EPHE 380 – MOTOR CONTROL

CONTROL OF RHYTHMIC MOTOR OUTPUT:

LOCOMOTION AND CENTRAL PATTERN GENERATORS

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Establishing accessible and affordable, yet effective rehabilitation strategies for people with neurological impairment

What do I mean by accessible and affordable?

WHY IS THE SPINAL CORD IMPORTANT FOR MOTOR OUTPUTS?

Mike the Headless Chicken

- Decapitated in 1945, but lived for another 18 months.
- Most of the ***brainstem*** **was left intact.**
- **The circuits for locomotion are located within the spinal cord**

NEURAL ORGANIZATION OF LOCOMOTION: HISTORICAL BACKGROUND

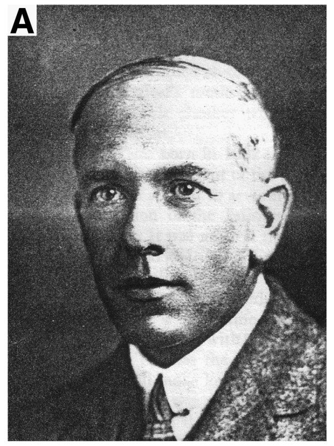
Locomotion possible without cortical input

Sherrington (1910):

– **Locomotion due to series of reflexes**

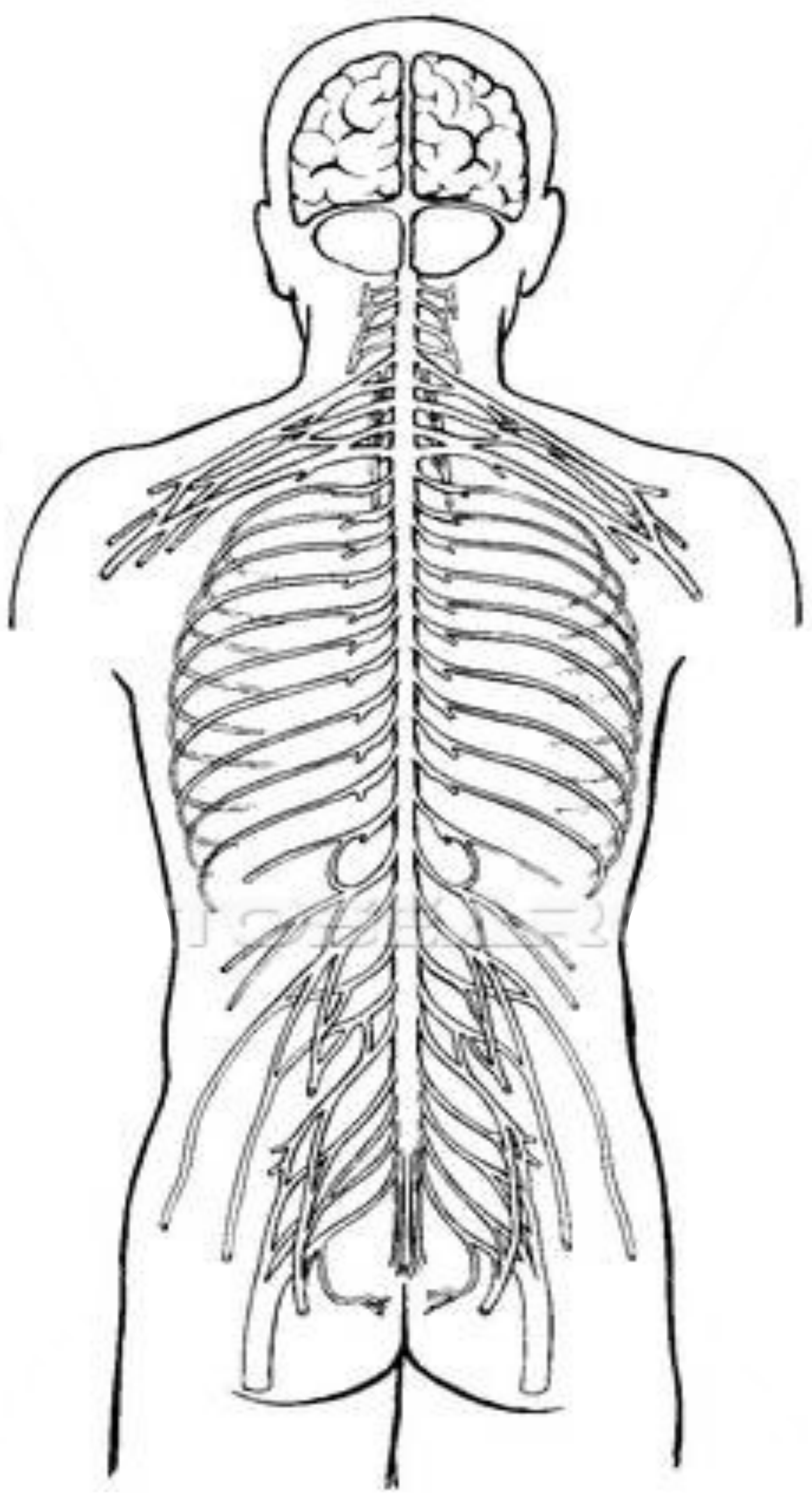
Graham Brown (1911):

– **Locomotion possible without afferent feedback**

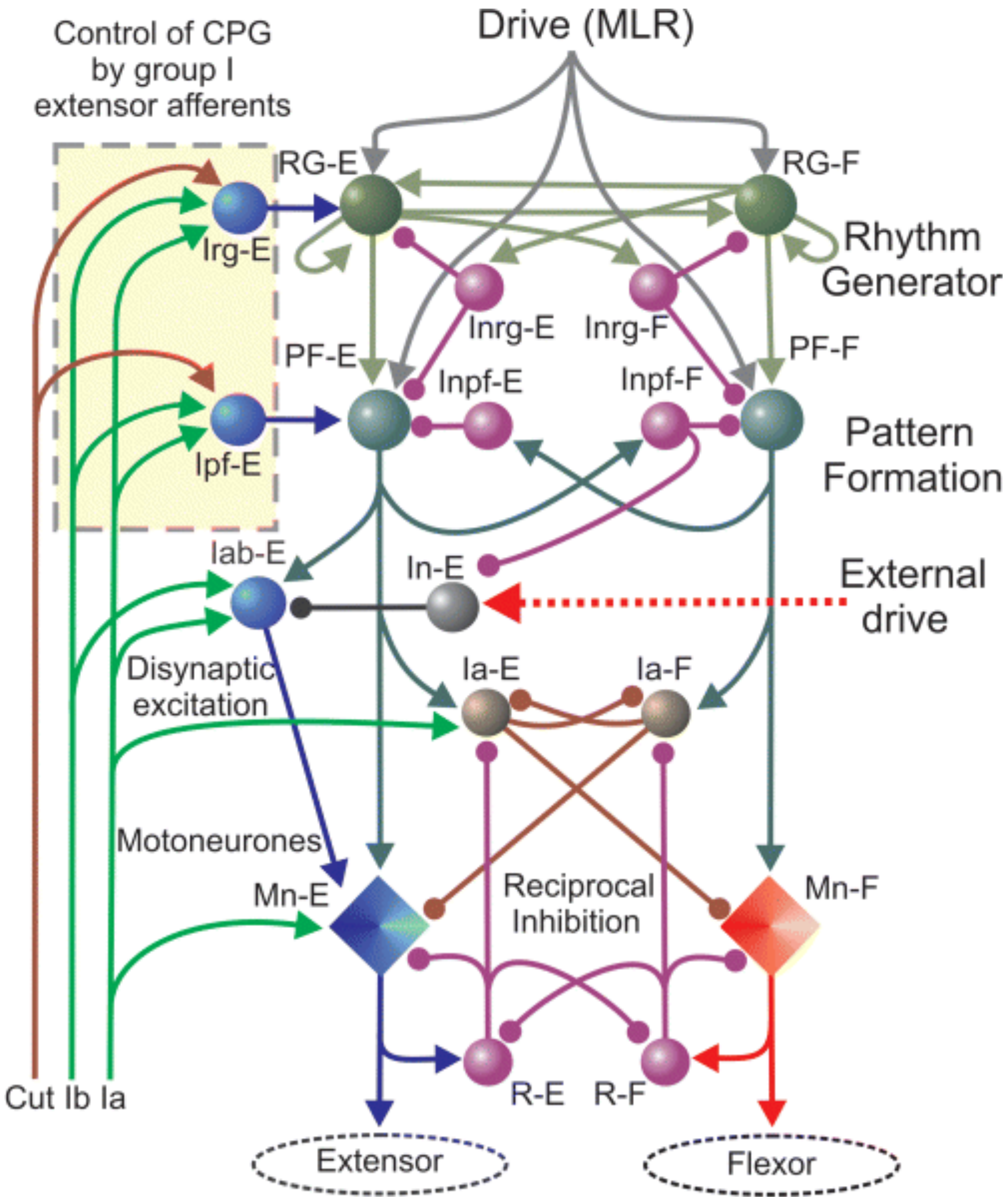


CENTRAL PATTERN GENERATORS (CPGS)...

- Most complex spinal networks
- Network of neurons in spinal cord that produce **rhythmic activity**
  - walking, breathing, vomiting, coughing
- Can autonomously generate repetitive patterns of movement
  - without sensory input
  - just get it started



"NEWEST CPG" FOR LOCOMOTION



Dr. David McCrea
Spinal Cord Research Centre
Winnipeg, Manitoba

CPGS CAN BE "BUILT" FROM REFLEXES

Remember the flexor withdrawal reflex?

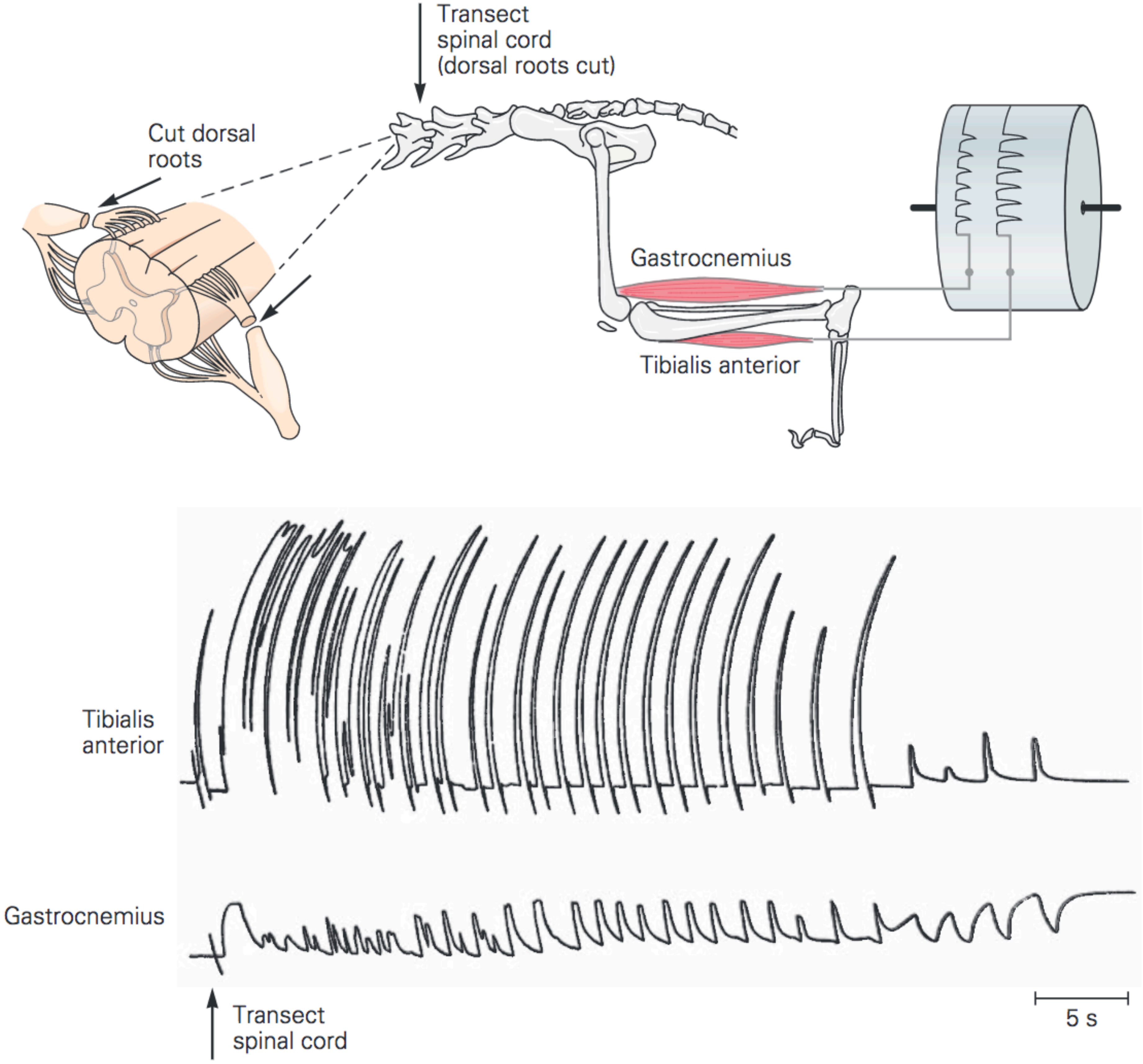
- complicated ipsi- and contralateral reflex coordination

Different reflex pathways can be integrated and used by the CPG

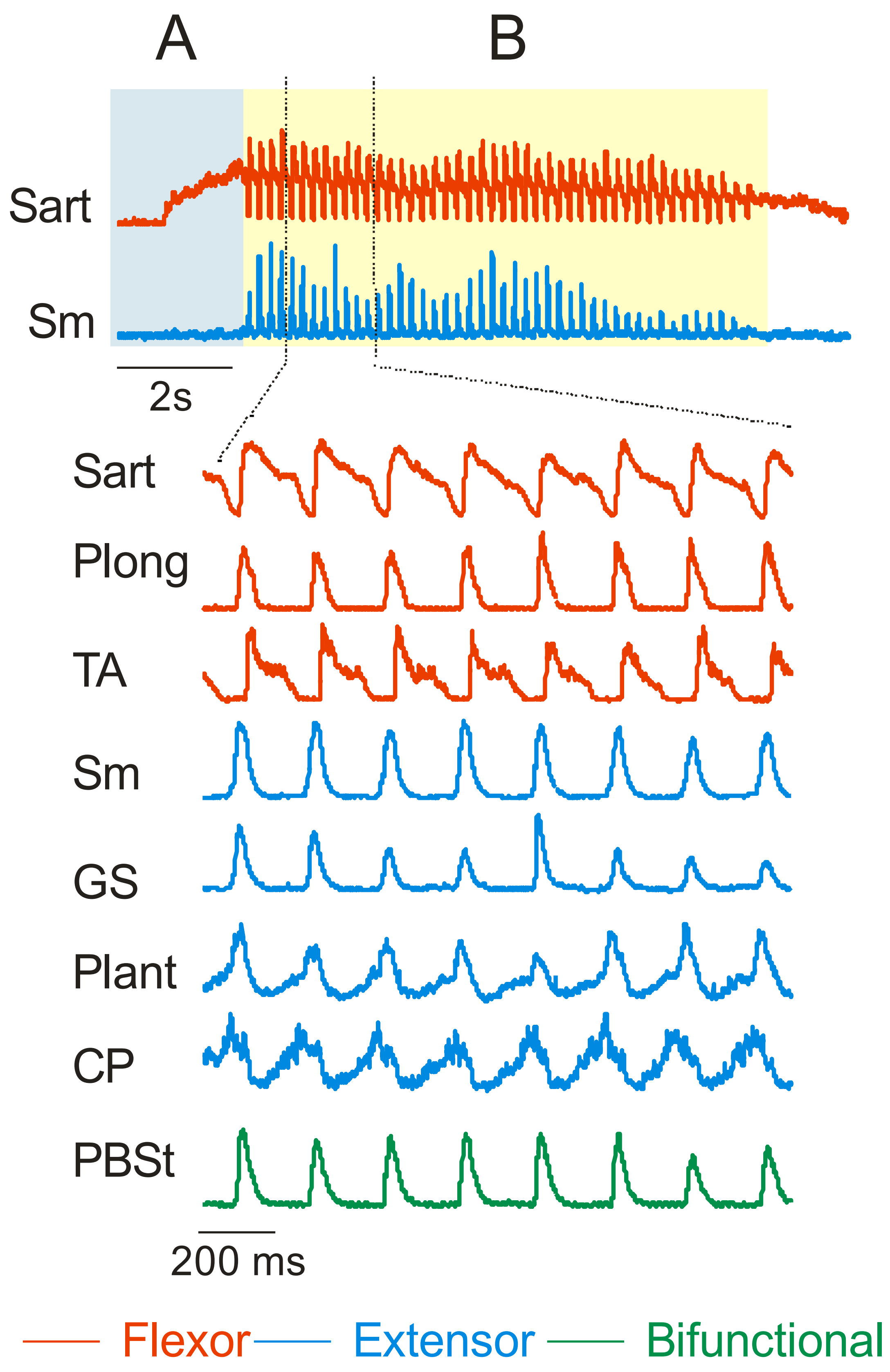
Thus spinal mechanisms can be used in complicated behaviours

One of the first demonstrations was in the "scratch reflex" of the dog

The OG Scratch Reflex



THE NEW SCRATCH REFLEX – FICTIVE SCRATCH

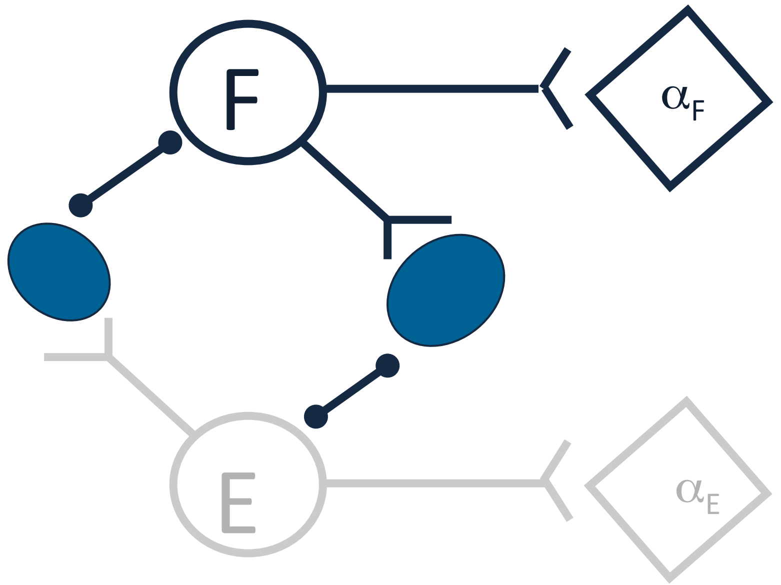


Scratch Reflex involves two general phases:

