Walking

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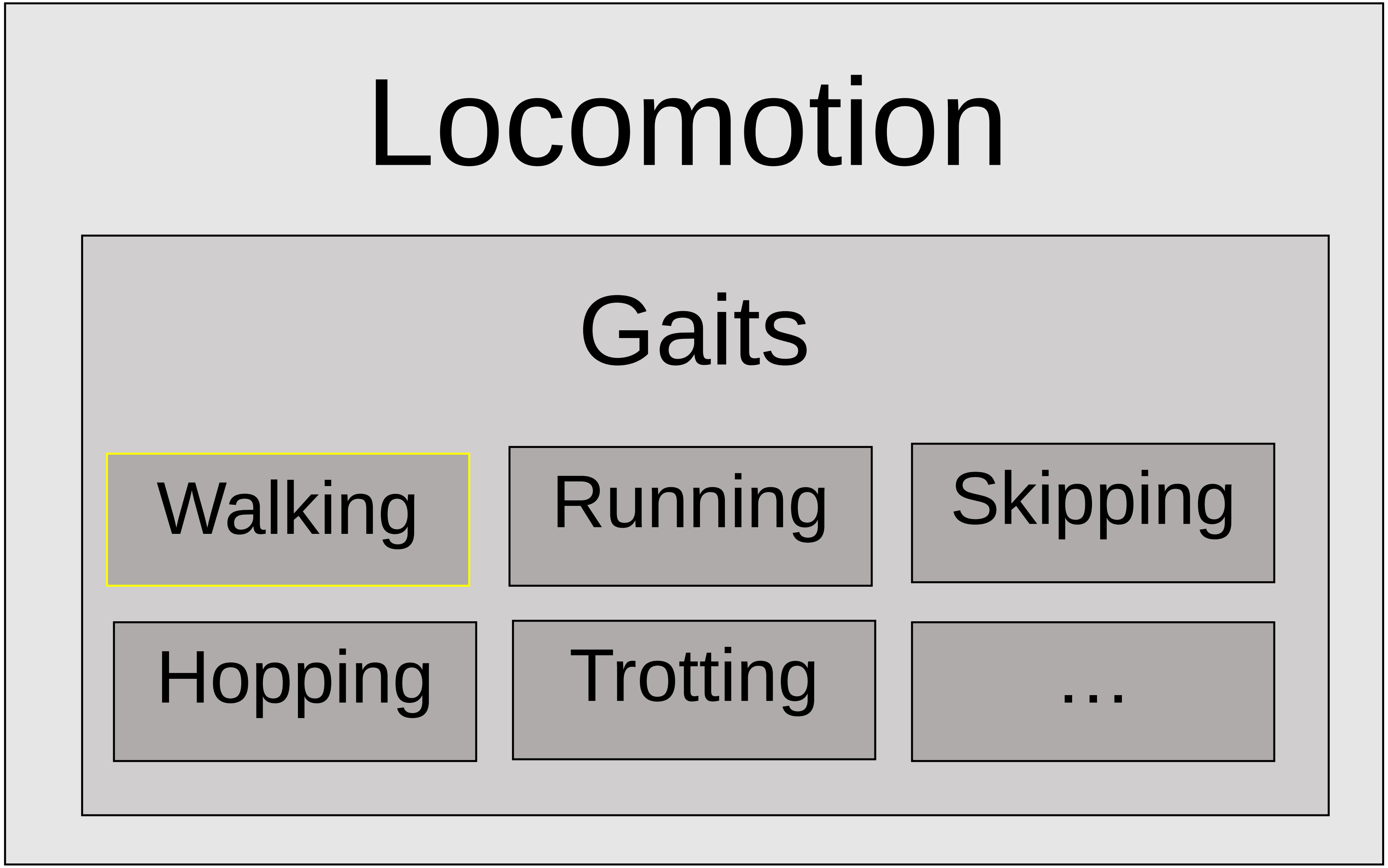

Locomotion
Gaits
Walking
Running
Skipping
Hopping
Trotting
...

Video from hhmi.org

- Some gaits come naturally to a species, others require conscious effort
- All gaits are typified by rhythmic coordination of various limbs

FUNDAMENTAL QUESTIONS:

1) How are the rhythmic motor patterns of locomotion generated?
2) How are those patterns modulated for complex locomotion?

FUNDAMENTAL ANSWERS

1) Central Pattern Generators
2) By ascending and descending input

Central Pattern Generators (CPGs)

CPG is a network of neurons, typically in spinal cord, that are capable of generating rhythmic pattern of movement *without requiring sensory feedback*

They are a shortcut for execution of complicated motor movement.

We will focus on walking but CPGs exist for *many* motor movements (breathing, chewing, yawning, swallowing, hiccupping…)

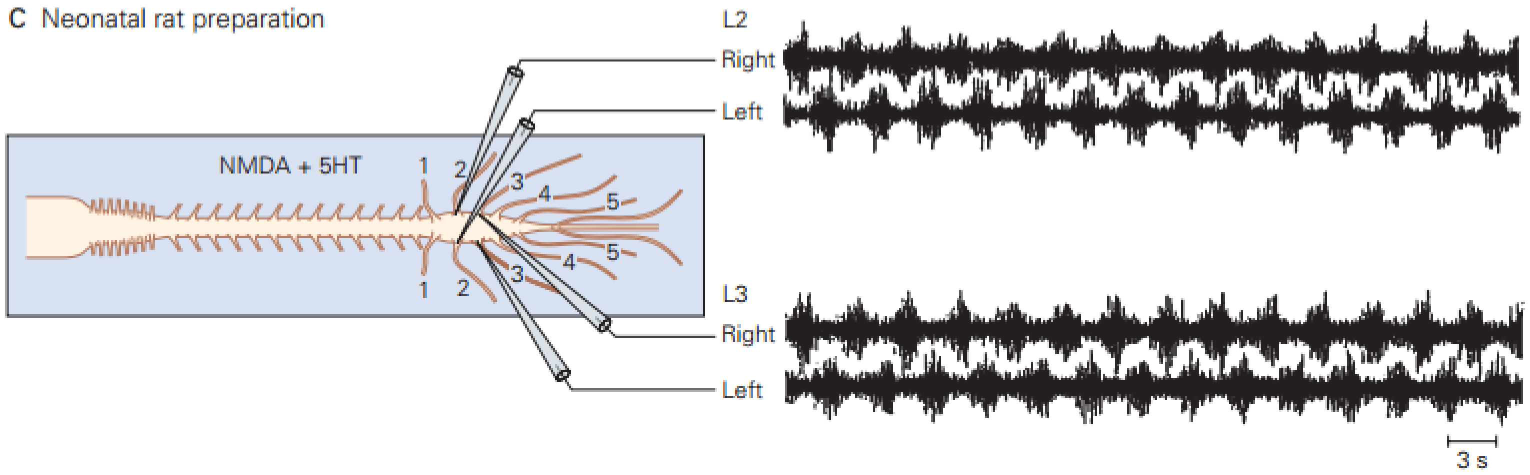


Image from Kandel

Locomotion requires rhythmic coordination of flexor (bending the limb) and extensor (straightening the limb) muscles

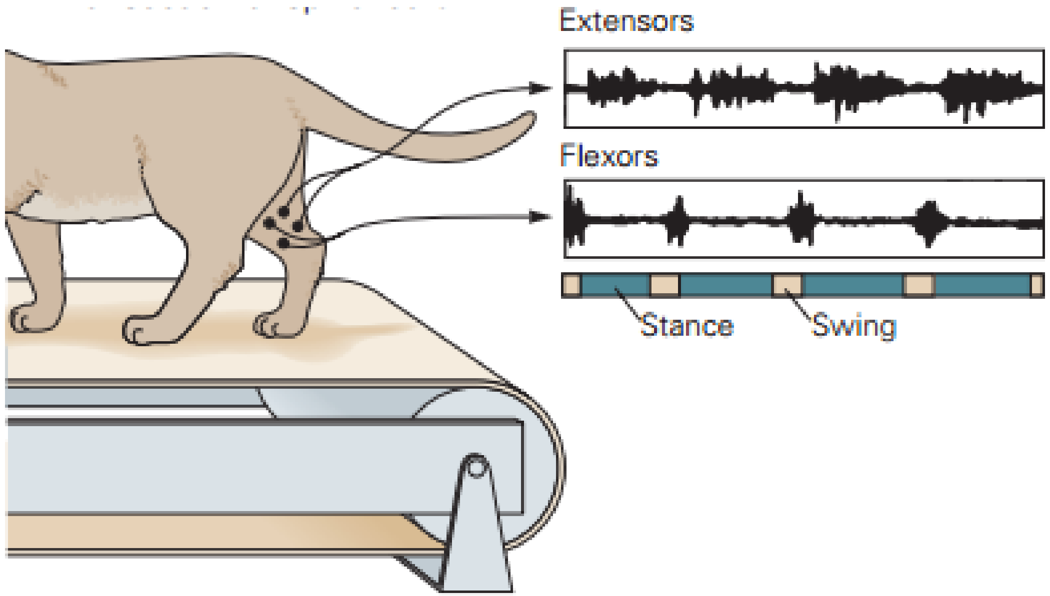


Image from Kandel

How does this coordination happen?

Mutually inhibiting spinal networks utilizing excitatory and inhibitory interneurons.

