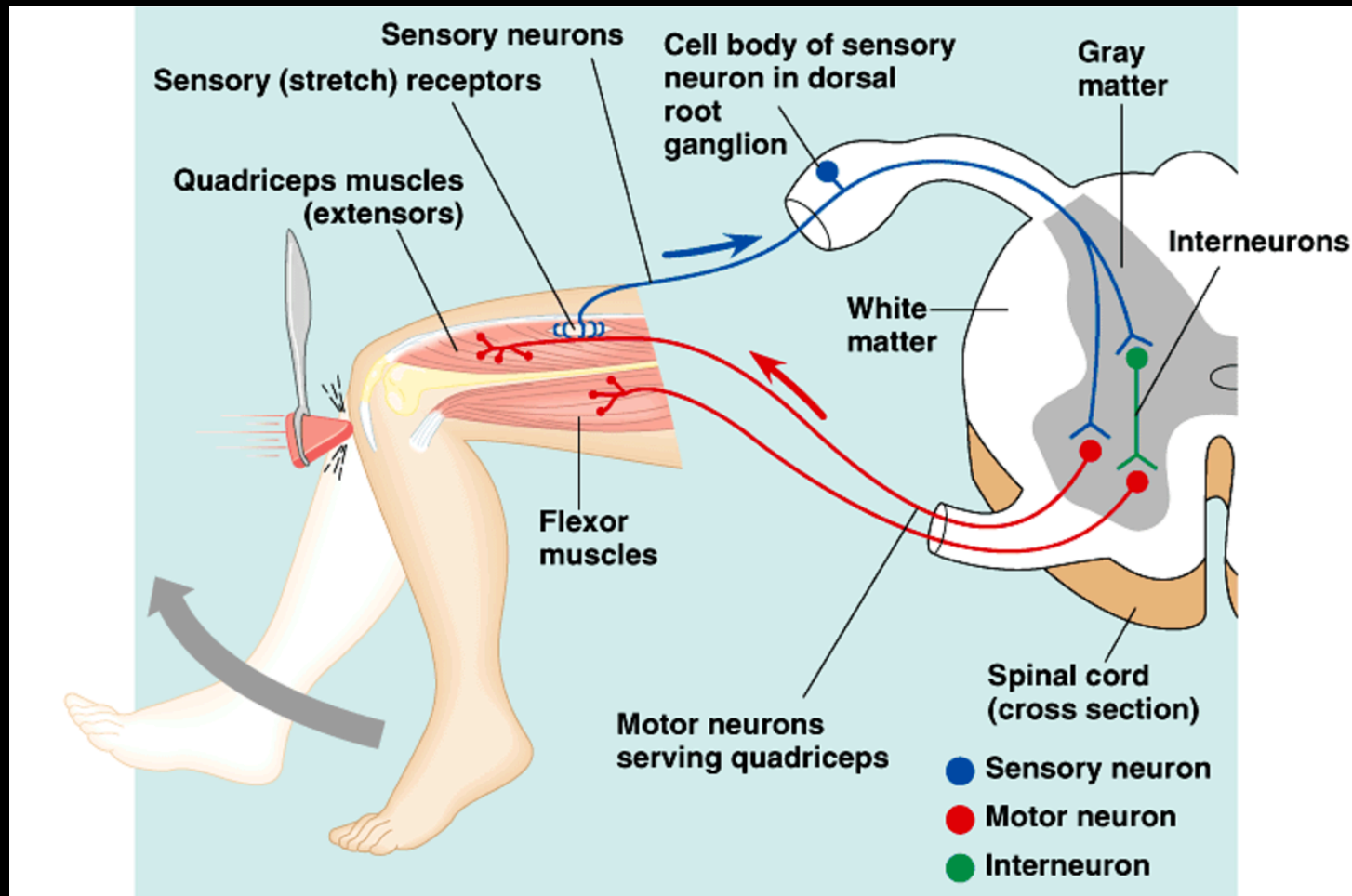




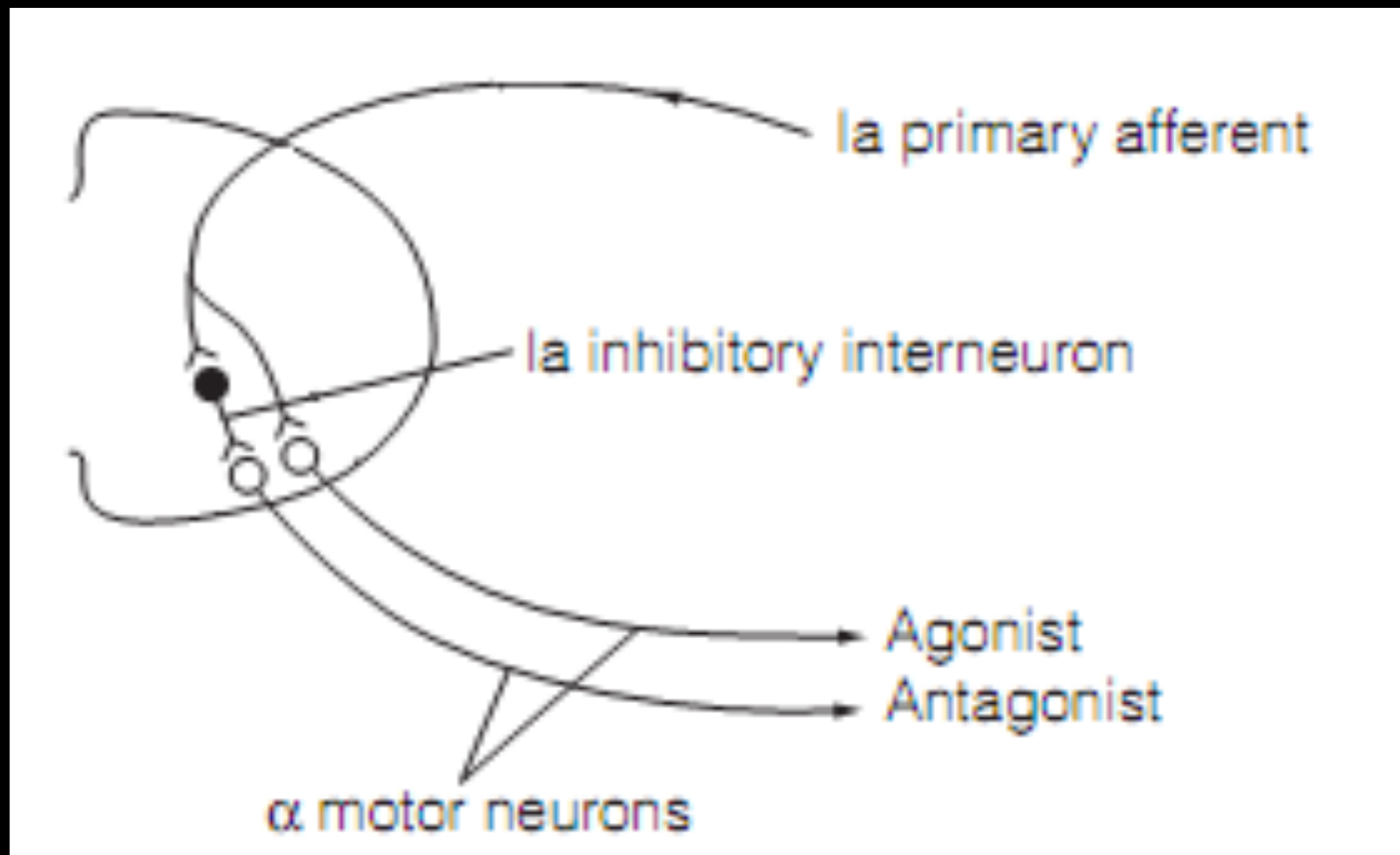




# Reciprocal Inhibition

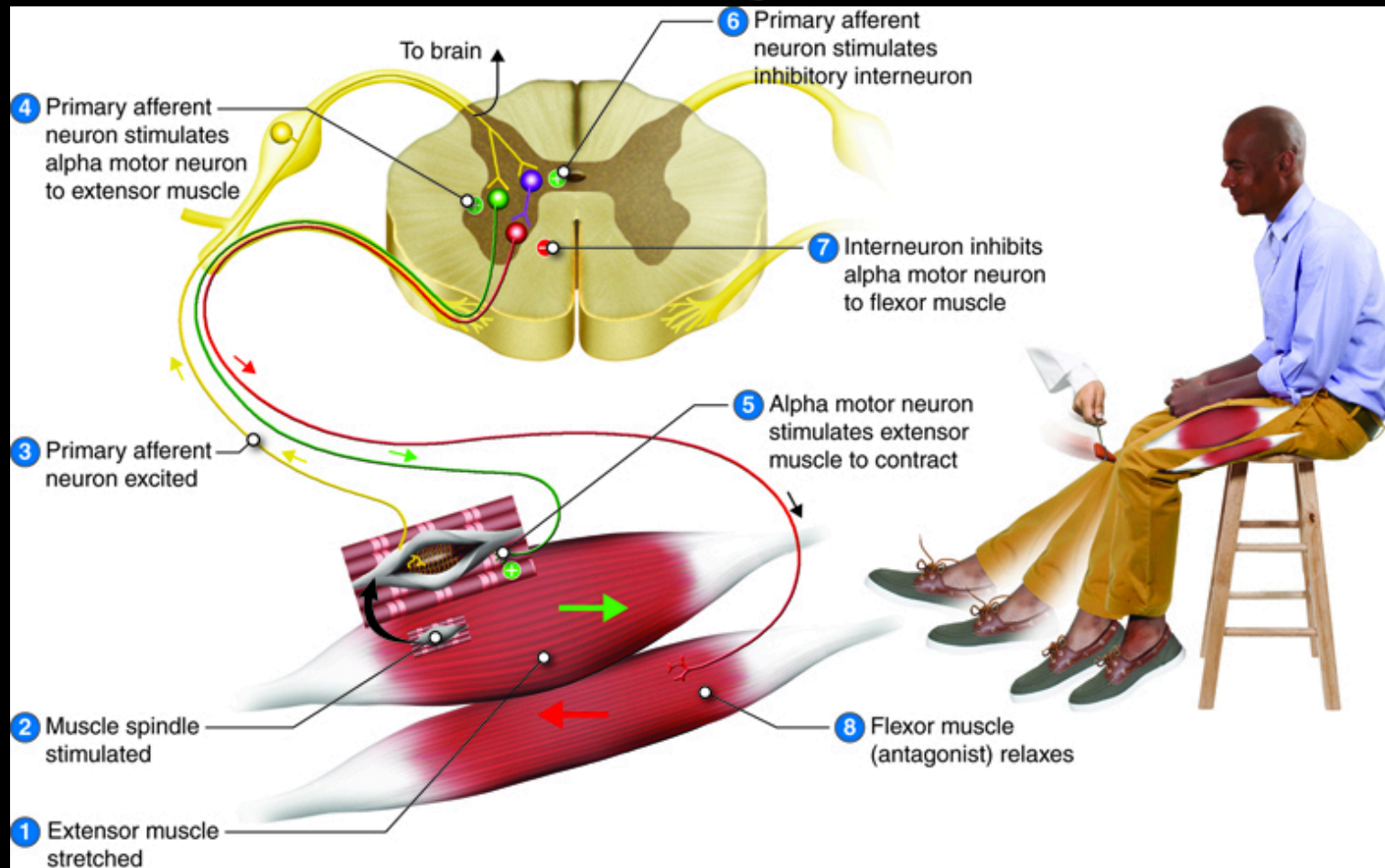








# Stretch Reflex (e.g. Tendon Tap)



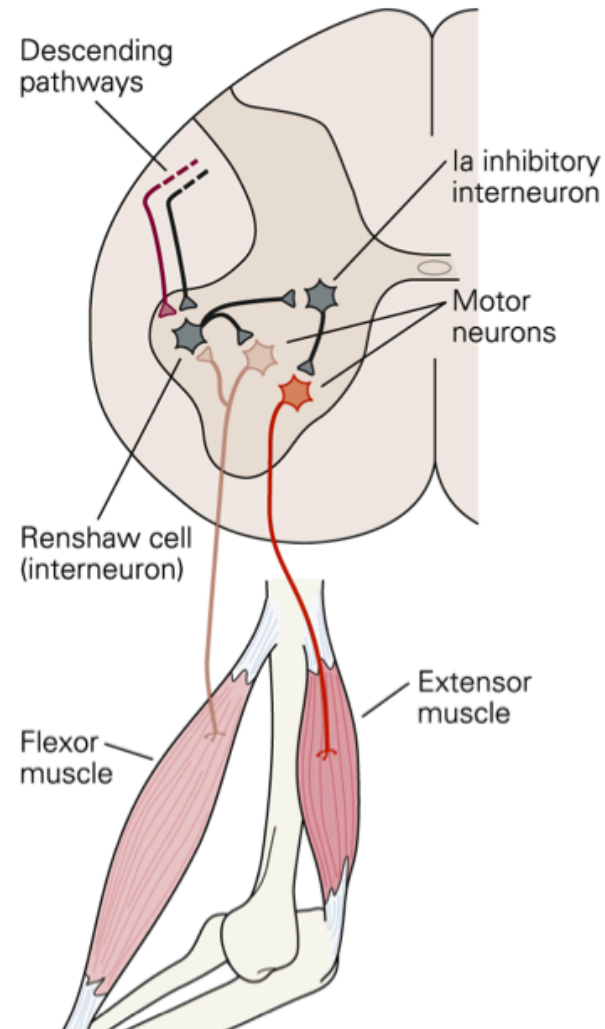


# Renshaw Cells

## RECURRENT INHIBITION

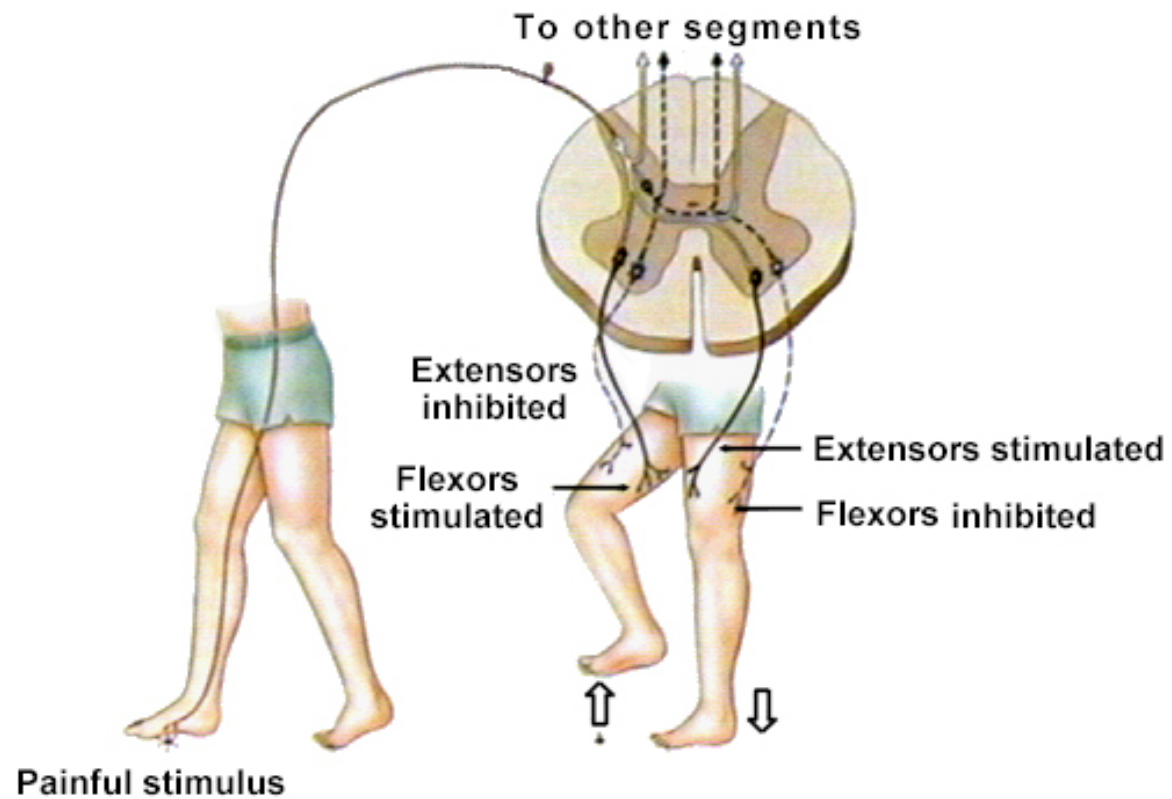
- regulates the firing of the alpha motor neuron (the MN can inhibit itself)
- removes “noise” by dampening the firing frequency of over-excited neurons
- prevents weakly excited alpha motor neurons from firing.

B Renshaw cell





## Flexion Withdrawal Reflex...





# Levels of Motor Control

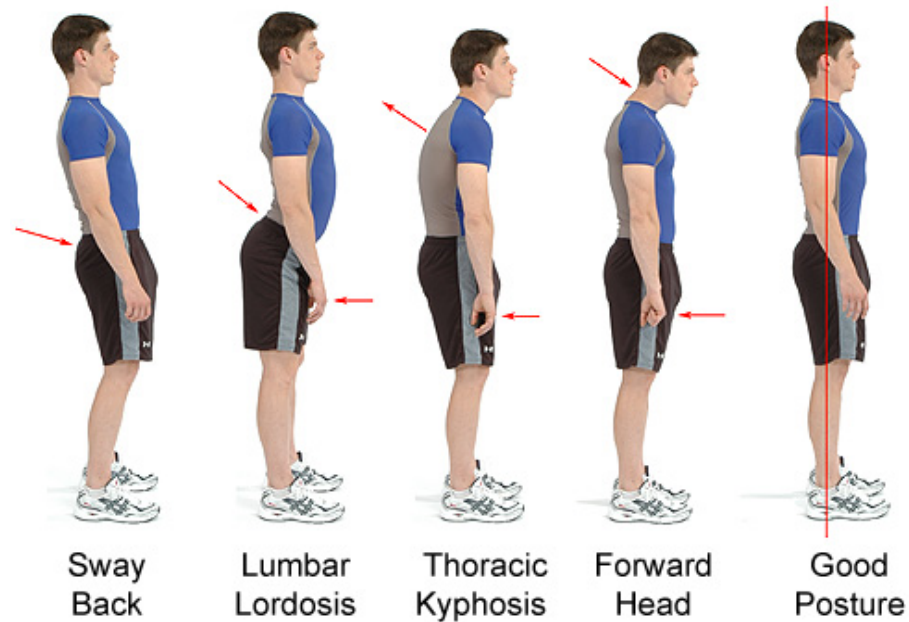
1. Reflexes
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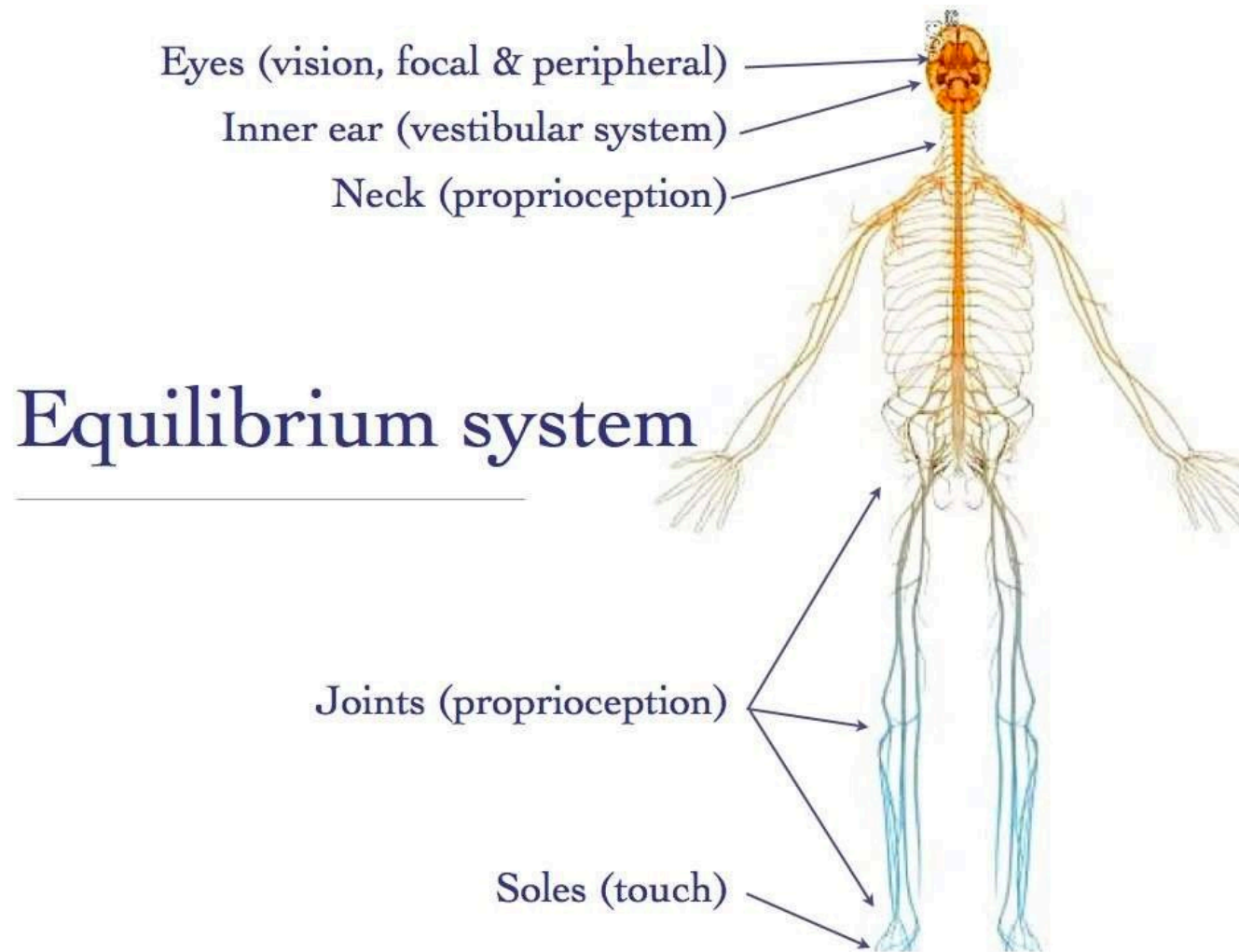
Posture:

relative position  
of various parts  
of the body with  
respect to each  
other

- Egocentric  
(within)
- Exocentric  
(with world)
- Geocentric  
(with gravity)

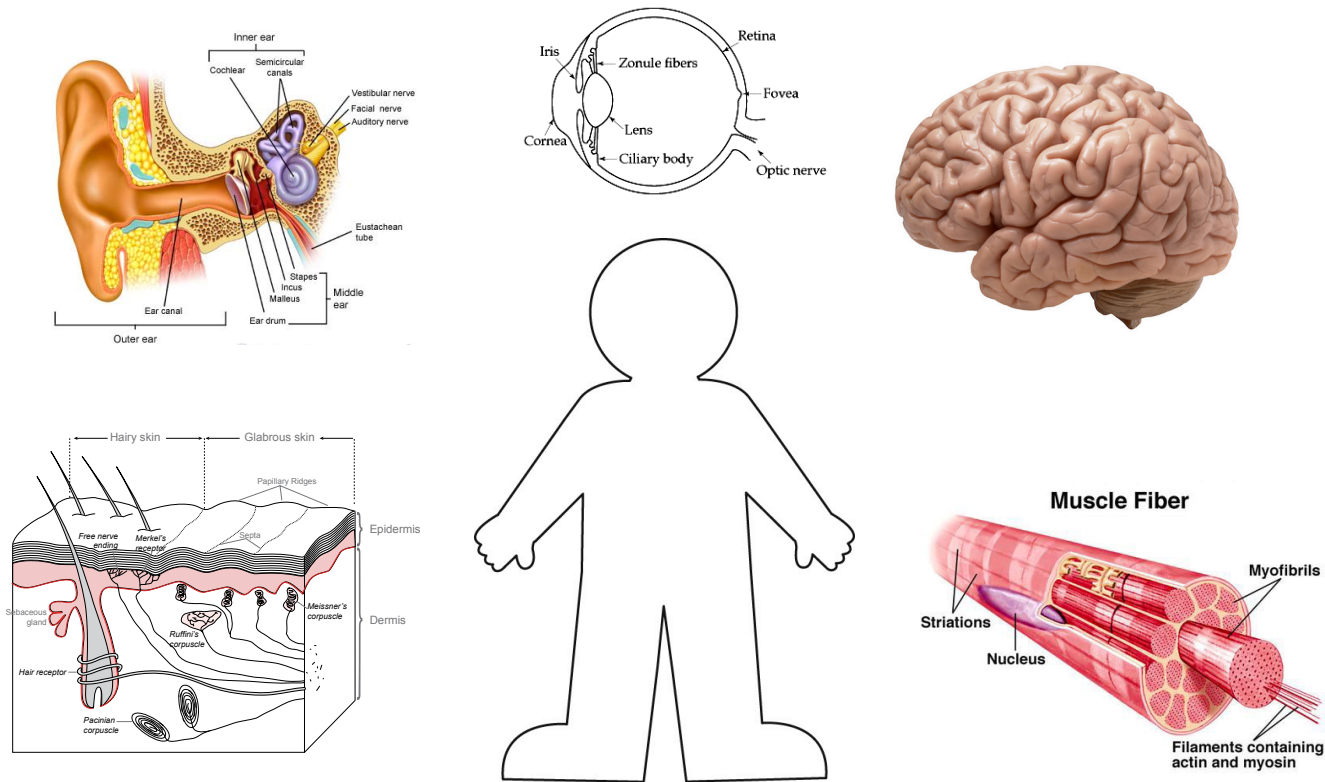








# How (Where) Does Postural Control Occur?



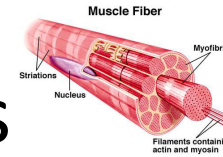


# Posture: Lines of Defense

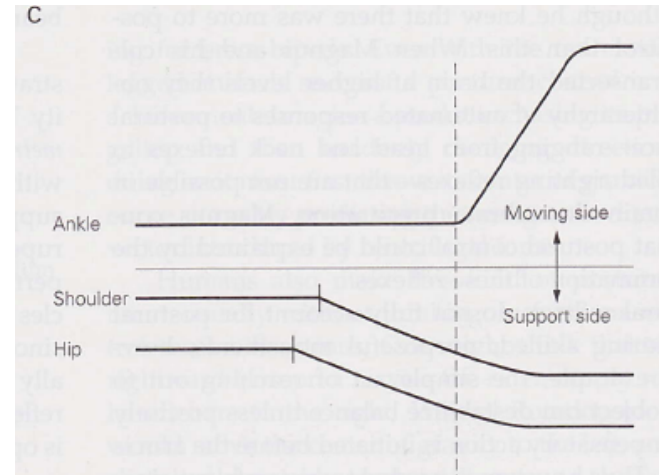
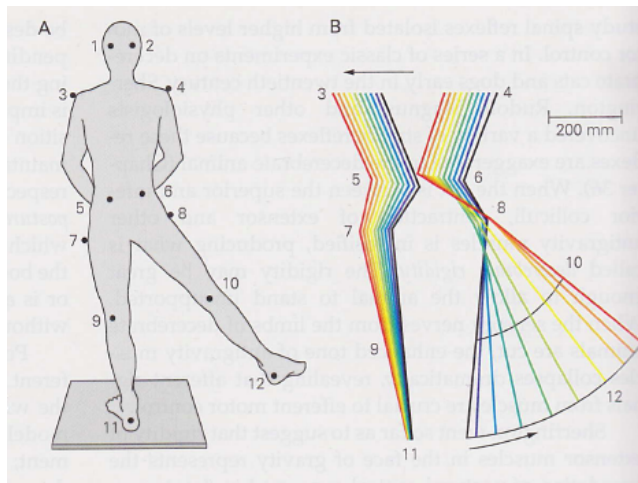
Mechanism	Typical Time Delay	Important Features
1. Anticipatory Postural Actions	-600 ms - 0 ms	Based on predicting a perturbation
2. Muscle and tendon elasticity	0 ms	Can be modulated (pre-flexes)
3. Equilibrial triad (vision, vestibular, proprioception)	20 ms -70 ms	Poorly controlled, low gain
4. Pre-programmed reactions	80 ms	Approximate correction
5. Voluntary actions	150 ms	Too late!