1) **Approach Phase (A in figure)**:
- Flexors are gradually depolarized and begin firing

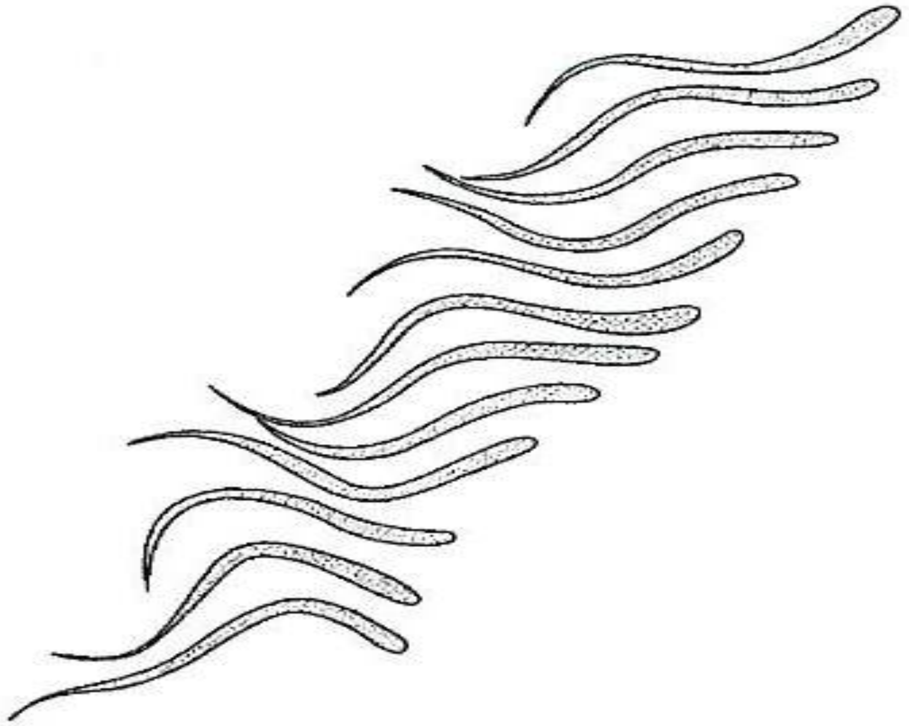
2) **Rhythmic Phase (B in figure):**
- Motor output alternating between flexors and extensors (~250ms):
  - Flexor phase ~ 200ms
  - Extensor phase ~ 50ms

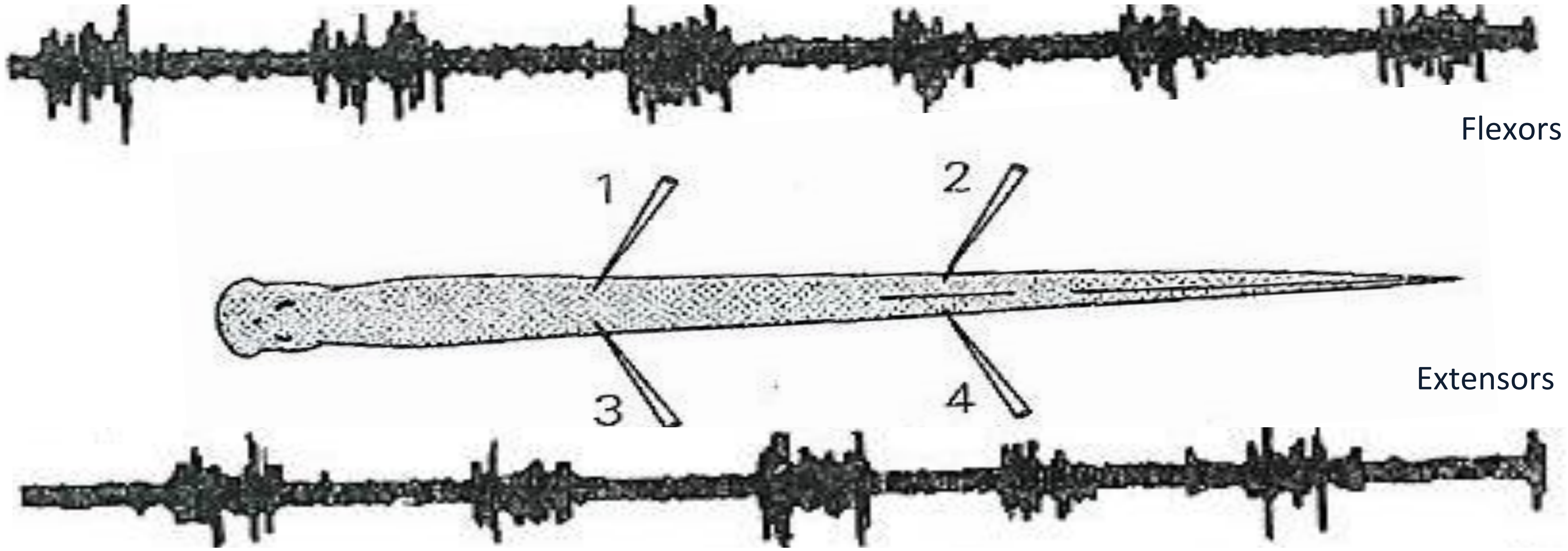
HALF-CENTRE MODEL
GRAHAM BROWN (1911)



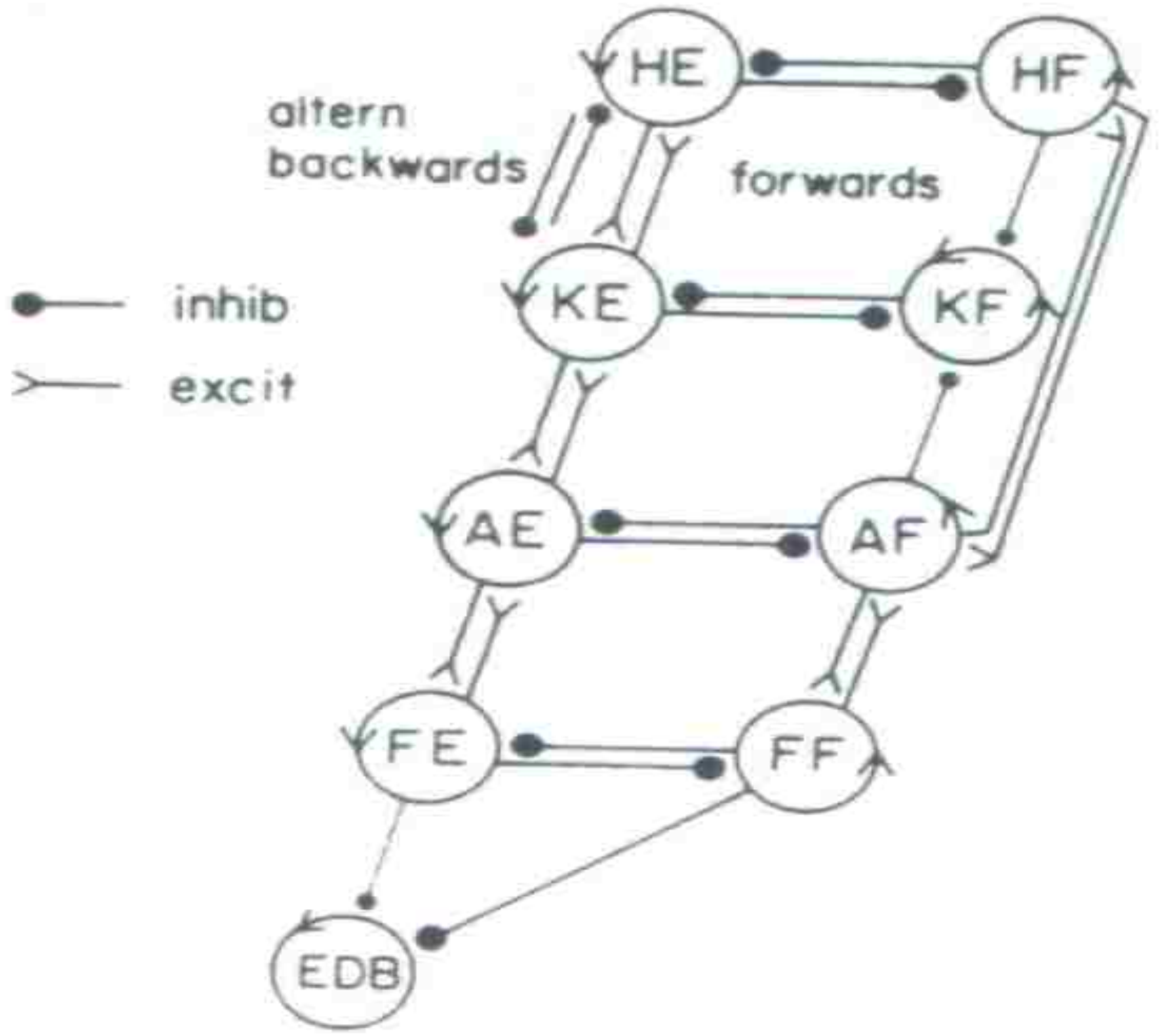
- Interneurons controlling flexor and extensor motor neurons
- **Reciprocal inhibition**

- Left-Right control in swimming (e.g. Lamprey)
- No sensory input, no brain





SCHEMA FOR CPG CONTROLLING QUADRUPED LOCOMOTION



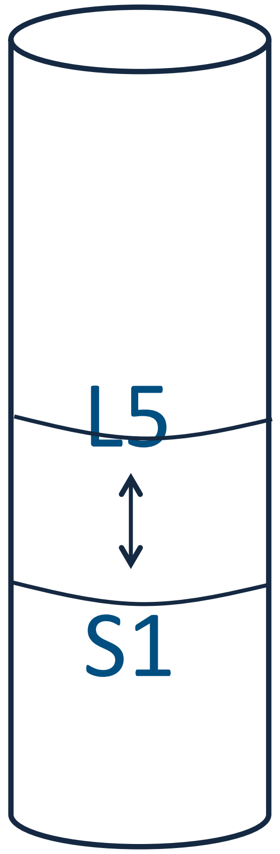
(Leonard, 1998)

Half center model

- reciprocal inhibition between flexors and extensors and between limb segments

Unit burst generators

- each joint is a "unit"
- recruited into a reciprocally-organized network in behaviour



RECIPROCAL INHIBITION IN CPGS

- When does switching from flexors to extensors occur?
- Duration of reciprocal inhibition limited by some intrinsic factors
    - “fatigue” of inhibitory synapses?
        - » Not likely
- More plausible mechanisms are:

  1) **accommodation**
     - » neuron responds to a constant excitatory input with a declining output (but it slowly tapers down)

  2) **post-inhibitory rebound**
     - » threshold for excitation of a neuron is transiently lower after inhibition (easier to turn on after inhibition)

MOTOR PATTERNS OF WALKING

Command for locomotion comes from the Mesencephalic locomotor region (MLR)

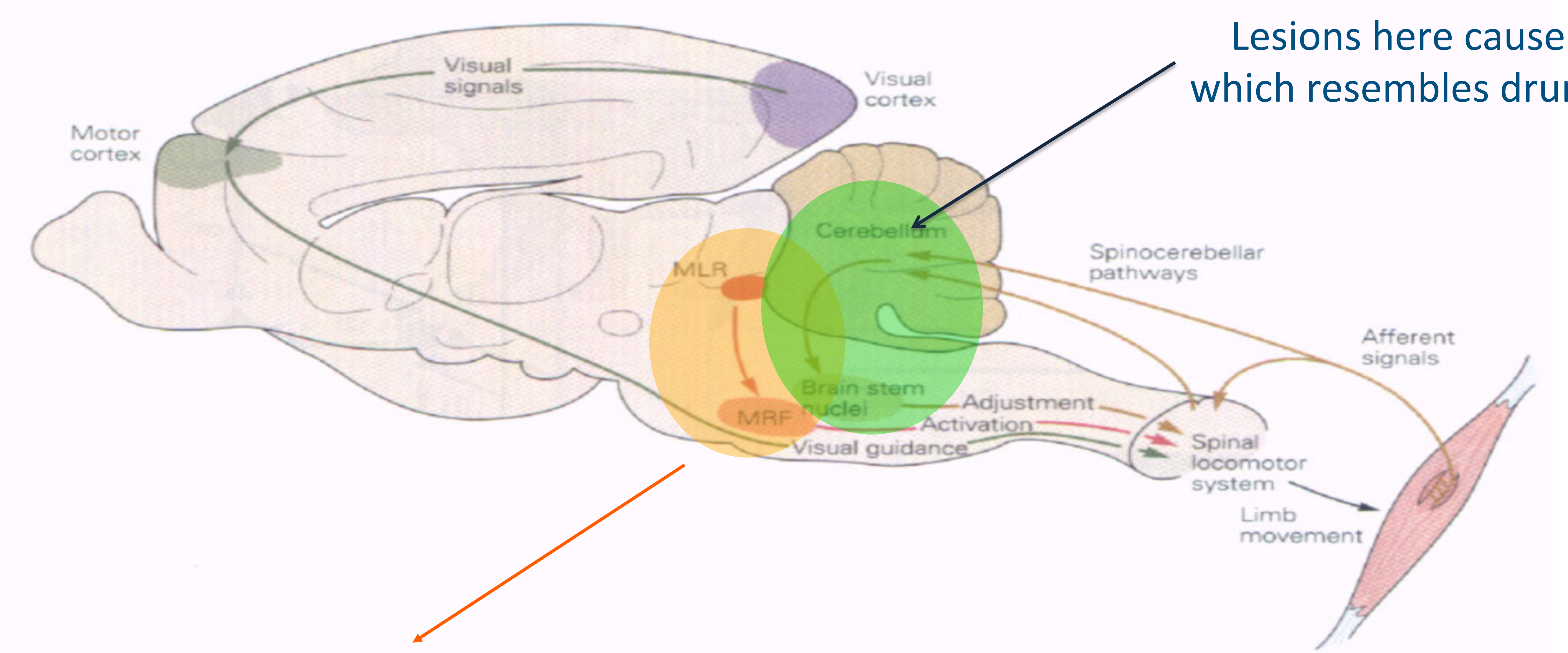
- Turns on CPG!

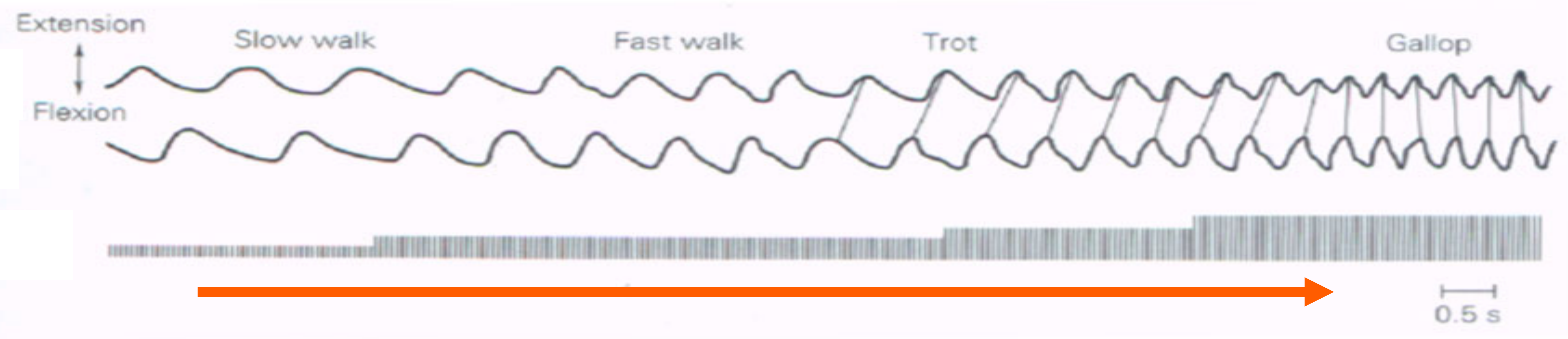
The **basic rhythm** is carried out by **CPG**…

- But there’s online control from **cortex**
  - e.g. hitting an obstacle with the foot

MOTOR PATTERNS OF WALKING

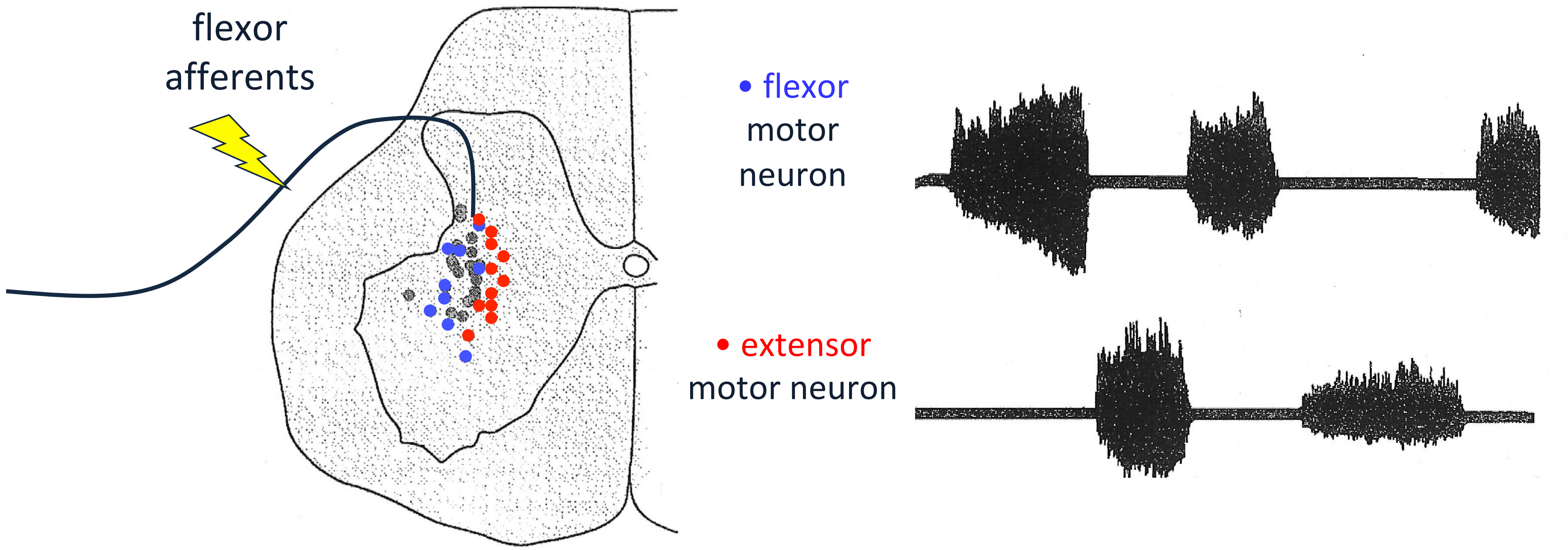
Lesions here cause ataxia which resembles drunken gait





Kandel (2000) Principles of Neural Science

Tonic input produces rhythmic output!