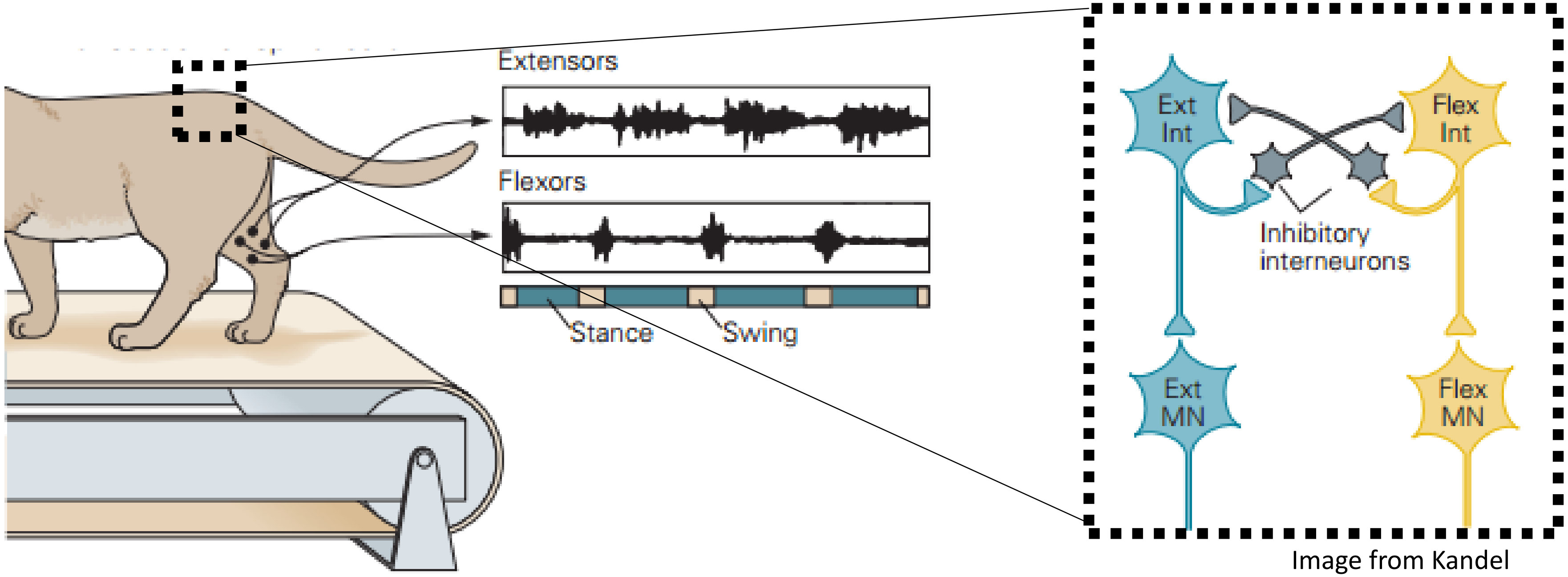
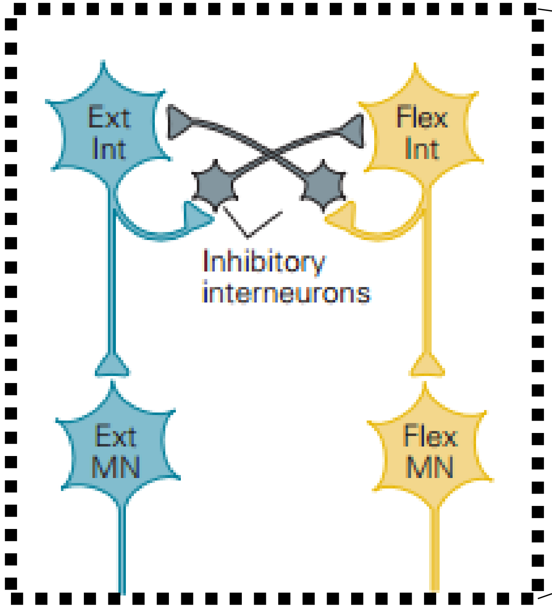


Image from Kandel

MN = Motor Neuron
Ext = Extensor muscle
Flex = Flexor muscle
Int = Internueron

Mutual inhibition coordinates ipsilateral flexor/extensor opposition as well as contralateral opposition



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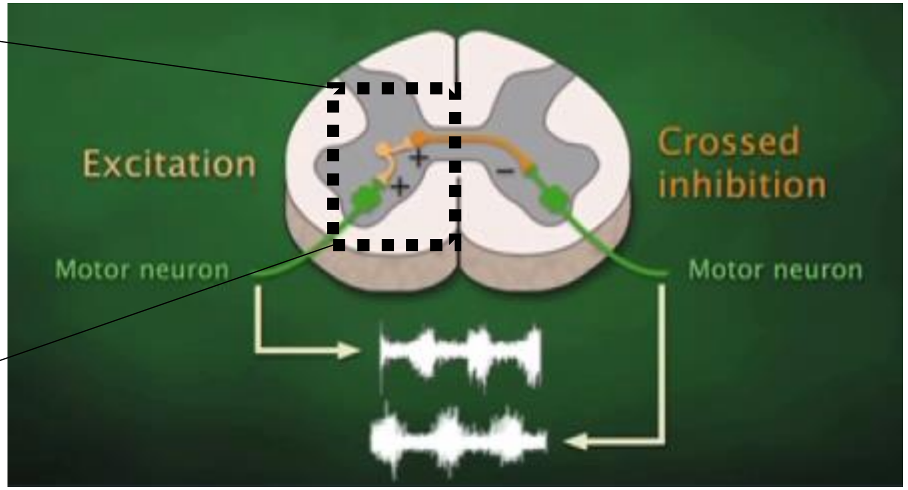

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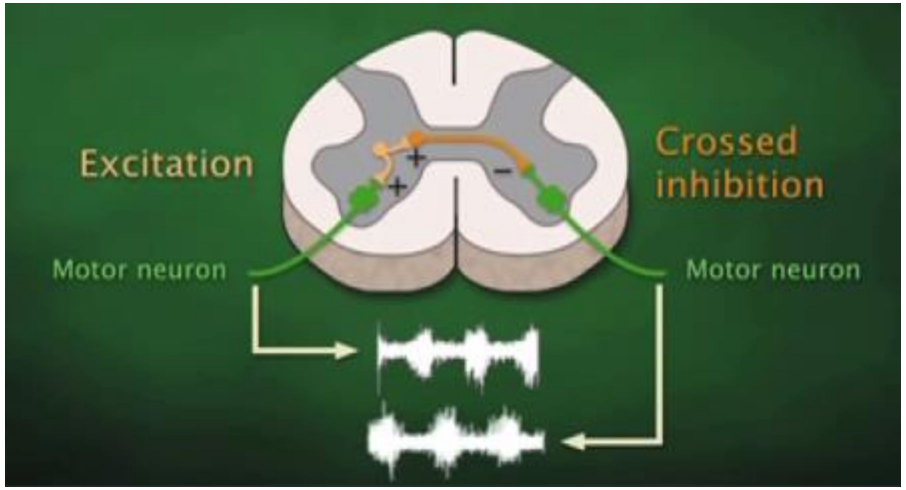
Example of contralateral motor neuron inhibition: walking in a wildtype mouse



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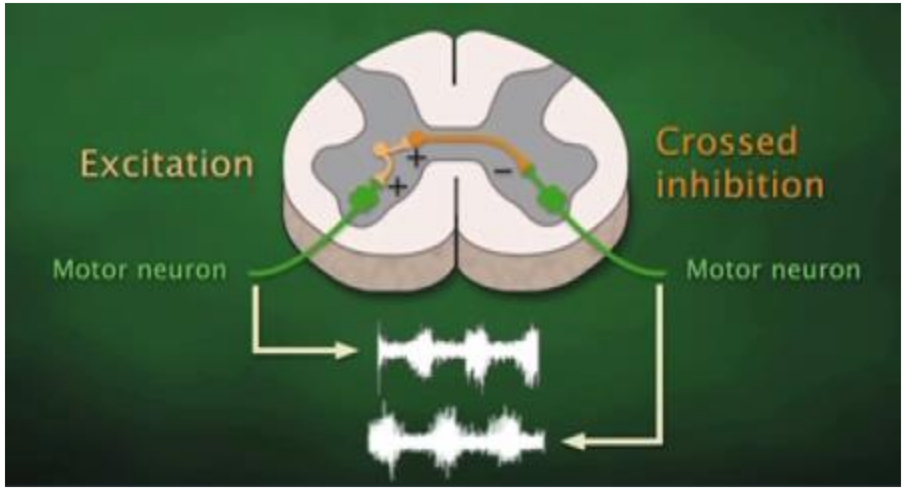
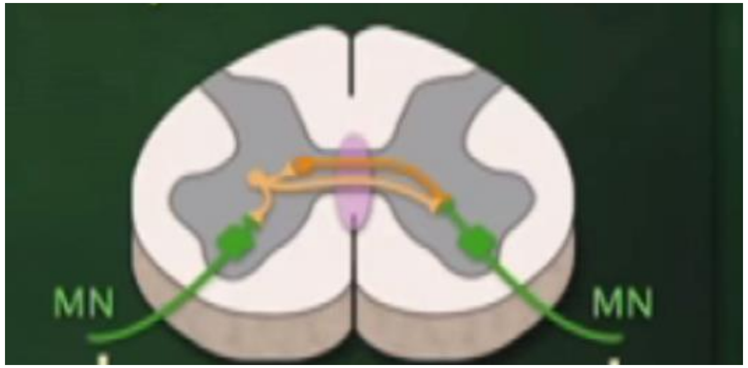
What would happen if instead of contralateral *inhibition*, the spinal walking circuit gave rise to contralateral *excitation*?





Images from hhmi.org

EphA4 is a gene that encodes a receptor for the protein family ephrin.

Ephrin is found in the middle of the spinal cord during development (purple oval in figure), and activation of the *EphA4* receptor repels axon growth, preventing excitatory interneurons from crossing.