# 1. Anticipatory Movements



Try at home experiment: stand against wall and raise outside leg



- Hip and shoulders move before ankle rises
- Counterbalancing movement 600 ms prior



## 2. Muscle and Tendon Elasticity

- Auto-stabilize movements
- Tensing muscles to enhance stiffness
- Agonist, antagonist pairs
- Visco-elastic properties
- CNS can control the baseline level of activation in postural muscles
- “Pre-flexes”
- Instantaneous response for unexpected perturbations



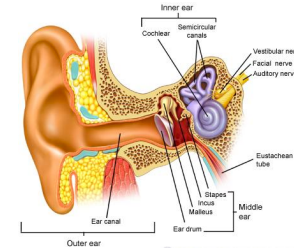


### 3. Equilibrial Triad

- A. Vestibular System
- B. Vision
- C. Proprioception



## A. Vestibular System



‘Which way is up?’

Major factor in the maintenance of upright posture with reflexive action

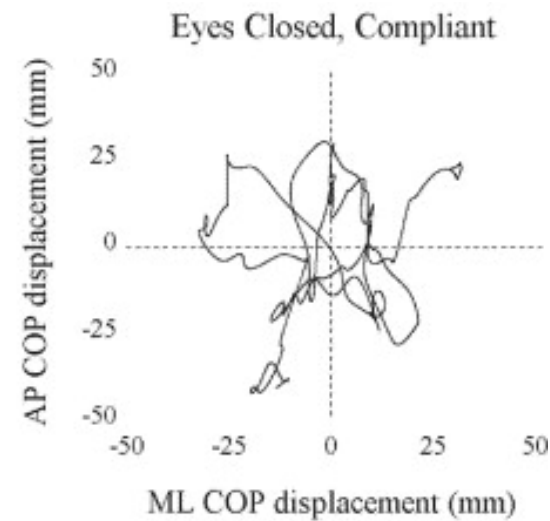
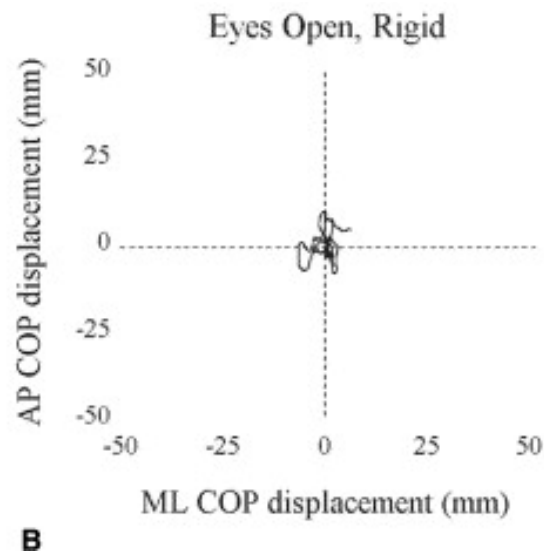
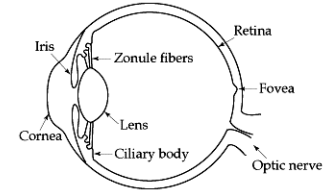
- To control upright posture
- To control eye movements

Normally, we are not conscious of this system



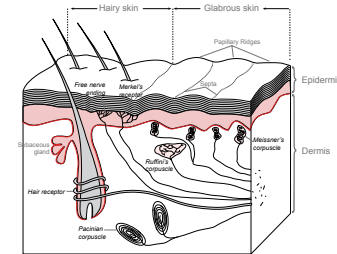
## B. Vision

- Most reliable sense
- Postural sway worsens without vision





## C. Proprioception



- In order make use of vestibular and visual circuits, you must have information about body position in space
- From peripheral receptors
  - Skin
  - Muscle
  - Tendon
  - Joint



## 4. Pre-Programmed Reactions

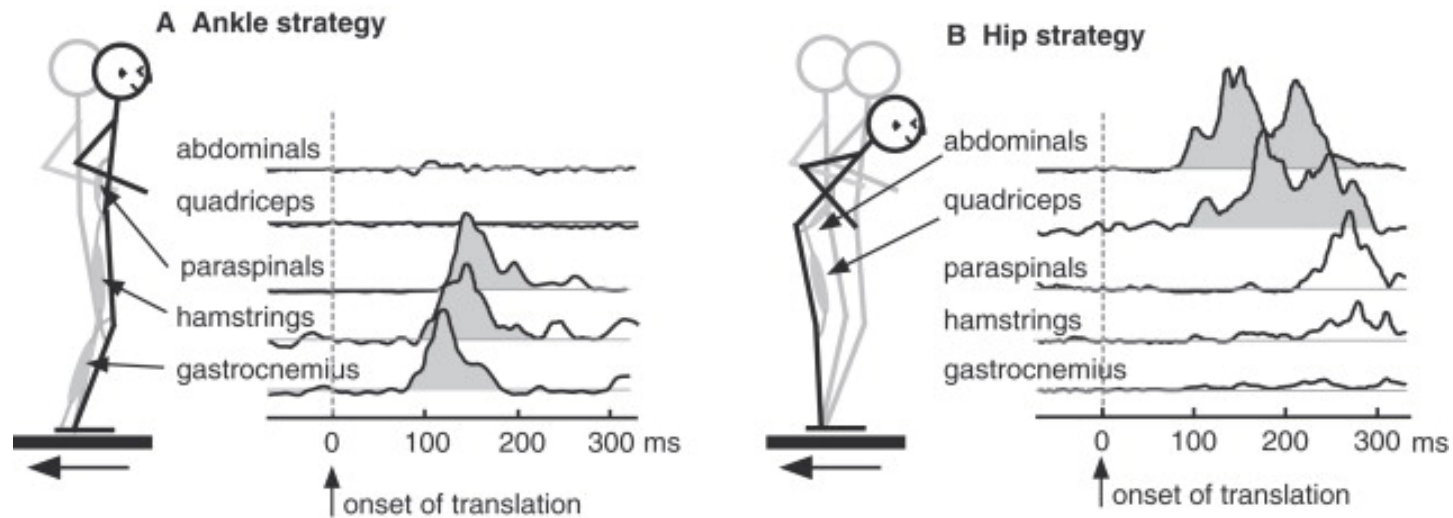


- Preferred patterns of corrective postural reactions
- Specific combination of muscle activity
- Longer delay; 80 ms
  - Too slow for reflex
  - Too fast for voluntary
- More powerful and more flexible
- Triggered by activation of visual, vestibular, and proprioceptive input
- Postural synergies: preferred pattern of muscle co-activation to maintain balance



(Ting, 2006 Prog in Brain Res)

# Postural synergies



- Forward body sway
- Dorsal muscles
- Distal to proximal
- Efficient, dangerous
- For slow perturbations

- Backward body sway
- Ventral muscles
- Proximal to distal
- Safe
- For fast perturbations



## 5. Voluntary Actions



### **Journal of Motor Behavior**

Publication details, including instructions for authors and subscription information:

<http://www.tandfonline.com/loi/vjmb20>

### **Hierarchical Error Evaluation: The Role of Medial-Frontal Cortex in Postural Control**

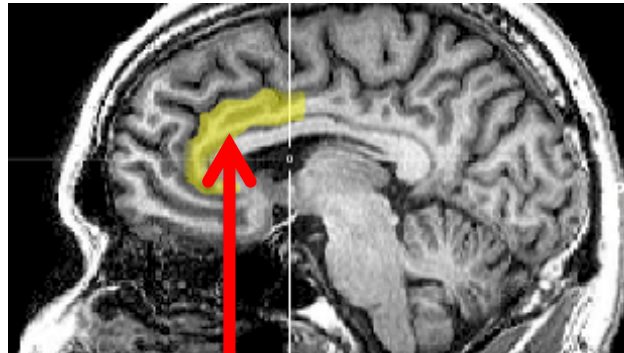
Cameron D. Hassall<sup>a</sup>, Stephane MacLean<sup>a</sup> & Olave E. Krigolson<sup>a</sup>

<sup>a</sup> Psychology and Neuroscience, Dalhousie University, Halifax, Nova Scotia

Published online: 10 Sep 2014.



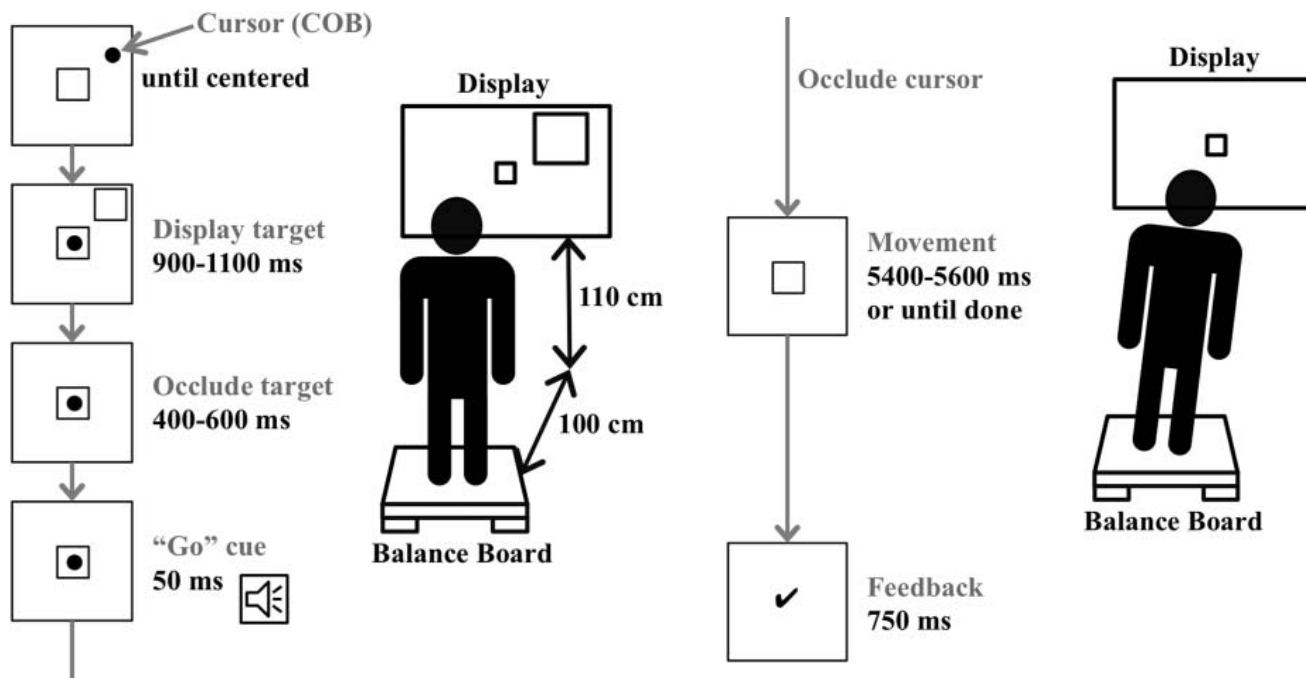
# Medial-Frontal Cortex



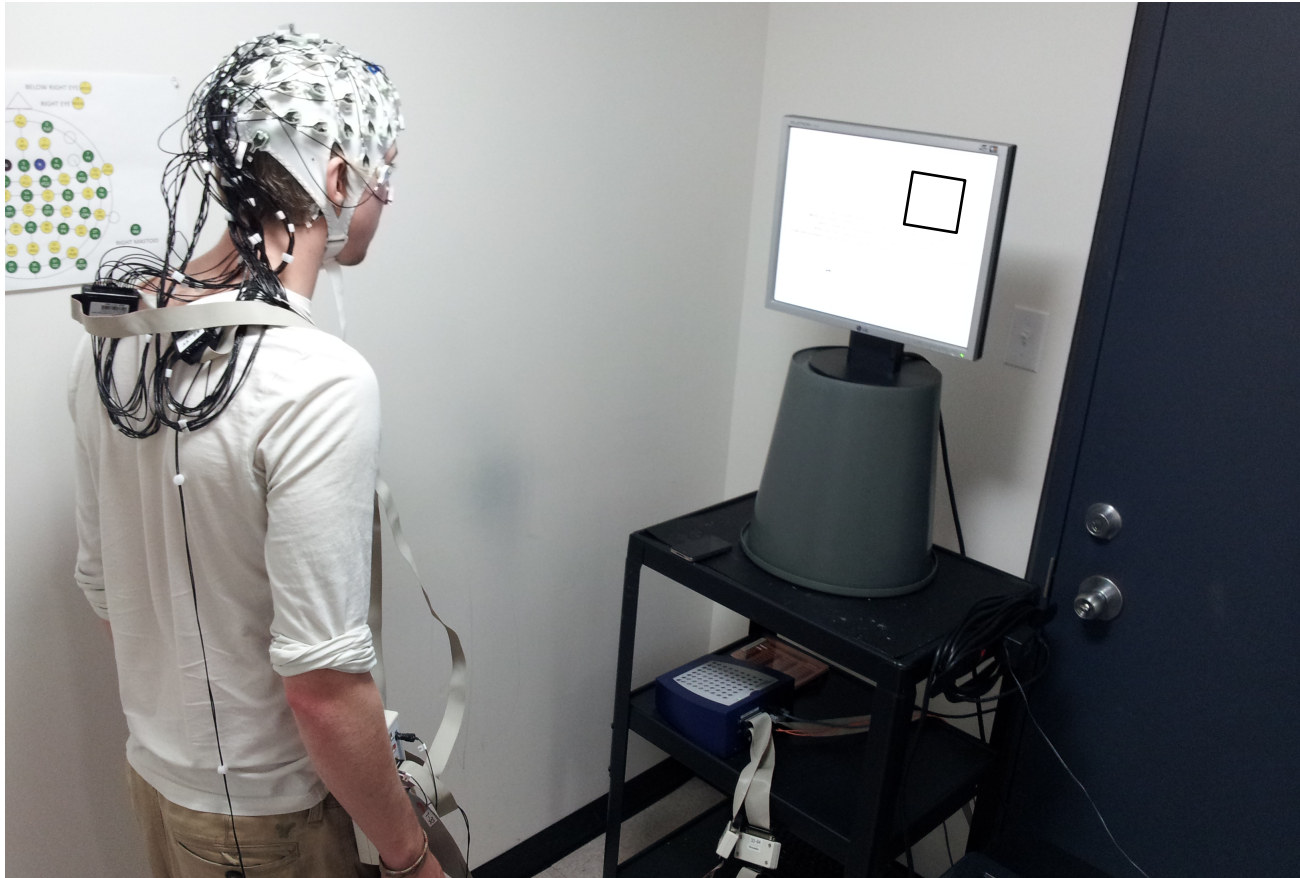
Cortical Control



# The Task



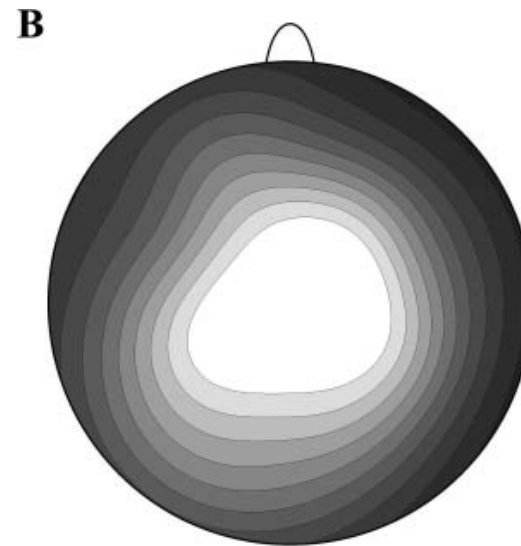
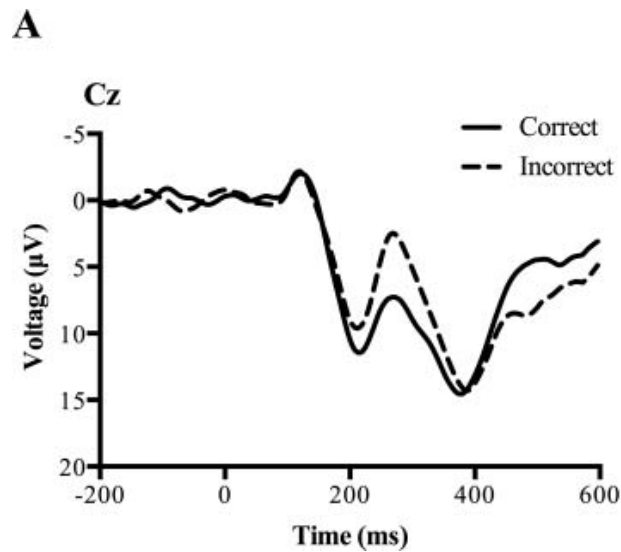






# ERP Results

- ERP: event-related potential – average scalp voltage response to an event





# Summary

1. Anticipatory postural actions
2. Muscle and tendon elasticity
3. Equilibrial triad
  - A. Vestibular
  - B. Vision
  - C. Proprioception
4. Pre-programmed reactions
5. Voluntary actions (Cortex)



# Levels of Motor Control

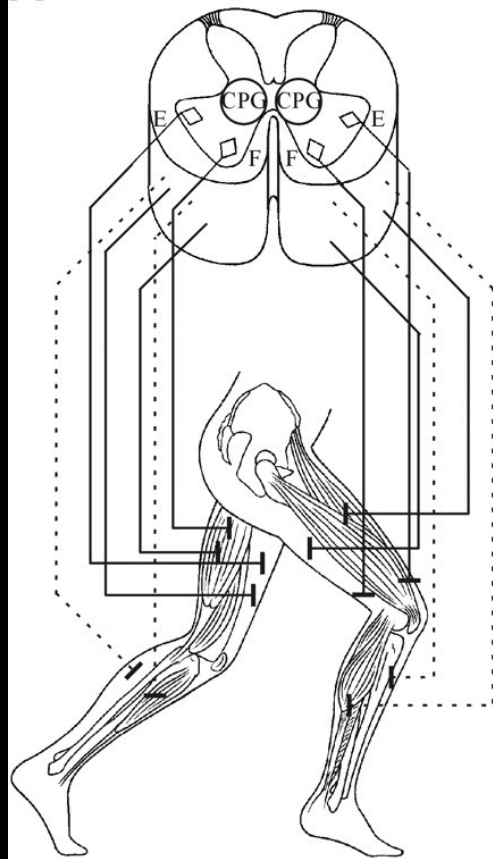
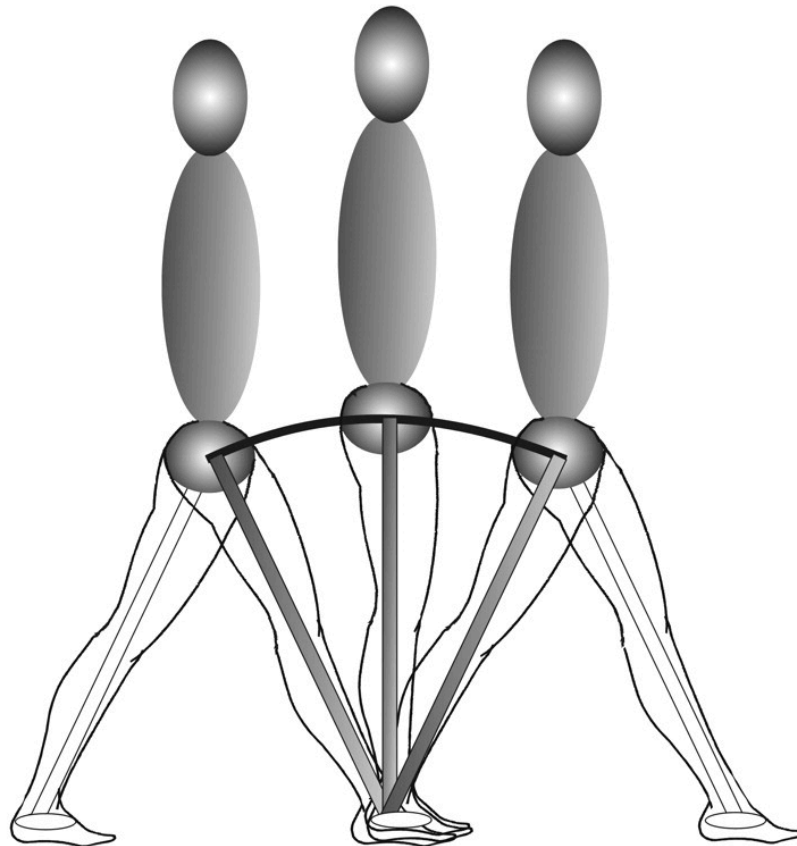
1. Reflexes
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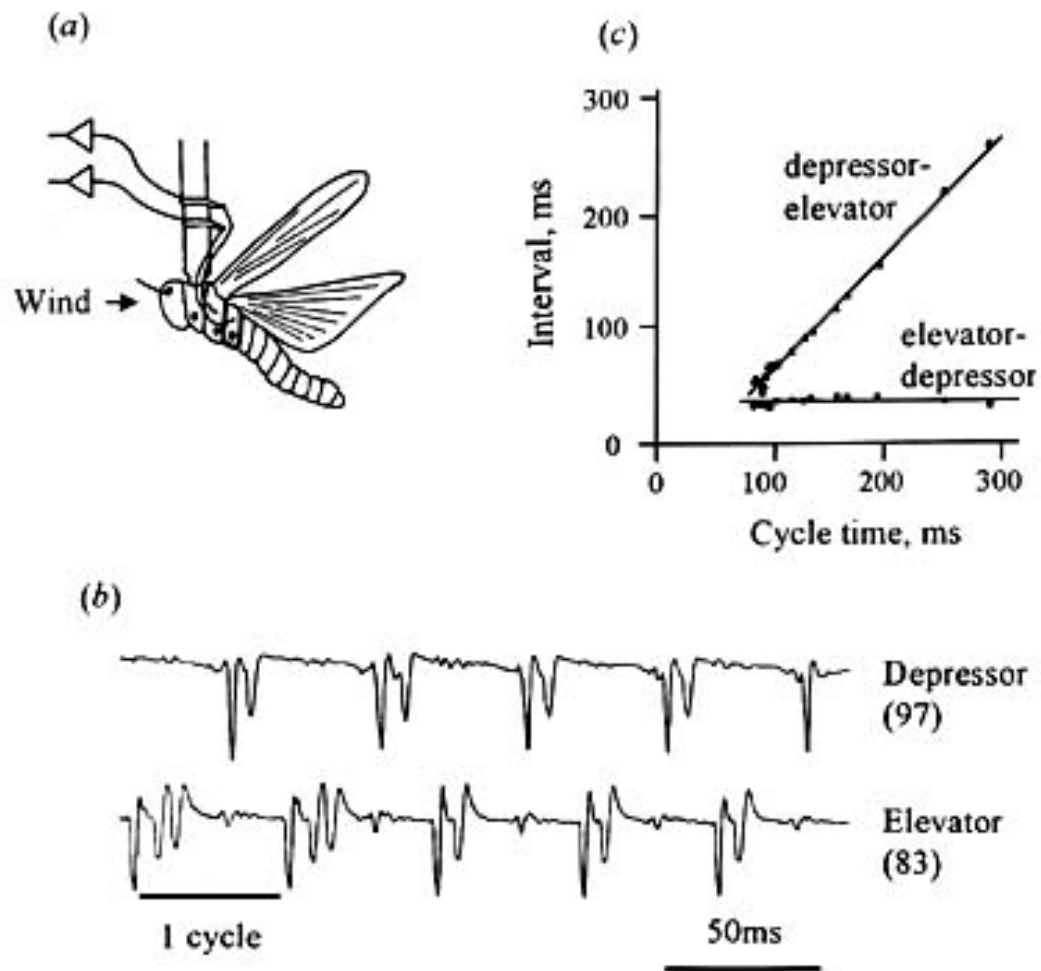
# Central Rhythm/Pattern Generators (CPGs)