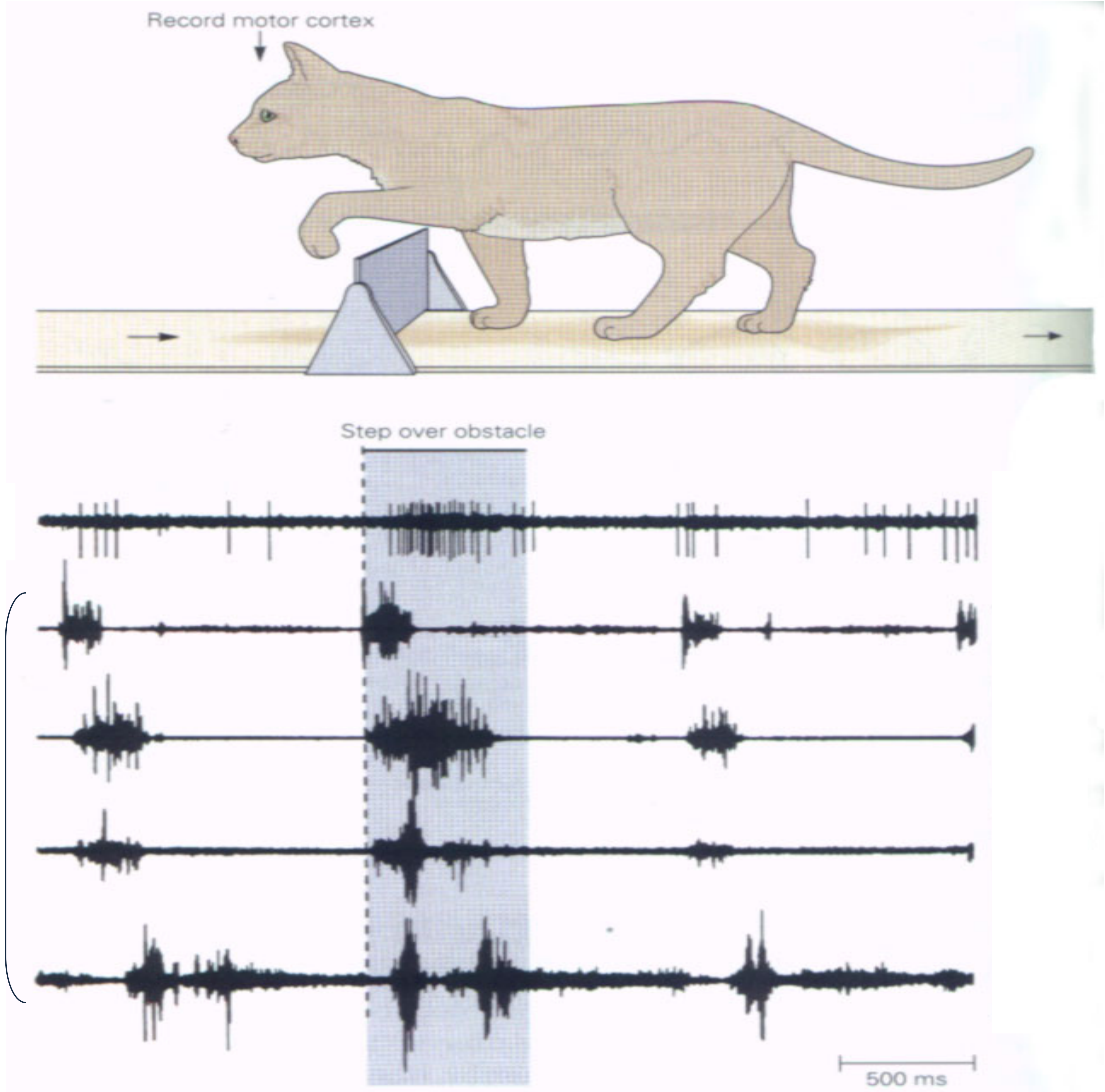


(Jankowska, 1967)

MOTOR PATTERNS OF WALKING

Motor cortex unit

EMG from foreleg muscles



Kandel (2000) Principles of Neural Science

Evidence of CPGs in humans

1. Infant walking

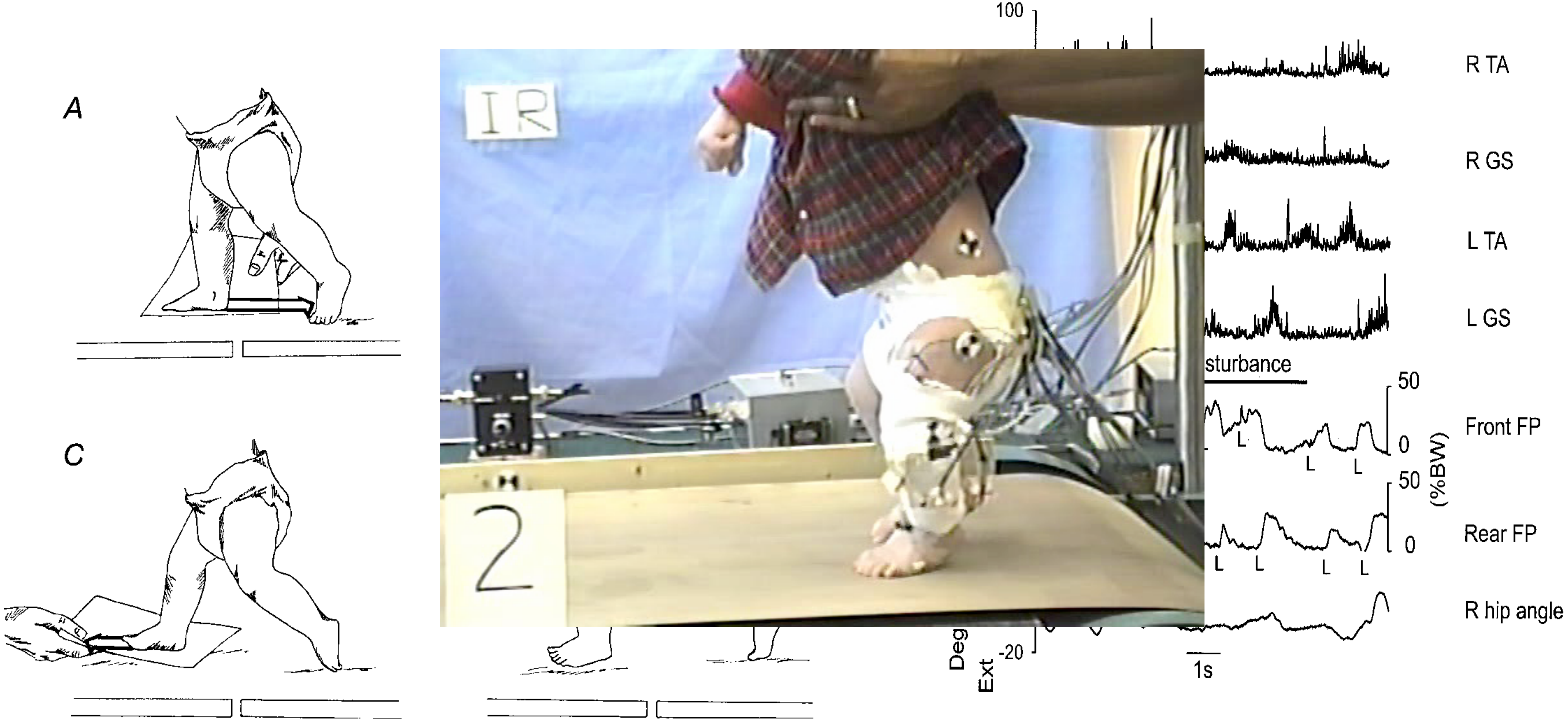
2. Rhythmic leg movements

3. Spinal cord stimulation

4. Drugs injected into the spinal cord

1) INFANT WALKING

- primitive step-like movements in newborn infants (birth - 3 mo) when supported externally
    - in utero coordinated movements too



Pattern modified by sensory feedback!

(Pang & Yang, 2000)

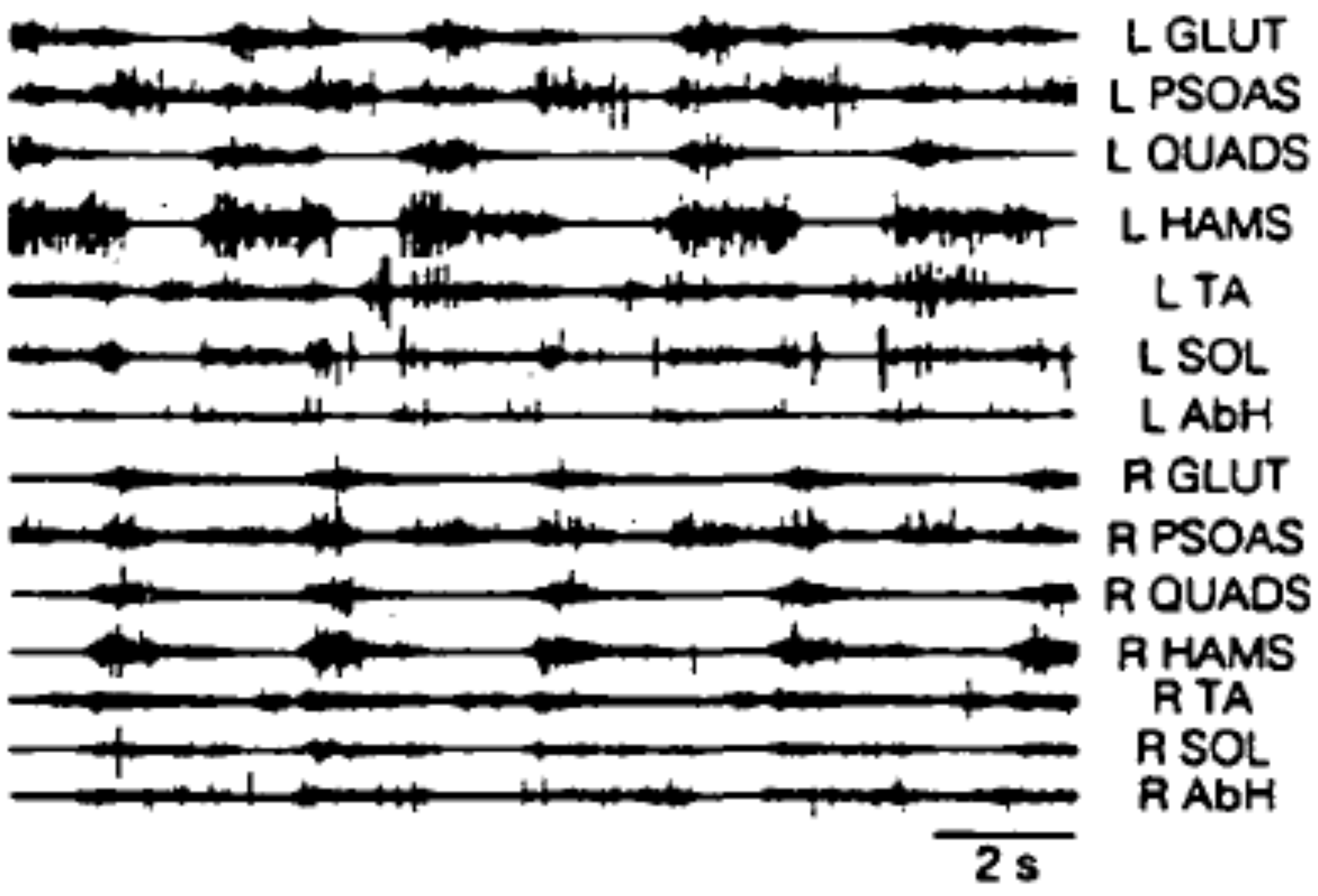
2) RHYTHMIC LEG MOVEMENTS IN ISCI PATIENTS

- 37 year old patient cervical neck injury
- Incomplete spinal cord injury
- Step training program after 17 years

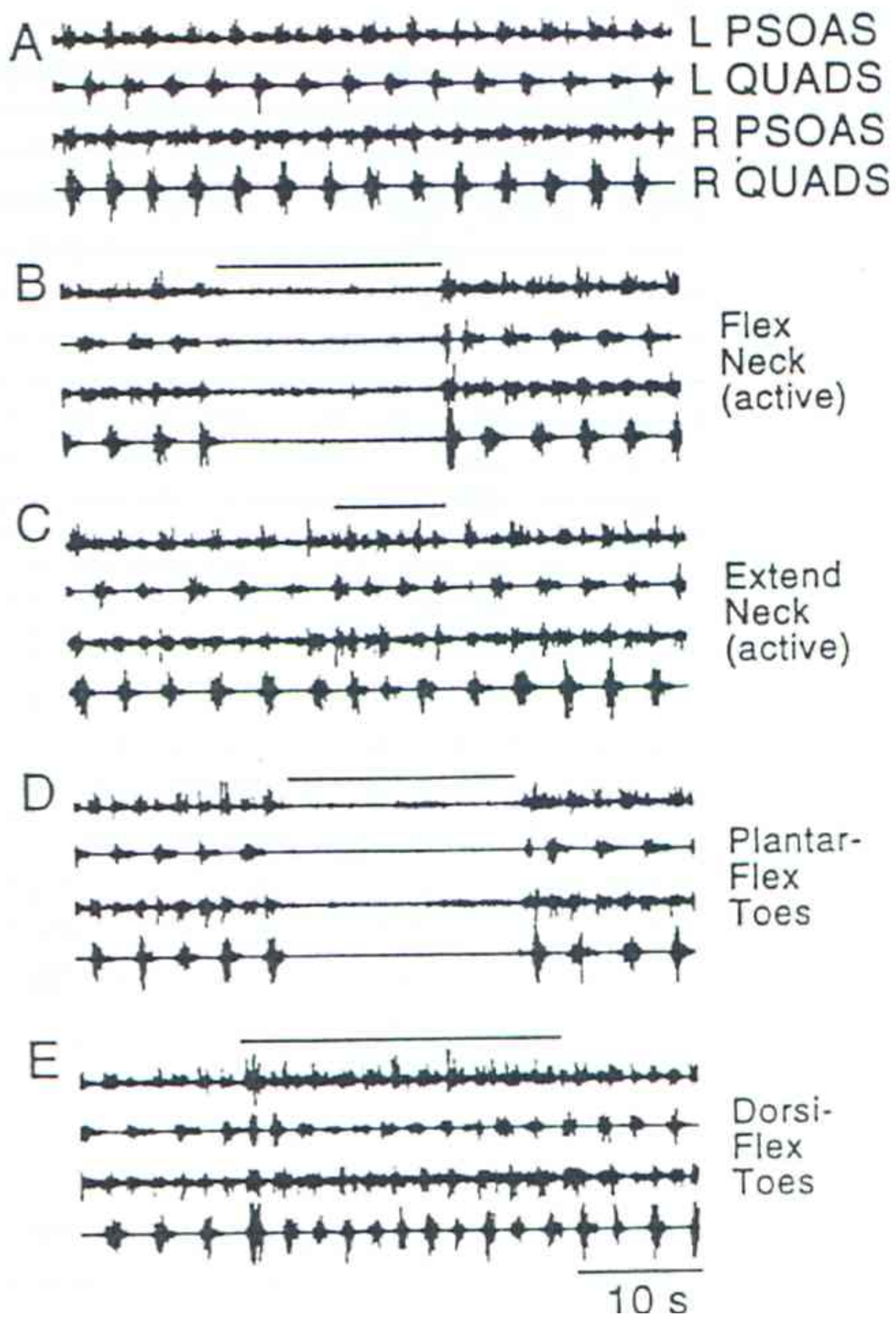
- Involuntary stepping movements
- Hip and knee flexion-extension movements at about 1Hz
- Evoked by lying supine and extending the hip

(Calancie et al., 1994)

2) Rhythmic leg movements in iSCI patients cont'd



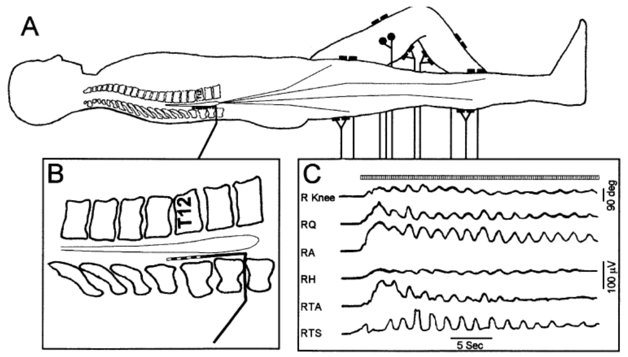
EMG very similar to walking
CPG modulates amplitude and timing



Peripheral feedback modifies the rhythm!