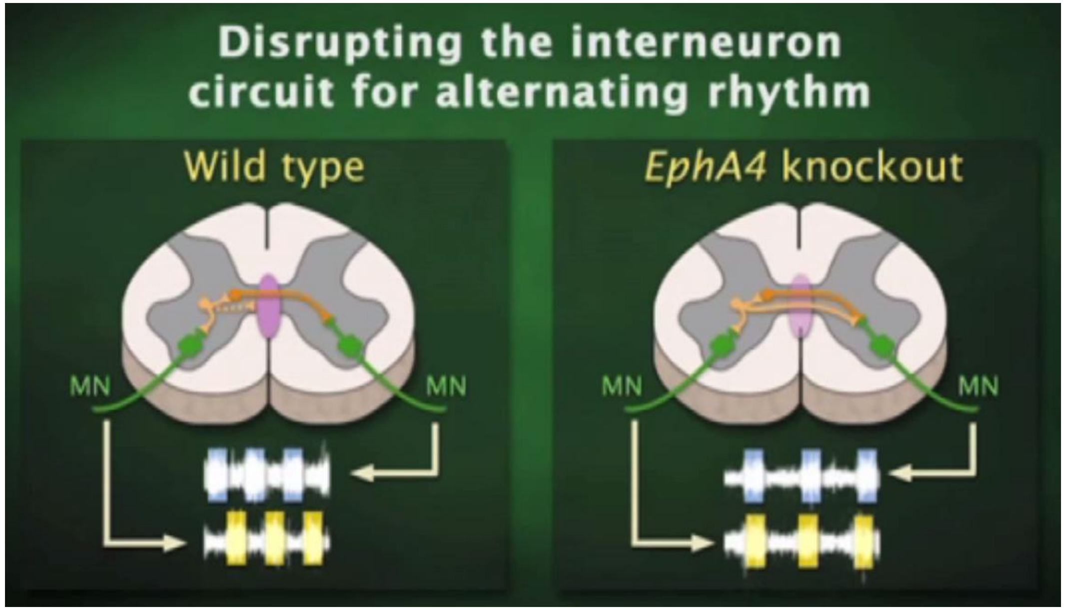
No *EphA4* gene

→

Growth of excitatory interneuron across spinal cord

→

Contralateral excitation



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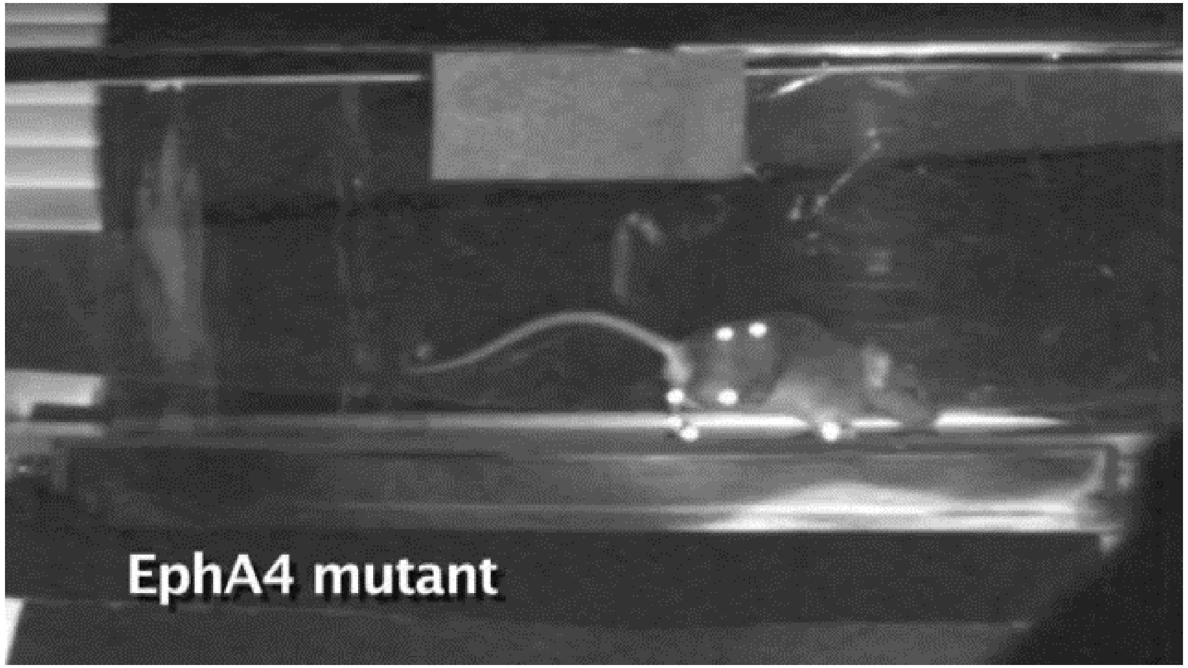

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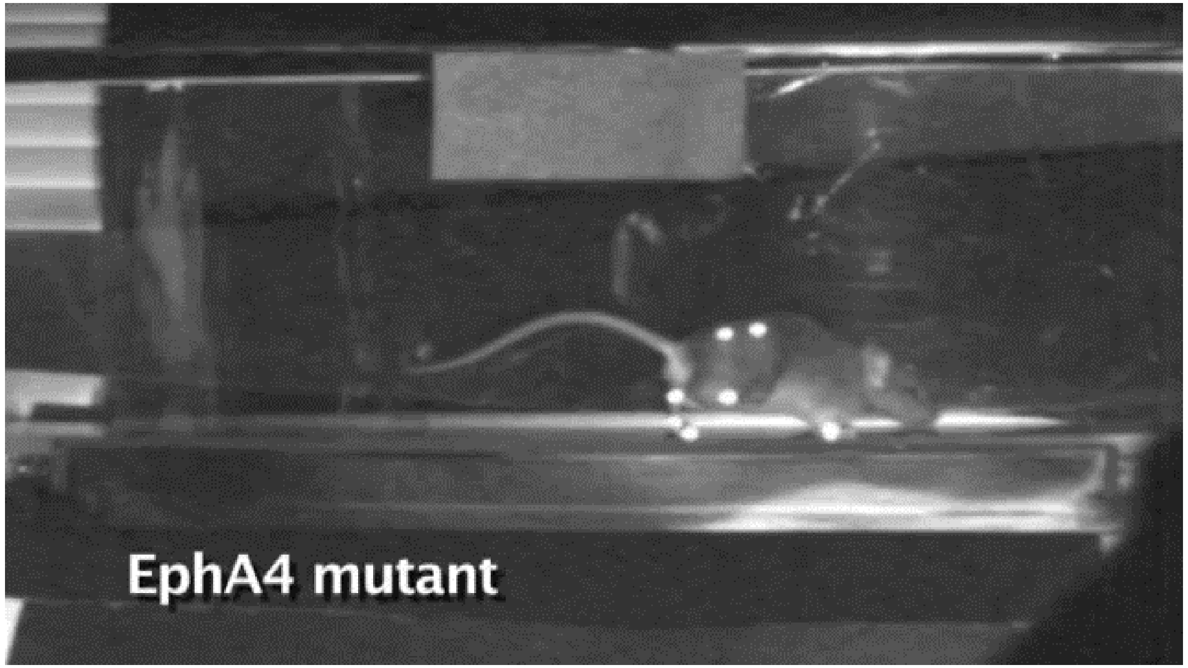
Contralateral inhibition leads to opposition of contralateral limb movement, while contralateral excitation leads to a mimicry of contralateral limb movement.

Hopping instead of walking



Video from hhmi.org

to recap

- CPGs can coordinate rhythmic motor neuron activity without sensory input.
- The coordination for stepping occurs both ipsilaterally among opposing muscles and contralaterally.
- The organization of excitatory and inhibitory interneurons in the spinal cord mediates this network.

FUNDAMENTAL QUESTIONS

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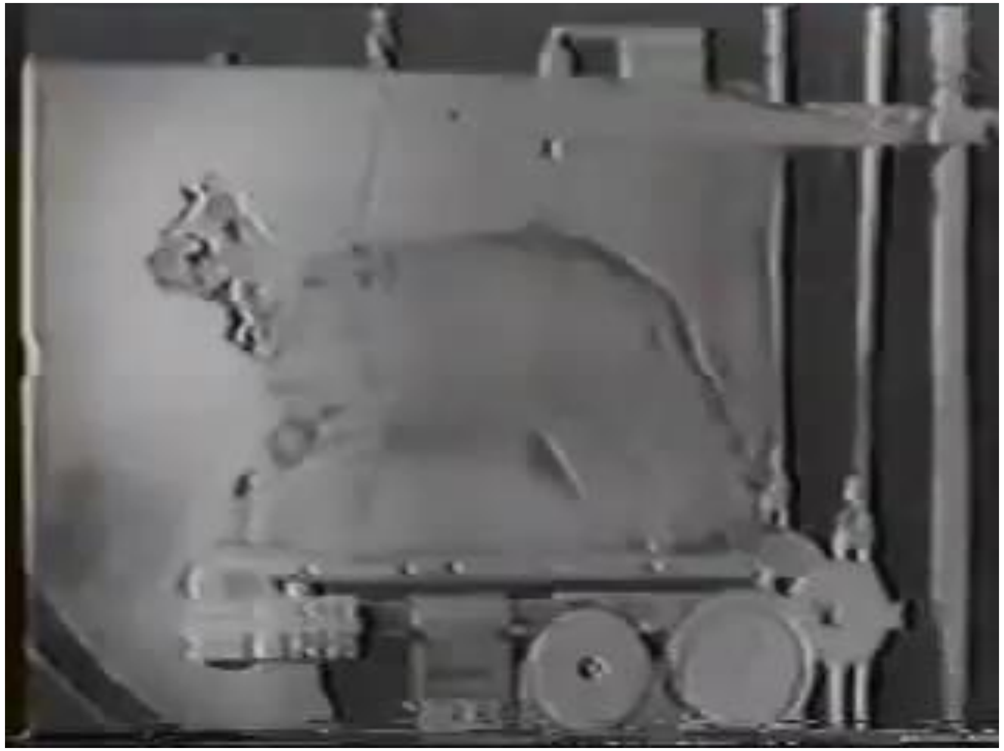
Walking is automatic and can be stereotyped, but it isn't rigid.