- Most complex spinal networks
- Patterns of neuronal connections in spinal cord
  - generate purposeful movements and behaviours
    - e.g. walking, breathing
- Can generate **spontaneous repetitive patterns** of movement without further sensory input

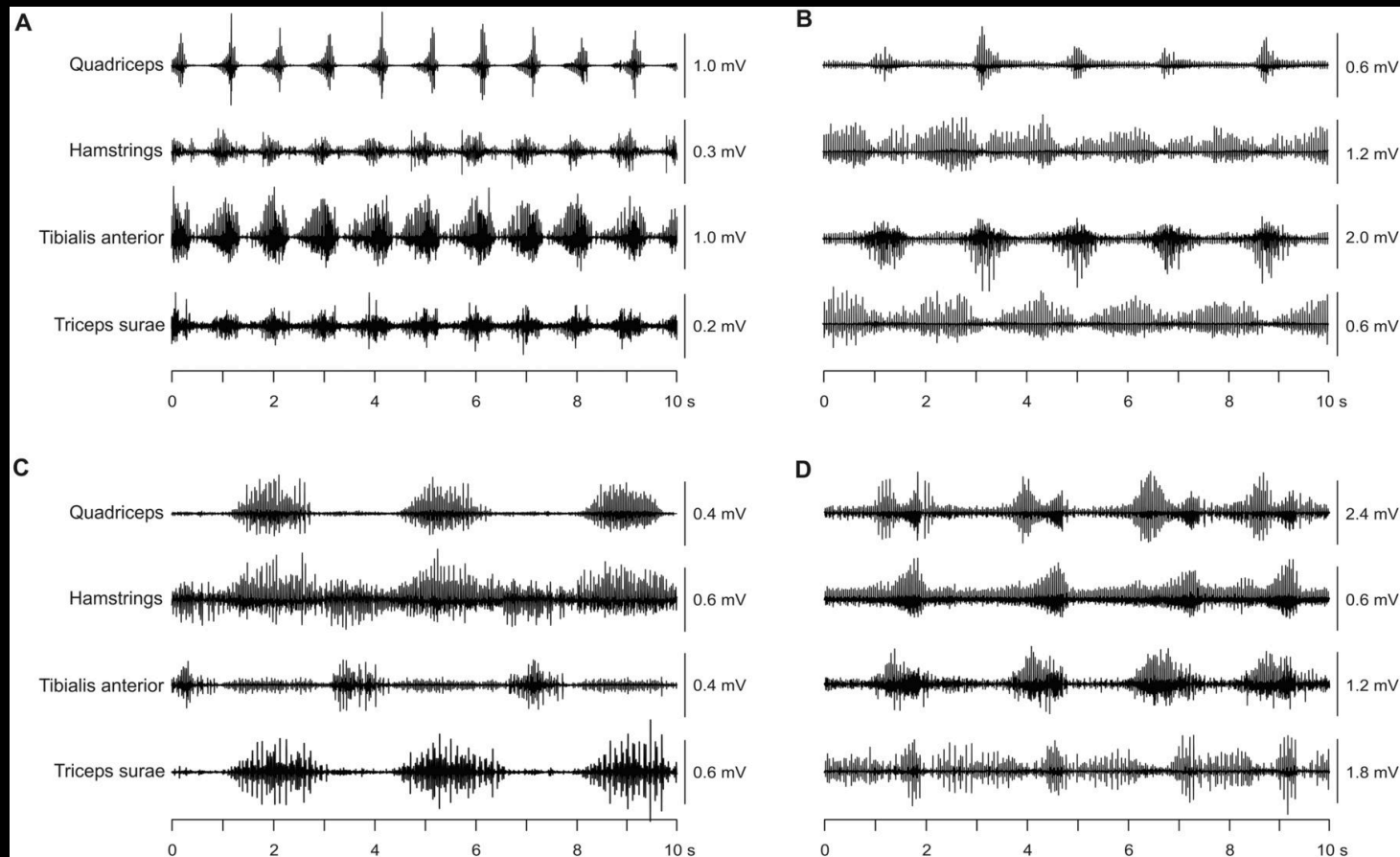


**A****B**











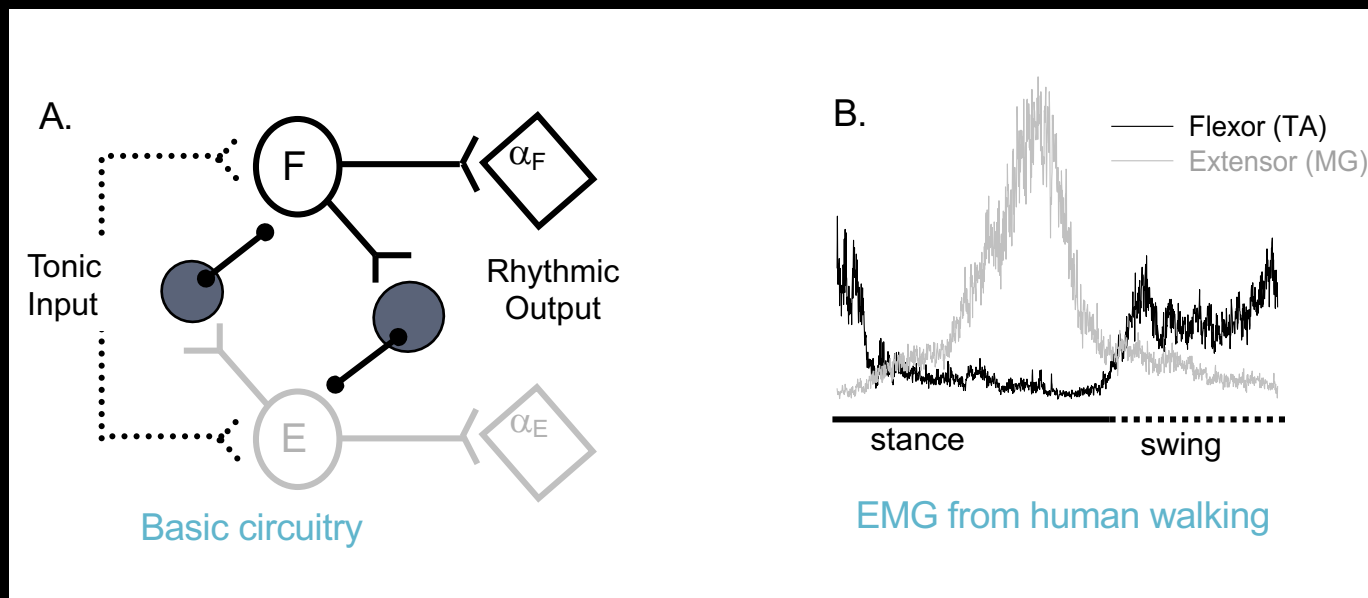
# CPGs are “built” from spinal reflexes

- Remember the flexor withdrawal reflex?
- Different reflex **pathways can be integrated** and used by the CPG
- Thus spinal mechanisms can be used in complicated behaviours
- One of the first demonstrations was in the “**scratch reflex**” of the dog



# CPGs: Half-Centre Model

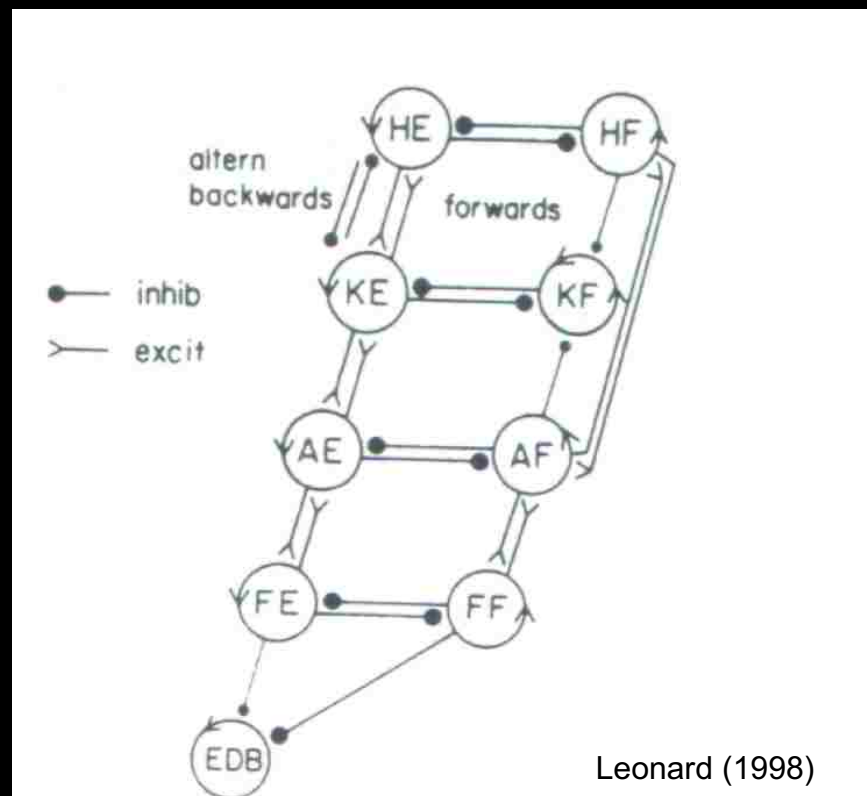
- generates rhythmic output from tonic input
- interneurons controlling flexor and extensor motor neurons have reciprocal inhibitory connections
  - also Left-Right control in swimming (e.g. Lamprey)





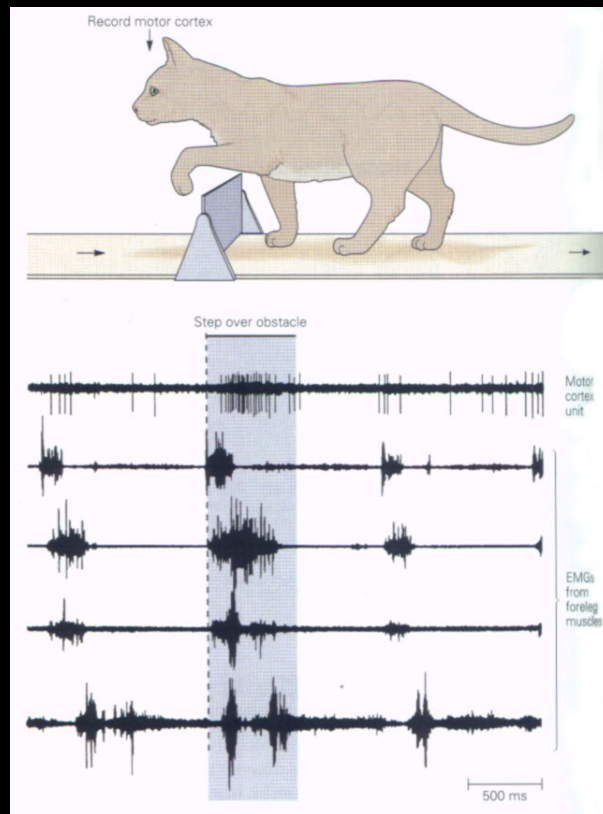
# Basic schema for CPGs controlling quadrupedal locomotion

- Note interactions between:
  - 1) flexors and extensors
    - Reciprocal inhibition
  - 2) limb segments
    - Ankle, knee, hip
- Each joint is a “unit”





# Connections with cortex...



- The **basic rhythm** is carried out by **CPG**
  - Online control from **cortex** is active
    - Cells in motor cortex respond when hitting an obstacle with the foot!

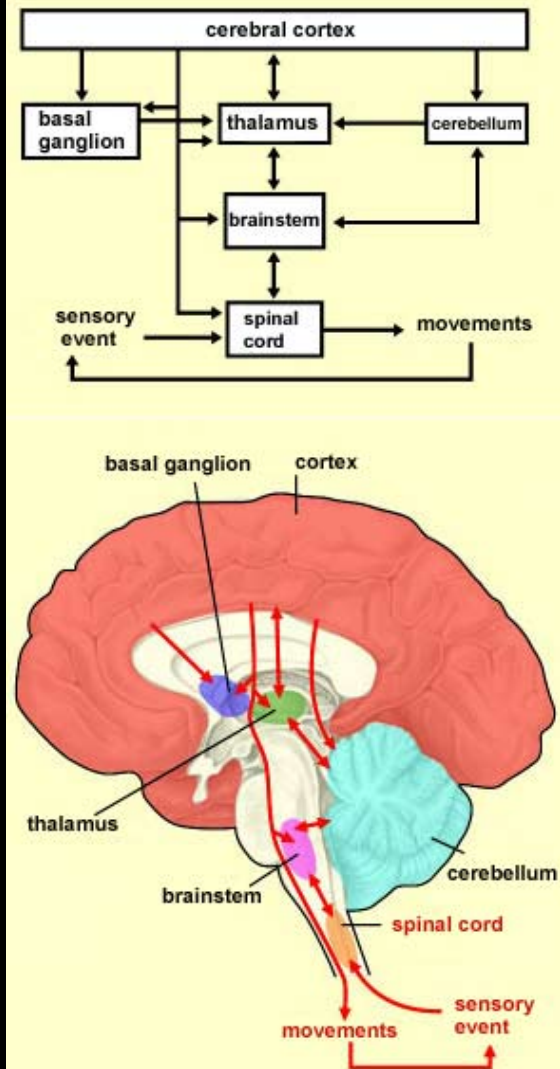


# Levels of Motor Control

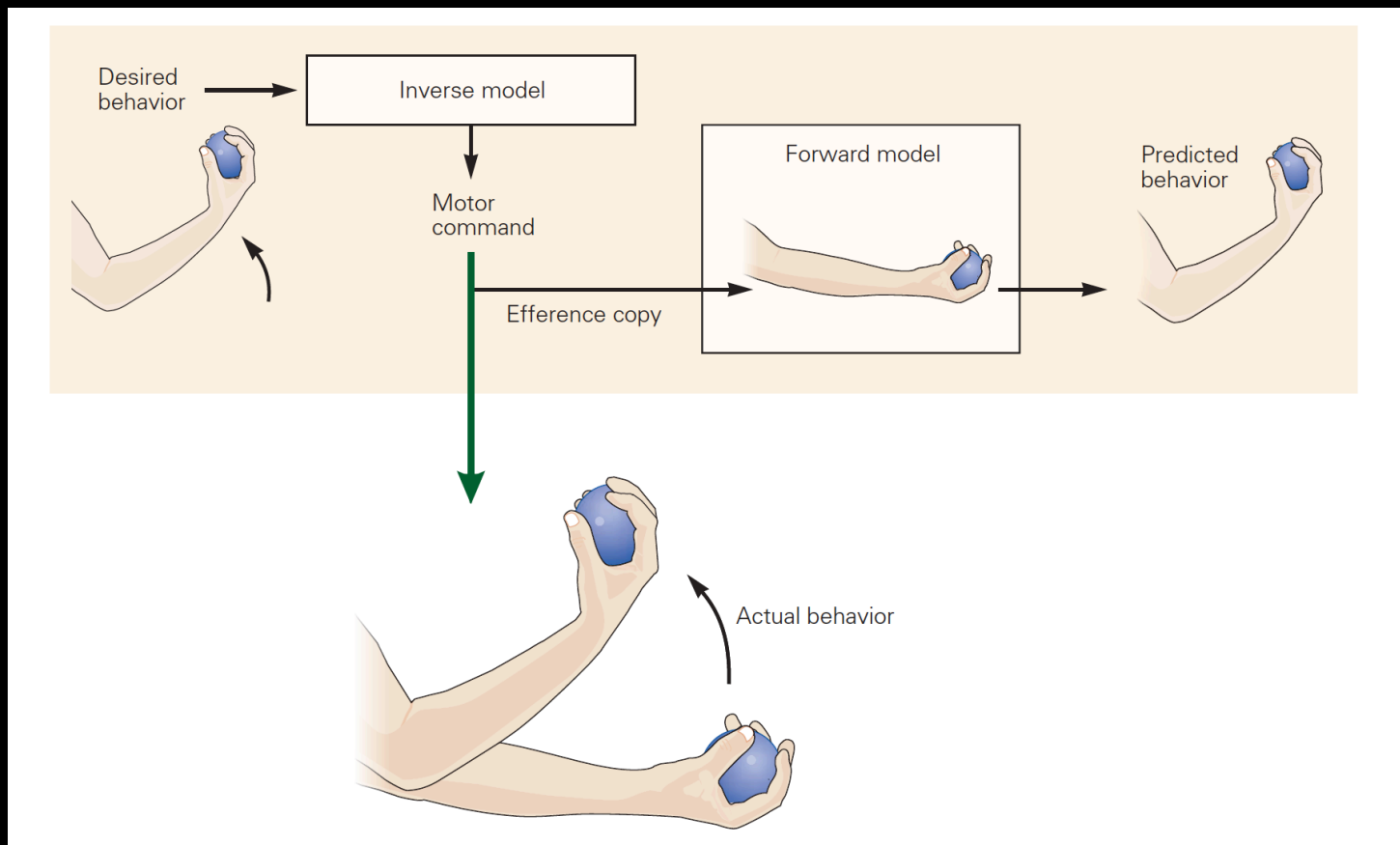
1. Reflexes
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The Flow of Information  
for Goal Directed Movements

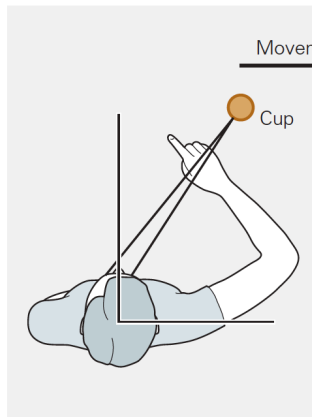




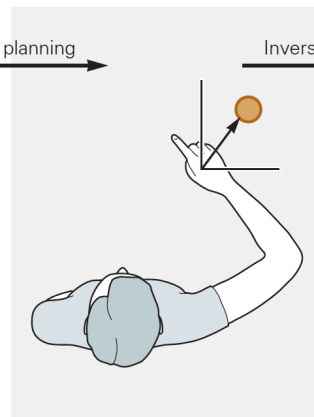




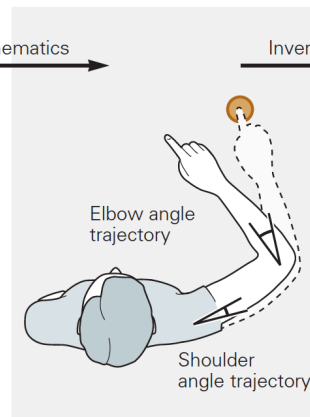
A Locate hand and cup  
(egocentric coordinates)



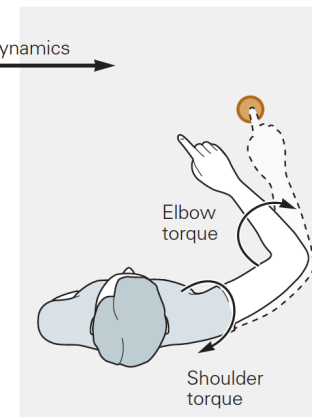
B Plan hand movement  
(endpoint trajectory)



C Determine intrinsic plan  
(joint trajectory)



D Execute movement  
(joint torques)

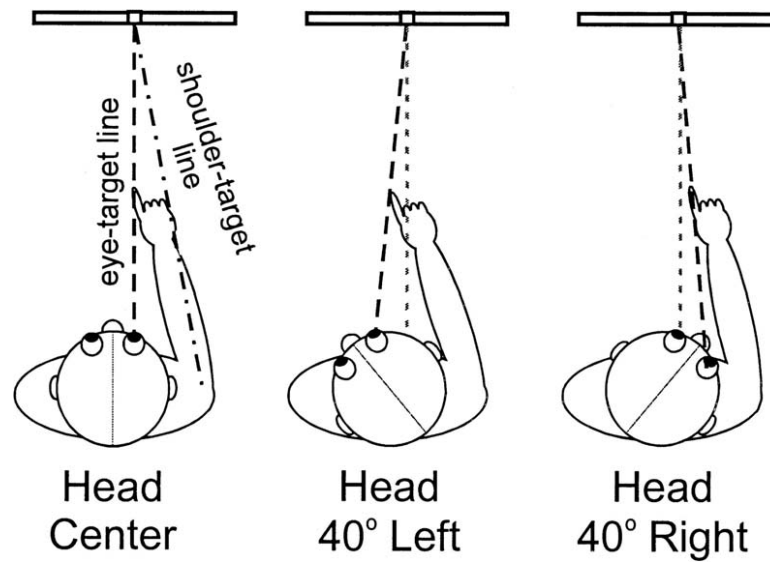




# Visuomotor Transformations

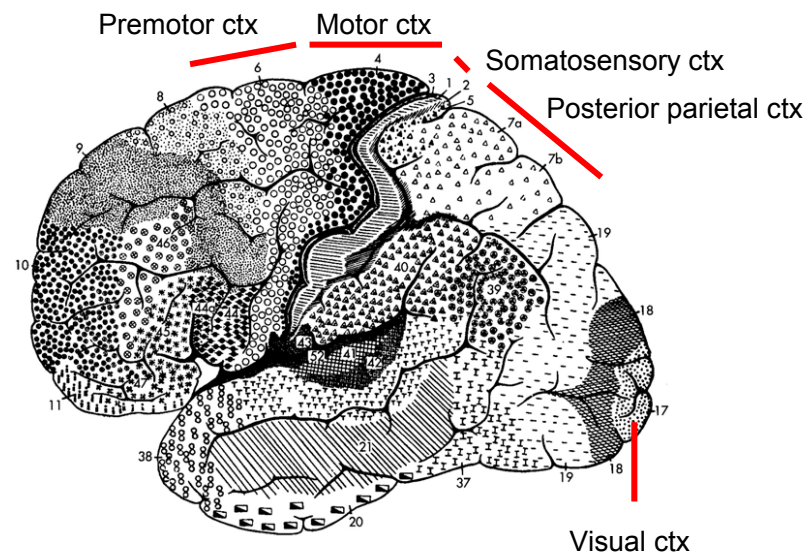
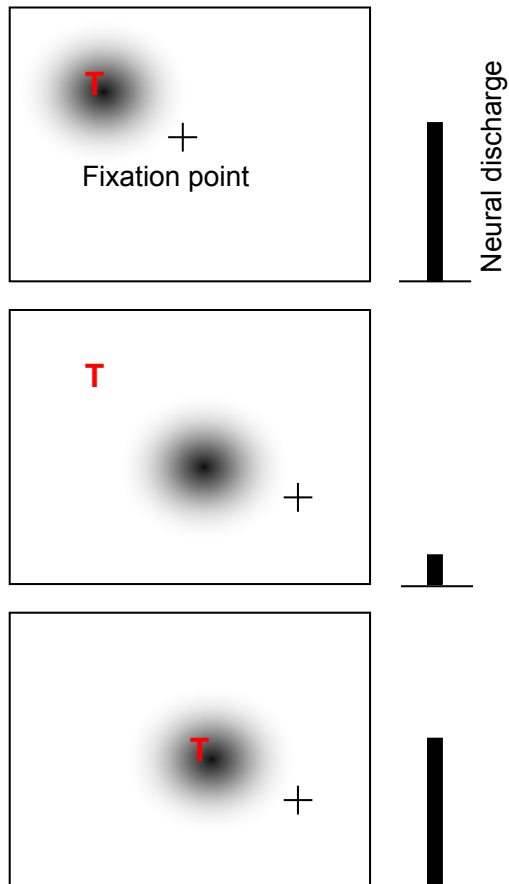