PLAY CALANCIE VIDEO

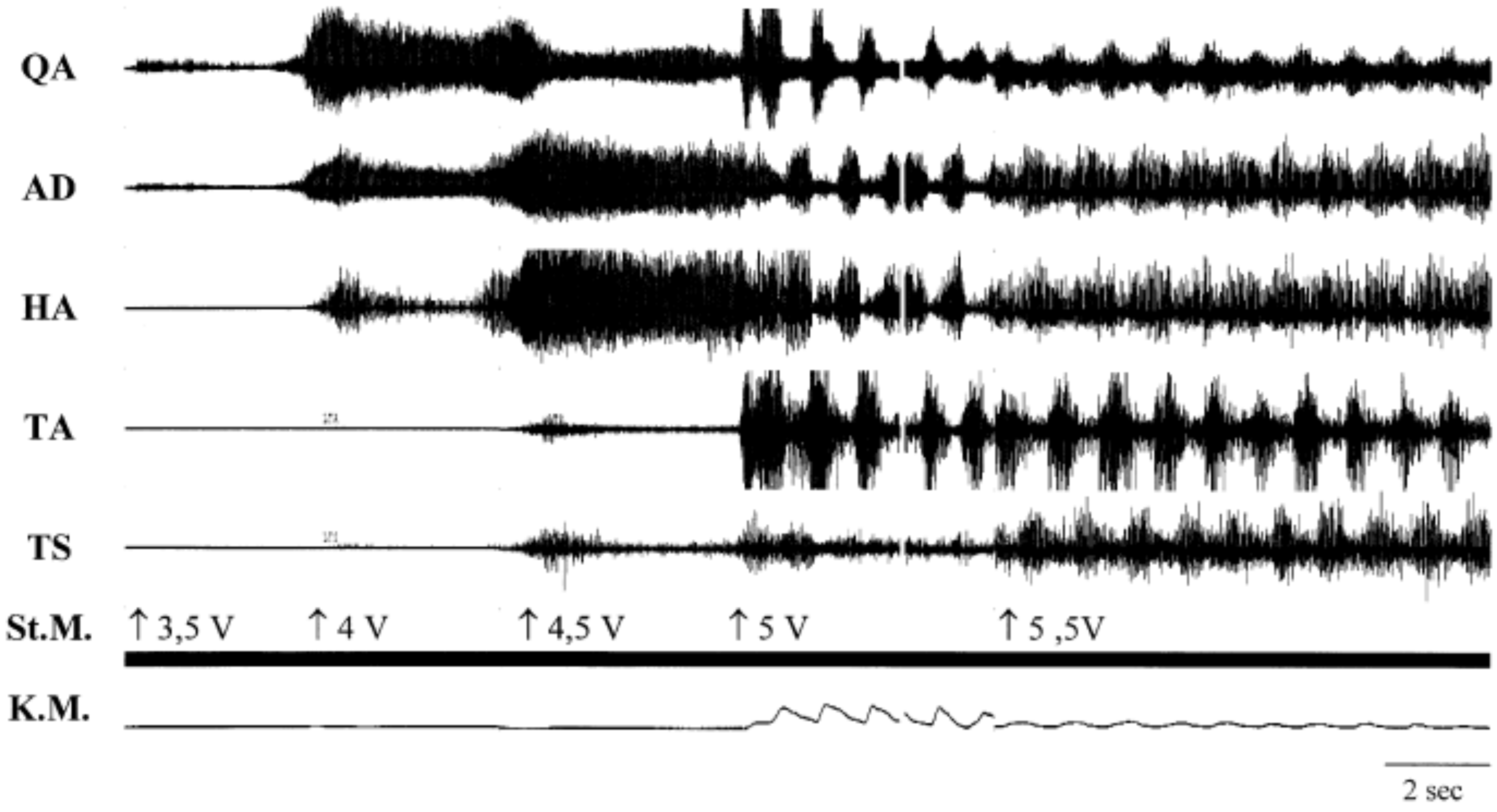
3) SPINAL CORD STIMULATION



(Dimitrijevic et al., 1998)

Thoracic injury, lumbar stimulation

Tonic input results in rhythmic output!

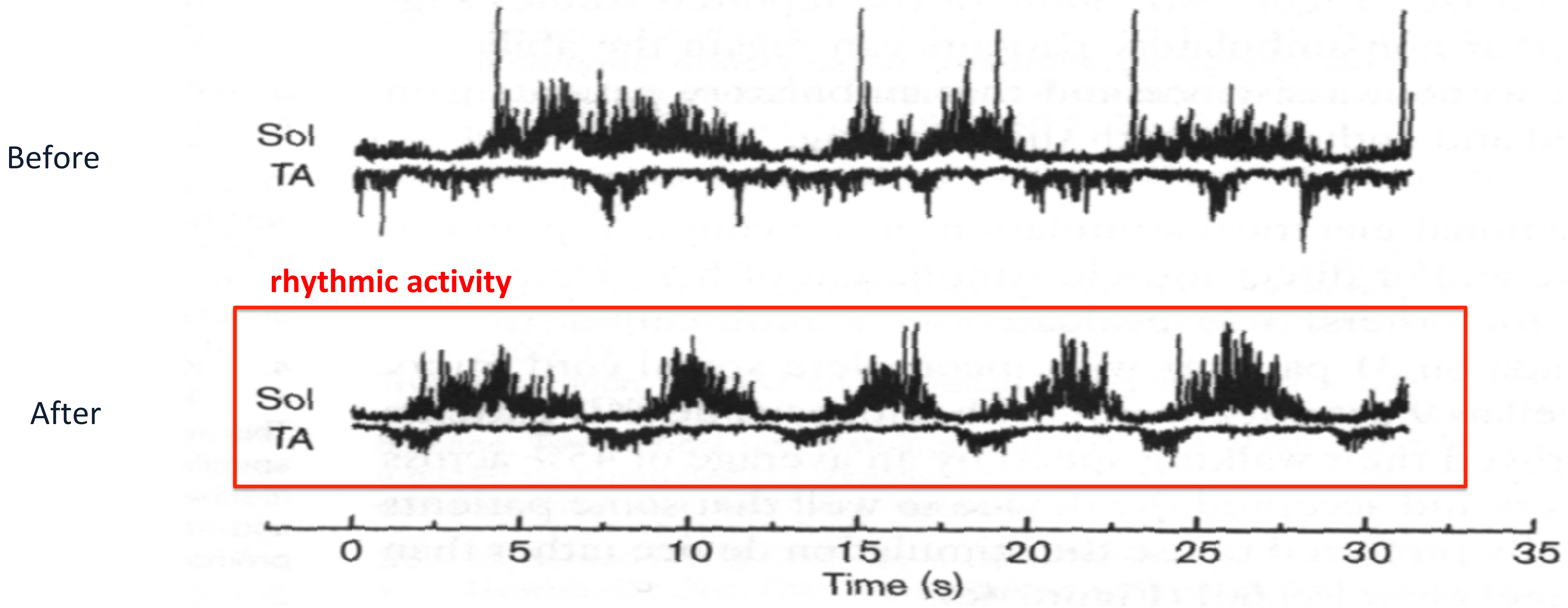


3) SPINAL CORD STIMULATION

PLAY GERISEMENKO VIDEO

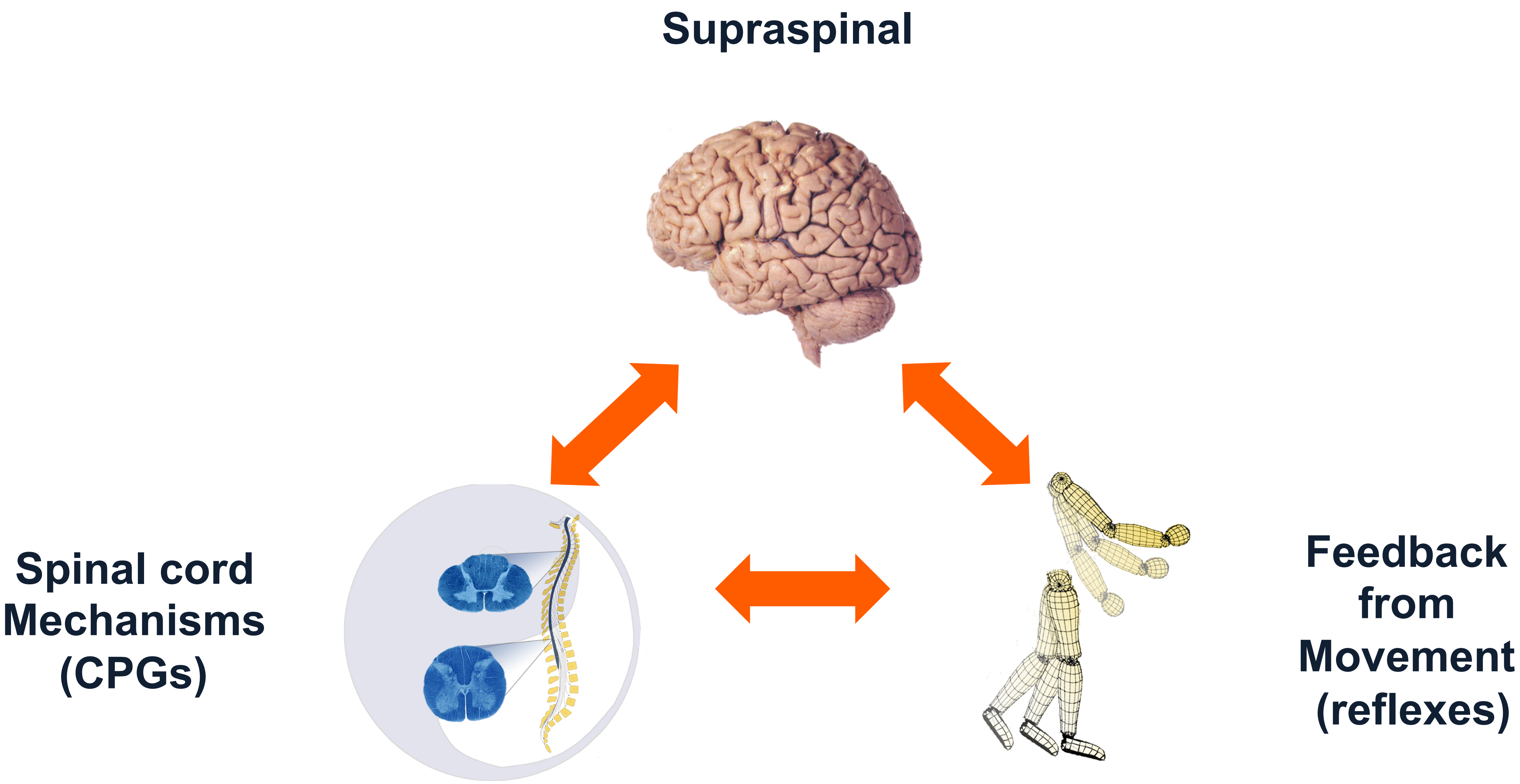
4) Drugs injected into spinal cord

INTRATHECAL INJECTION OF CLONIDINE (ADRENERGIC AGONIST) IN HUMANS



(B.Bussel 1999)

CONTROL OF WALKING; THE TRIPARTITE SYSTEM



Zehr & Duysens (2004) The Neurroscientist

WHAT ABOUT SENSORY FEEDBACK?

1)Rhythmic motor pattern can be produced by CPG's without any sensory feedback

However…

2) CPG's can be strongly influenced by signals from peripheral receptors

GENERAL PRINCIPLES OF HOW SENSORY FEEDBACK IS INTEGRATED DURING LOCOMOTION:

1) Sensory feedback contributes to the generation and maintenance of rhythmic activity

2) Sensory signals initiate major phase transitions

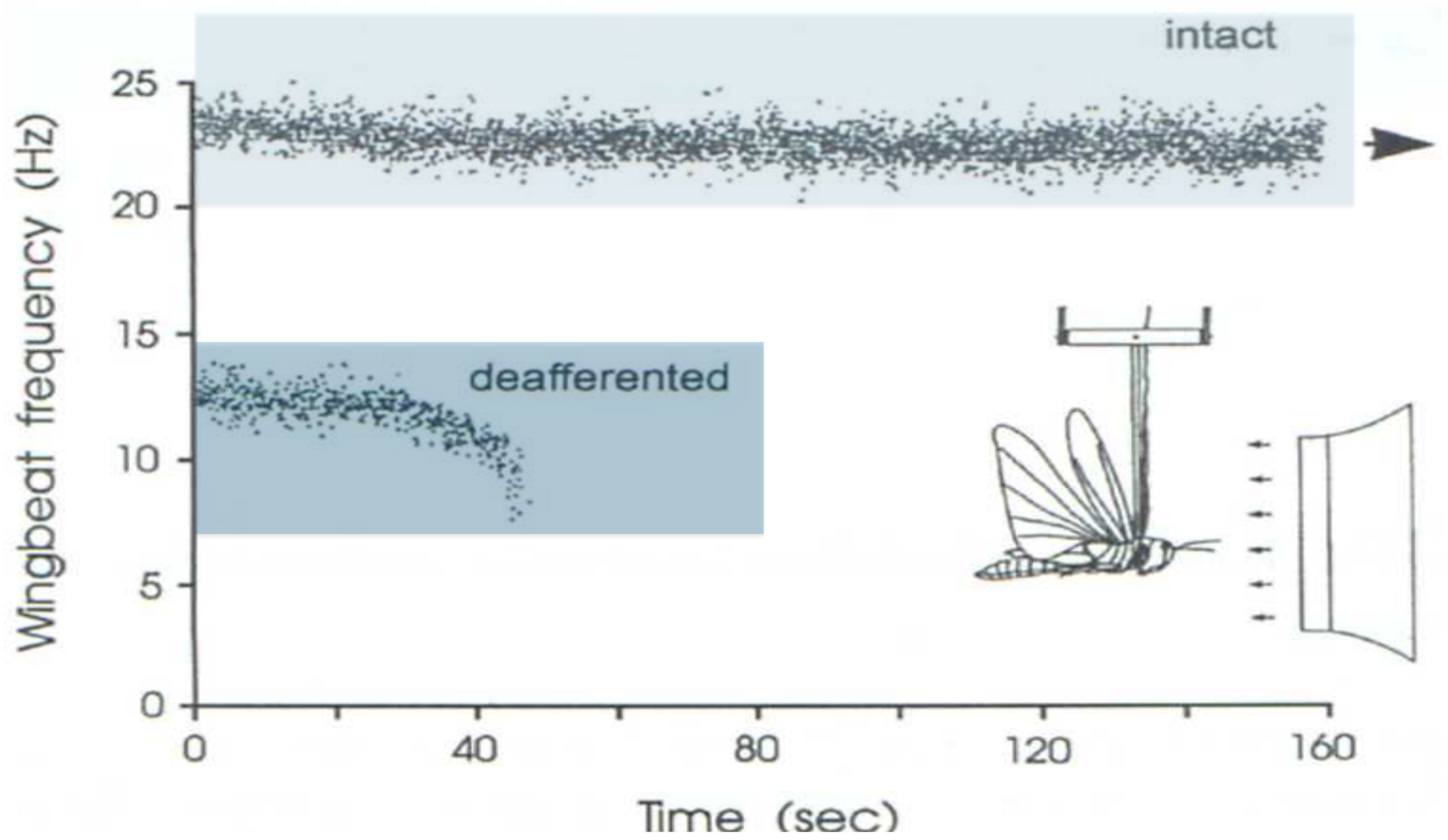
3) Sensory signals regulate the magnitude of ongoing motor activity

4) Transmission in reflex pathways is extremely flexible
    - Task dependent and phase dependent

5) Sensory feedback is usefully integrated during locomotion

1) GENERATION AND MAINTENANCE OF RHYTHMIC MOTOR ACTIVITY

Flight system of the locust



- **Deafferented: removal of feedback**
- **Removing sensory feedback causes rhythmic pattern to be weaker**
- **Eventually disintegrates**

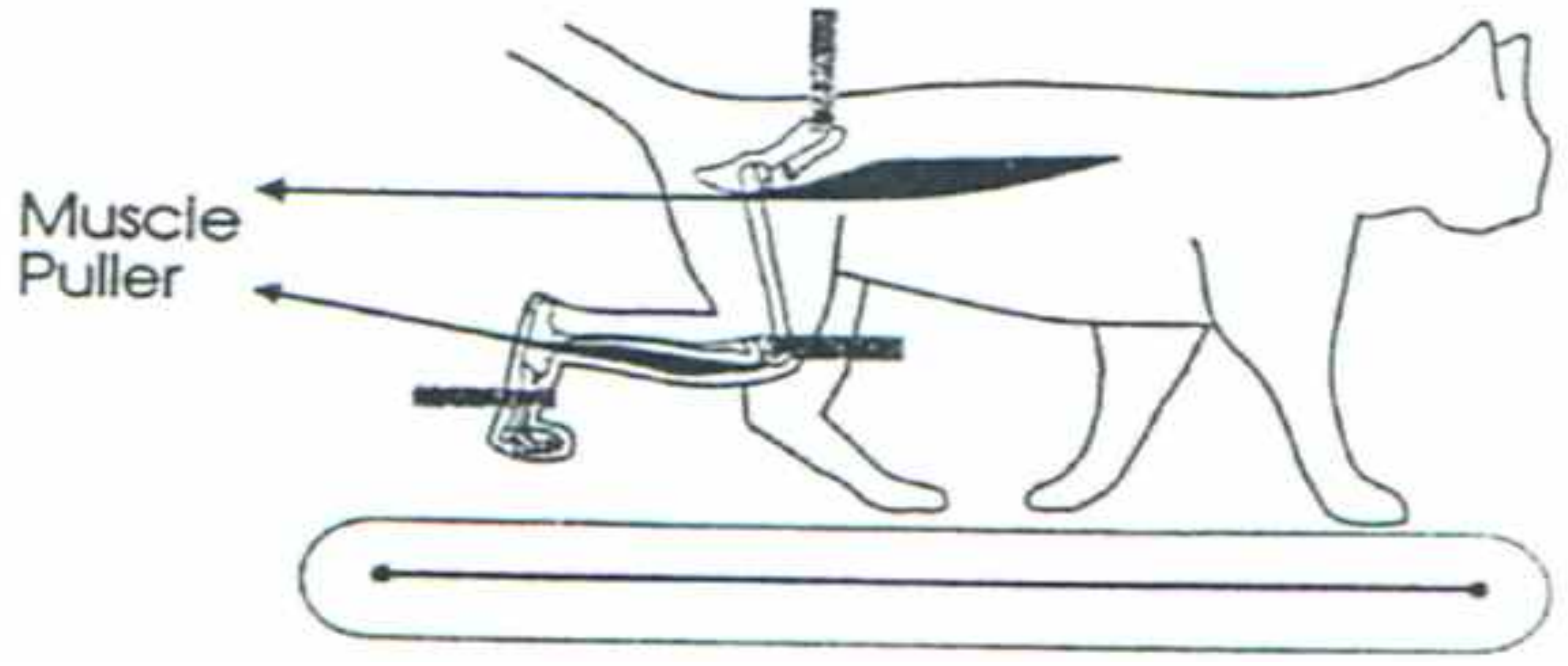
(Stein et al. 1997)