Sensory feedback modulates timing, amplitude of steps

Walking is automatic and can be stereotyped, but it isn’t rigid.
Sensory feedback modulates timing, amplitude of steps

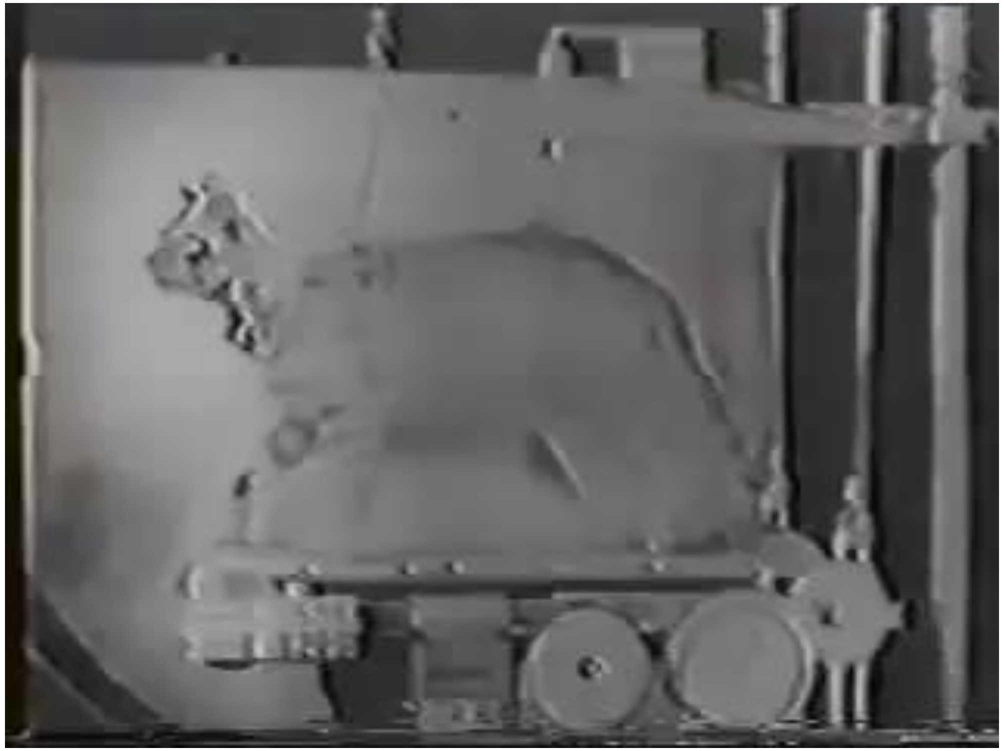
- Decerebrate cat prep (cortex disconnected from brainstem/cerebellum/spinal cord)
- Cannot voluntarily walk
- Held up by a harness and placed onto treadmill



Video from Youtube user 0zxr; from work of K.G. Pearson

Walking is automatic and can be stereotyped, but it isn’t rigid.
Sensory feedback modulates timing, amplitude of steps

- No descending input to regulate the gait
- The rate of stepping adjusts to the speed of treadmill
- Ascending sensory info, without cortical involvement, is sufficient to control step speed



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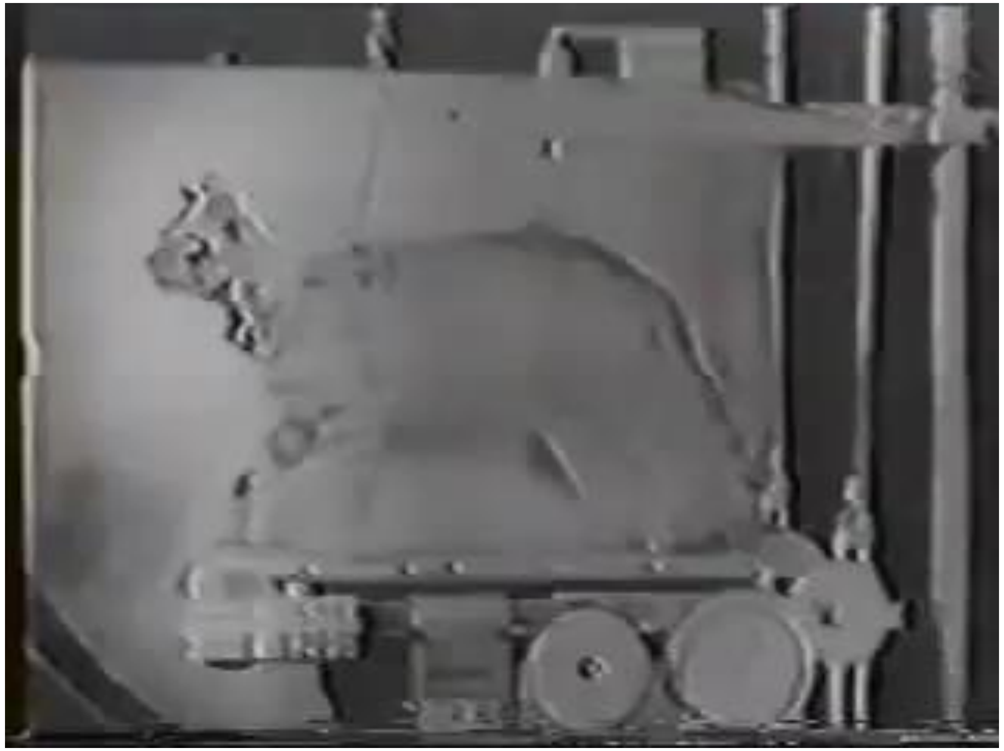
What sensory information is still being utilized in the decerebrate cat?



Video from Youtube user 0zxr; from work of K.G. Pearson

What sensory information is still being utilized in the decerebrate cat?

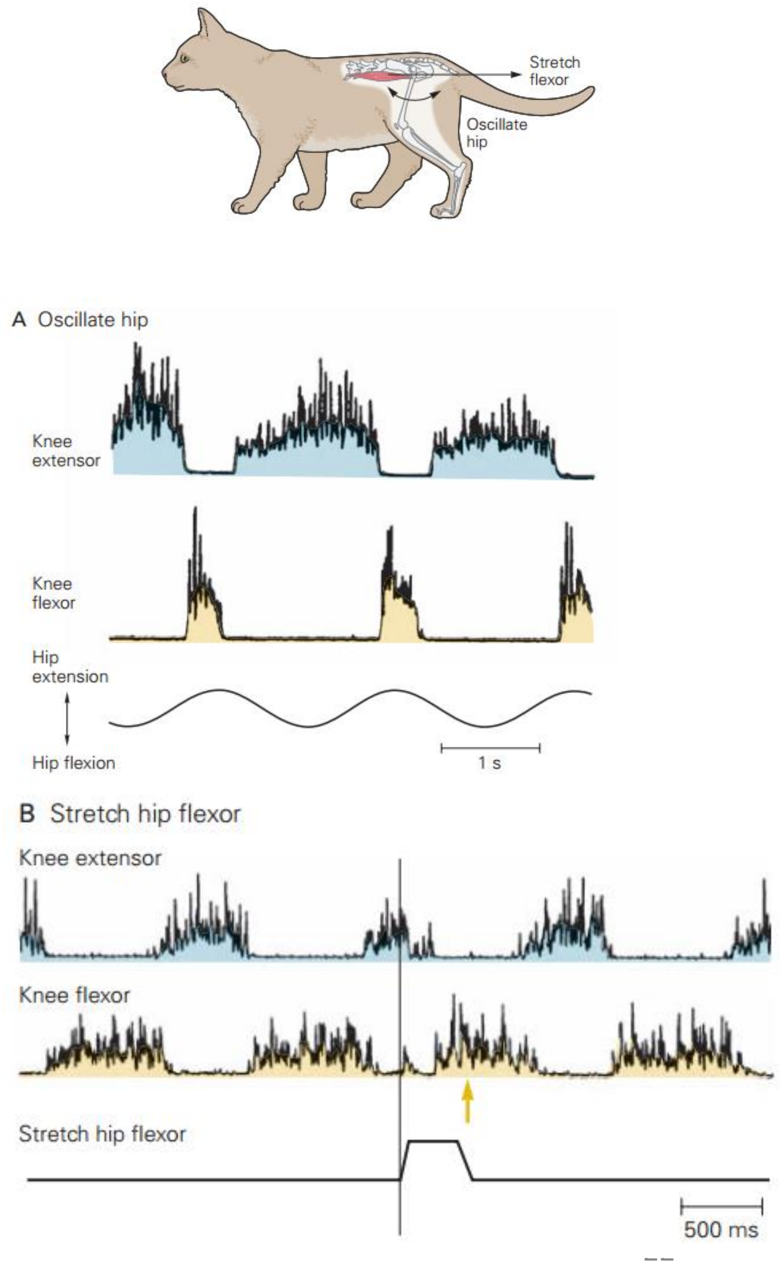
Proprioceptive (ie body position) information

- Ia afferents from muscle spindles (muscle stretch reflex)
- Ib afferents from Golgi Tendon Organs (muscle contraction)

Proprioceptive information

Stretching the hip flexor muscle →
Activates muscle spindle in flexor muscle →
Excite MN to contract flexor muscle →
Inhibit MN to relax extensor muscle