When you point, you align your finger with the retinal location of the target



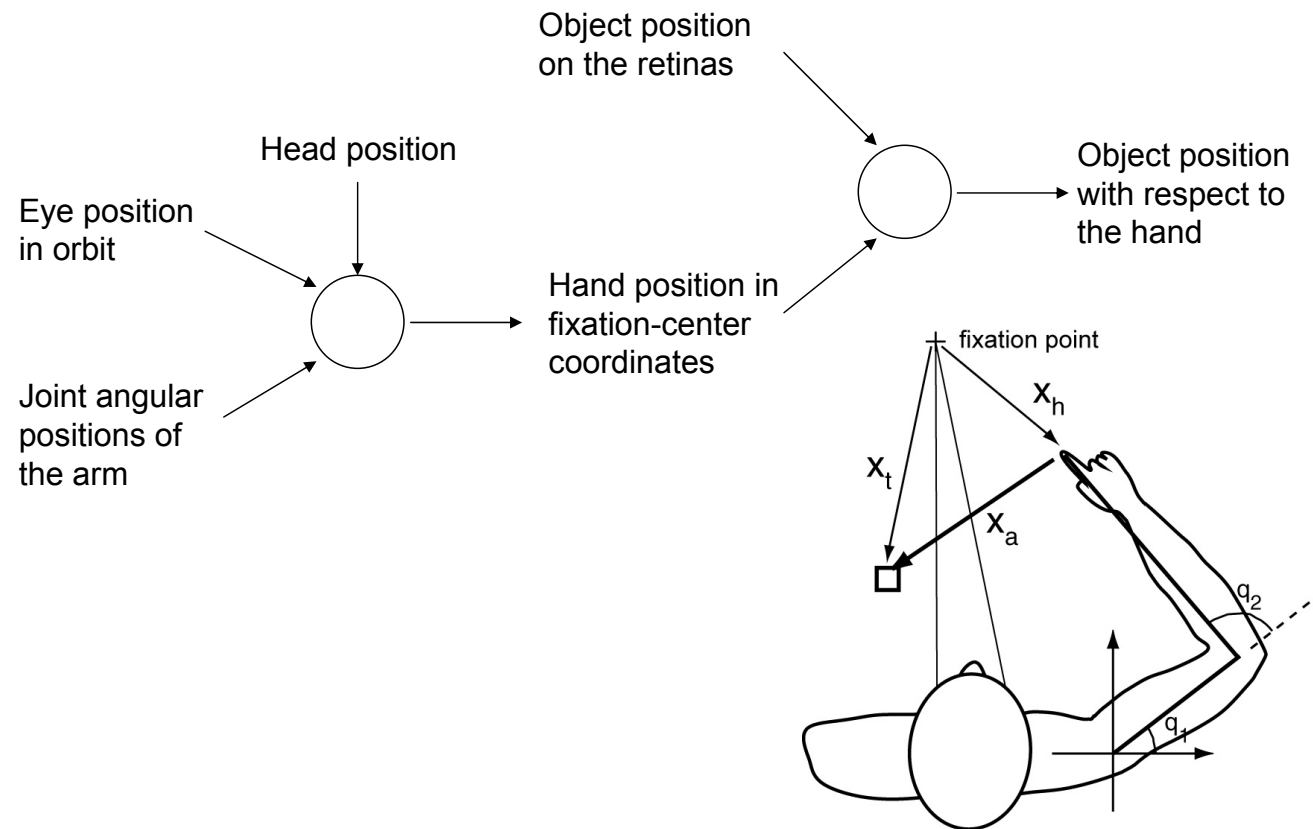


## Coding location of target with a retinocentric receptive field

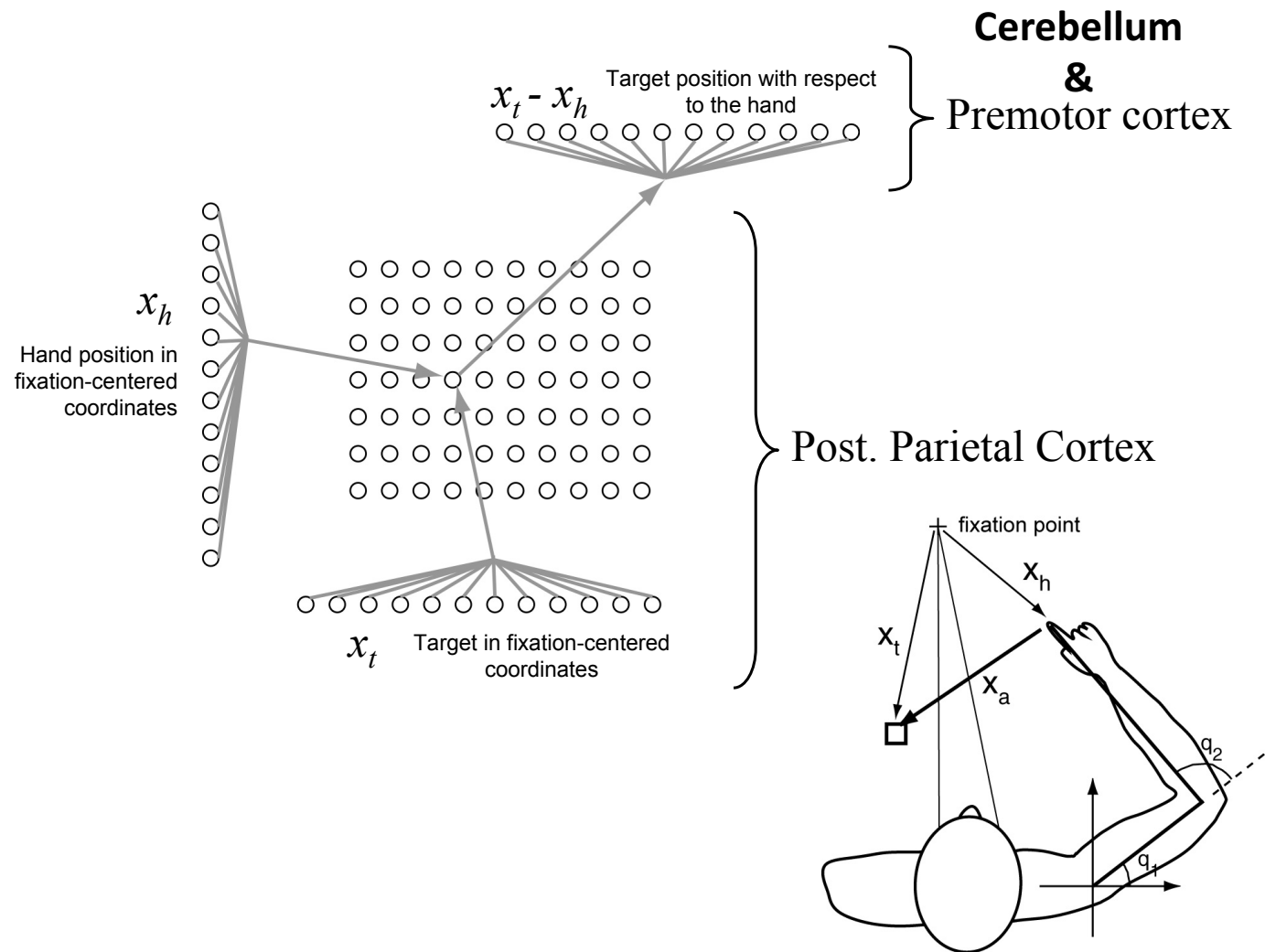




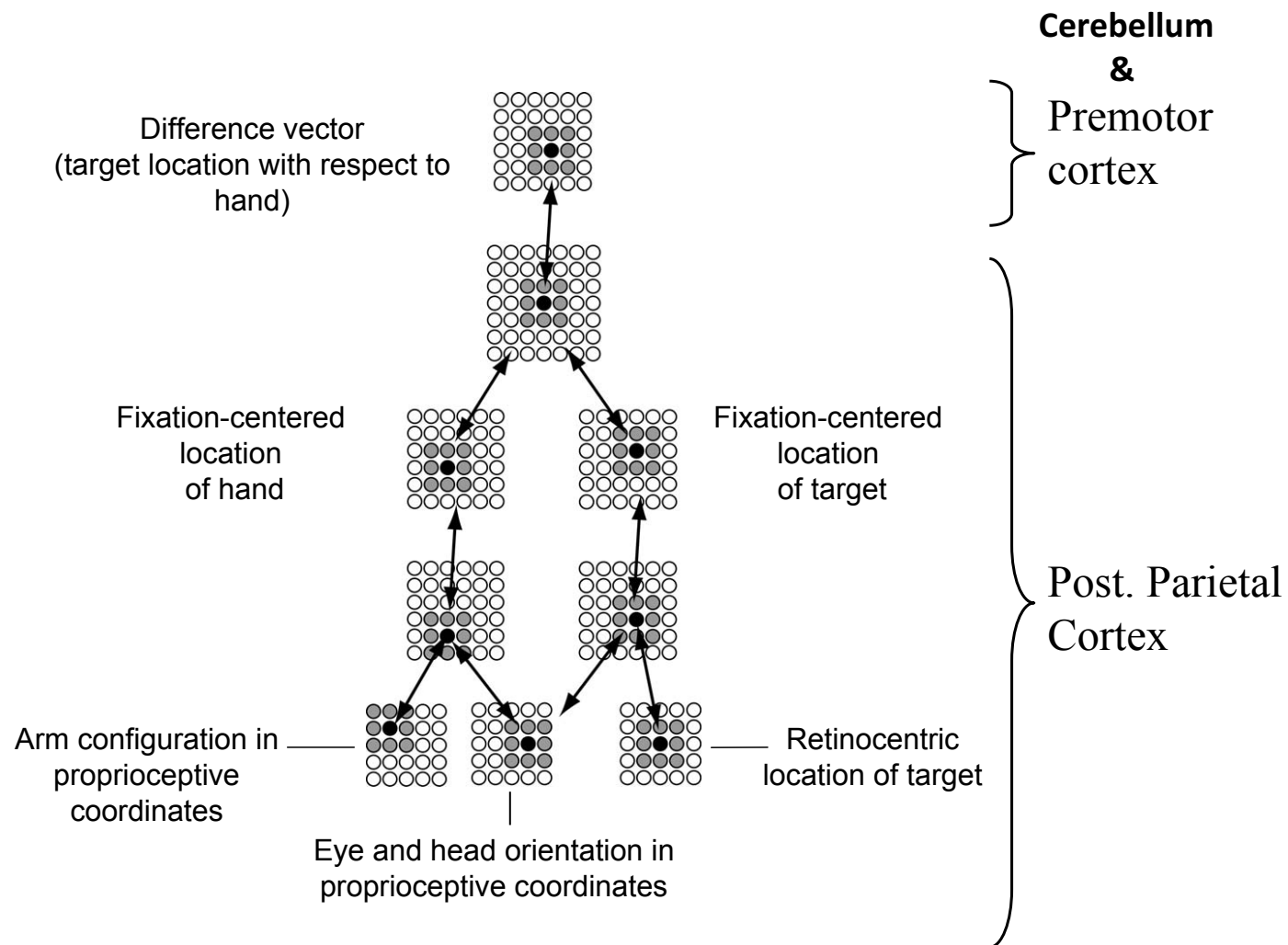
**To reach a target, hand position is computed in fixation-centered coordinates**





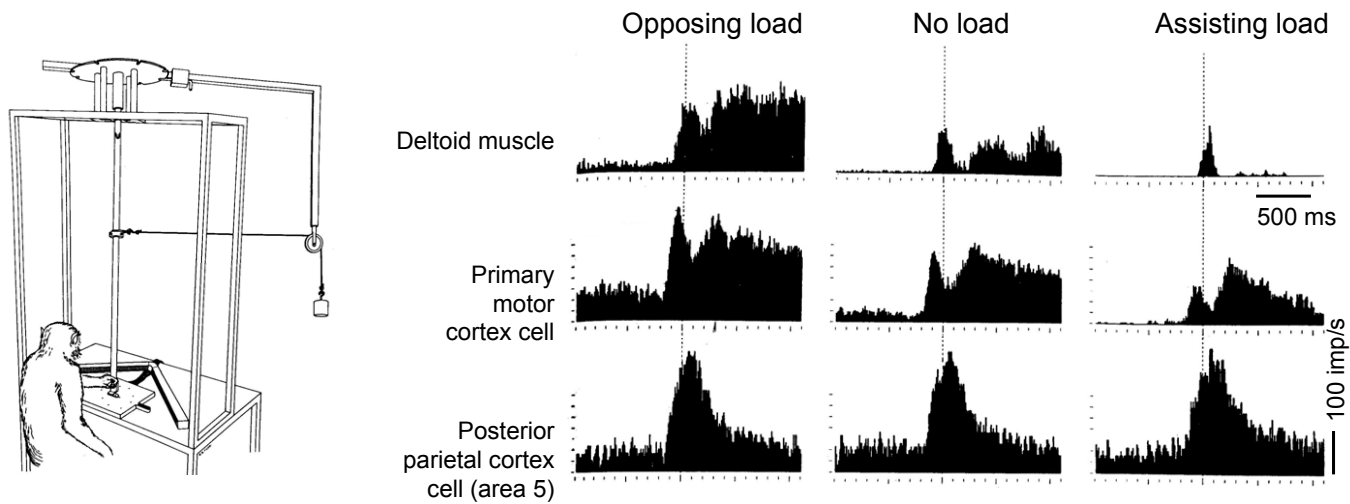








## PPC neurons encode target location and not the forces necessary to reach that target





# So...

The PPC is all about computing the visuomotor transformations necessary to generate:

$x_h$ : the position of the hand in fixation centered coordinates

$x_t$ : the position of the target in fixation centered coordinates

The movement vector can be expressed mathematically

as:  $X_{\text{movement}}$  or  $X_m = X_t - X_h$

\* NB,  $X_m$  would be expressed as a three dimensional vector but for simplicities sake we simplify to one dimension



So, we know we need  $X_m$  what's the  
next step?

We know the vector to the target, now we meet a  
motor command – a trajectory to the target  
location that takes into account:

Muscles involved

Joints involved

Relative force needed

Relative timing

I.E., the MOTOR PROGRAM (Invariant & Variant  
Parameters)



# Determining the Motor Command: The Inverse Model

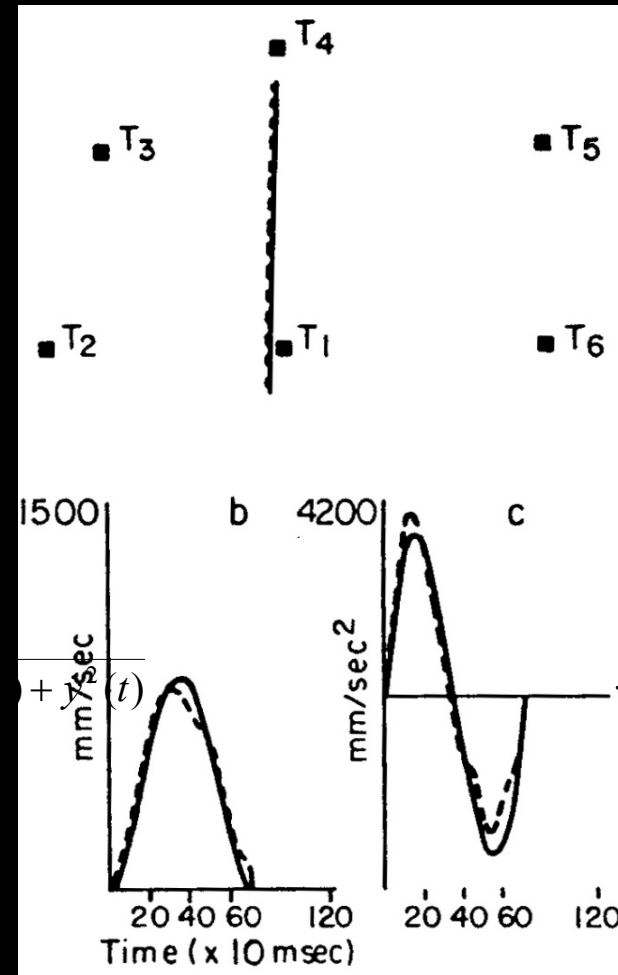




Why an Inverse Model?  
(and to be fair, Forward Models too)

Point to point movements generally exhibit similar characteristics:

- hand trajectory is along a straight line
- hand speed follows a smooth, bell shaped time course
- hand speed is typically symmetric about the midpoint of the movement.



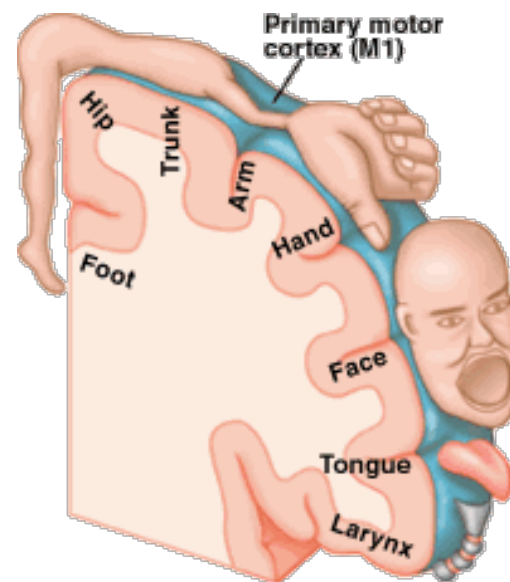
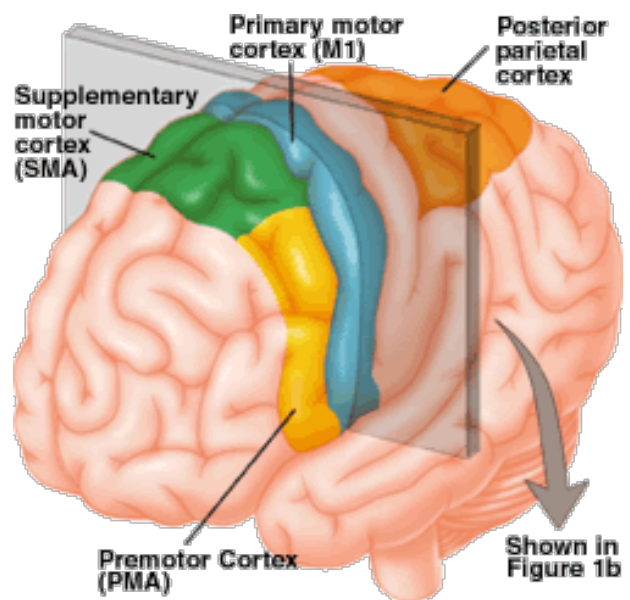


## Let's step back a second...

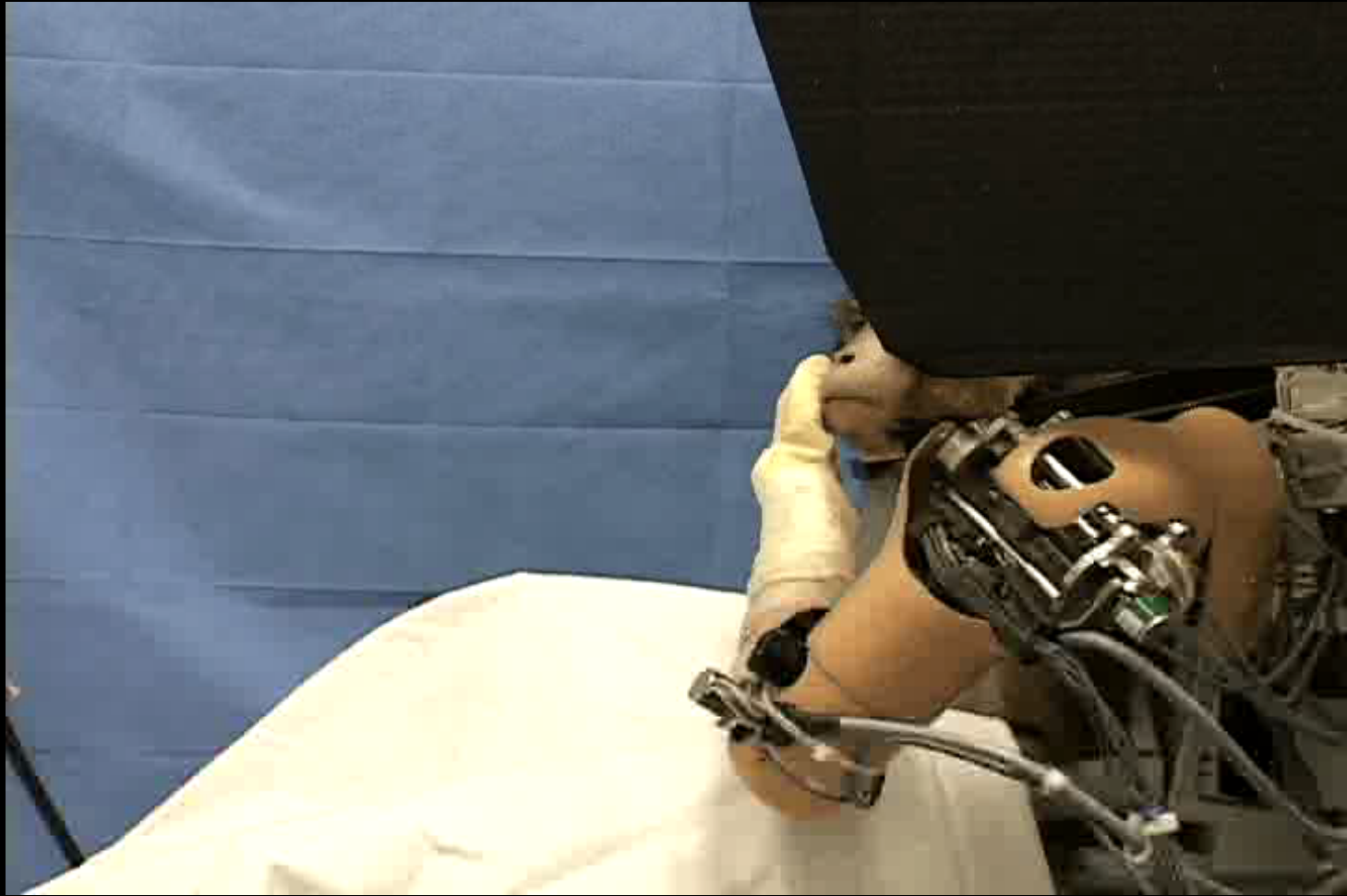
What is a “motor command”

- the neural activity that results in muscular contraction
- which muscles, how long, how much, sequencing, etc















# **BRAIN-COMPUTER INTERFACE RESEARCH**

**UPMC Rehabilitation Institute and the  
University of Pittsburgh School of Medicine**

## **Study participant Jan Scheuermann feeds herself**

- 1) Nov. 28, 2012 - Chocolate bar
- 2) Nov. 30, 2012 - Chocolate bar
- 3) Nov. 30, 2012 - Chocolate truffle
- 4) Nov. 30, 2012 - String cheese
- 5) Nov. 30, 2012 - Red pepper

December 2012

TRT 05:27

©2012 UPMC/Pitt Health Sciences



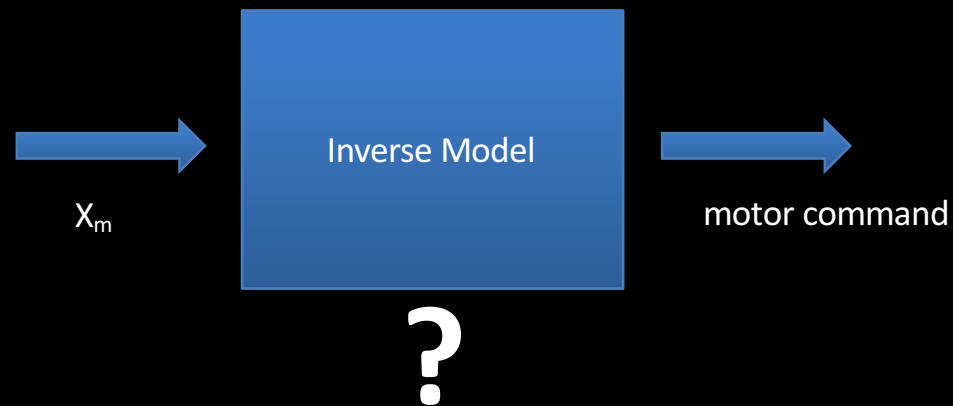
## So what is the motor command?

It is the set of instructions sent to M1 that result  
in muscular contraction

In the Schwartz Lab they place an electrode  
array over M1 so that they can use the brains  
neural activity in M1 to control the various  
motors in the “arm”.