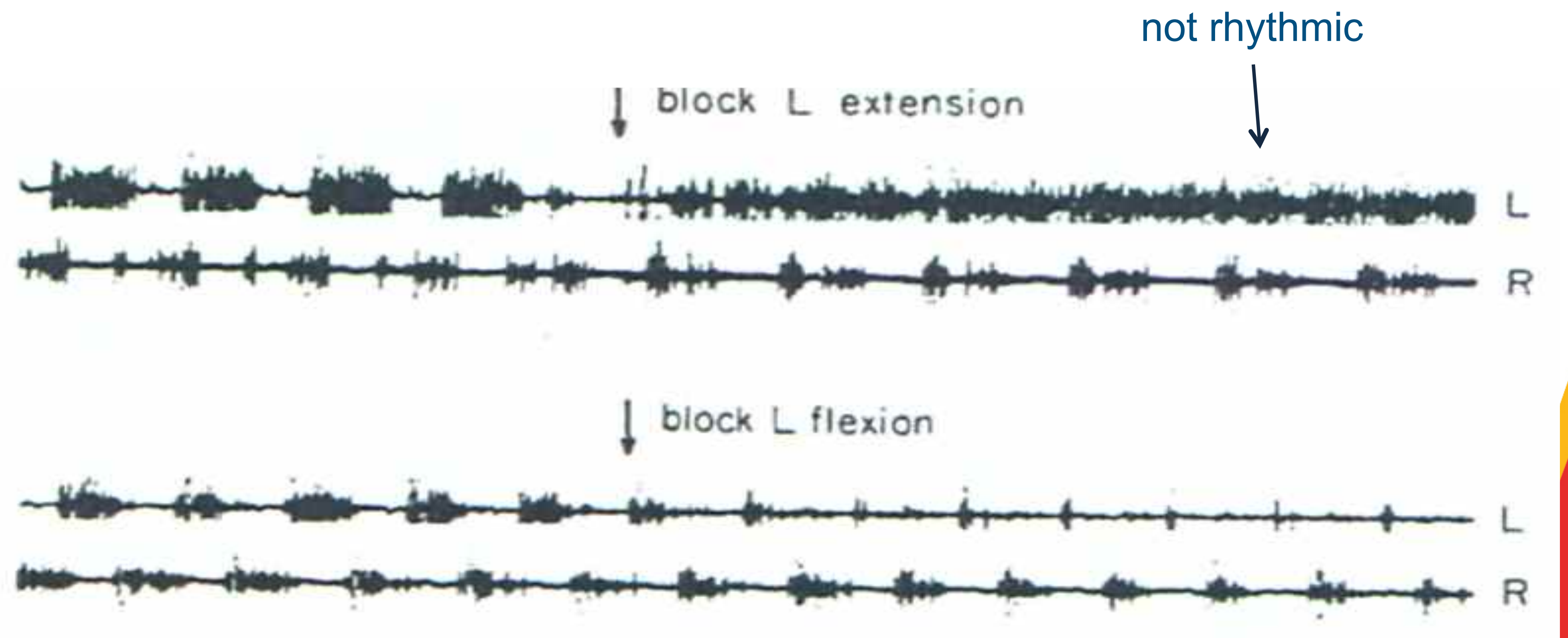
2) PHASE SWITCHING BY SENSORY SIGNALS

From stance to swing

Hip extension VIP

- Extending the hip (stretching the muscles around the hip) could initiate transition
- Muscle spindles in hip flexor muscles!
- Locomotor rhythm can be blocked by holding hindlimb in extension in cats





(Duysens & Pearson, 1998)

3) AFFERENT REGULATION OF THE MAGNITUDE OF MOTOR ACTIVITY

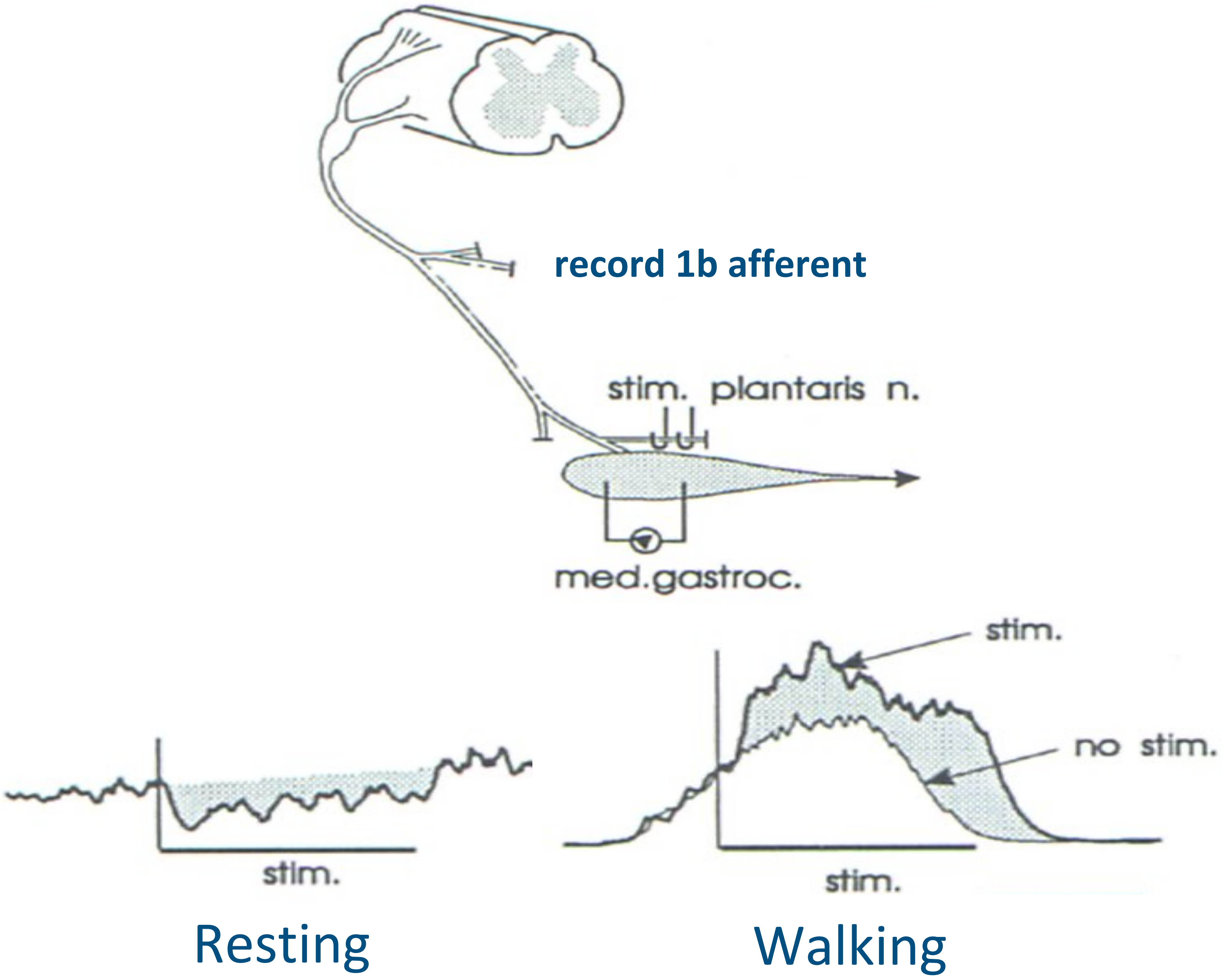
From stance to swing - Plantarflexion VIP

- Activation of medial gastrocs during stance activates group Ib afferents (from golgi tendon organs)

Resting: disynaptic inhibition

Walking: excitatory pathway to med. Gastrocs

Ib input can reset and entrain the rhythm of a CPG

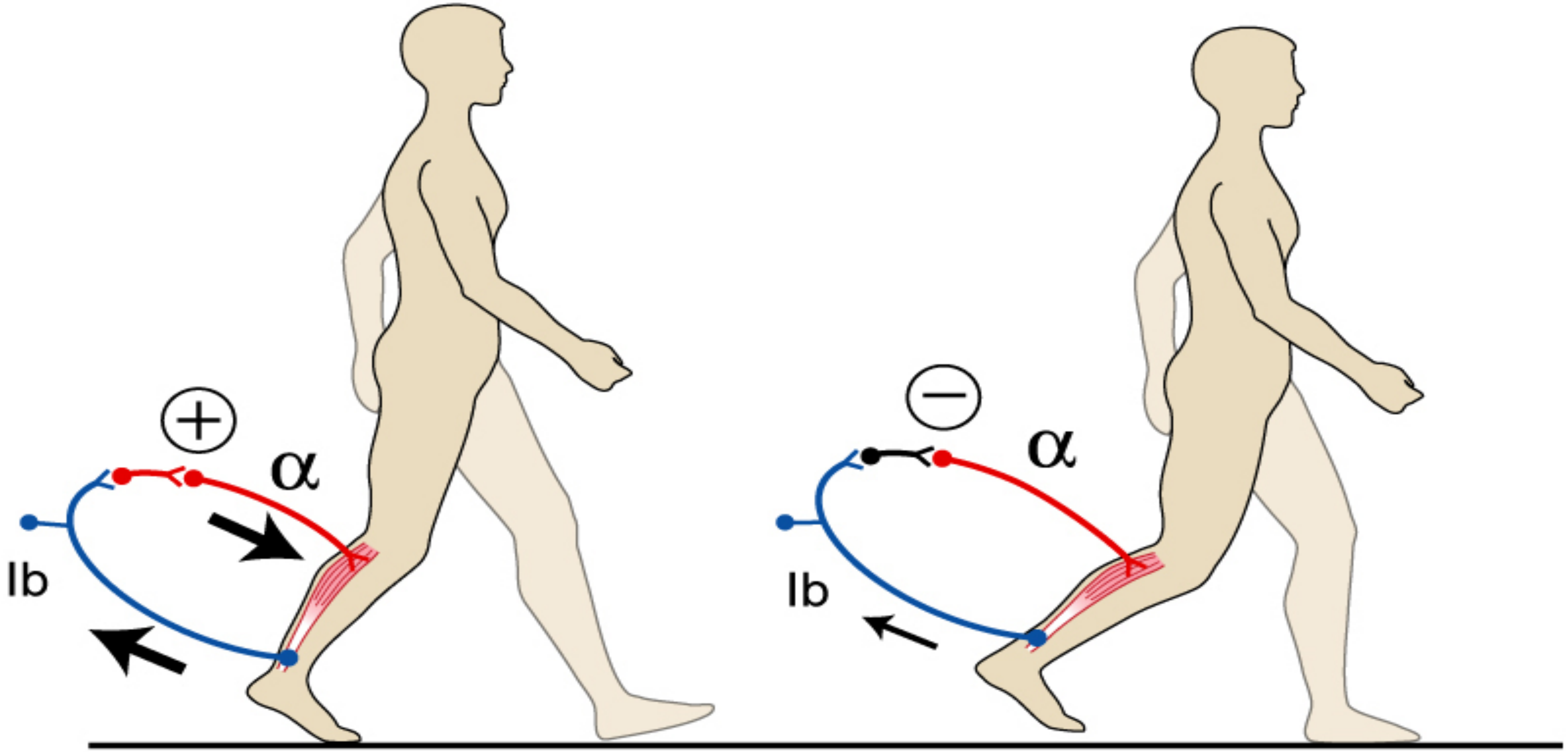


(Stein et al., 1997)

3) AFFERENT REGULATION OF THE MAGNITUDE OF MOTOR ACTIVITY

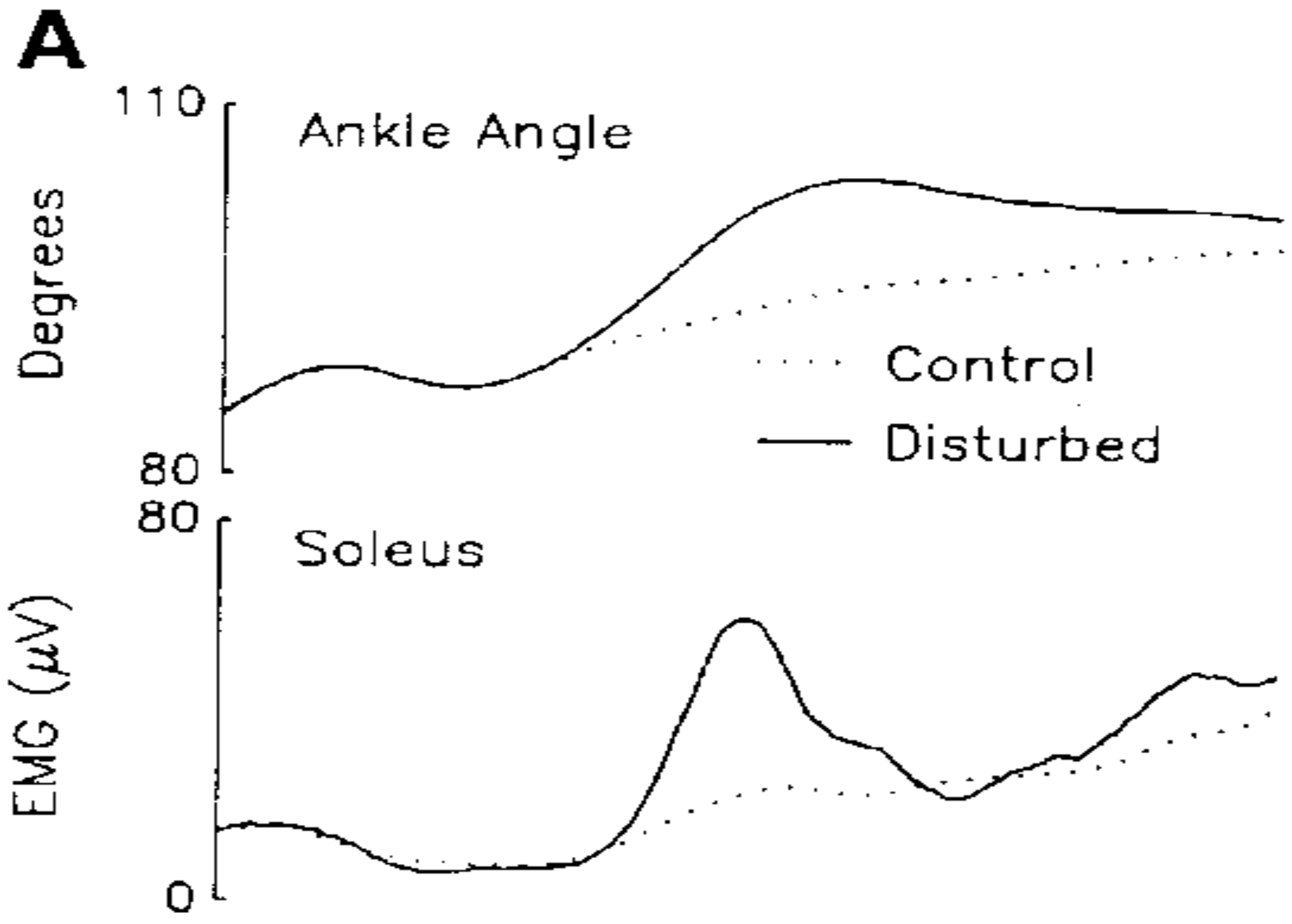
Stance Phase: GTO excitatory to muscle. Helps maintain force output

Swing Phase: GTO inhibitory to muscle. Helps relax muscle.



3) Afferent regulation of the magnitude of motor activity

Stretch reflexes ↑ force production during stance



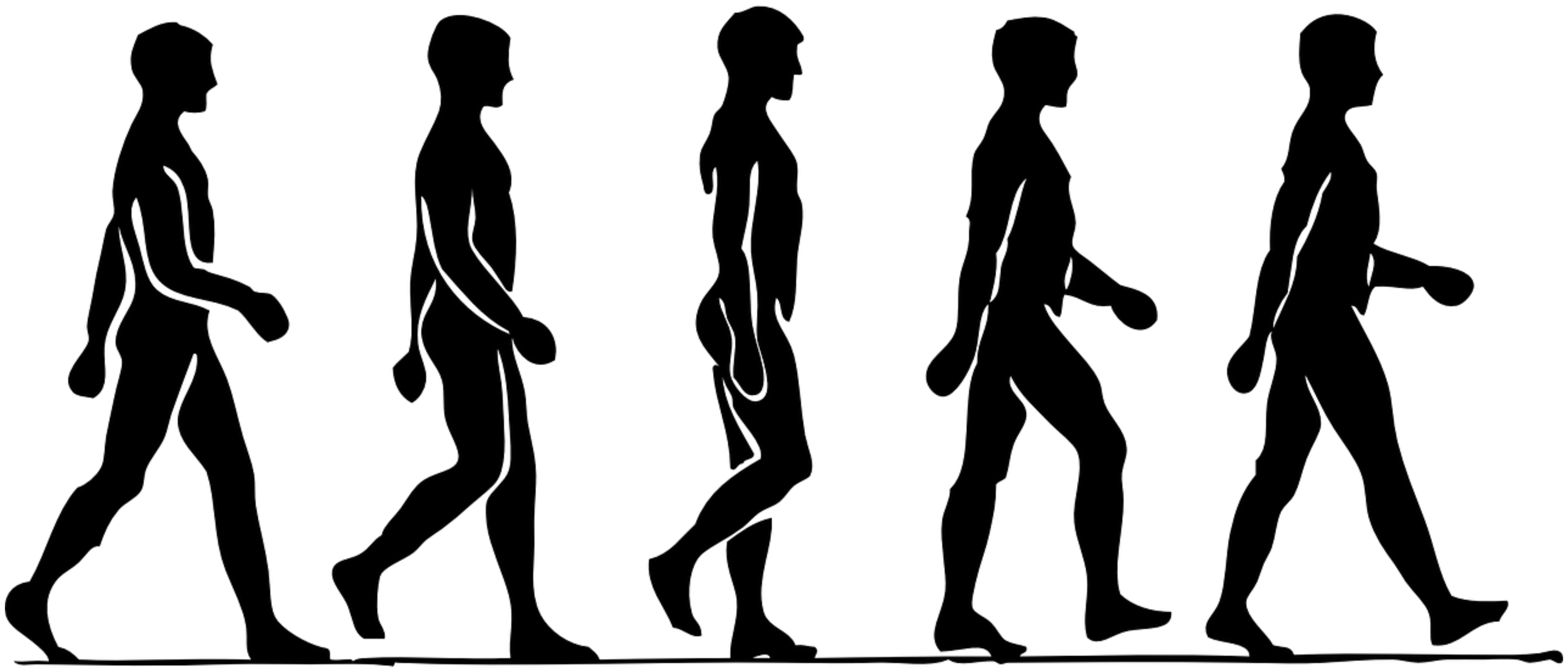
30-60% of SOL activation due to velocity sensitive reflex component during stance (e.g. muscle spindle primaries, Group Ia; also Group II afferent contributions)

Yang et al. (1991) Exp Brain Res

4) Transmission in reflex pathways is flexible

3 major concepts:

1) Task-dependent reflex modulation
2) Phase-dependent reflex modulation
3) Reflex reversal



4) Transmission in reflex pathways is flexible

Three main mechanisms:

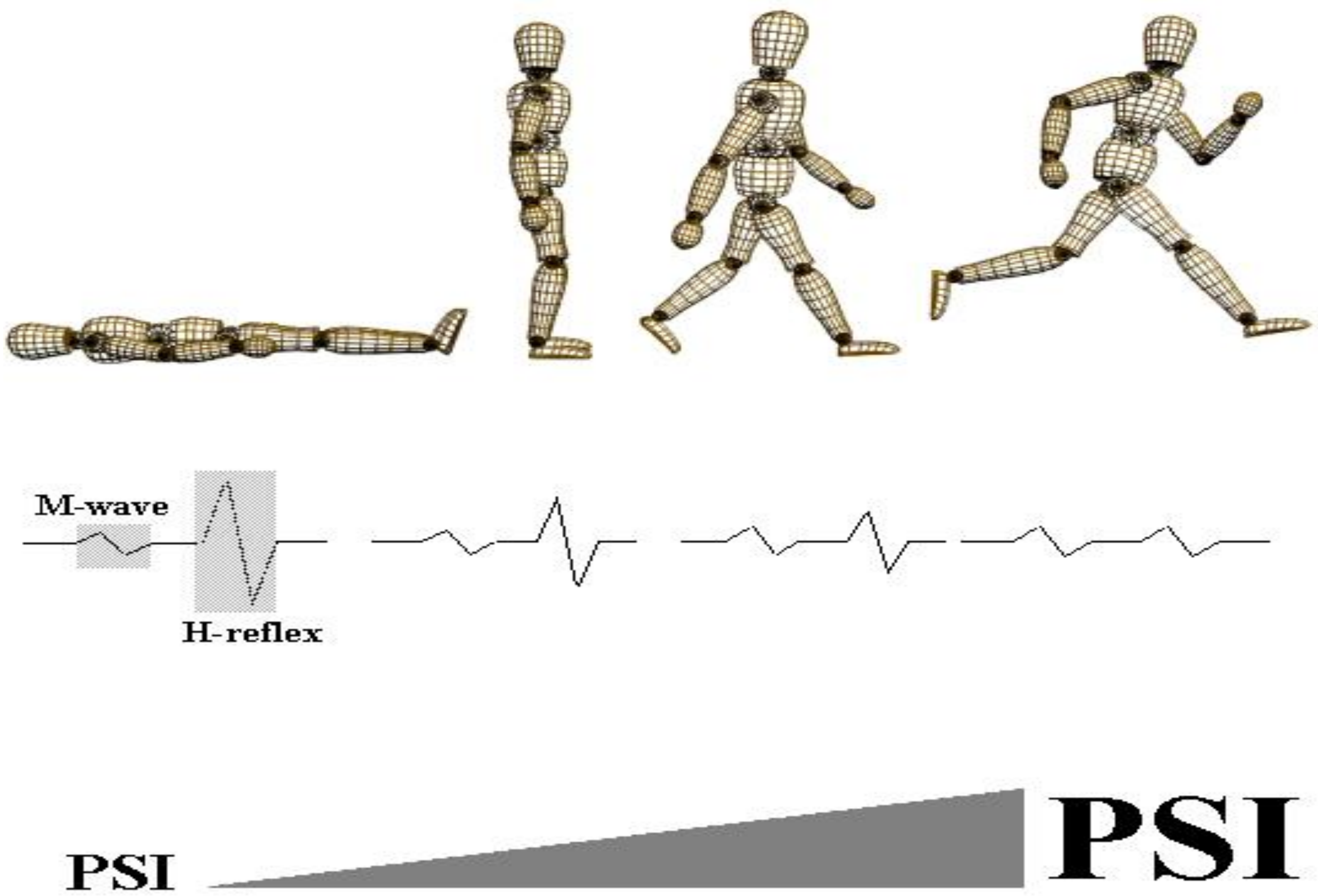
1) Efferent modulation of afferent feedback
   - CPG opening and closing interneuronal pathways
2) Pre-synaptic modulation
   - presynaptic inhibition of afferent transmission
3) State-dependent release of neuromodulators
   - switching, reflex reversal, and reflex gain

A. TASK-DEPENDENCY OF REFLEXES…

H-reflexes progressively decreased from standing, to walking, to running

- Likely mechanism? **Presynaptic inhibition**

Task-dependency also observed in cutaneous pathways



Zehr (2002) Eur J Appl Physiol

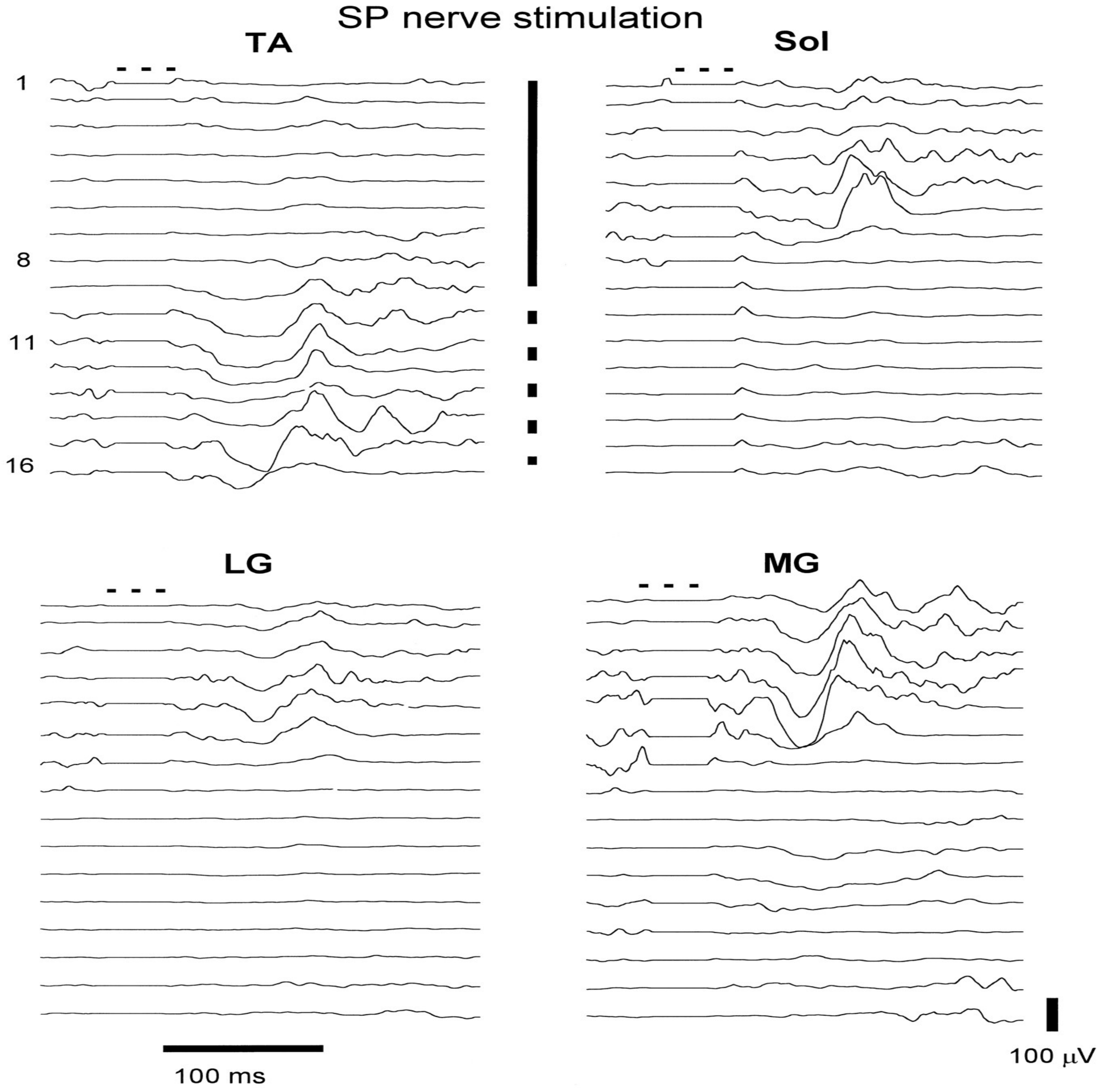
B. PHASE-DEPENDENT MODULATION…

Cutaneous reflex size can vary throughout step cycle

Differences within functional synergists (e.g. Sol, LG, MG muscles)

Modulation due to…

- Outflow from CPG?
- Movement-related modulation?

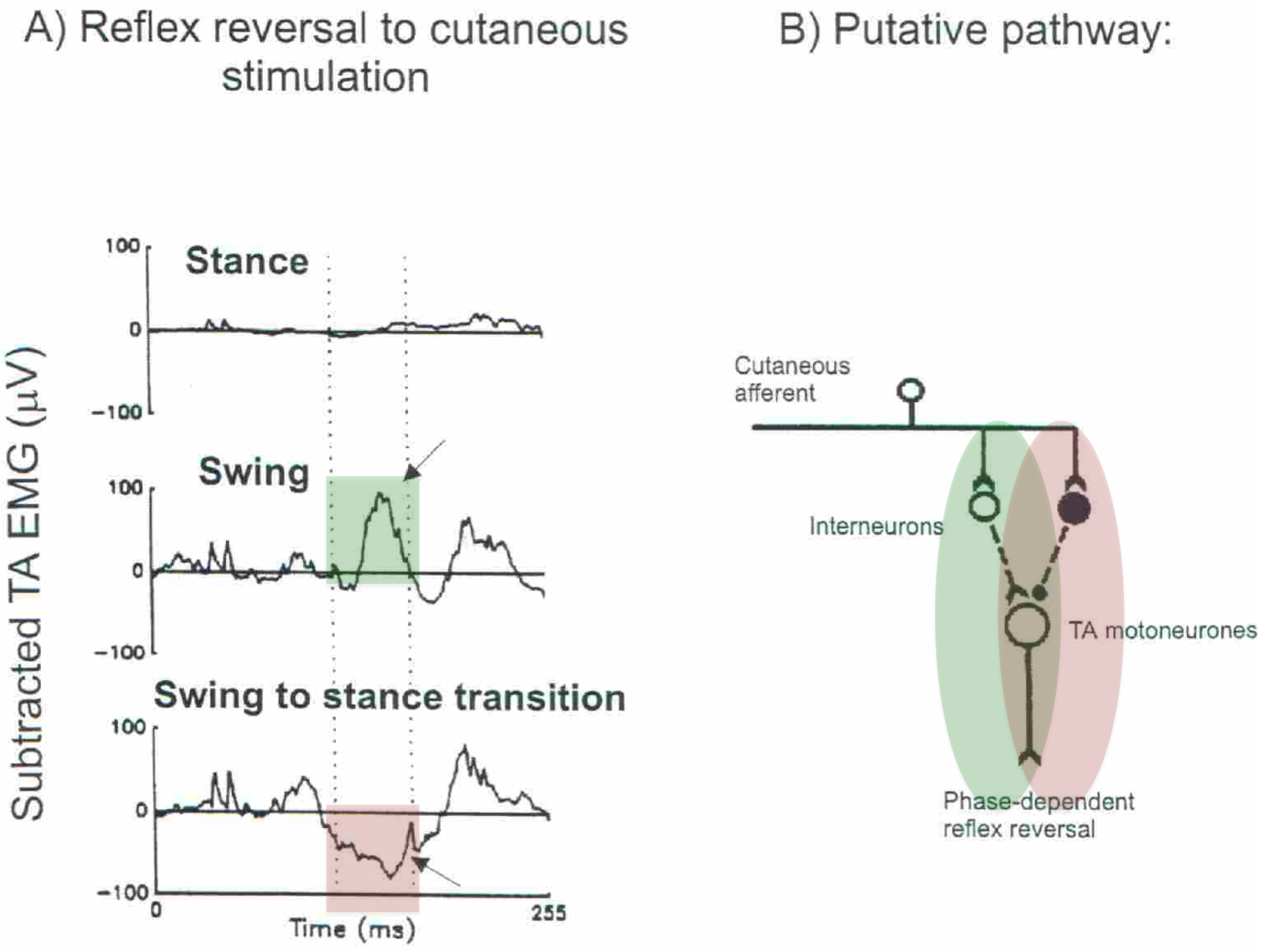


Zehr et al. (1997) J Neurophysiol

PHASE DEPENDENT MODULATION CAUSES REFLEX REVERSAL…

Cutaneous reflexes can be excitatory at one part of step cycle & inhibitory at another

“Sign” of the reflex reverses



Zehr & Stein (1999) Prog Neurobiol

5) REFLEX FUNCTION DURING WALKING

What do reflexes contribute in controlling, adapting or modifying the human locomotor cycle?

Muscle reflexes:

Stretch & H-reflexes (muscle spindle; group Ia & II afferents)

Ib reflexes (GTO, i.e. load receptor)

Cutaneous reflexes:

Nerves innervating the dorsal, lateral, & plantar aspects of the foot

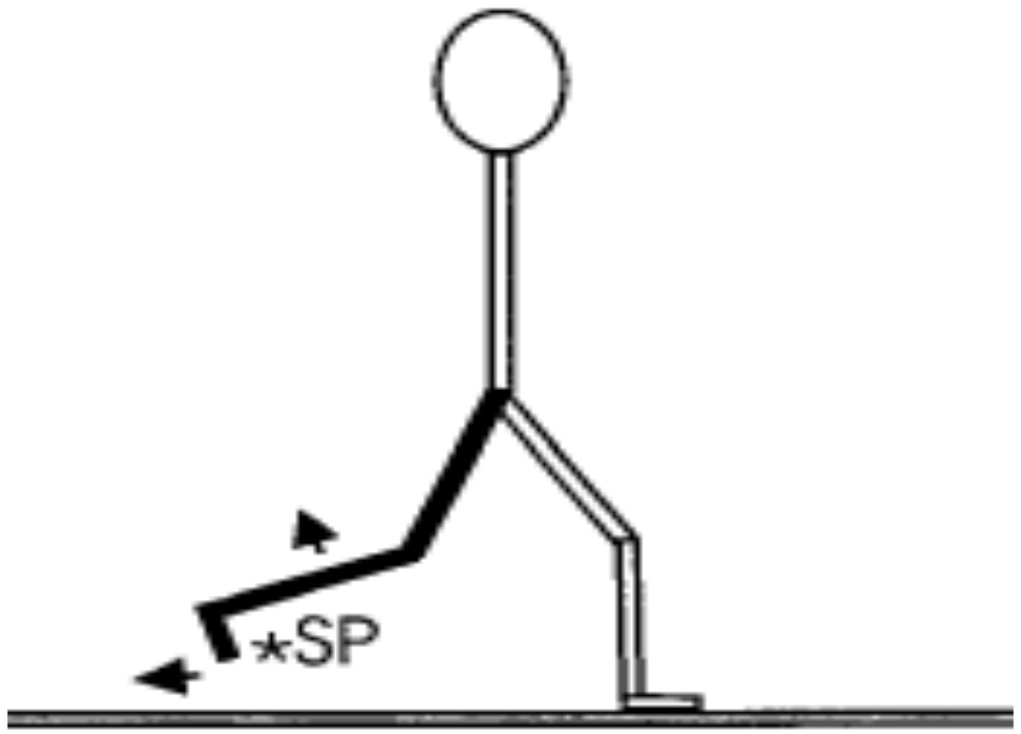
5) REFLEX FUNCTION DURING WALKING

Stumble Correction Reflex

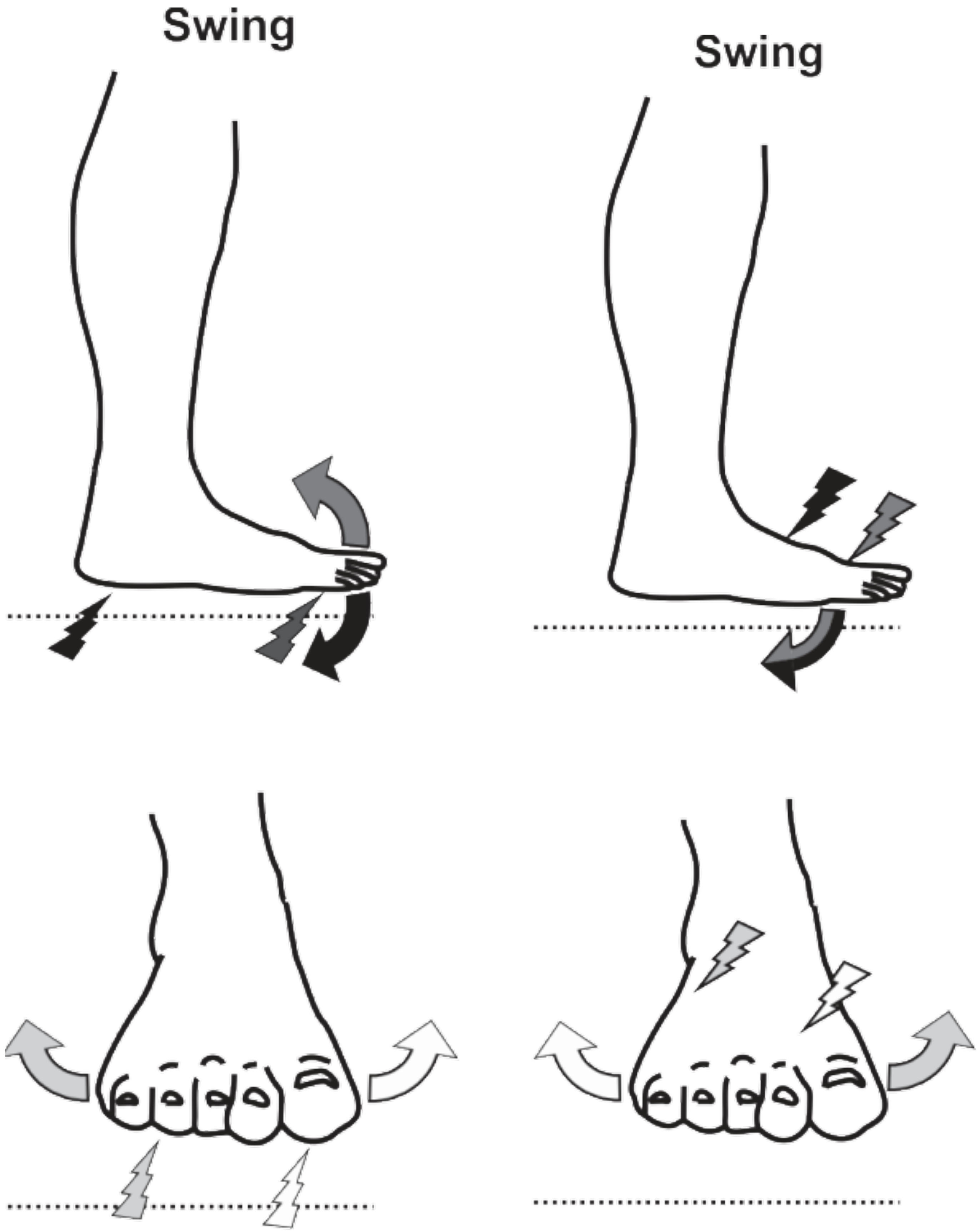
contact to top of foot during swing

- Excitation of knee flexor
- Inhibition of ankle flexor

Allows for smooth walking



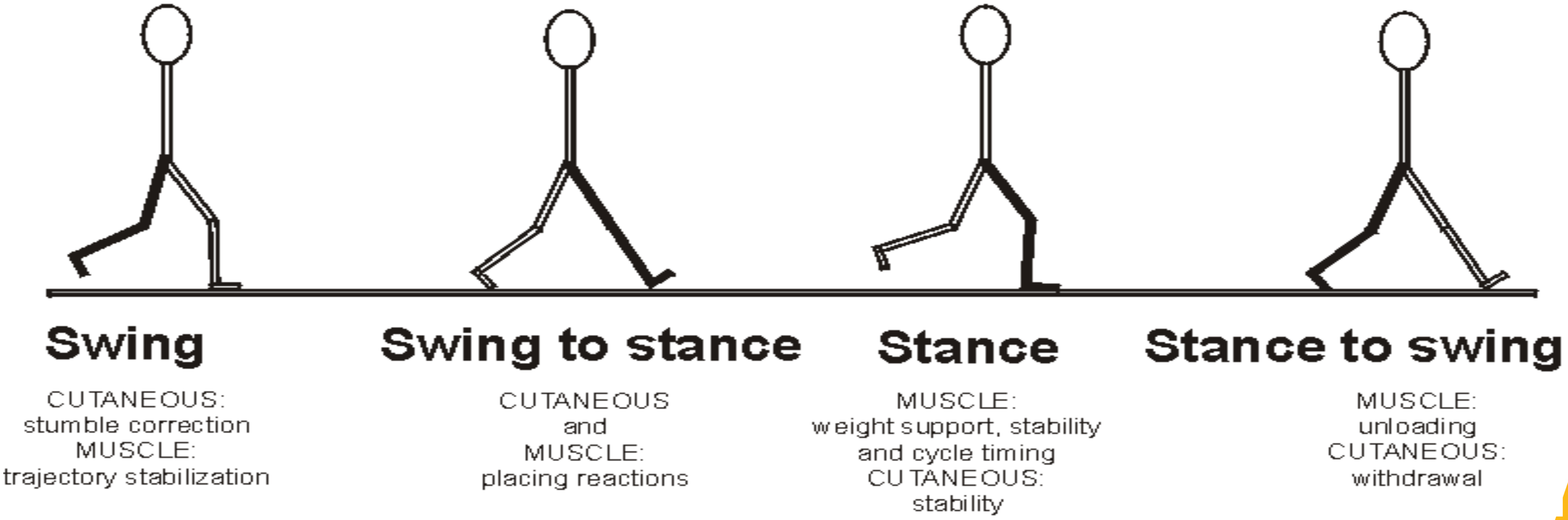
Zehr & Stein (1999) Prog Neurobiol



Pearcey and Zehr (Under Review)