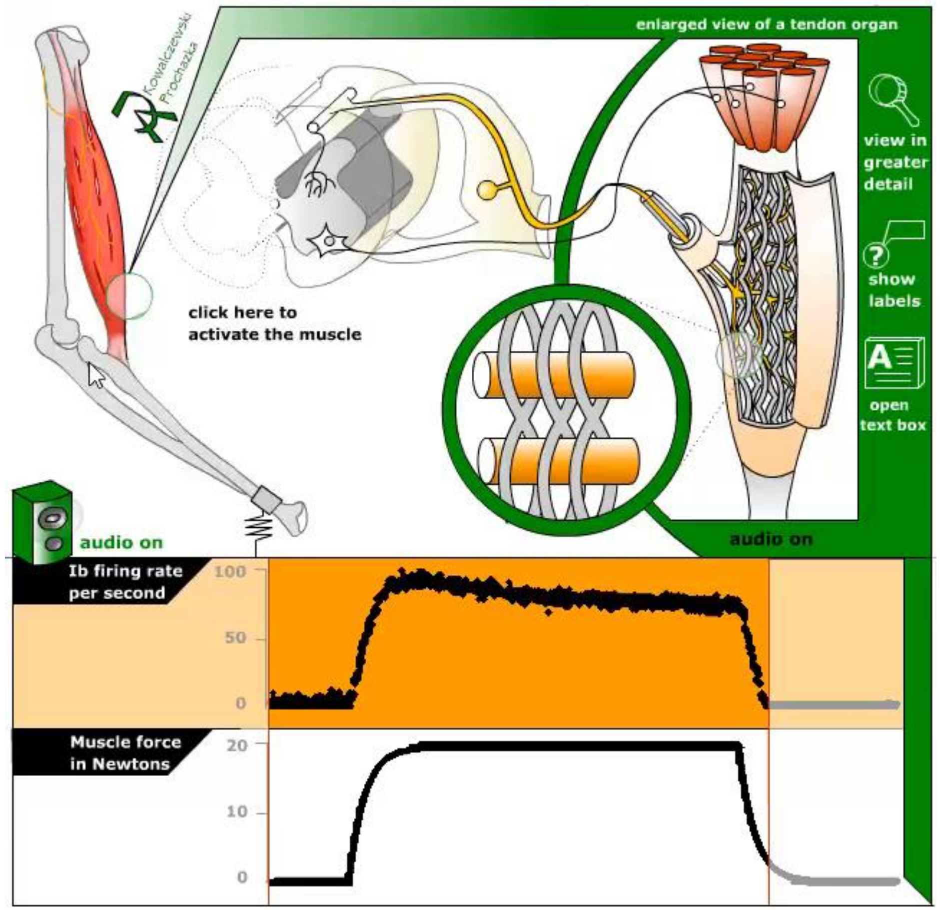
The hip muscle can transmit information about the stance phase during walking (swing vs. stance)



Proprioceptive information

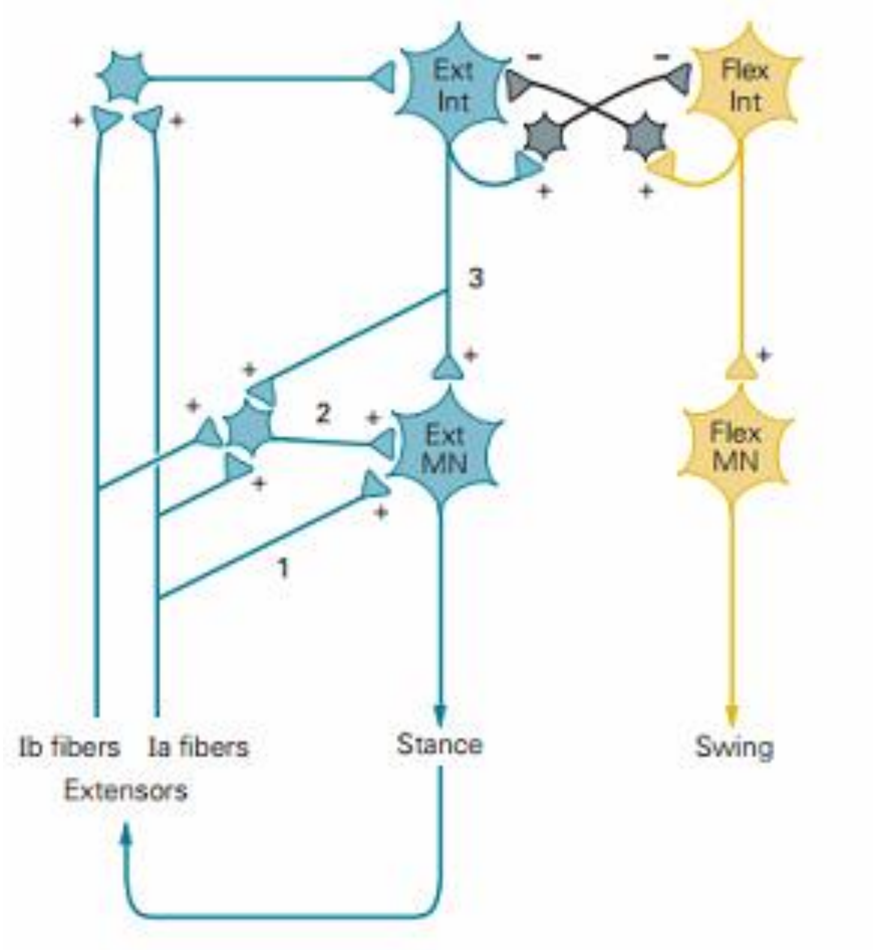
The Golgi Tendon Organ (GTO) sends signals to the spinal cord when it is squeezed during muscle contraction.

This transmits information on muscle load (weight bearing)



Animation by the Prochezka lab at University of Alberta

Proprioceptive information, including tension and extension information from the muscle, takes mono-, bi-, and polysynaptic routes to regulate the CPG.



to recap

- CPG activity can generate rhythmic motor movement by itself, but is modulated by sensory feedback
- Proprioceptive information can control pace and timing of walk

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FUNDAMENTAL ANSWERS

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Descending pathways can initiate walking and control speed

Mesencephalic locomotor region (MLR) can initiate walking, even in decerebrated prep.

MLR →

Reticular formation (medulla) (axons in ventrolateral funiculus →

CPG

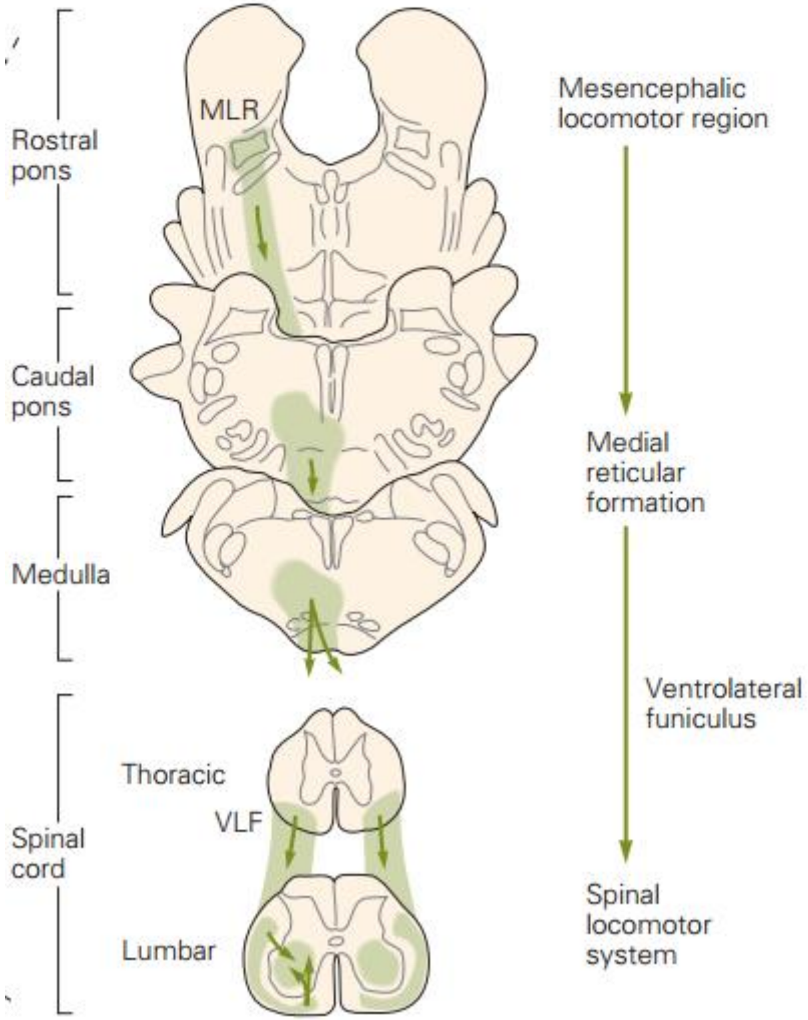
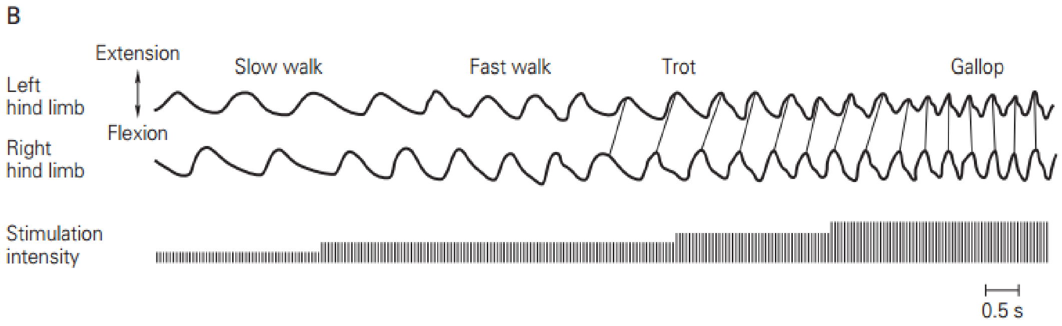


Image from Kandel

Descending pathways can initiate walking and control speed

Stimulation of MLR can modulate speed of walking.