# The Inverse Model



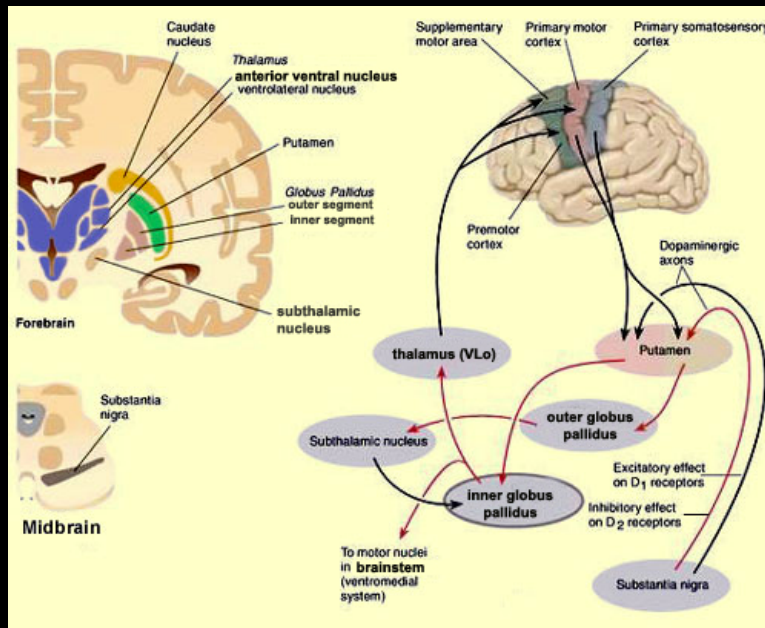


## What We Believe...

The inverse model helps with the computation of  $X_m$  (cerebellum) and outputs a motor command (premotor cortex)



# What we do know...

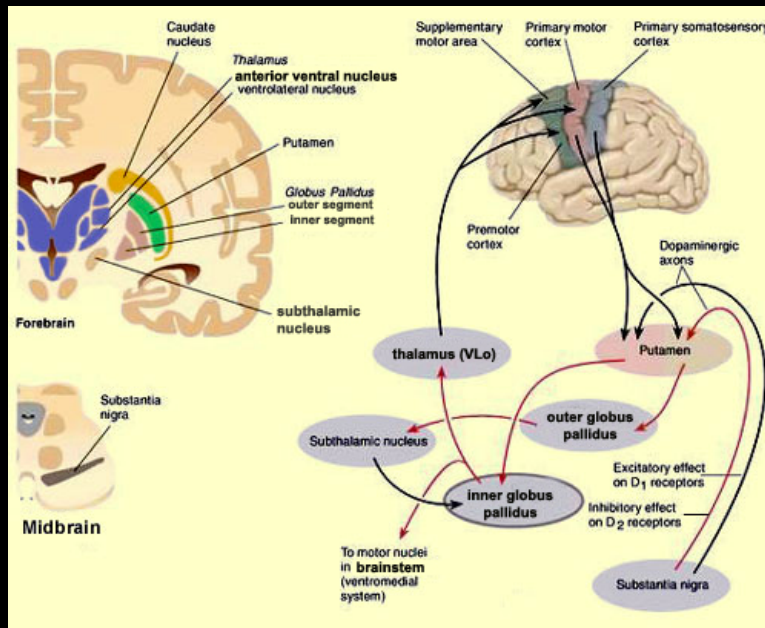


## The Basal Ganglia

- a collection of nuclei in the midbrain
- definitely play a role in movement planning and control (Parkinson's)
- (also play a role in reinforcement learning and motivation)
- implicated in postural stability and control (and that may be their role in goal directed action – to stabilize the body for movement?)
- but very few in any direct connections to descending pathways
- another idea is that the BG is a gateway system that only allows activity in SMA (voluntary movement) if a sufficient level of firing is achieved.



# What we do know...

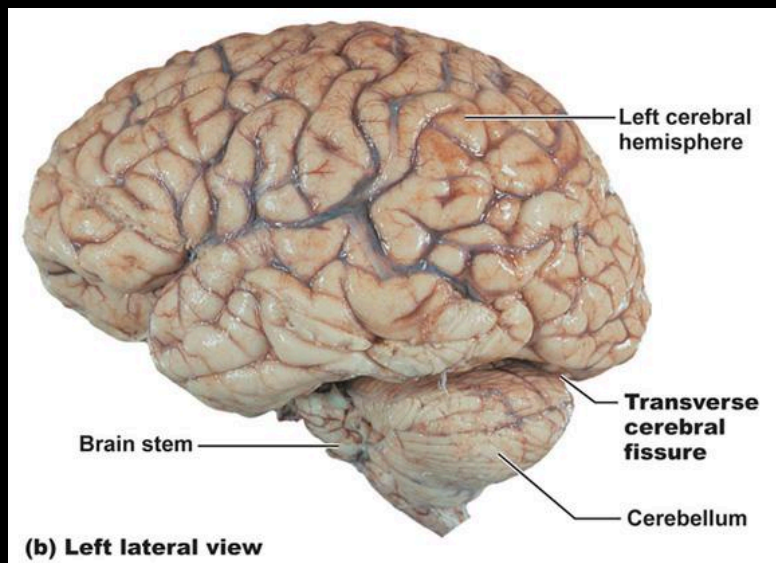


## The Basal Ganglia

- to expand on that:
- a **direct pathway** selectively facilitates certain motor (or cognitive) programs in the cerebral cortex that are adaptive for the present task, whereas an **indirect pathway** simultaneously inhibits the execution of competing motor programs. An upset of the balance between the direct and indirect pathways results in motor dysfunction



# What we do know...



## The Cerebellum

- control of timing
- estimation
- prediction

(some argue this is the “home” of forward and inverse models

- we do know that movement deficits such as cerebellar ataxia result in uncoordinated and poorly controlled movements

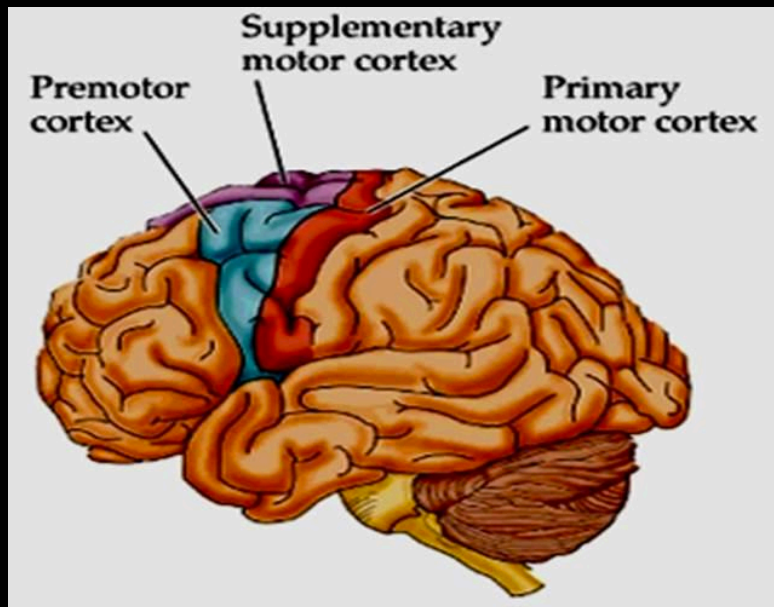


# Cerebellar Axatia





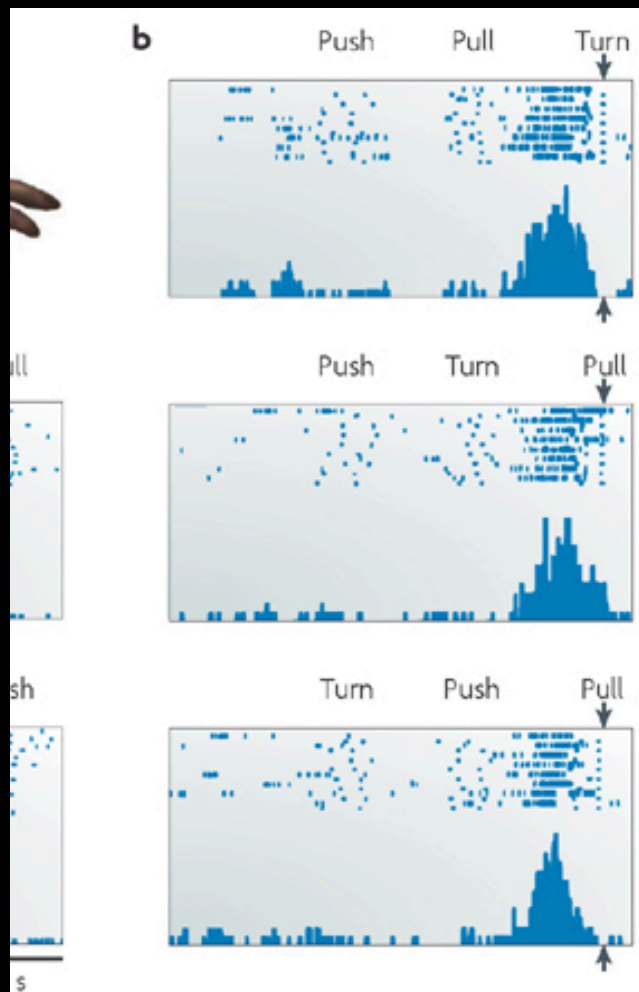
# What we do know...



## SMA & PMC

- the secondary motor areas (PMC and SMA) work with the cerebellum to specify the precise sequence of contractions of the various muscles that will be required to carry out the selected motor action
- recall  $X_m$ , this still needs to be converted into a set of intrinsic coordinates in muscle terms, this could be part of what the SMA does with the help of the Cerebellum, the same is true for Premotor Cortex
- SMA also seems crucial for well learned movements and internally generated movements
- additionally movement sequencing

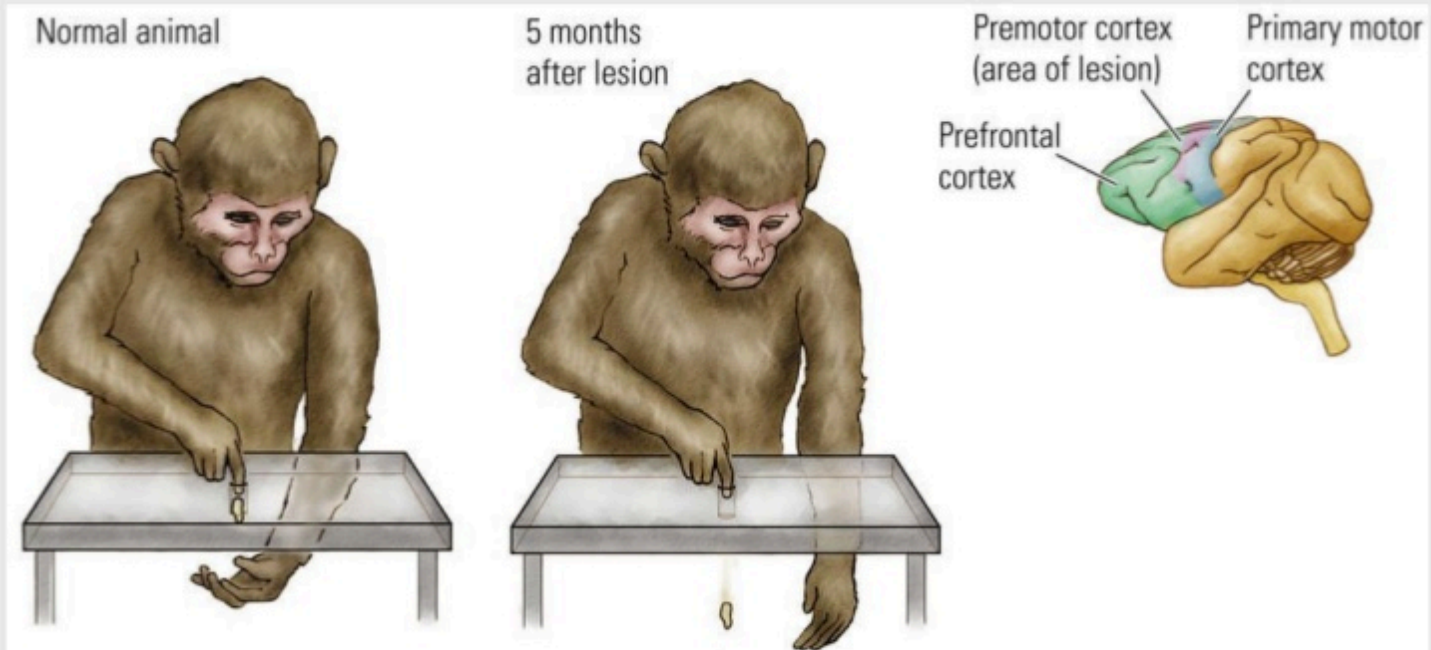




An interesting study where one particular neuron in SMA only fired before the third movement in a sequence, but note, irregardless of what the third movement was

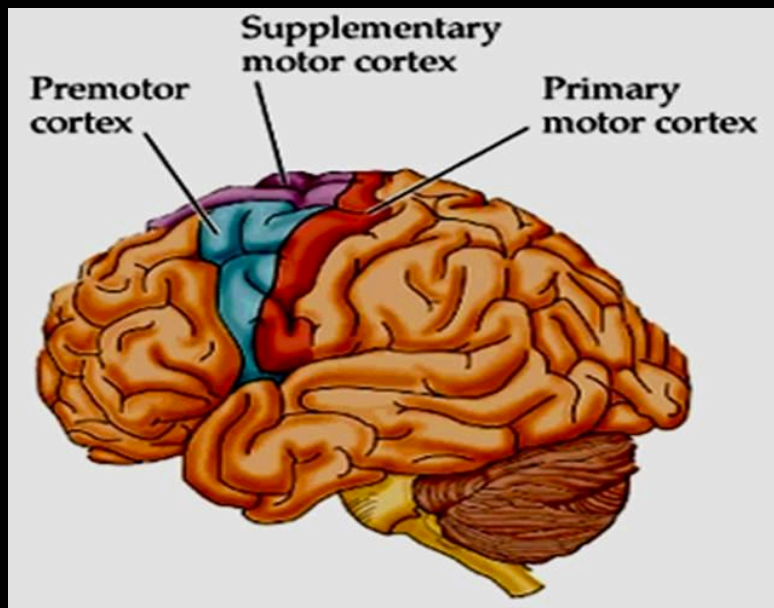


## Animals with damage to the premotor cortex cannot put motor sequences together





# What we do know...



## PMC

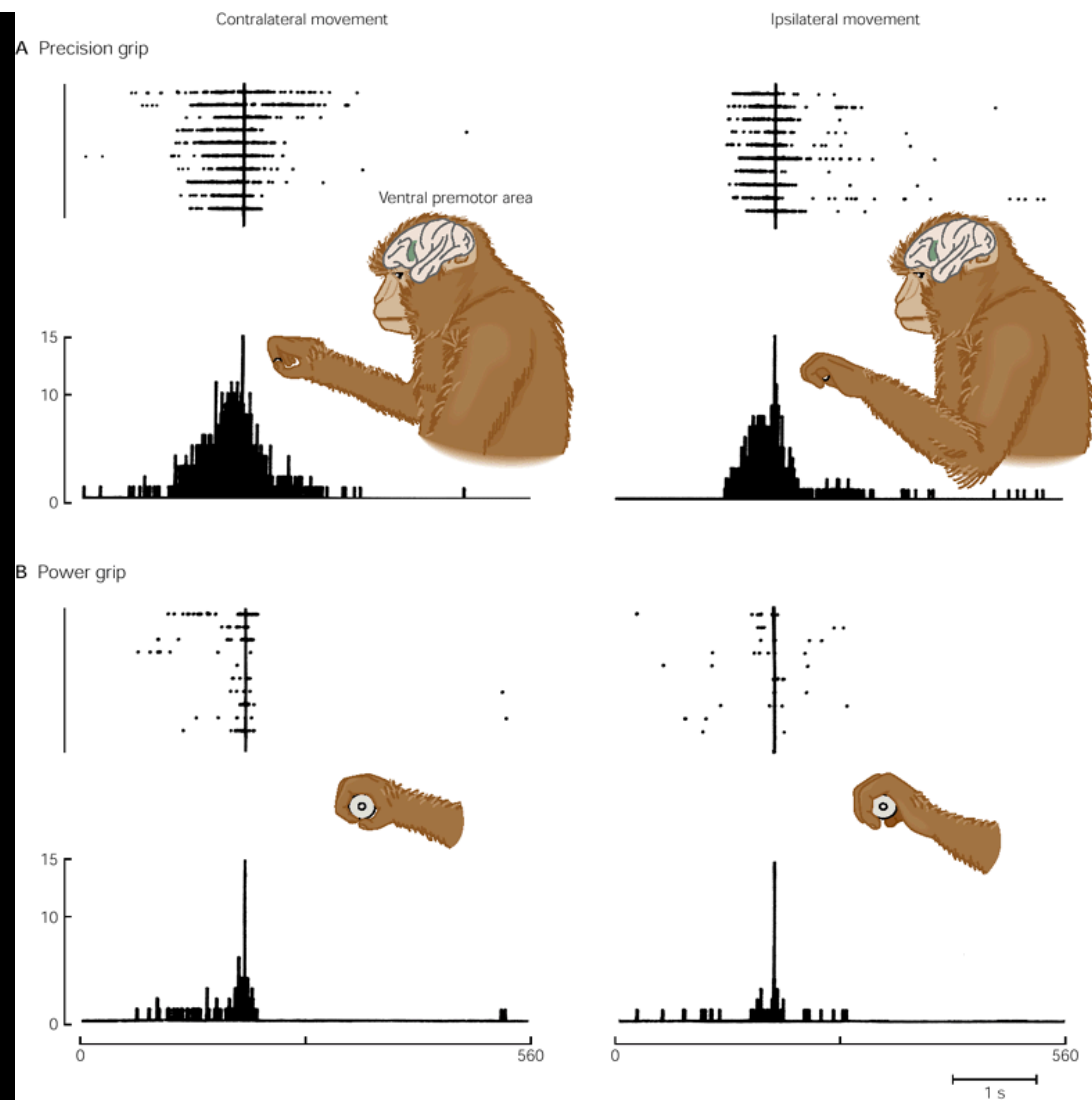
- the secondary motor areas (PMC and SMA) work with the cerebellum to specify the precise sequence of contractions of the various muscles that will be required to carry out the selected motor action

- recall  $X_m$ , this still needs to be converted into a set of intrinsic coordinates in muscle terms, this could be part of what the SMA does with the help of the Cerebellum, the same is true for PMC

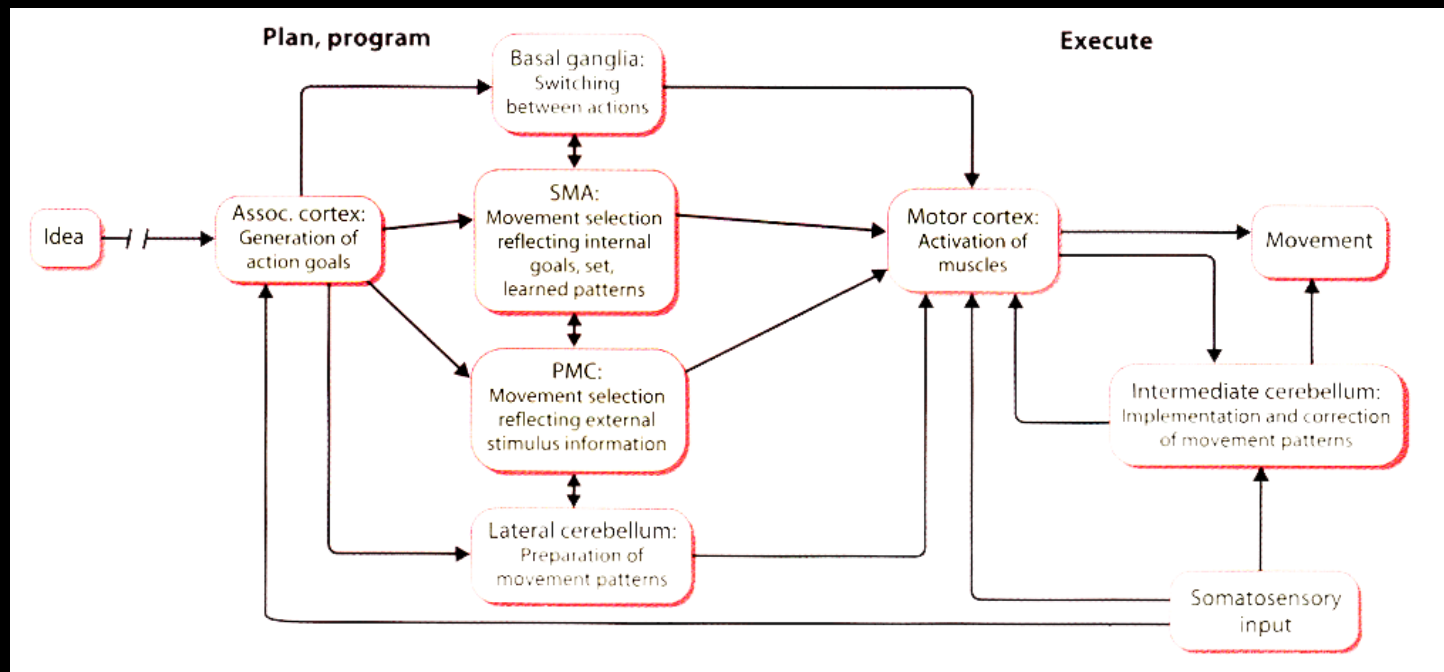
- PMC also seems crucial for externally driven actions