5) Reflex function during walking

- Summary of reflex function while walking



Zehr & Stein (1999) Prog Neurobiol

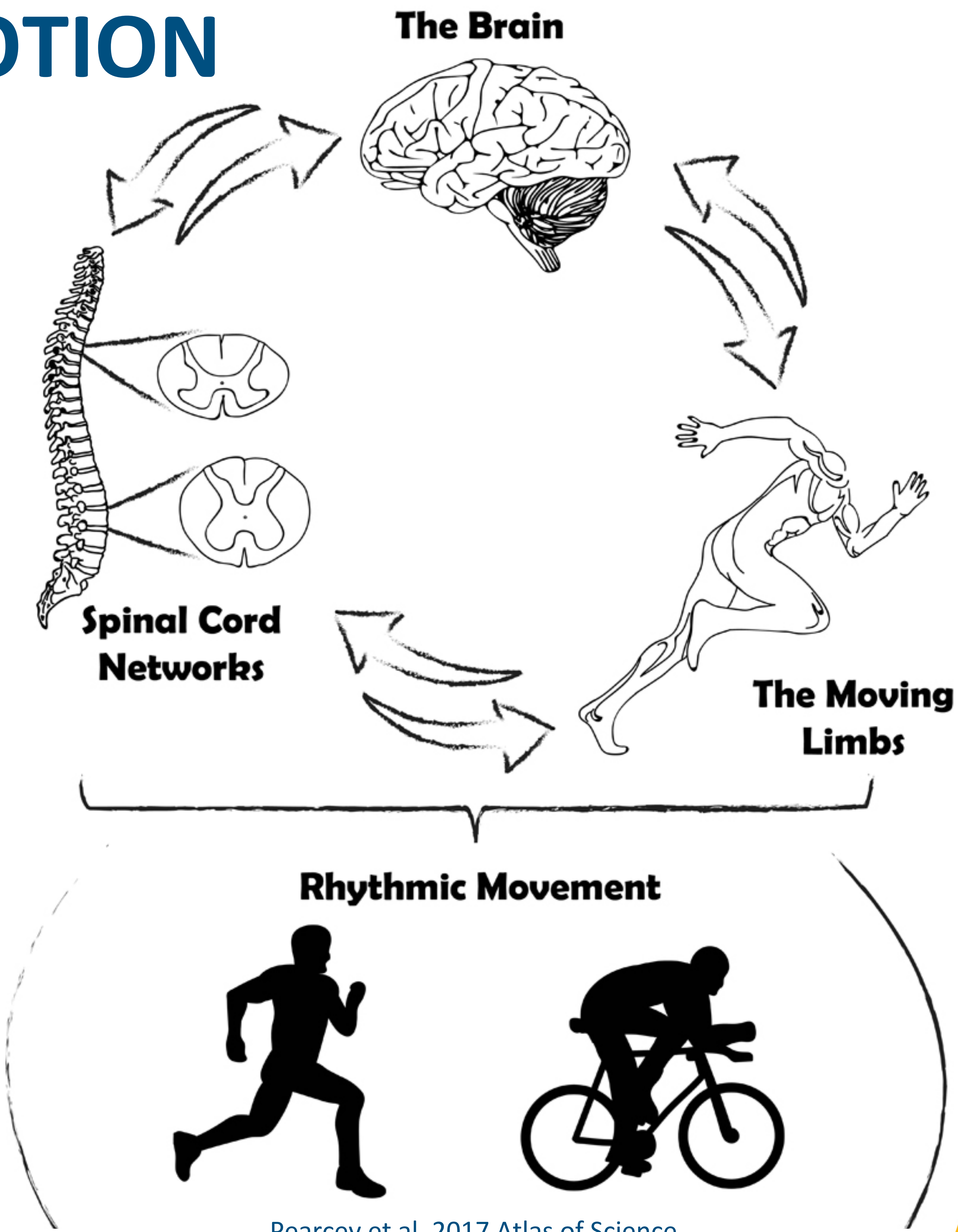
RECAP: CPG'S FOR LOCOMOTION

CPG: pool of neurons in spinal cord responsible for rhythmic movement

Brain required to turn CPG on, but can run independently

Sensory feedback sculpted by CPG:

1. Maintains CPG output
2. Helps initiate phase transitions
3. Enhances ongoing muscle activity
4. Reflex response is task and phase dependent
5. Serves a function during locomotion



Pearcey et al. 2017 Atlas of Science

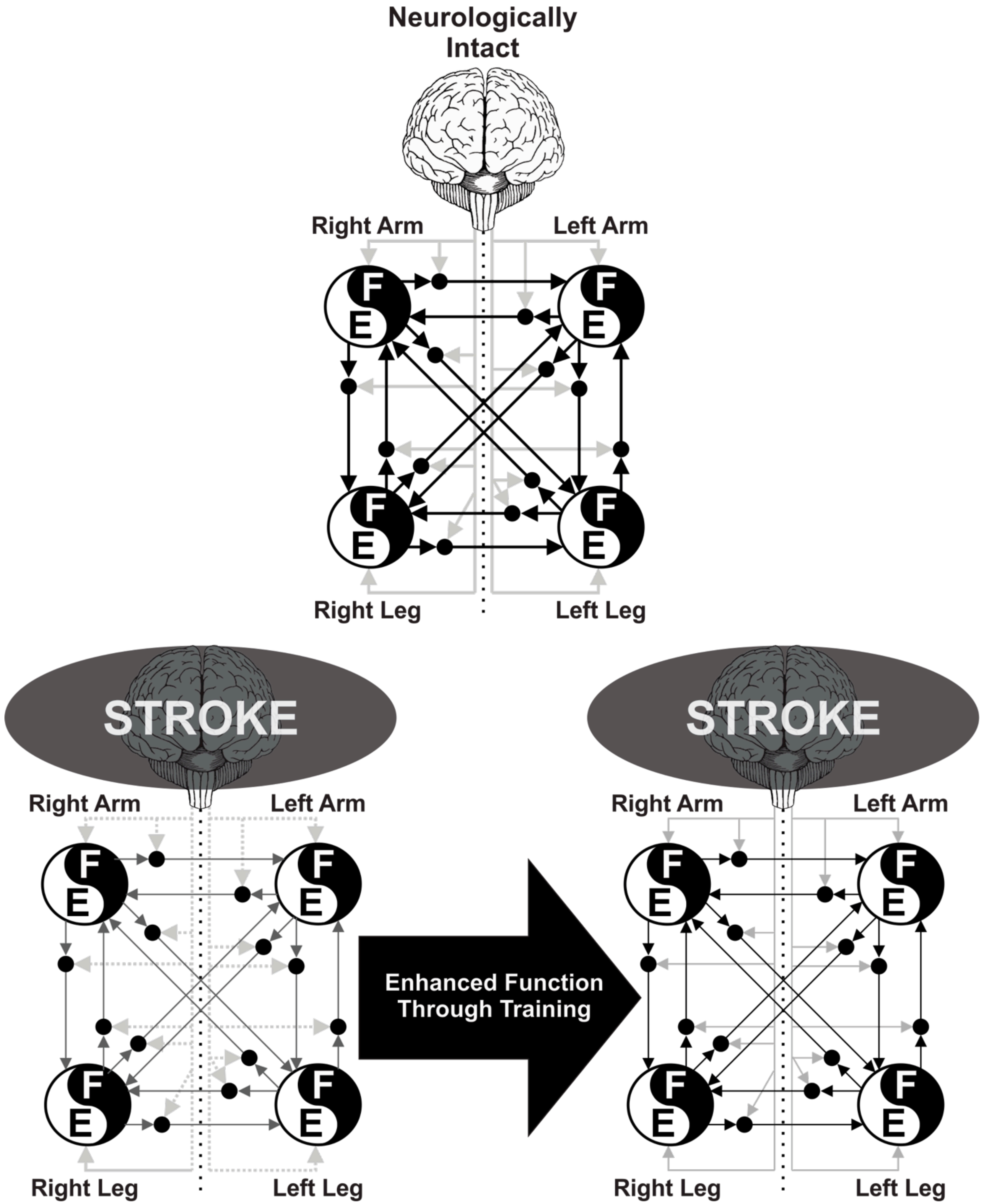
IMPLICATIONS FOR WALKING REHABILITATION

If CPG for walking exists in humans, can we use these networks to improve walking?

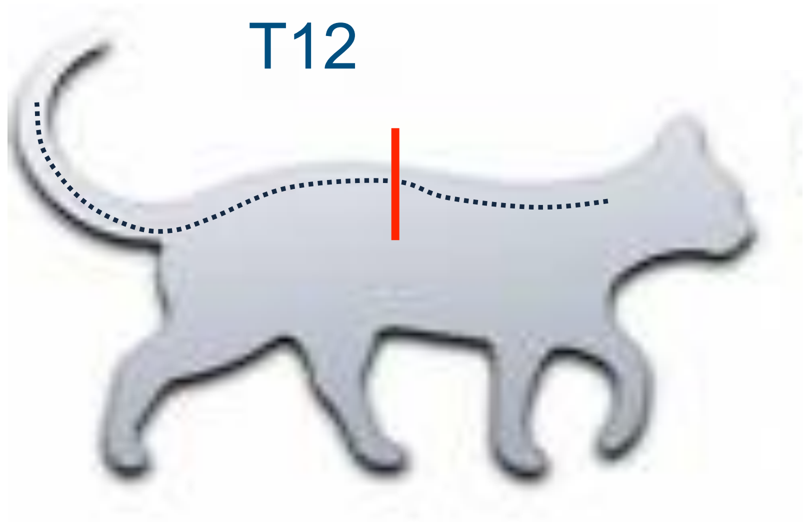
CNS lesion results in two forms of damage:

1. Neuronal cell death
    - At site of lesion and in close proximity
2. Denervation resulting from interruption of activity in neural networks

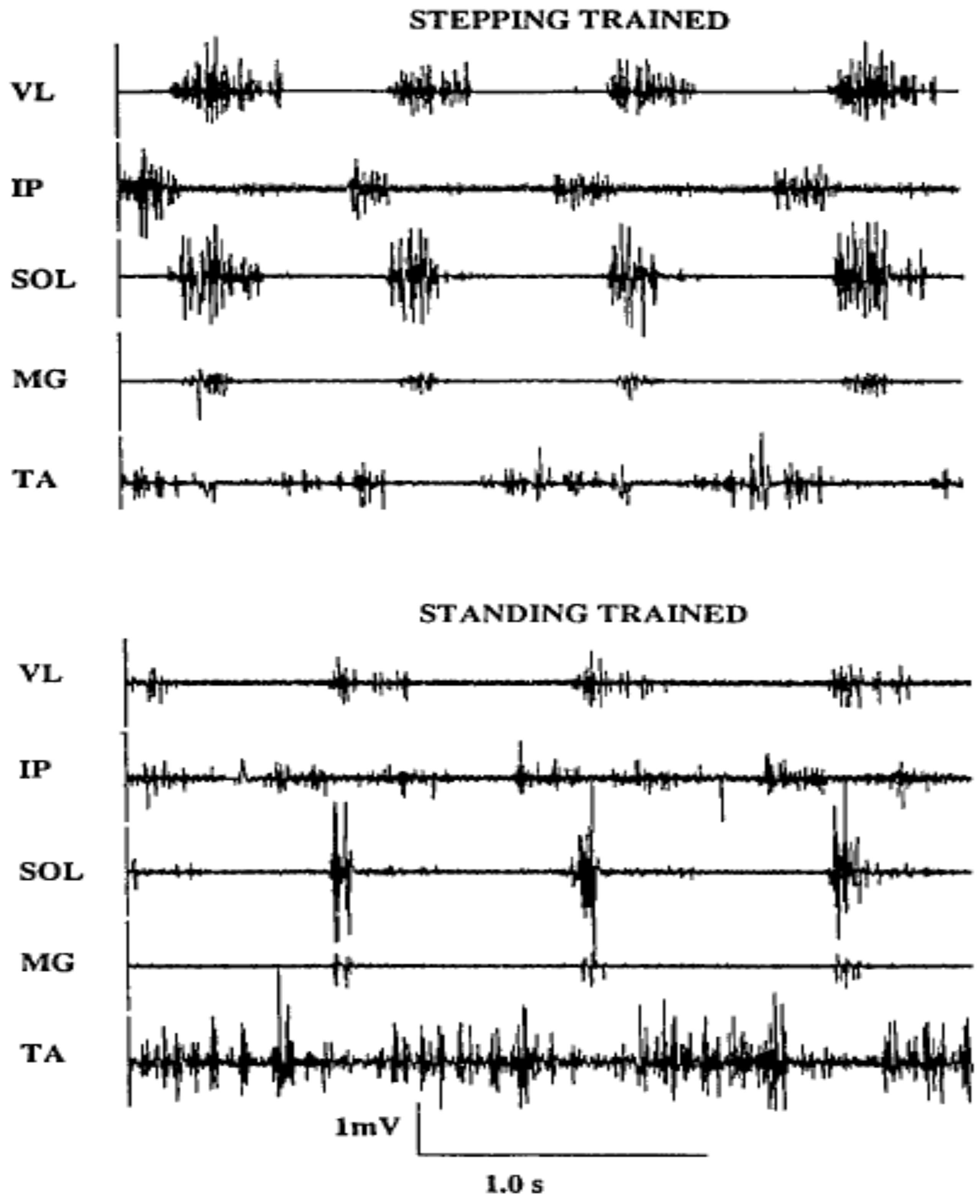
Most studied in stroke, spinal cord injury and multiple sclerosis


Neurologically Intact
Right Arm
Left Arm
F
E
Right Leg
Left Leg
STROKE
Enhanced Function Through Training

LOCOMOTOR RETRAINING OF THE ISOLATED SPINAL CORD: CAT



1. No training
2. Stepping training
3. Standing training



- Consistent locomotor patterns seen only in stepping trained cats
- Reversal if animal than undergoes standing training
- Reorganization due to training

(Hodgson et al., 1994)