Higher intensity stimulation → faster speed



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- subthalamic locomotor region (in the subthalamic nucleus)
- pontine pedencular nucleus (in the pons)

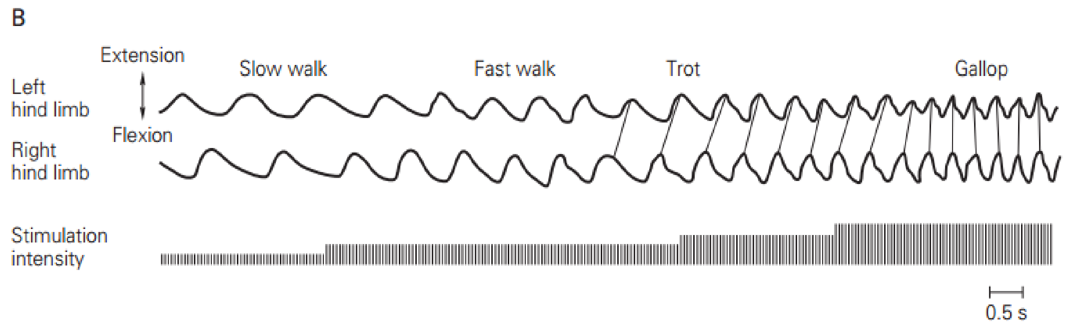
both involved in gait *modulation* but not critical for *initiation*

Descending pathways can initiate walking and control speed

Descending pathways require glutamatergic activation to initiate walking.

Norepinephrine (NE; from the locus coeruleus) and serotonin (5-HT; from raphe nucleus) can be sufficient to initiate stepping, not necessary.

NE and 5-HT thought to play modulatory role



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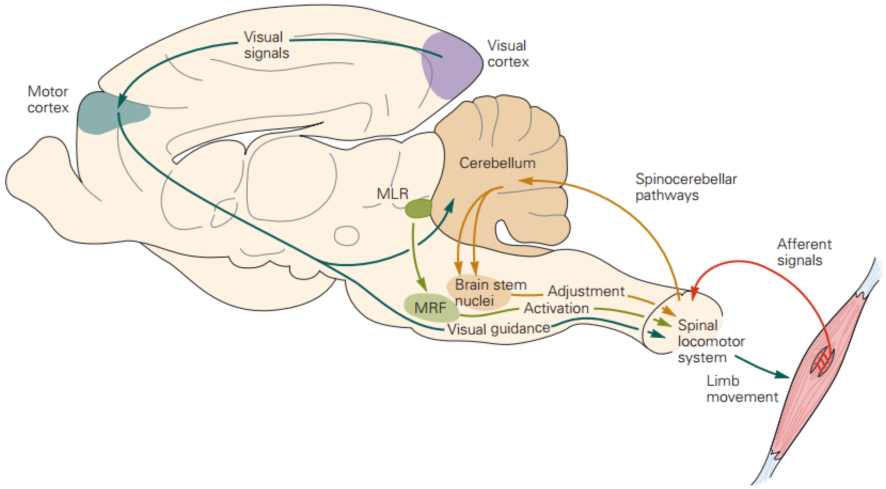
Cerebellum fine-tunes locomotor patterns

Cerebellum receives proprioceptive information from the spinocerebellar tract

- Dorsal spinocerebellum tract: proprioception
- Ventral spinocerebellum tract: afferents from CPGs

This gives the cerebellum information on:

- Where the limbs are
- What the pattern of limb movement is



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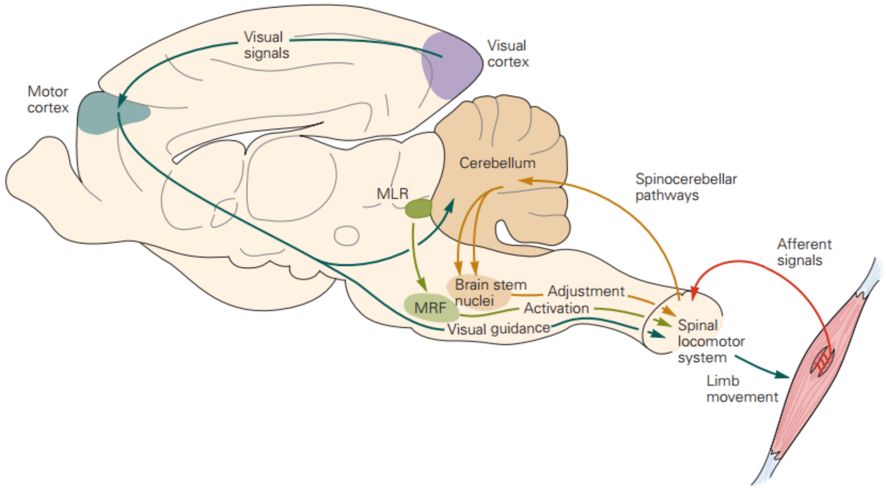
Cerebellum fine-tunes locomotor patterns

Cerebellum receives descending motor information from motor cortex

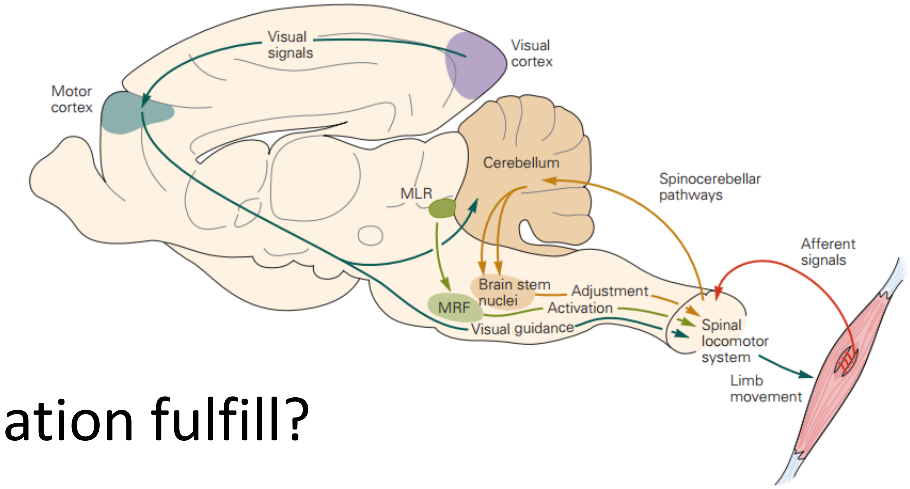
- Transmits plans for intended and upcoming motor movements



Cerebellum fine-tunes locomotor patterns

The cerebellum combines information on:

- Current limb position
- Current motor pattern
- Intended motor commands
- Upcoming motor commands

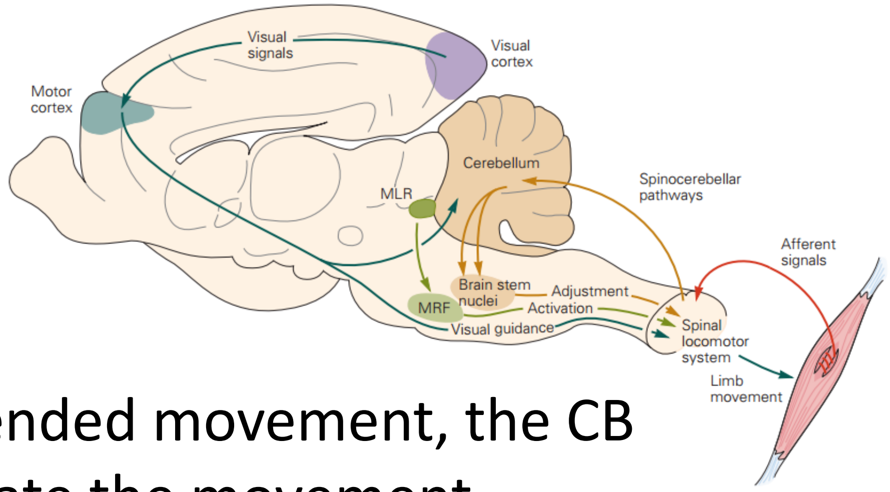


What functional role would combining all this information fulfill?

Cerebellum fine-tunes locomotor patterns and corrects errors

The cerebellum combines information on:

- Current limb position
- Current motor pattern
- Intended motor commands
- Upcoming motor commands



If an error is detected in the current compared to intended movement, the CB issues commands to other brainstem nuclei to modulate the movement.

Visuomotor coordination requires motor cortex

Subjects with motor cortex lesions can walk on simple surfaces just fine

But deficits exist with complex, visuomotor tasks (climbing a ladder, stepping over an object)

When stepping over an object (out of sight), its position relative to the limbs is kept in working memory.

The posterior parietal cortex is critical for this function.