- additionally movement direction







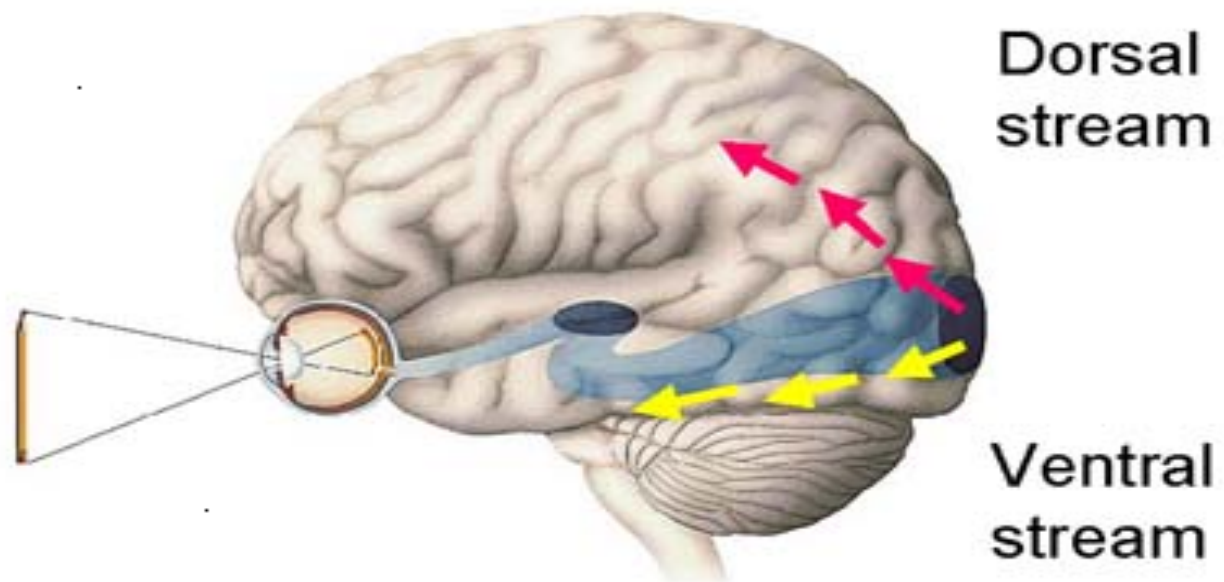




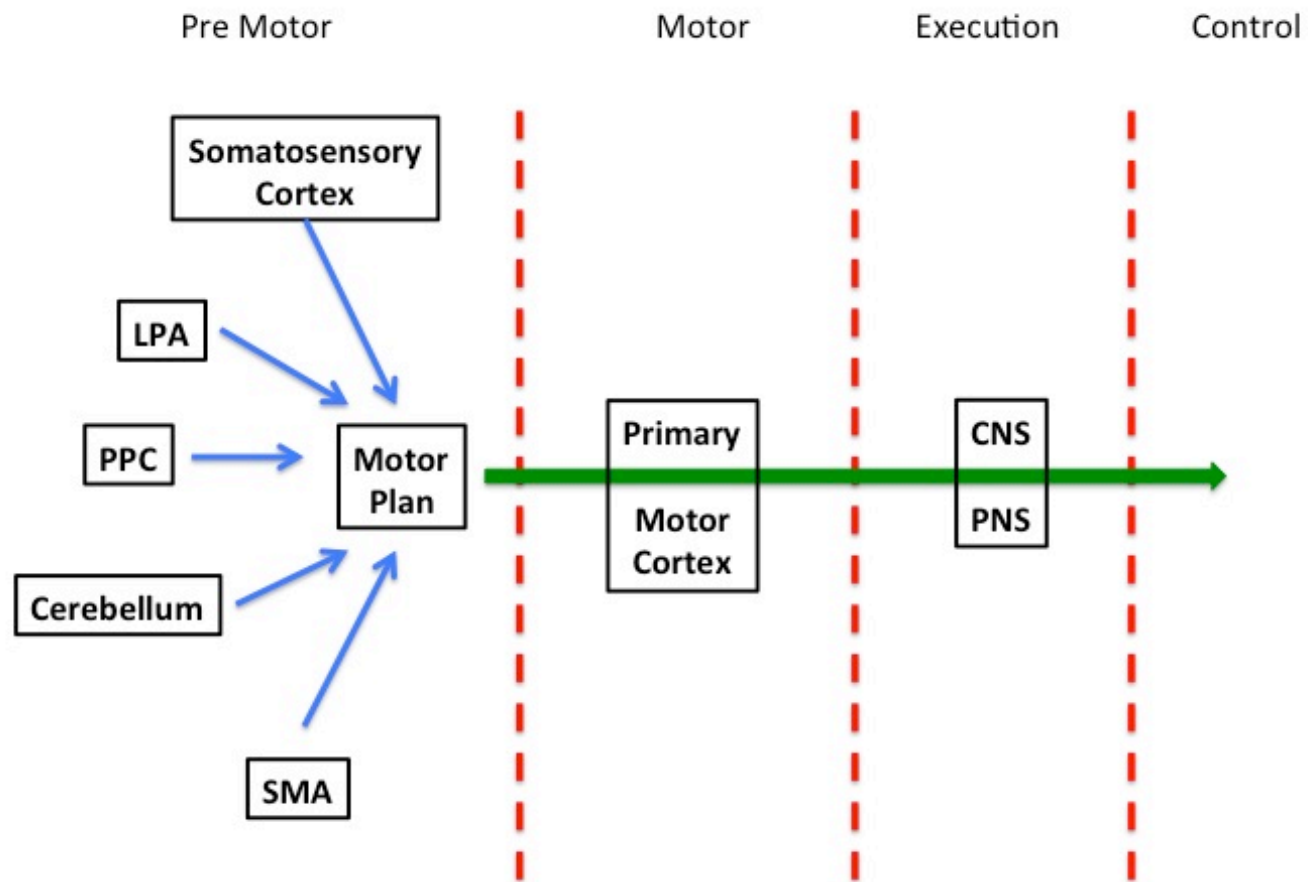
# Levels of Motor Control

1. Reflexes
2. Postural Control
3. Cyclical Movements
4. Goal Directed Action
5. Motor Control







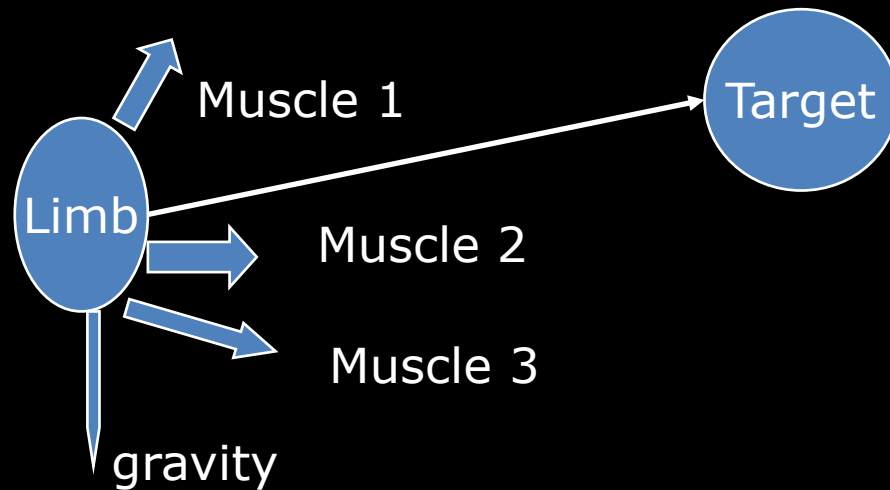




# The Need for Control



There are errors in a motor command





# Three Sources of Errors

1. A Poor Motor Command (imperfect memory)
2. Neuromotor Noise
3. Changes in the Environment



# **Goodale, Pelisson, & Prablanc (1986)**









## **Goodale, Pelisson, & Prablanc (1986)**





DESIRED STATE



TARGET





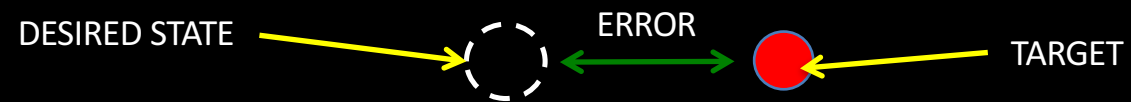
DESIRED STATE



TARGET



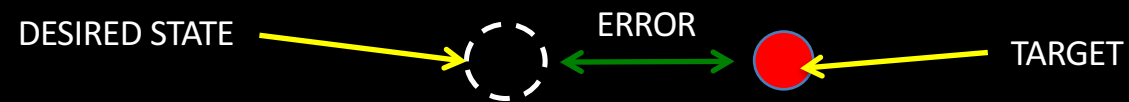




$$\text{ERROR} = X_t - X_d$$

The motor system is continually working to minimize ERROR





But never forget it takes time to COMPUTE  $X_d$  and  $X_t$ , thus corrections are not instantaneous, but occur after a visual processing delay (100 – 150 ms)



DESIRED STATE

ERROR

TARGET



$$\text{ERROR} = X_t - X_d$$

The motor system is continually working to minimize ERROR



# Two Types of Control

1. Feedback Based
2. Forward Control (maybe...)



Westwood, Heath, Roy (2001)

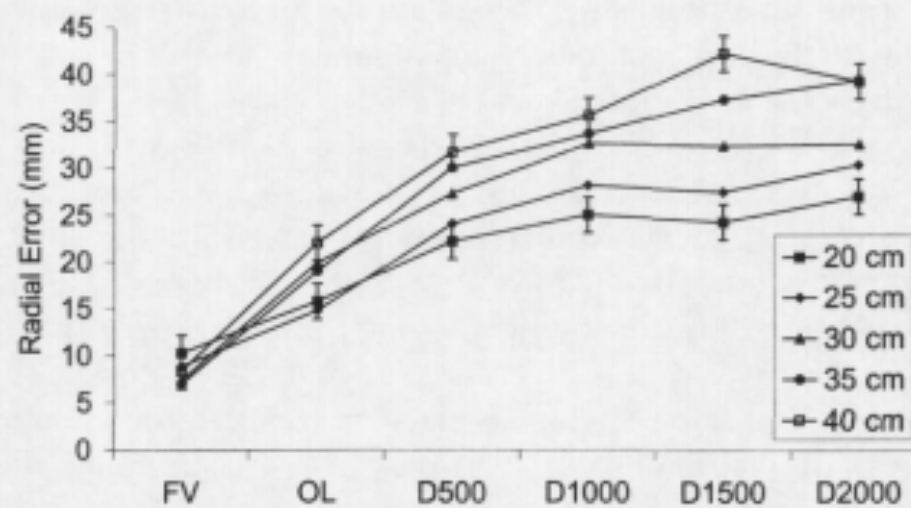












*Figure 1.* Radial error (mm) for reaching movements to 20, 25, 30, 35, and 40 cm target amplitudes in full vision (FV), open-loop (OL), and 500-2000 ms delay conditions (D500-D2000). Bars represent within-subjects SEM; for clarity, bars are only shown for the 20 cm and 40 cm targets.



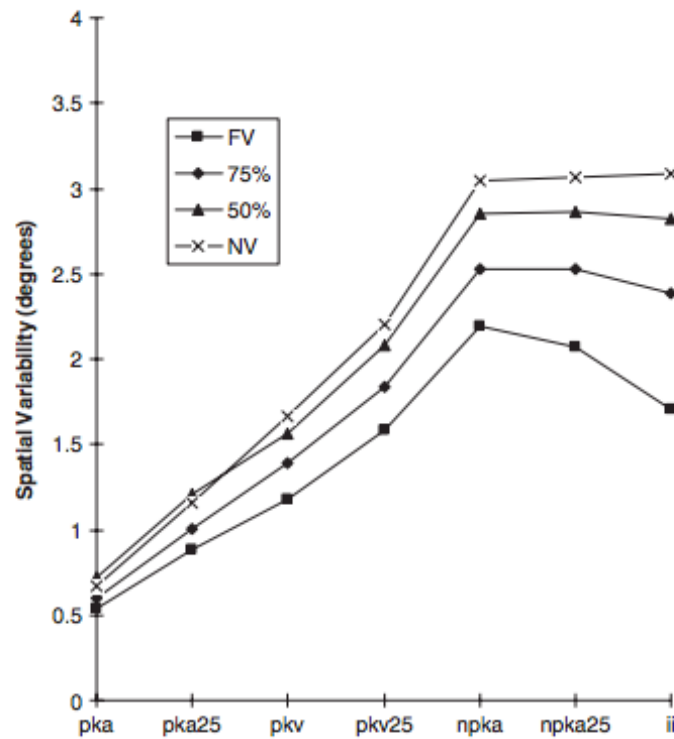


Fig. 2. Variability in distance traveled at peak acceleration (pka), peak acceleration + 25 ms (pka25), peak velocity (pkv), peak velocity + 25 ms (pkv25), negative peak acceleration (npka), negative peak acceleration + 25 ms (npka25), and at the end of the initial impulse (ii) for the FV, 75%V, 50%V and NV conditions (adapted from Khan and Franks (2003)).



Heath 2005





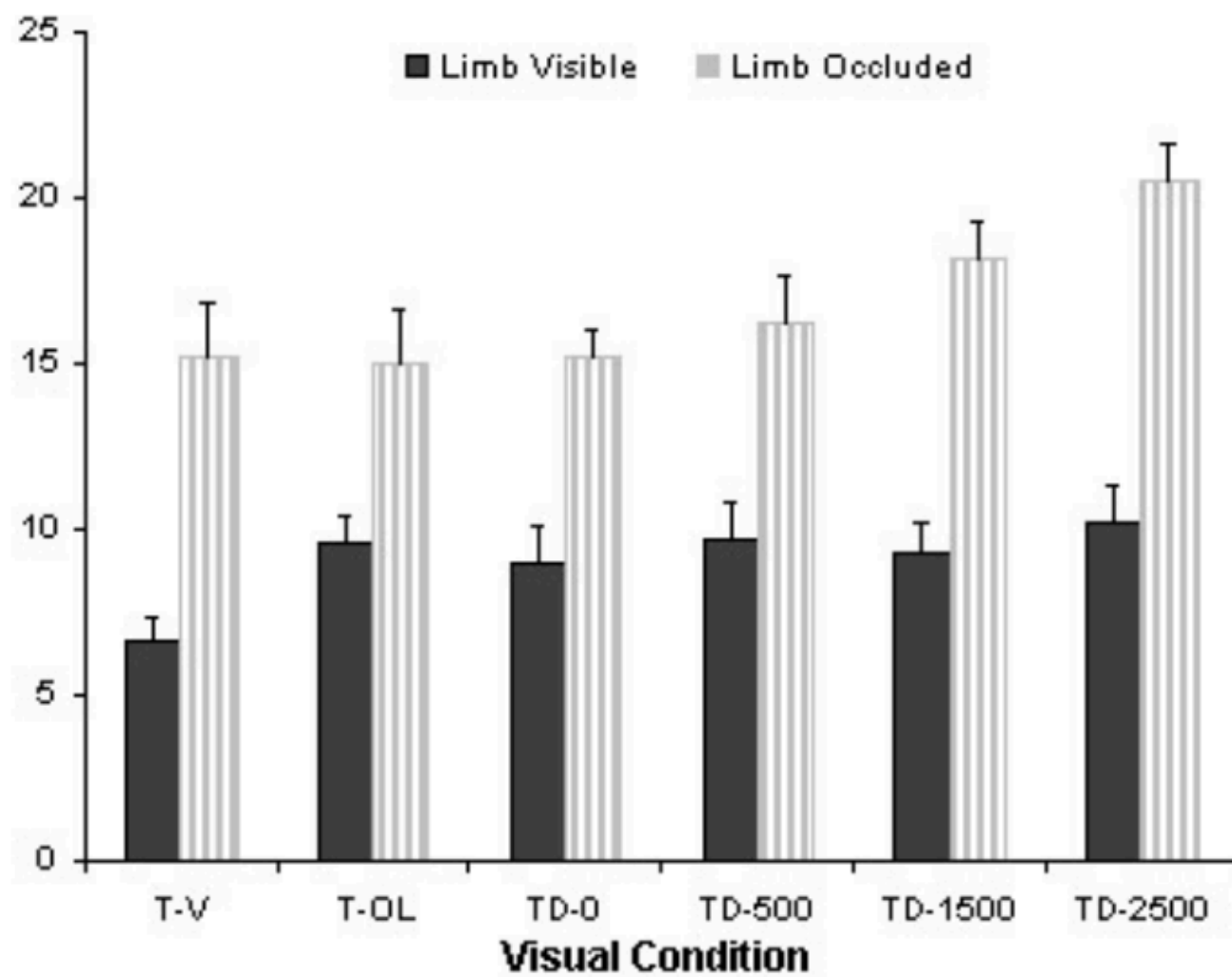






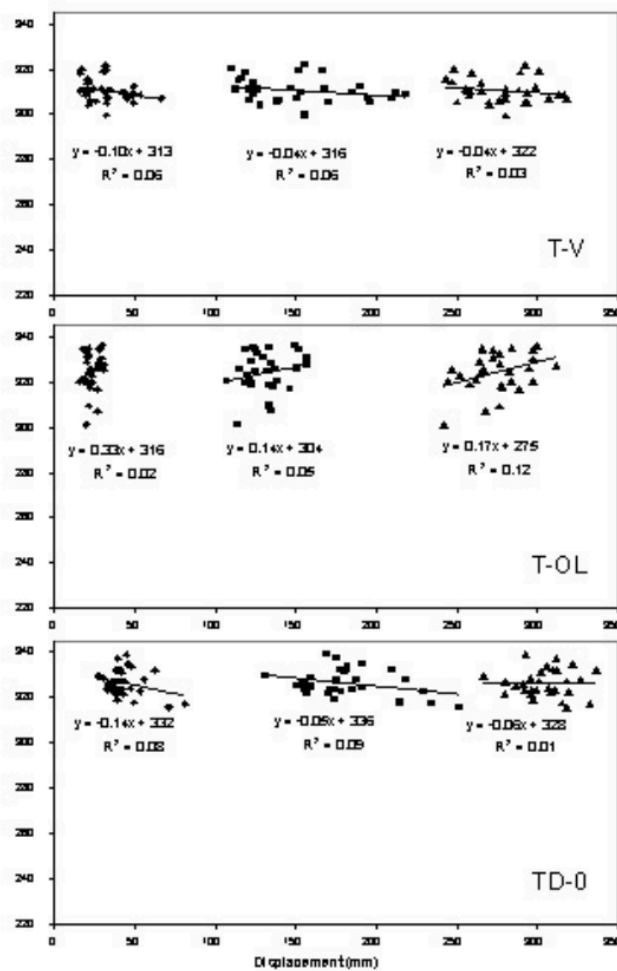




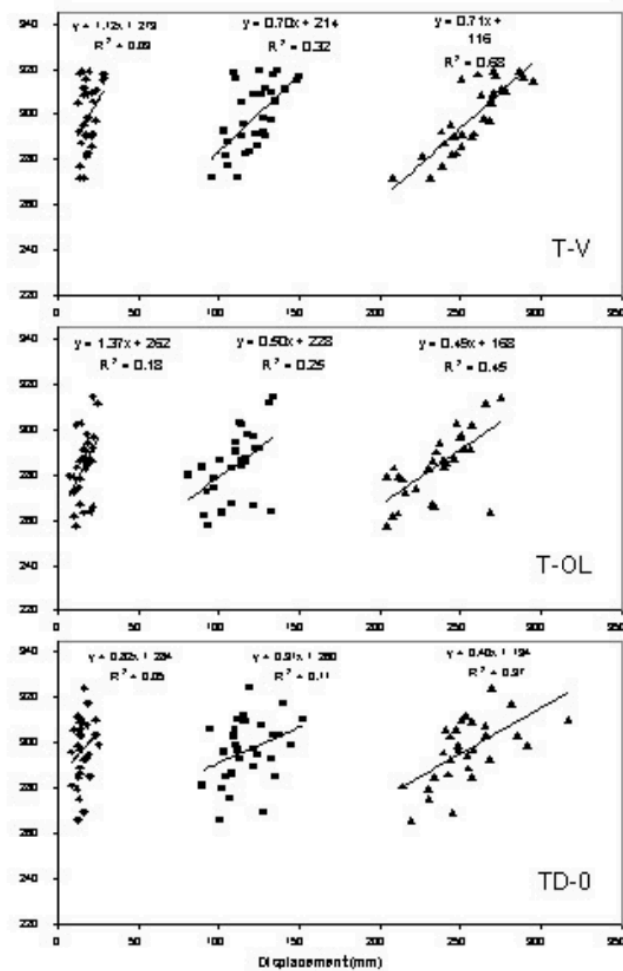




Limb Visible



Limb Occluded



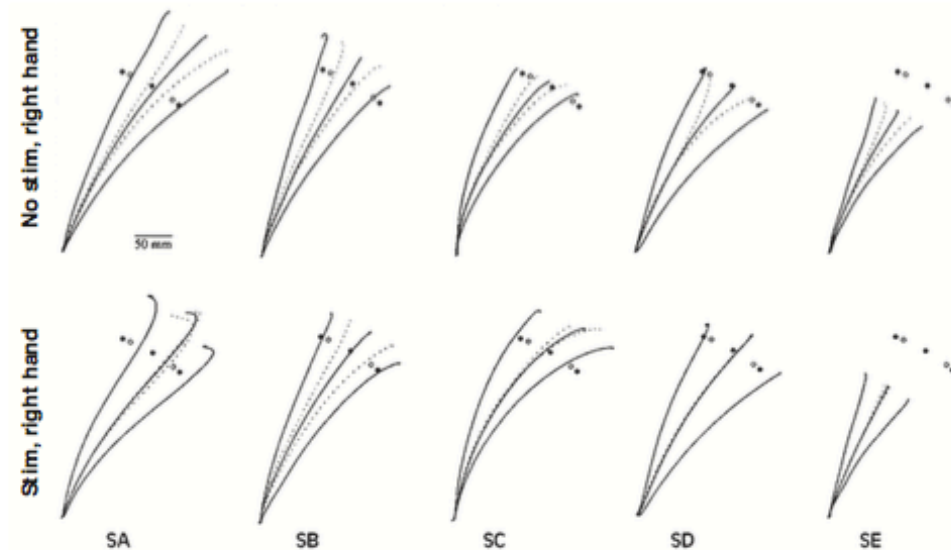


Desmurget et al. 1999









**Fig. 1.** Mean hand paths produced by all subjects (SA–SE) with the right, dominant hand in the non-stimulated (upper row) and stimulated (lower row) conditions. Mean trajectories were computed after temporal normalization of the individual trials ( $n = 10$ ). The black continuous curves represent the mean paths directed at stationary targets (20, 30 and 40 degrees). The gray dashed curves represent the mean paths directed at jumping targets (30  $\rightarrow$  22.5 and 30  $\rightarrow$  37.5 degrees). Black circles indicate stationary target locations, whereas white circles represent jumping target locations.