LOCOMOTOR TRAINING OF THE ISOLATED SPINAL CORD: CHICK

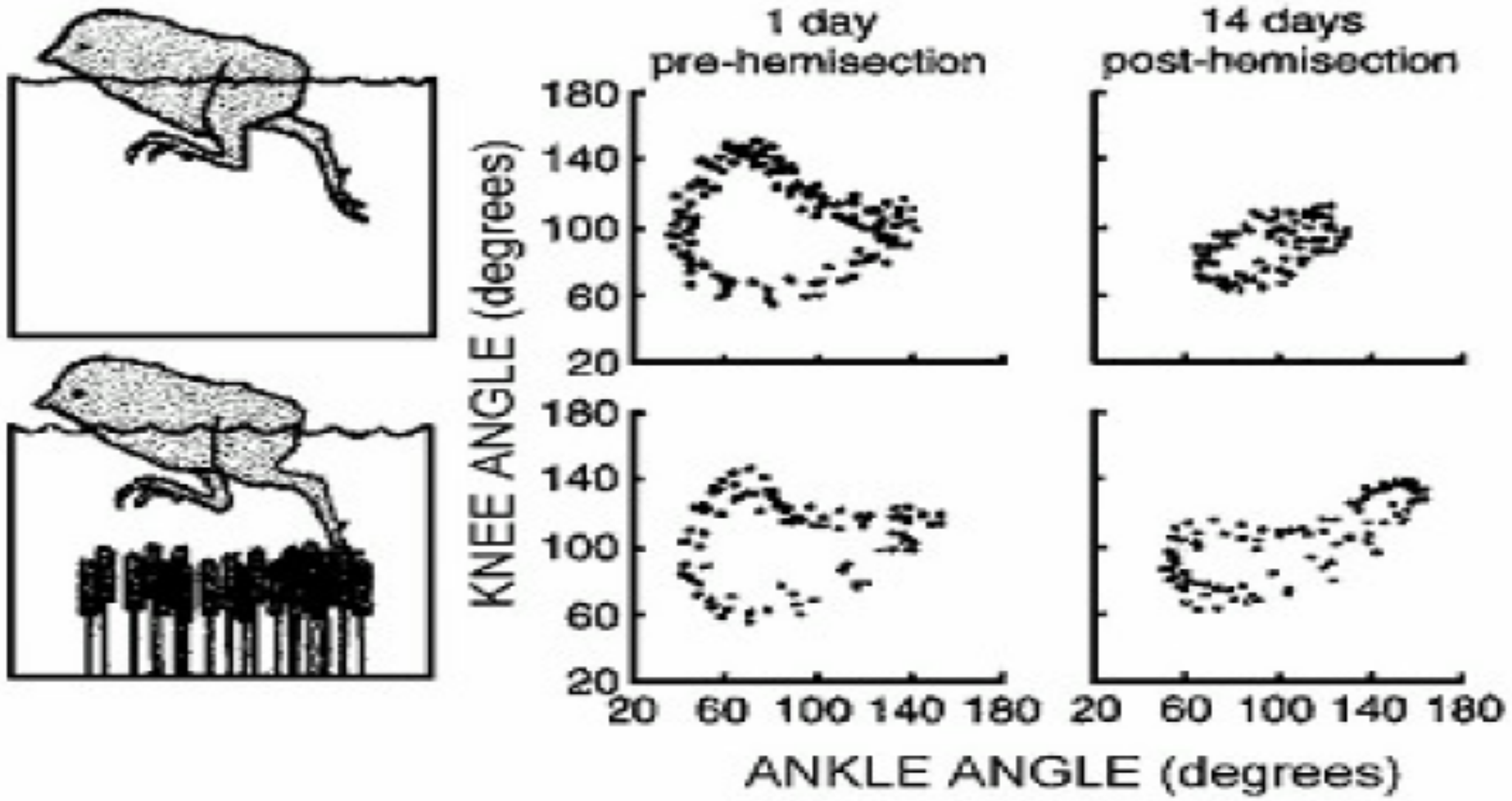
Swimming chicks

Knee and ankle excursions

Spinal hemi-section

Swim training with and without enhanced cutaneous feedback

- Better recovery with sensory input



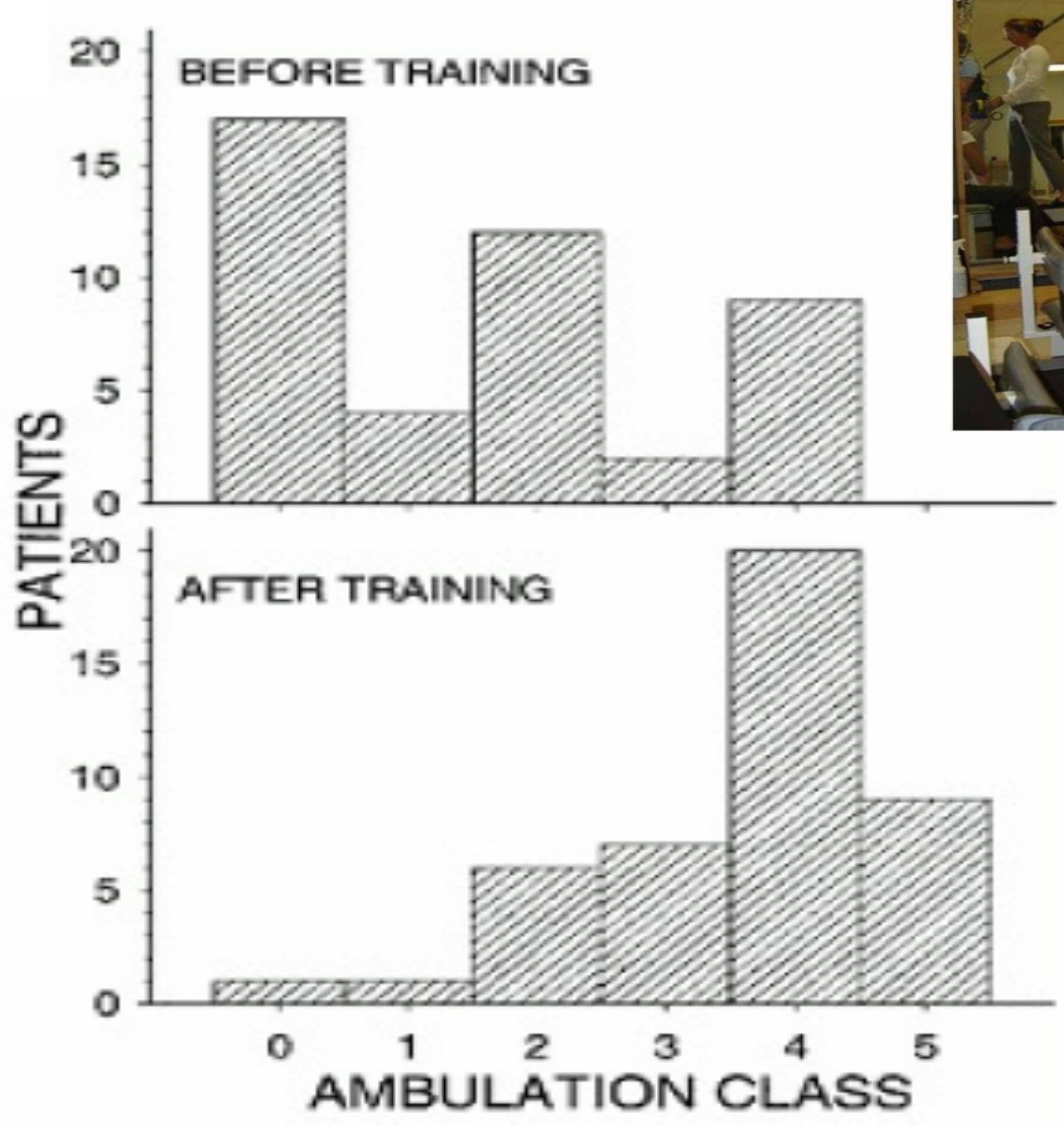
Wolpaw & Tennissen (2001) Annu Rev Neurosci

LOCOMOTOR TRAINING OF THE ISOLATED SPINAL CORD: HUMAN

Body weight supported treadmill training in complete and incomplete SCI

Changes in “ambulatory class” with locomotor training

- 0-2 = wheelchair
- 5 = > 5 steps w/o assistance



Wolpaw & Tennissen (2001) Annu Rev Neurosci

WALKING ROBOTS

Rhythmic movement

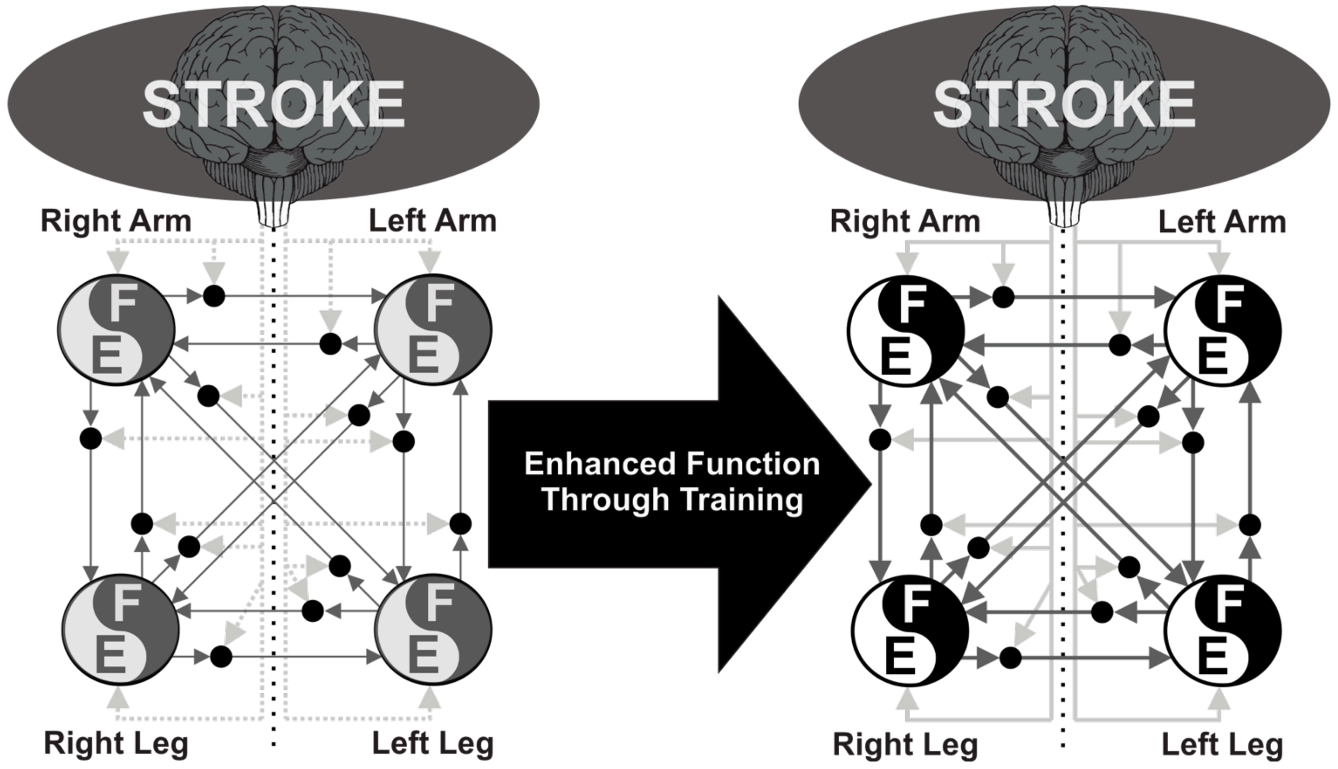
Integrate sensory feedback

Improve walking

ARM AND LEG CYCLING TRAINING AFTER STROKE

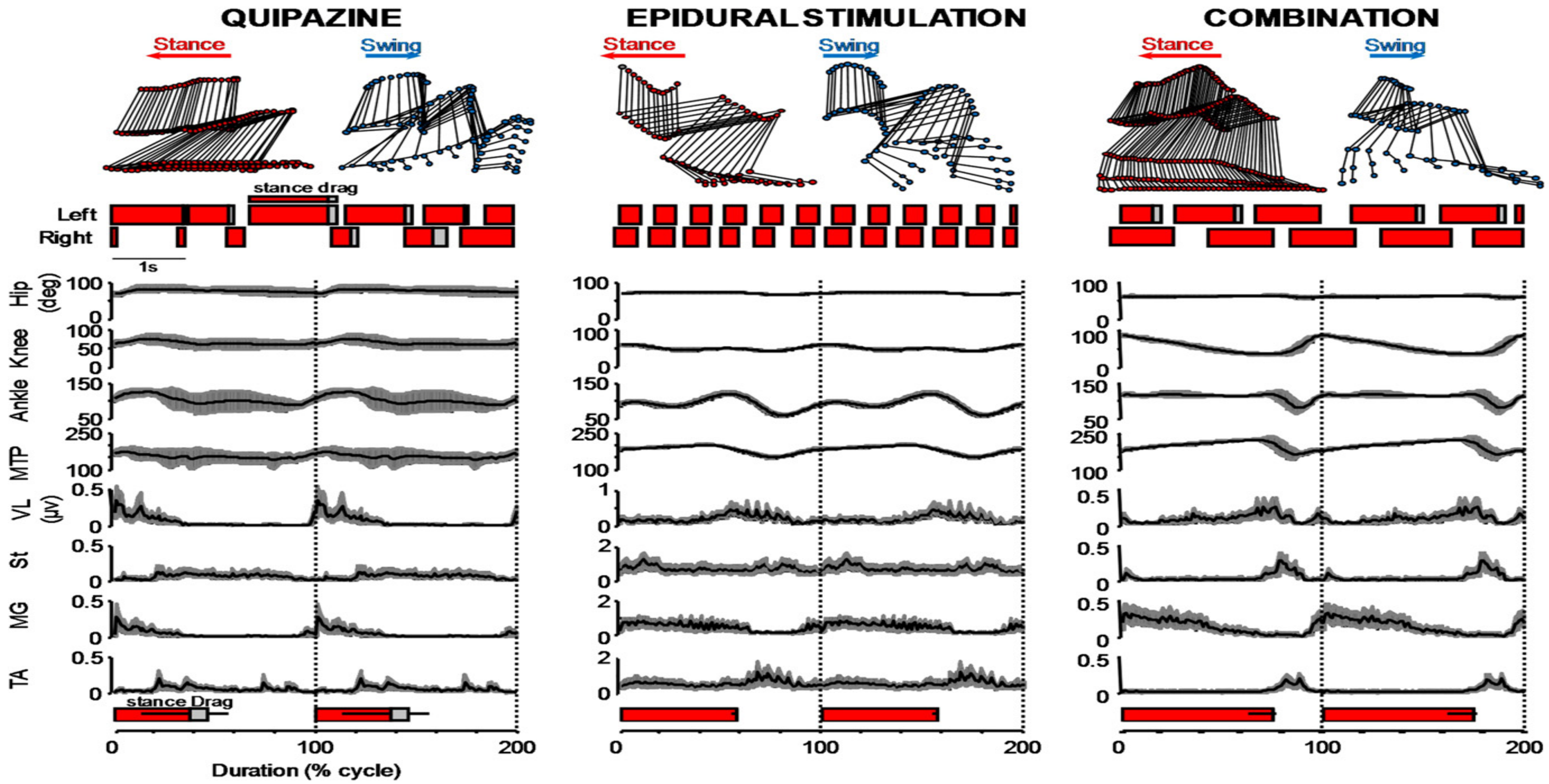
Combined arm and leg (or just arm) movement at 60rpm

- Activate locomotor networks in spinal cord (non-fatiguing)
- Shared propriospinal connections



Where next?

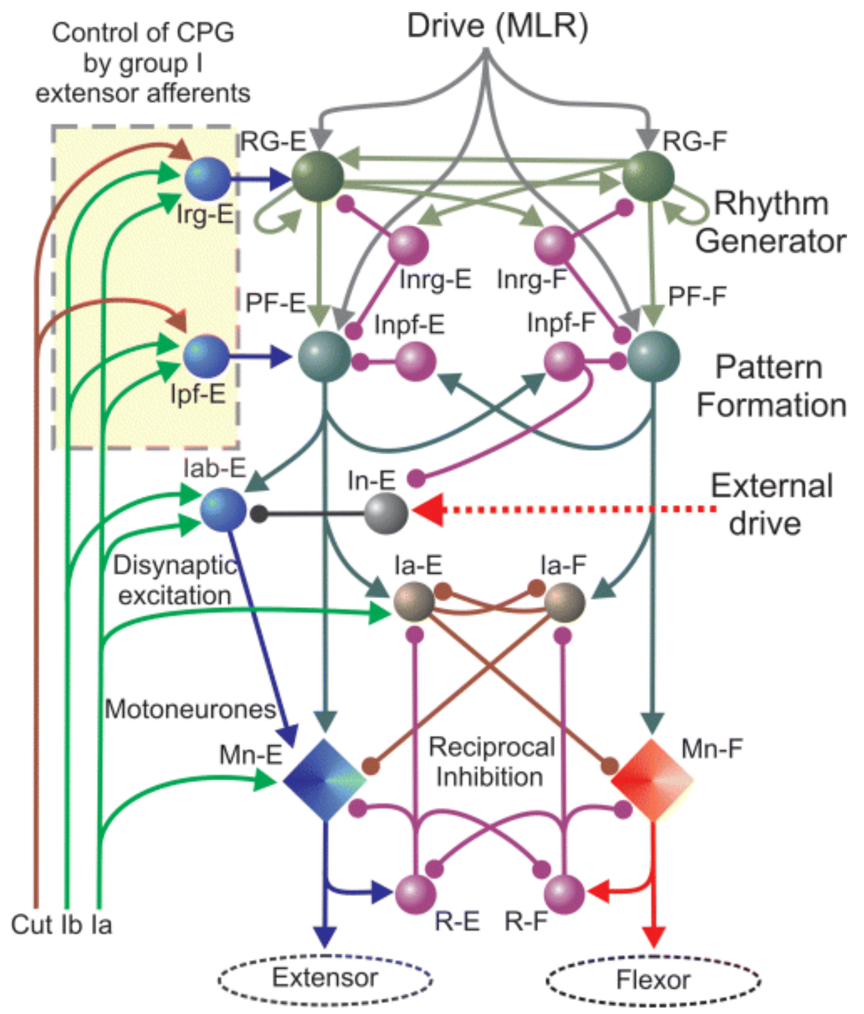
Play big idea video



*Use of drugs to improve neural activity—Quipazine is a serotonergic agonist (Edgerton et al 2008)

Edgerton video

CPG REVIEW



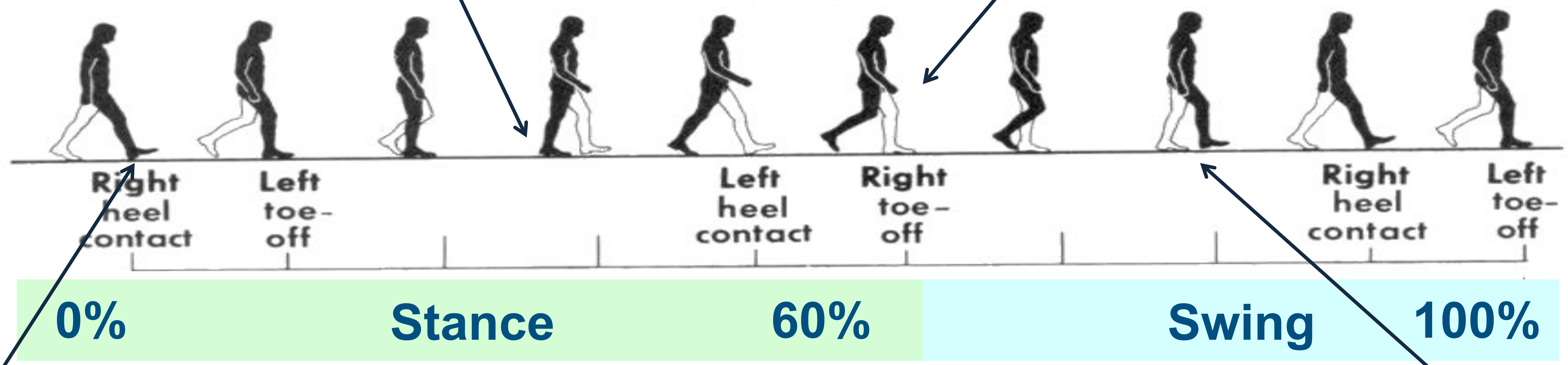
Central pattern generators in the spinal cord produce the building blocks of rhythmic activity

Tonic input from supraspinal centres causes rhythmic motor output (also adjustments from brain for skilled walking/adjustments)

Sensory feedback sculpts rhythmic activity

Force feedback (Ib) to increase plantar-flexion

Hip stretch (Ia) initiates swing phase



Cutaneous feedback for heel placement

Cutaneous feedback to avoid tripping

FOR FURTHER READING ON THE TOPIC:

Sherlock Holmes and the Curious Case of the Human Locomotor Central Pattern Generator

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