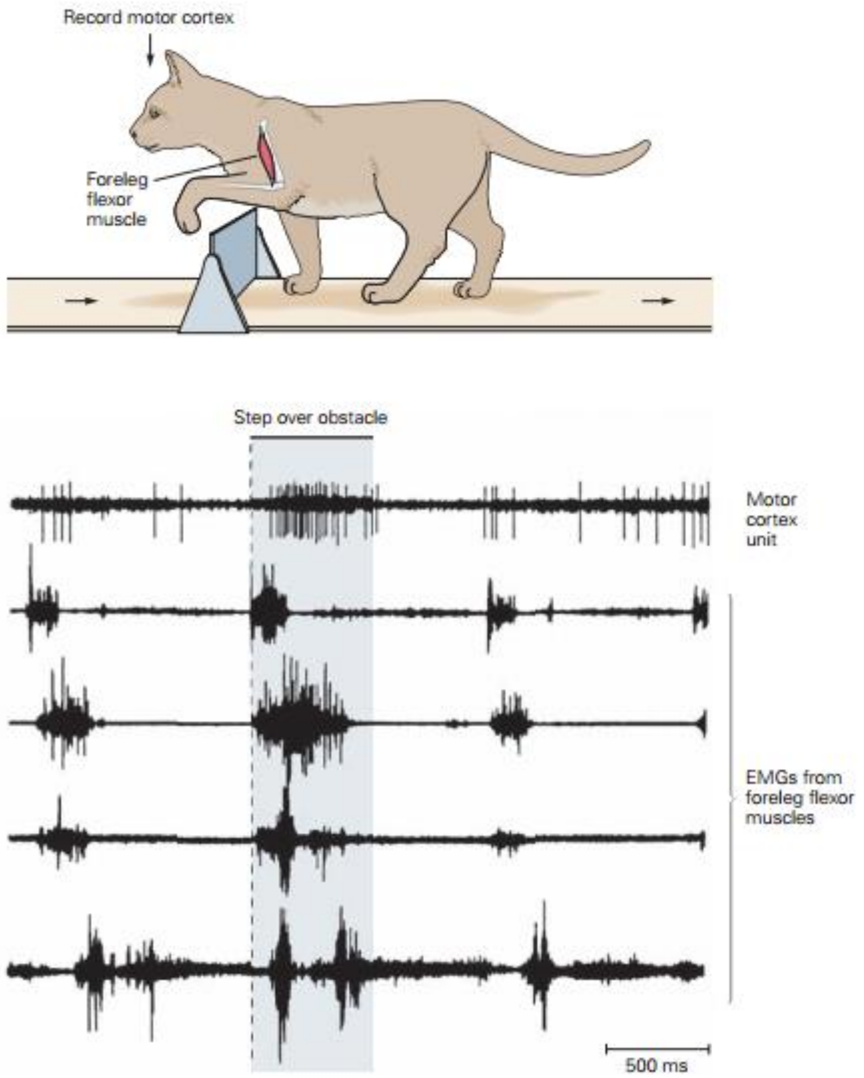


Image from Kandel

Locomotion in humans

- Basic mechanics of locomotion (CPGs, ascending and descending modulation) thought to be similar
- Greater reliance on <u>descending</u> modulation, especially balance information from vestibular nuclei (harder to balance on two vs. four legs)
- Evidence for innate locomotor CPGs in human newborns

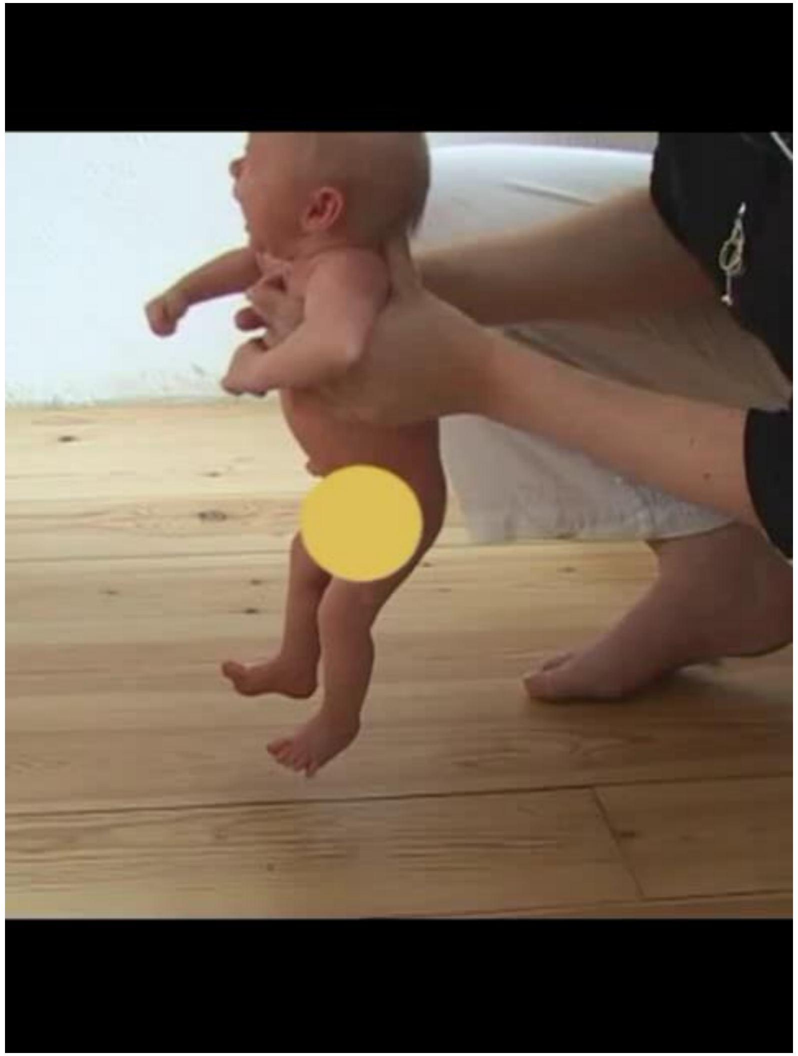
Locomotion in humans

Human newborns, held upright against flat surface, show walking behavior.

Even occurs in babies with anencephaly.

To walk independently, babies need cortical development (~1 yr)

Horses, by comparison, can stand and walk within hours of being born.



Video via Youtube user onemedicalvideo

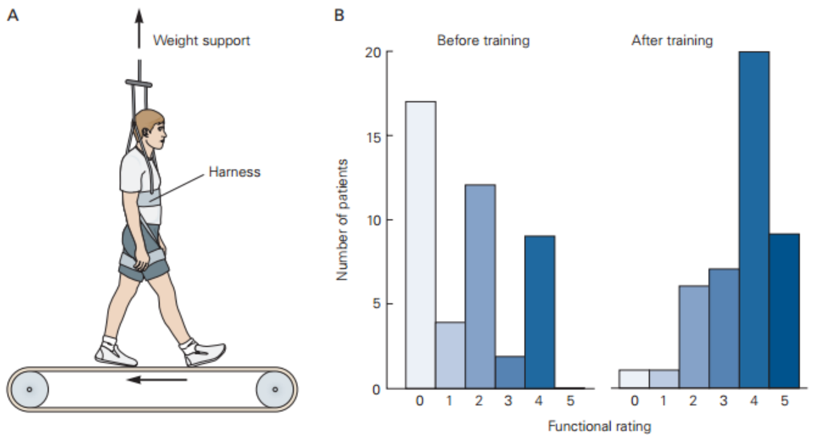
Locomotion in humans

Humans with spinal cord injuries can regain some walking ability (if injury is moderate)

Require a harness to ease burden of balancing

Training on a treadmill improves walking ability; thought to depend on plasticity of CPGs

These therapeutic practices came directly from basic science – studying locomotion in cats



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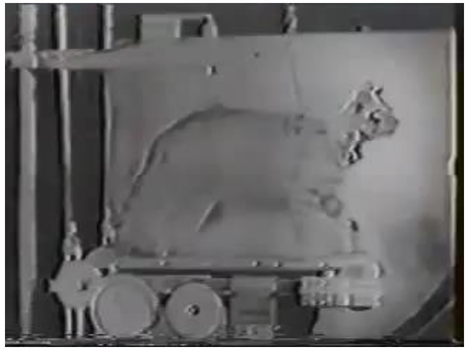

Restoring locomotion in humans

*Very** recent research has used patterned, electrical stimulation of the spinal cord to restore locomotion in paraplegic humans – even with total lower limb paralysis

Source: Nature Videos

*Wagner et al. (November 2018) Nature

Restoring locomotion in humans

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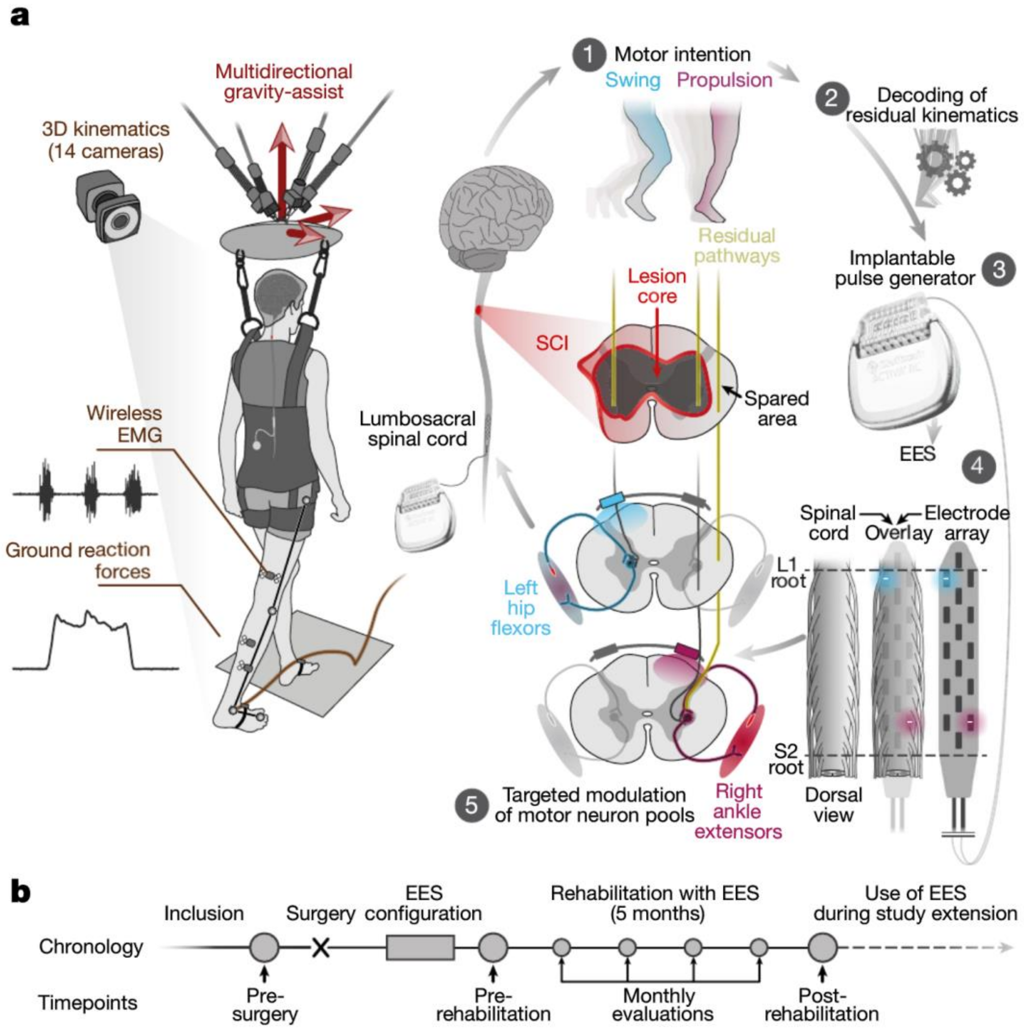
(a) Schematic of experimental design