Krigolson & Holroyd 2007



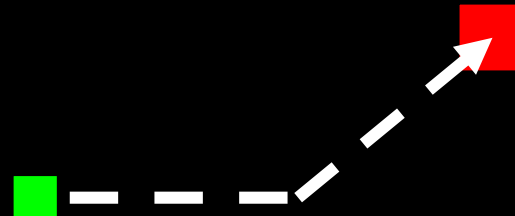
# Target Errors



**Condition One:  
Control**

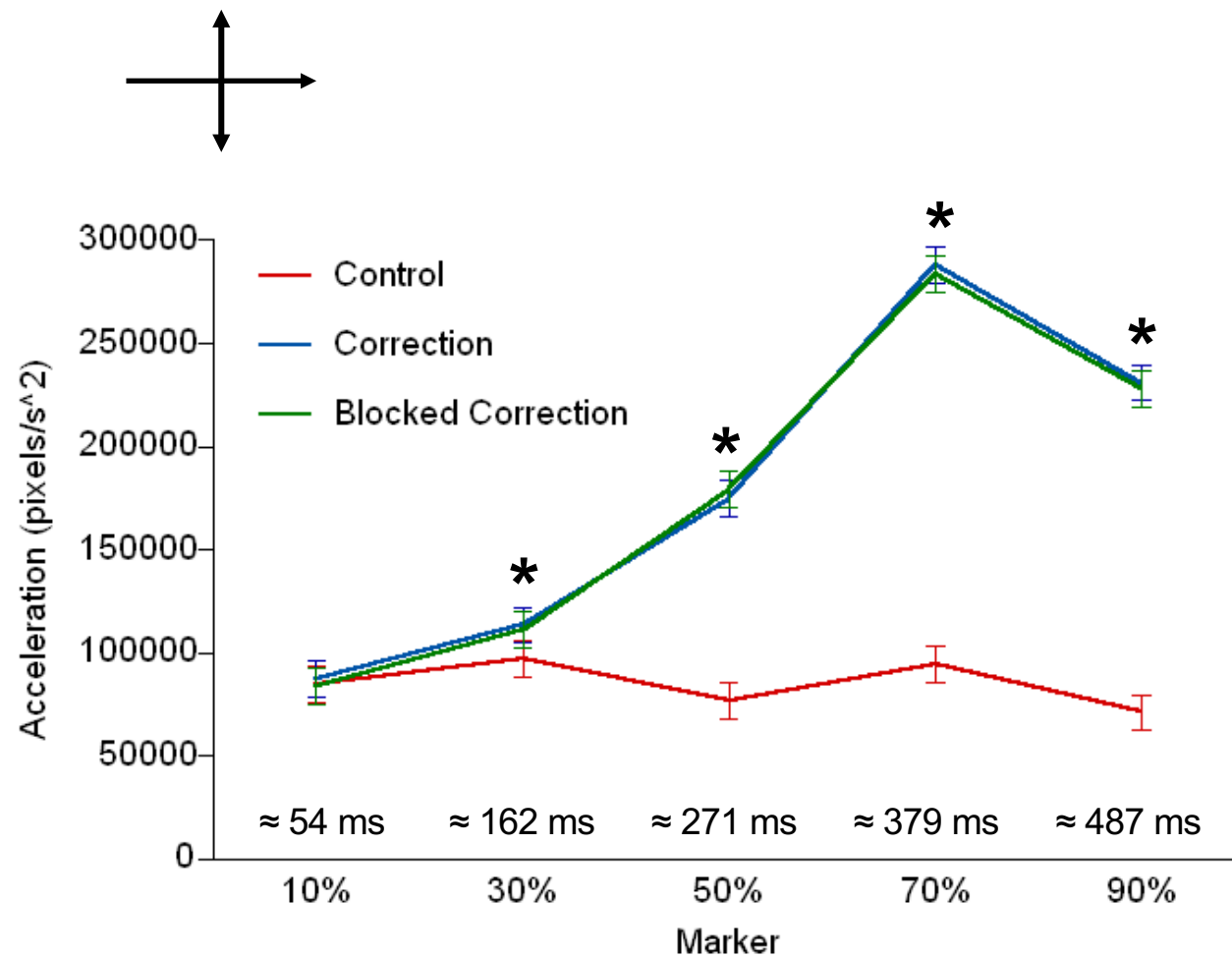


**Condition Two:  
Target Jump**

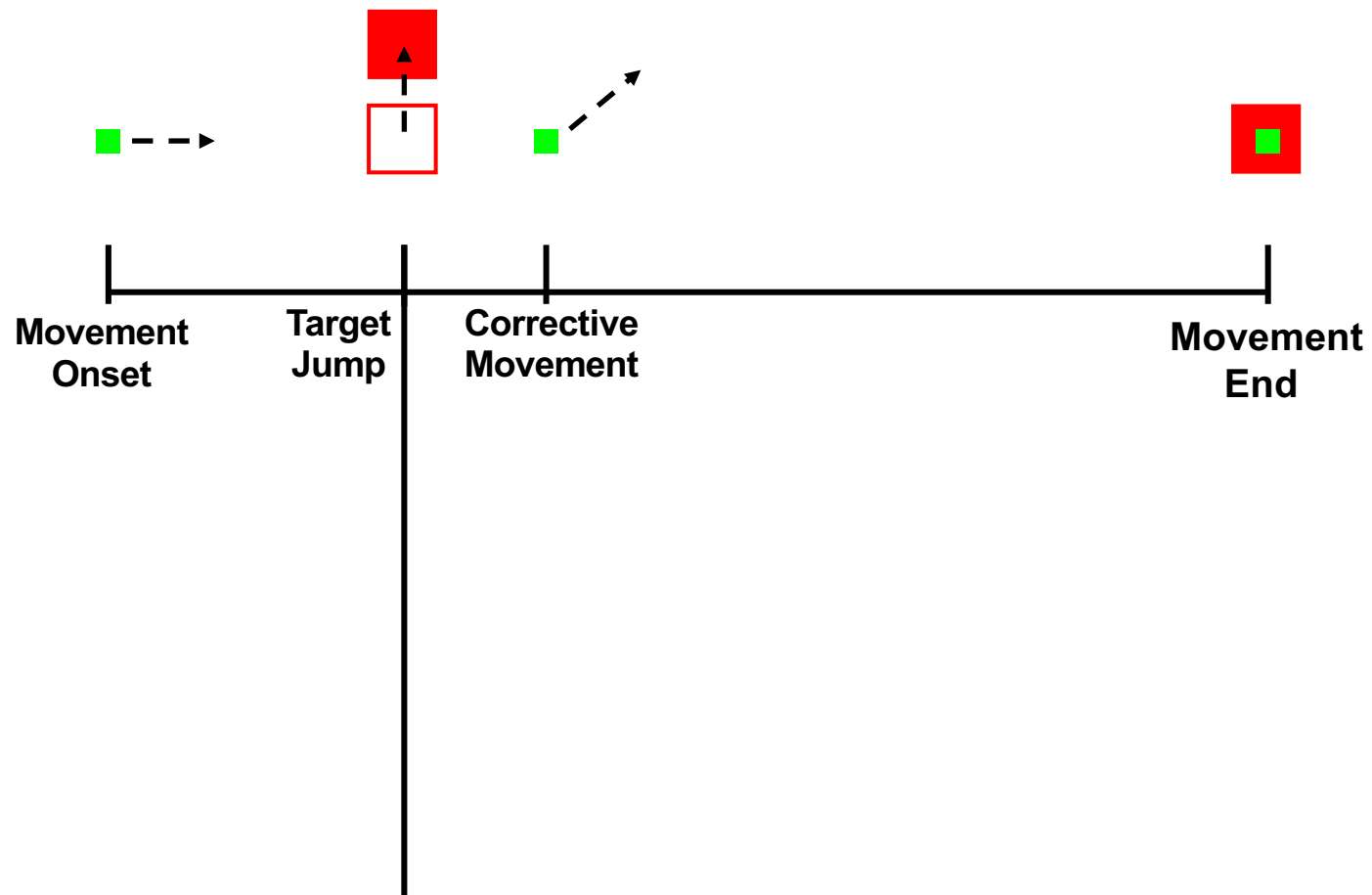




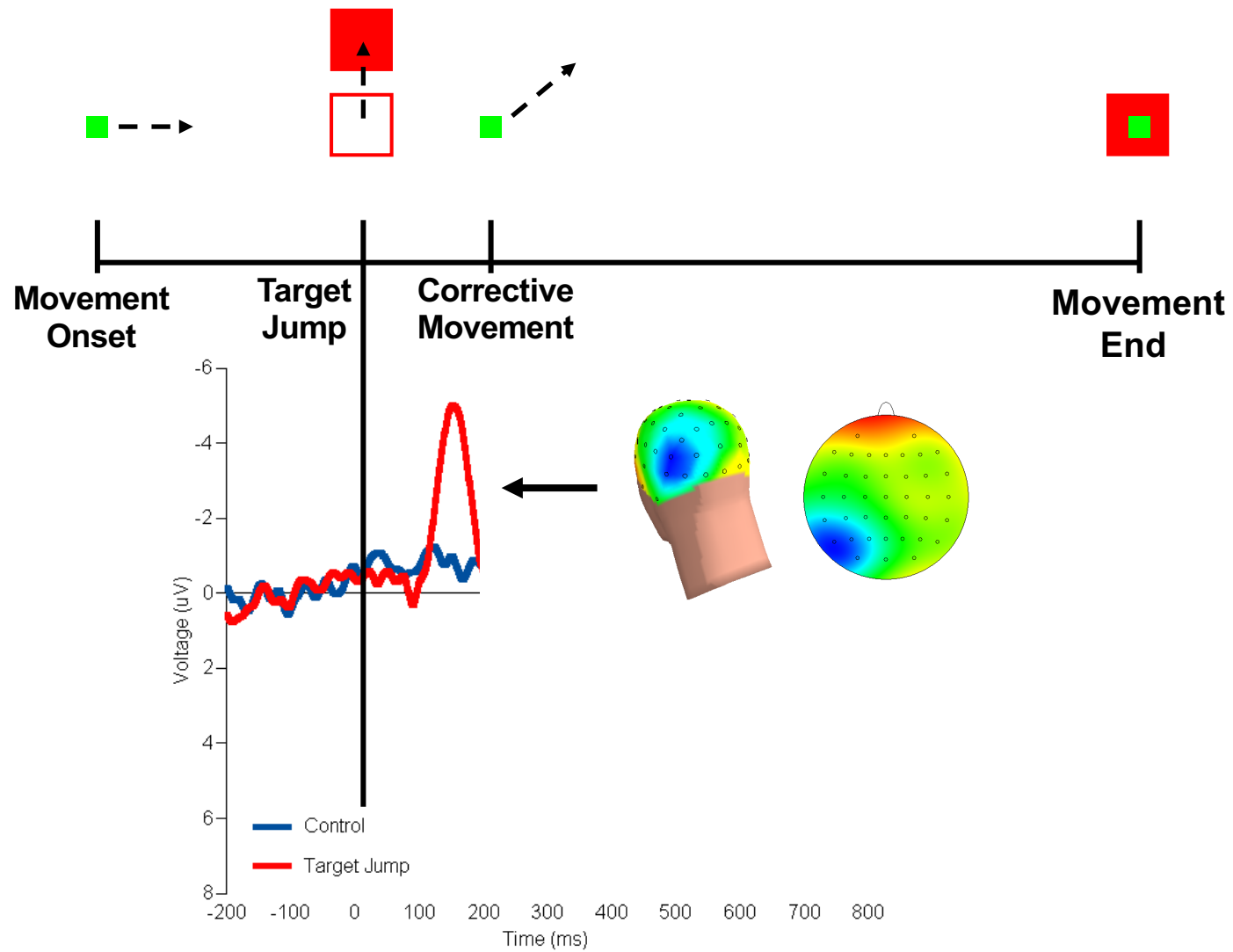
Secondary Movement Axis: Acceleration as a Function of Experimental Condition



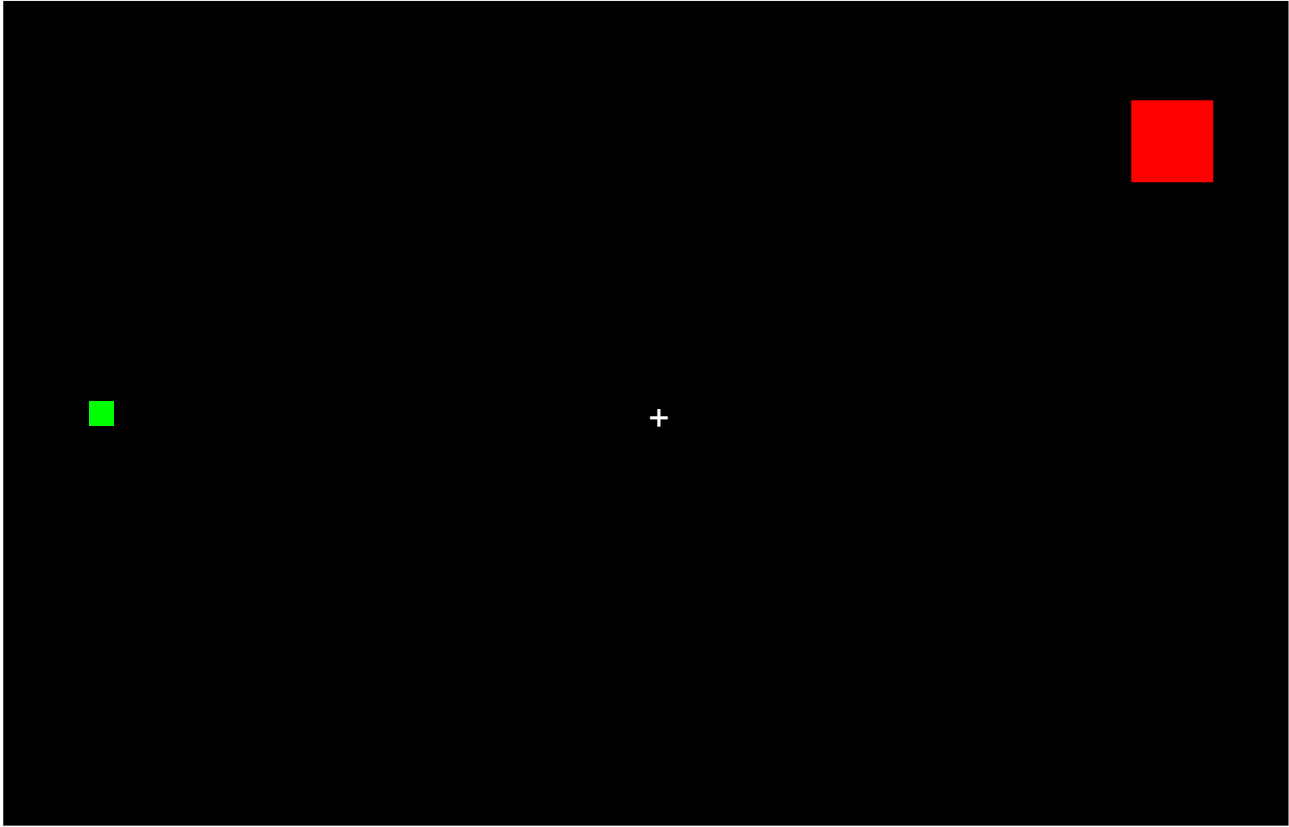




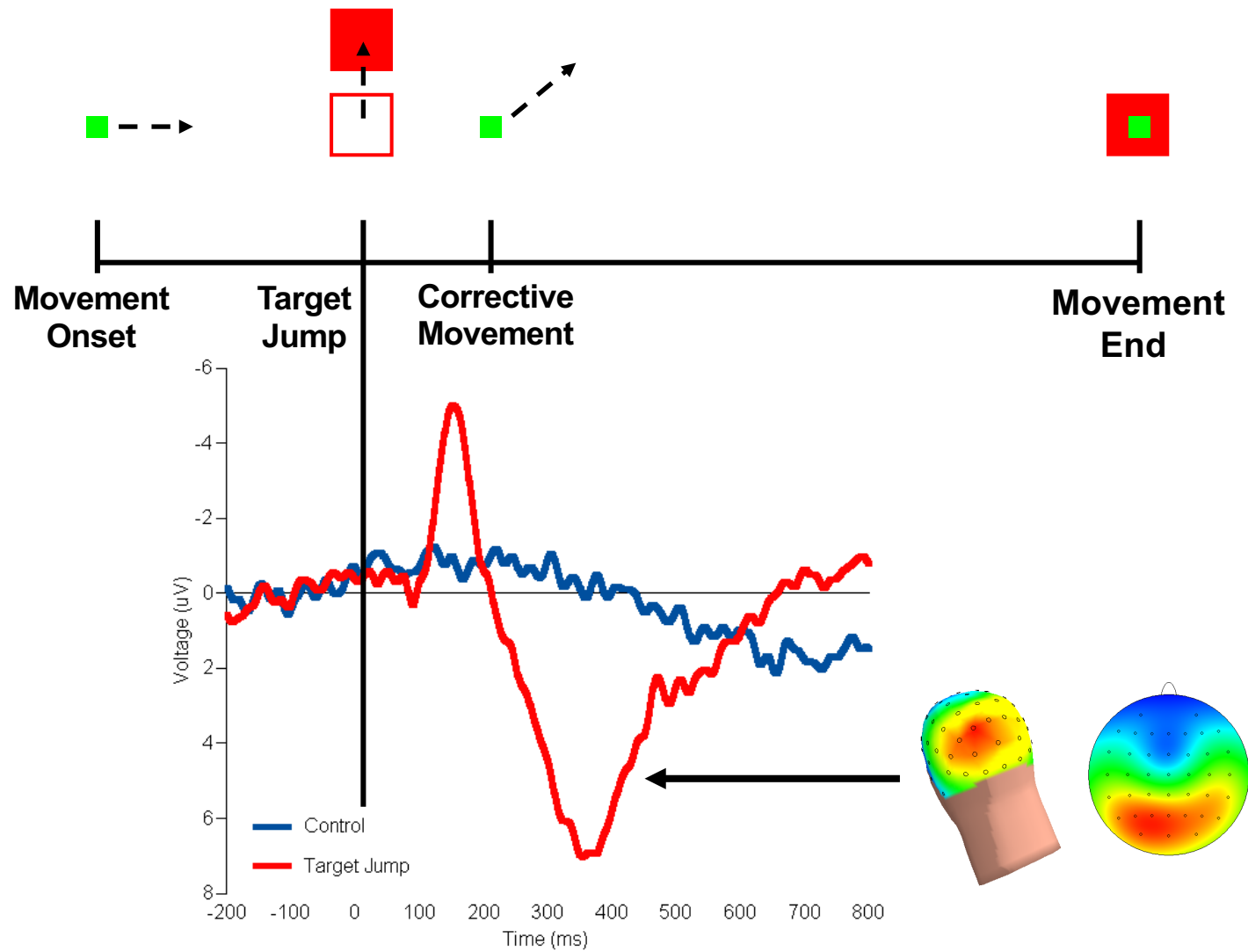












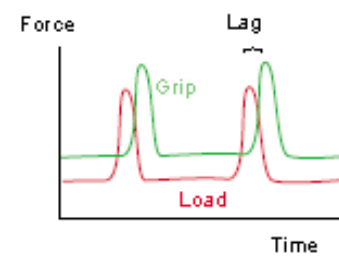
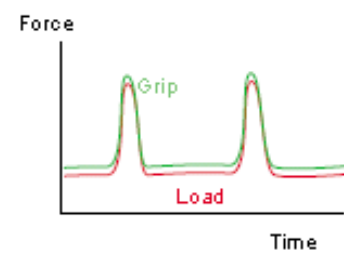
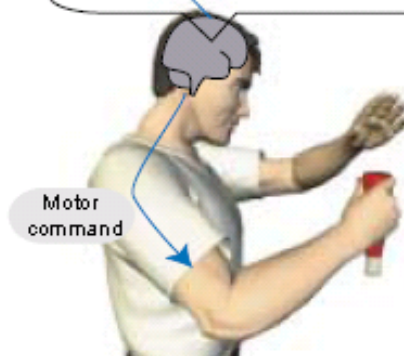
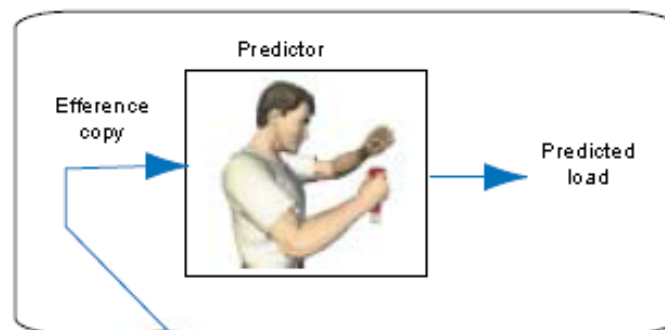


# FORWARD CONTROL

Why aren't feedback loops enough?

(another way to think of this is what is an inherent problem with feedback loops)

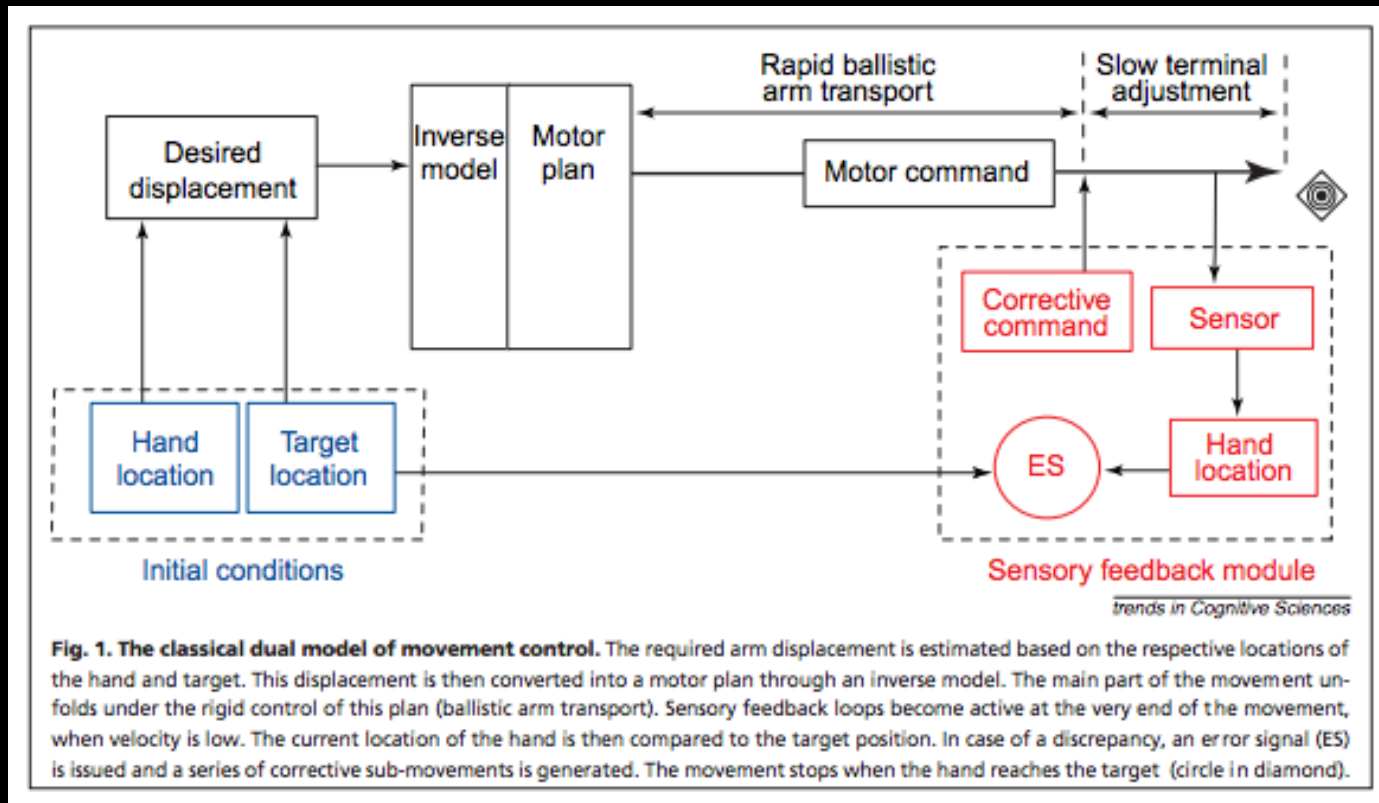









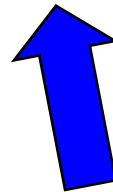
How does predictive control work?







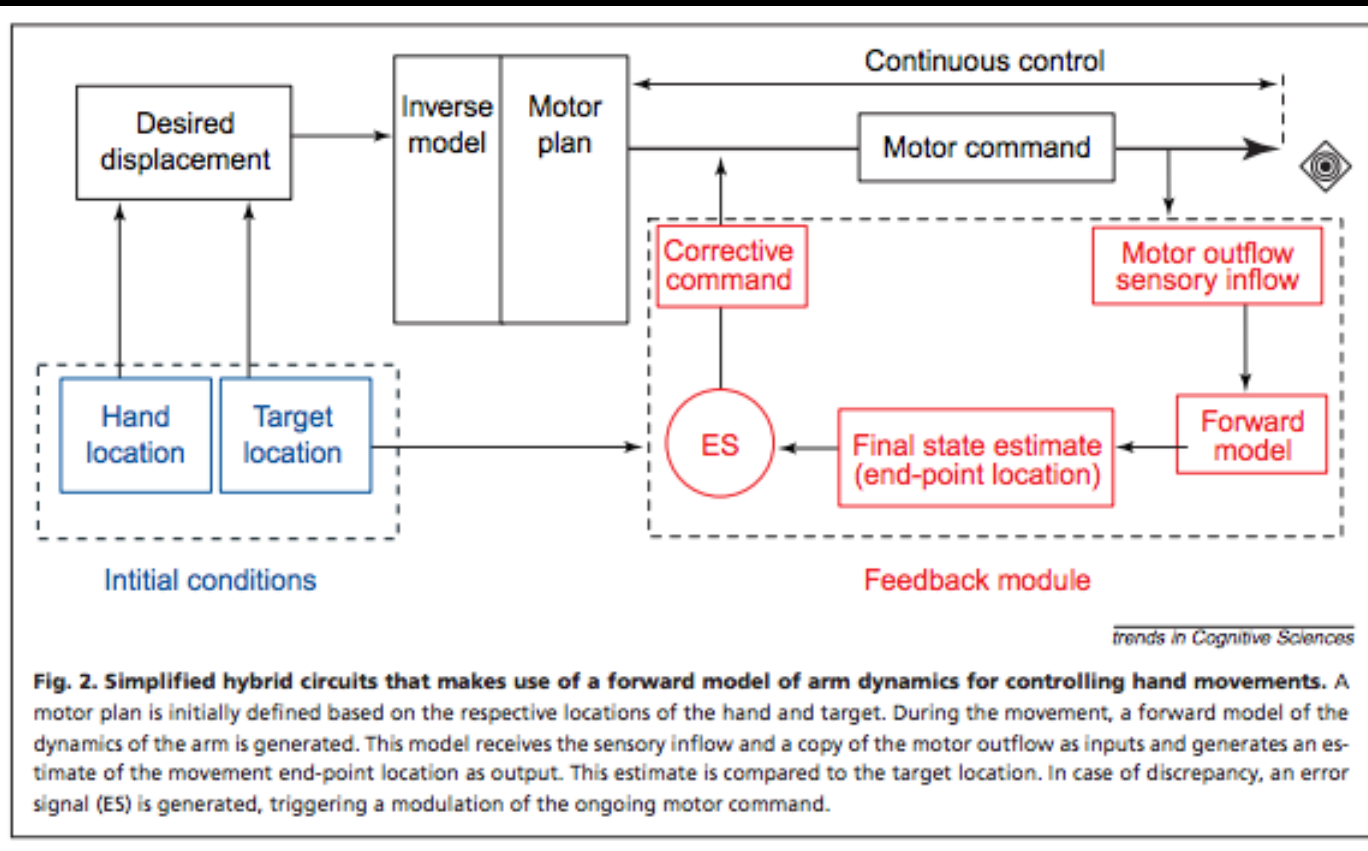
-  Predicted State
-  Estimate of Target Location
-  Physical Target Location






ERROR!  
ERROR = Predicted – Estimate  
ERROR  $\approx$  0  
Minimize Error!

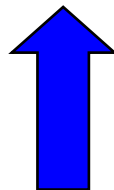
What system is fixing  
this problem?








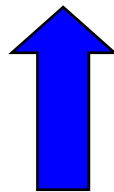


-  Predicted State
-  Estimate of Target Location
-  Physical Target Location






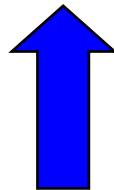


-  Predicted State
-  Estimate of Target Location
-  Physical Target Location








-  Predicted State
-  Estimate of Target Location
-  Physical Target Location






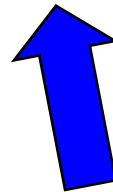


-  Predicted State
-  Estimate of Target Location
-  Physical Target Location








-  Predicted State
-  Estimate of Target Location
-  Physical Target Location

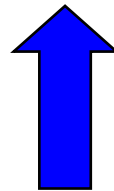


ERROR!  
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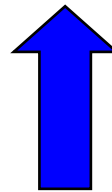
-  Predicted State
-  Estimate of Target Location
-  Physical Target Location



No ERROR!  
 $\text{ERROR} = \text{Predicted} - \text{Estimate}$   
 $\text{ERROR} = 0$






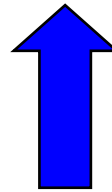
-  Predicted State
-  Estimate of Target Location
-  Physical Target Location



No ERROR!  
 $\text{ERROR} = \text{Predicted} - \text{Estimate}$   
 $\text{ERROR} = 0$






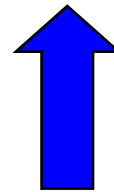
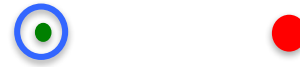
-  Predicted State
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 $\text{ERROR} = \text{Predicted} - \text{Estimate}$   
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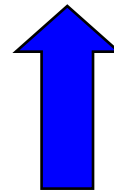
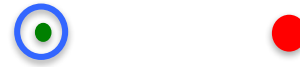
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No ERROR!  
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 $\text{ERROR} = 0$






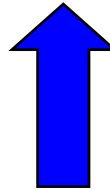
-  Predicted State
-  Estimate of Target Location
-  Physical Target Location



No ERROR!  
 $\text{ERROR} = \text{Predicted} - \text{Estimate}$   
 $\text{ERROR} = 0$



-  Predicted State
-  Estimate of Target Location
-  Physical Target Location

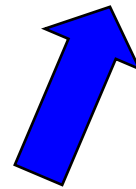


ERROR!  
ERROR = Predicted – Estimate  
ERROR  $\approx$  0  
Minimize Error

Why the delay this time?  
What system fixes this?






- Predicted State
- Estimate of Target Location
- Physical Target Location

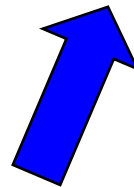


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-  Physical Target Location

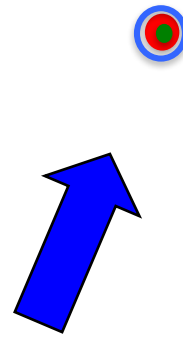


ERROR!  
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 $\text{ERROR} \approx 0$   
Minimize Error

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ERROR!  
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 $\text{ERROR} \approx 0$   
Minimize Error

Why the delay this time?  
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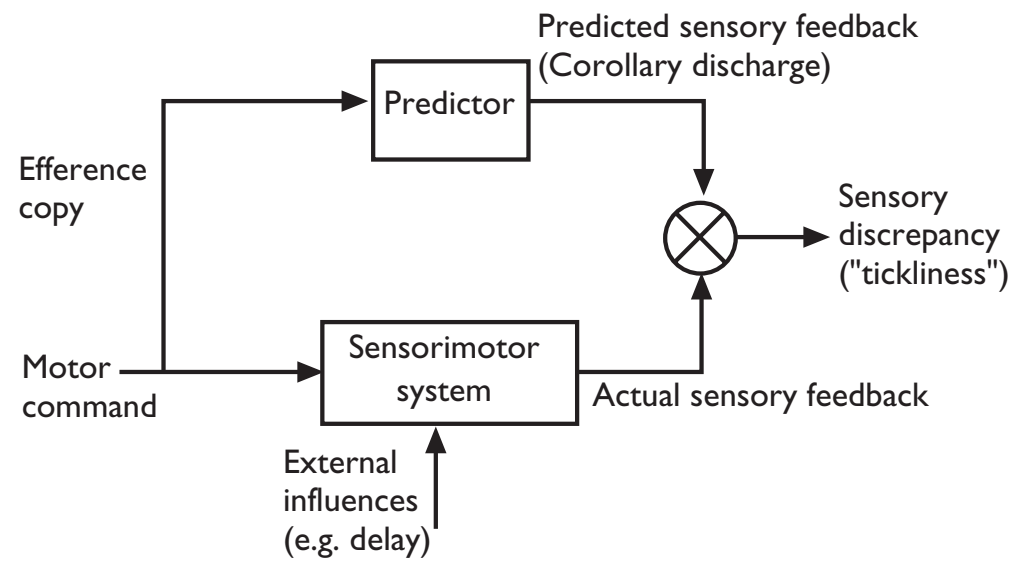
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ERROR!  
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 $\text{ERROR} \approx 0$   
Minimize Error

Why the delay this time?  
What system fixes this?







# Parkinson's Disease



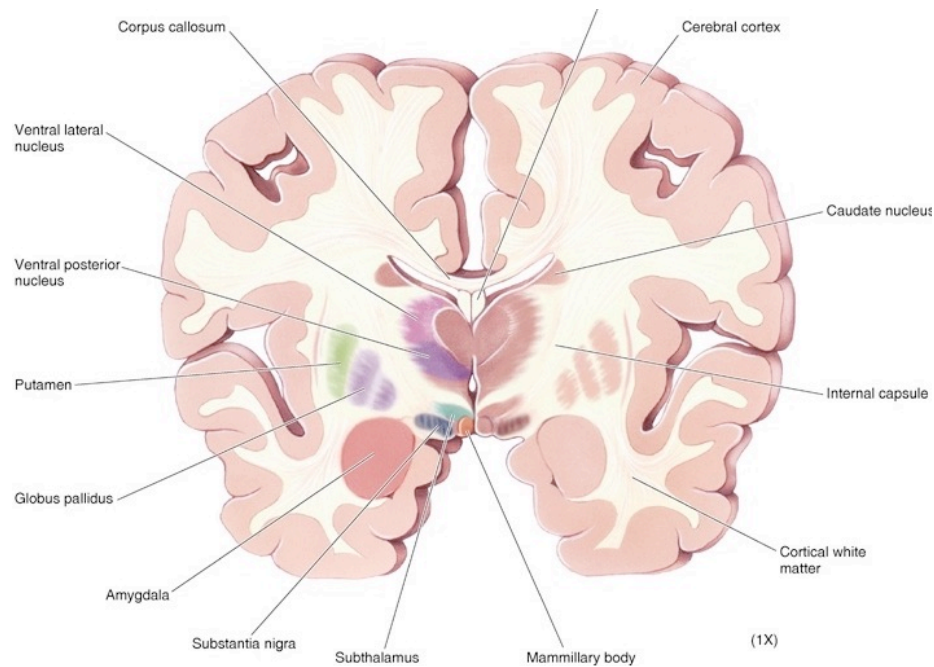
# Basal Ganglia - Role in Movement

- Many hypotheses
  - 1) BG are involved in feedback control
    - Honing of motor program by enhancing activity of target movement and inhibiting activity of non-target movements
  - 2) BG disinhibit areas of the motor system to allow movement to occur
  - 3) BG turn off postural control to allow voluntary movement to occur
  - 4) BG are involved in sequencing of movement fragments or whole movements



# Basal Ganglia Nuclei

- Consist of 5 pairs of nuclei: (interconnected and subcortical)
- 1) caudate
- 2) putamen
- 3) subthalamic nucleus
- 4) globus pallidus (GP) internal/ external
- 5) substantia nigra (SN) - pars compacta/ pars reticulata





## **Inputs to basal ganglia:**

Receive input from cerebral cortex (corticostriate pathway).

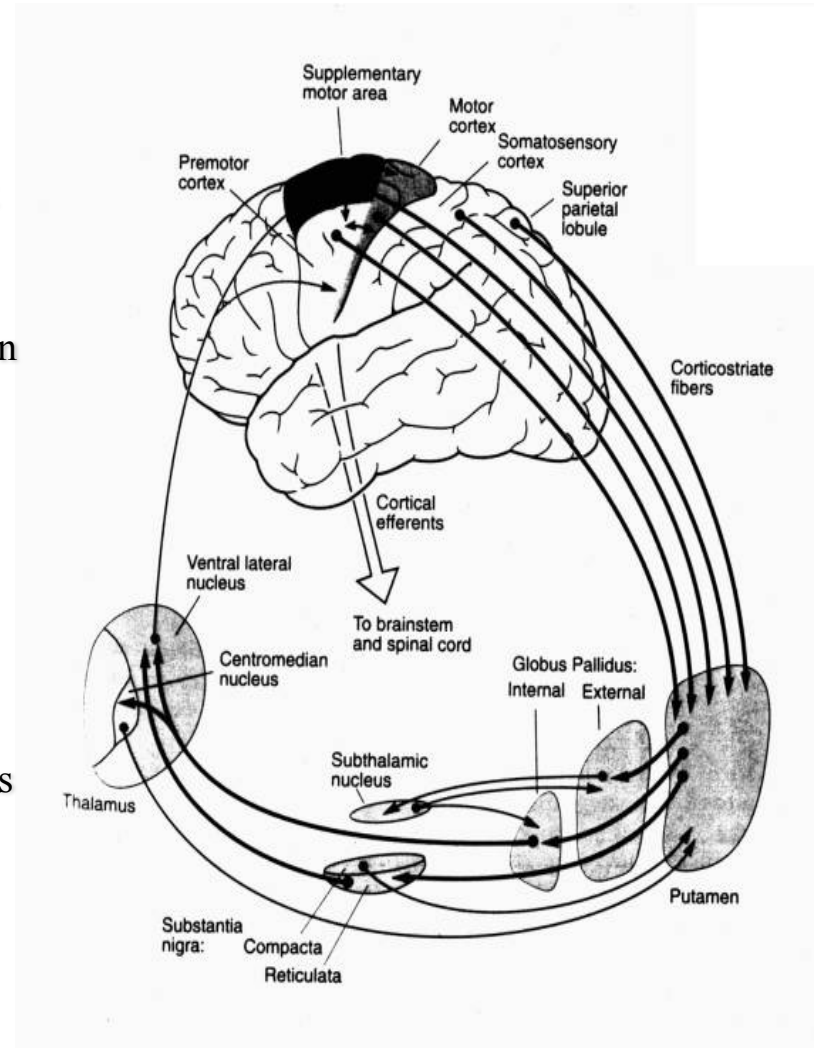
Via striatum = caudate and putamen

Caudate -cognitive/behavioral

Putamen - motor

From caudate and putamen nuclei to:

- globus pallidus
  - internal and external segments
- substantia nigra
  - pars reticulata





## **Symptoms of Parkinson's Disease**

- “TRAP”
  - (T)remor
  - (R)igidity
  - (A)kinesia (bradykinesia)
  - (P)ostural disturbance



## Symptoms of Parkinson's Disease

### 1) Tremor:

-“resting” vs. “intention”

-pillrolling (thumb & forefinger motion)

-magnified by stress, fatigue

-involuntary oscillation

### 2) Rigidity:

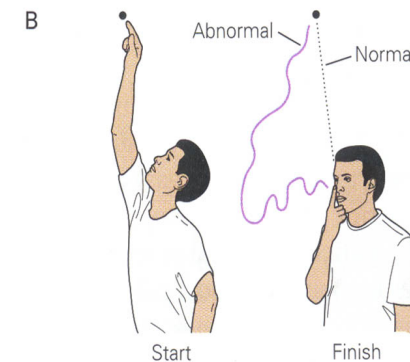
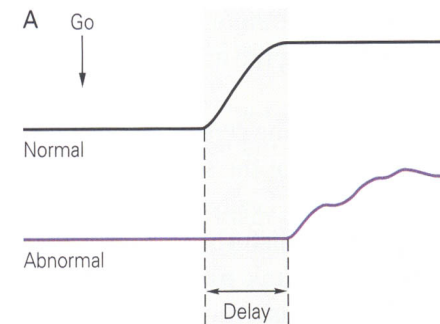
-increased resistance to passive stretch

-(“cogwheel”)

-facial expression (mask-like- hypomimia)

-decreased arm swing

-Long latency stretch reflex is enhanced in Parkinson's Disease.



Cerebellar Patient



## Symptoms of Parkinson's Disease

### 3) Akinesia (and bradykinesia and hypokinesia)

- increased Reaction time & Movement time
  - alleviated with external cues
  - This may also be due to muscle weakness observed in patients.
  - Increased speed accuracy trade-off.
- Simple RT is longer, however results from choice RT studies are conflicting.
- Bradyphrenia– slowness of thought



## Symptoms of Parkinson's Disease

### 4) Postural deficits

- flexed posture
- decreased efficiency during postural perturbations

### 5) Gait Disorders

- problems to initiate
- “freezing”
- shuffling pattern
- increased speed leads to “festination”



## Treatments for Parkinson's Disease

### 1) Pharmacological - increase dopamine levels with L-DOPA

- precursor of dopamine
- “On-Off” effects
- Dose must be increased because disease is degenerative.
  - 3-5 years
- Currently, no cure.

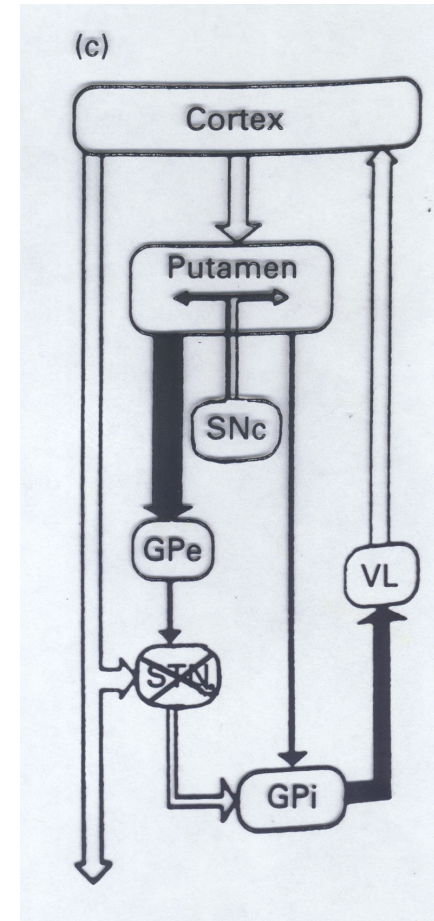
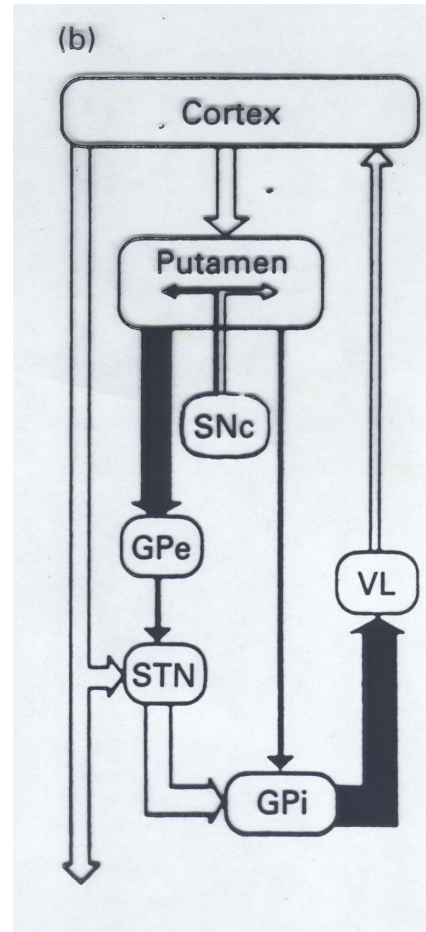


## Treatments for Parkinson's Disease

2) Neurosurgical - restore balance of inputs to thalamus by lesioning/stimulating specific sites in basal ganglia.

### 3) Deep Brain Stimulation

- importance of placement within basal ganglia
- maintain excitation/inhibition balance





# Transcranial Magnetic Stimulation

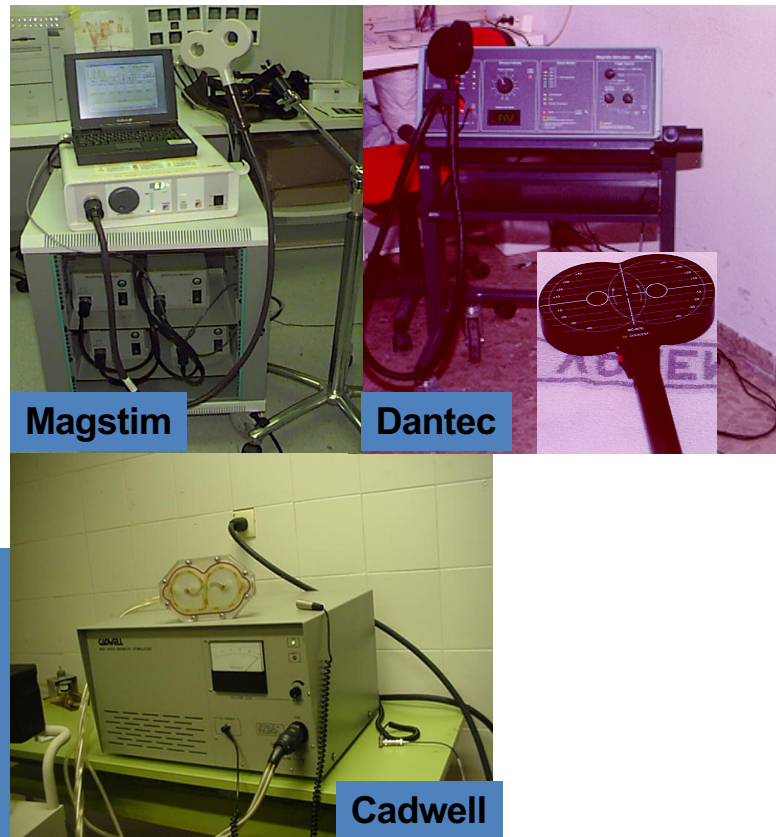




Barker, 1984

Transcranial Magnetic Stimulation allows the Safe, Non-invasive and Painless Stimulation of the Human Brain Cortex.

### Common rTMS machines



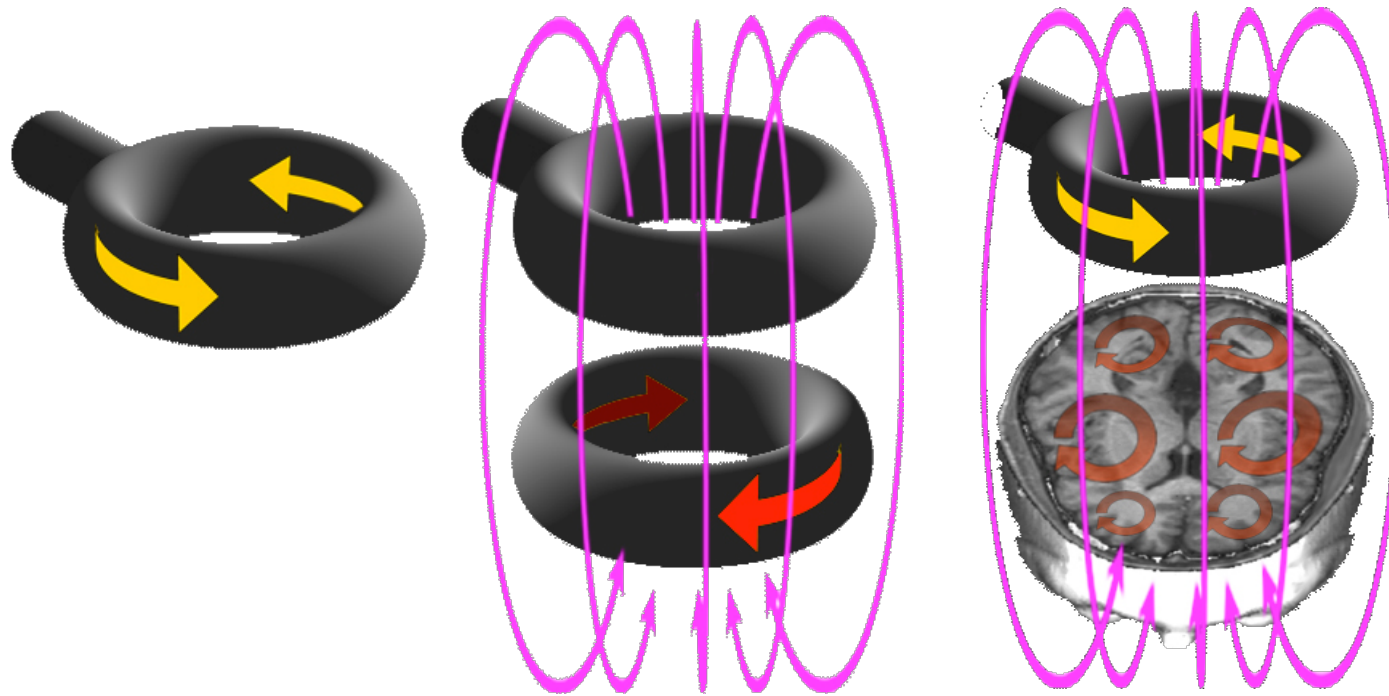
Magstim

Dantec

Cadwell



# Electromagnetic Induction



Introduces disorder into a normally ordered system

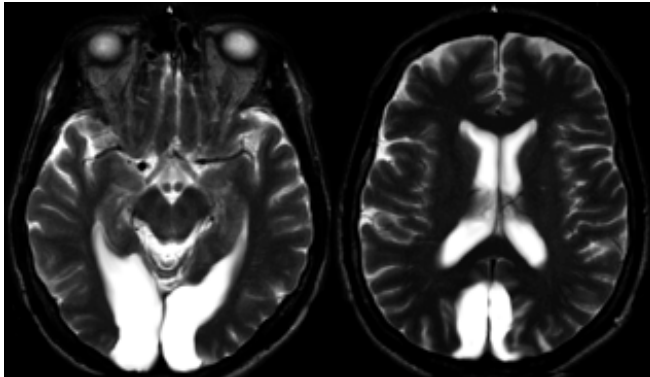


# Advantages of TMS: Virtual Patients

causal link between brain activity and behaviour

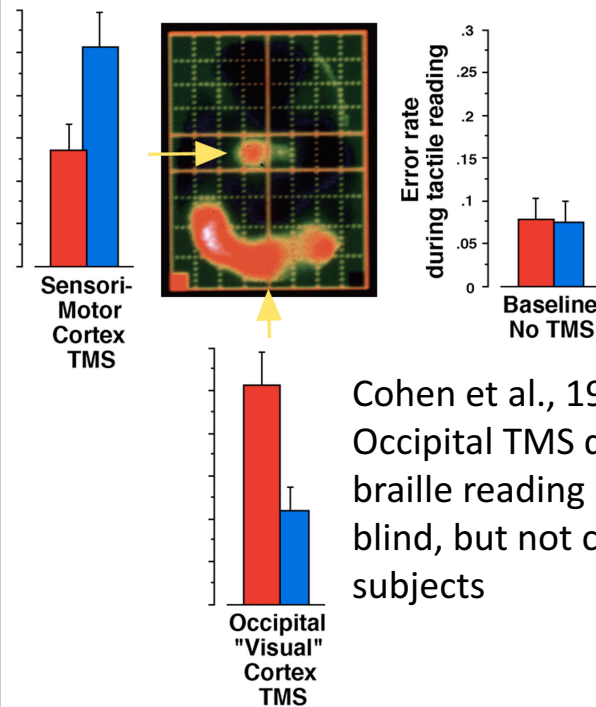
## Braille Alexia

### Real lesion



Hamilton et al., 2000. Reported case of blind woman who lost ability to read braille following bilateral occipital lesions

### TMS lesion

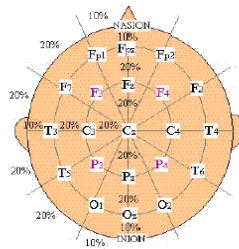
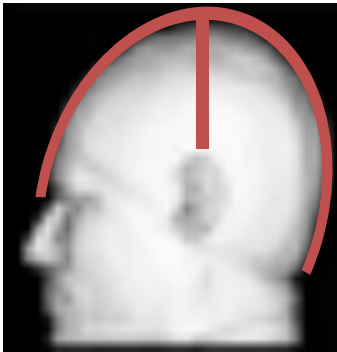


Cohen et al., 1997. Occipital TMS disrupts braille reading in early blind, but not control subjects

Blue = sighted; Red = E blind



# Coil localisation - hitting the right spot



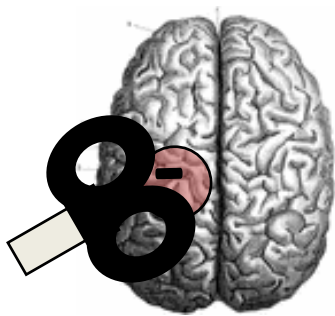
Find functional effect  
M1 - hand twitch (MEP)  
V5 - moving phosphenes

Find anatomical landmark  
inion/nasion-ear/ear vertex  
EEG 10/20 system

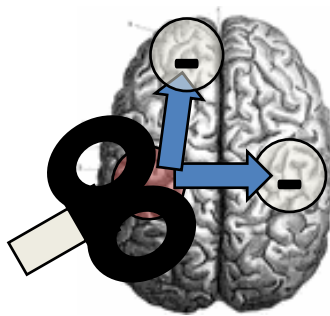
Move a set distance along and across (e.g. FEF =  
2-4 cm anterior and 2-4 cm lateral to hand area)



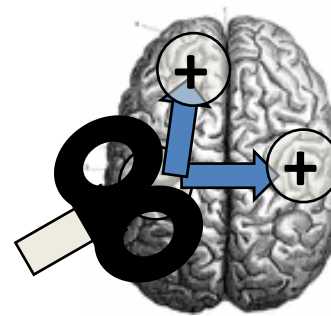
# Stimulation techniques and possible effects



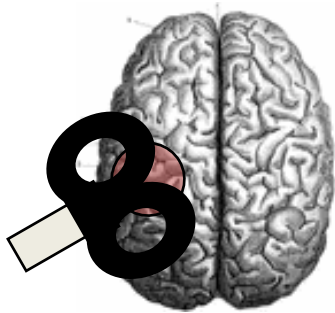
Expected effect



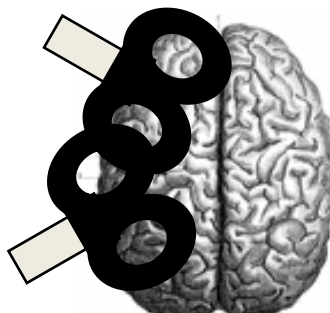
Connected effects



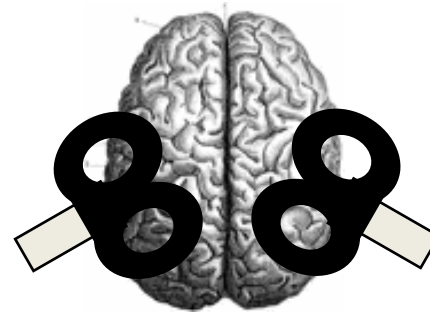
Paradoxical effects



Single pulse  
rTMS (low/high fr.)



Paired pulse



Paired pulse