(b) Timeline of experiments



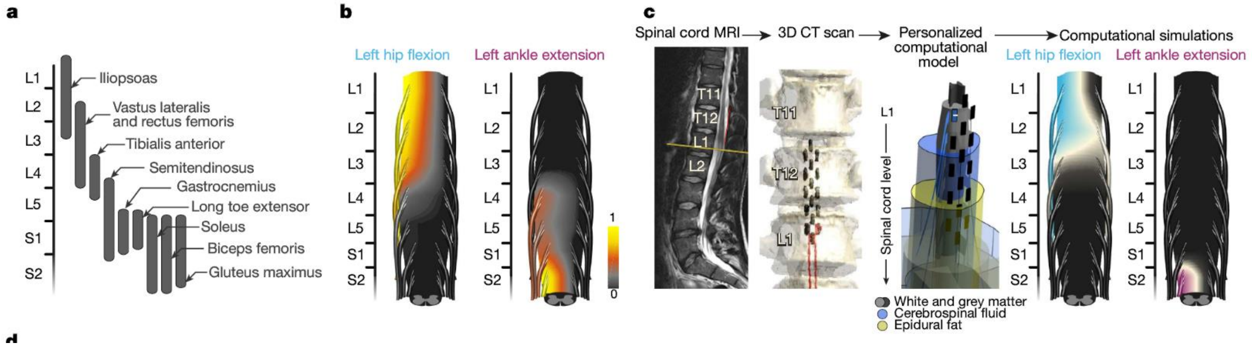
*Wagner et al. (November 2018) Nature

Restoring locomotion in humans

(a) Identifying which muscles are controlled by what level of the spinal cord

(b) Reading out spinal nerve activity in healthy people during movement

(c) Creating models for electrical stimulation to approximate healthy spinal activity



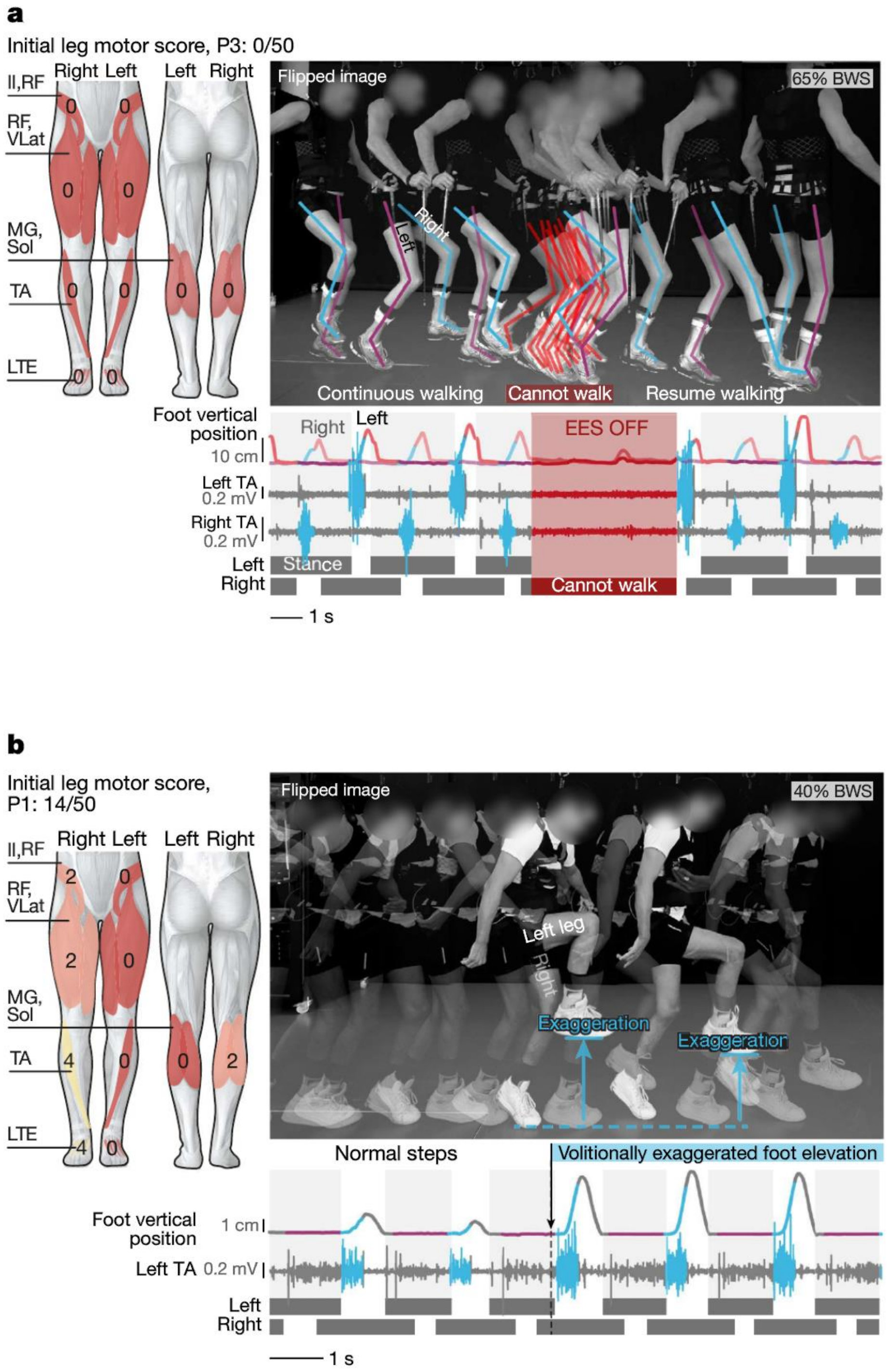
*Wagner et al. (November 2018) Nature

Restoring locomotion in humans

(a) Patient #3: completely paralyzed before treatment. Epidural electrical stimulation (EES) allows walking

(b) Patient #1: Complete left paralysis, major right paralysis. EES enables walking and even gait modulation

*Wagner et al. (November 2018) Nature



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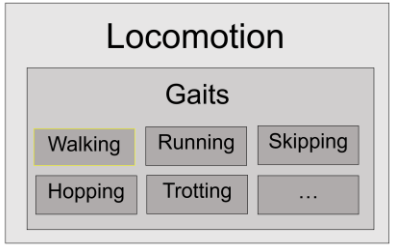
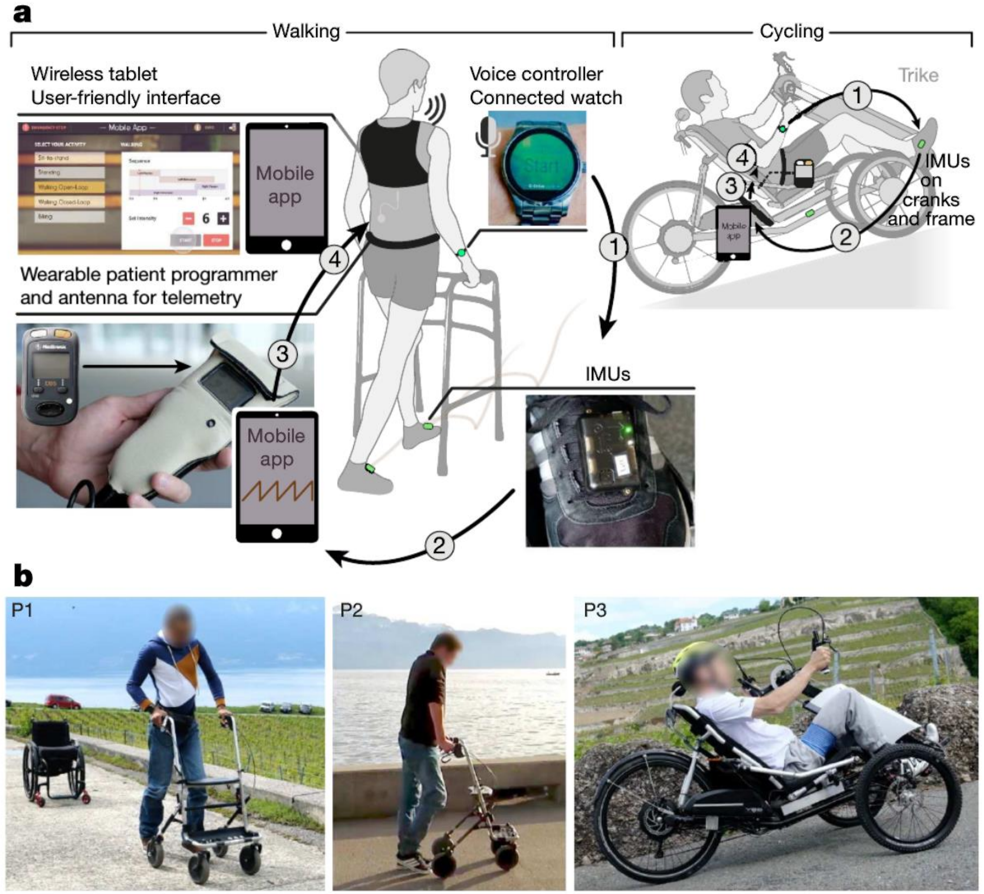


Different gaits require different patterns of muscle coordination



Walking and cycling were enabled in patients by programming different patterns of electrical stimulation, automatically detected by foot position.

Wireless electrical stim device is paired with smartwatch app to allow patient to control when to turn stimulation on and off

*Wagner et al. (November 2018) Nature