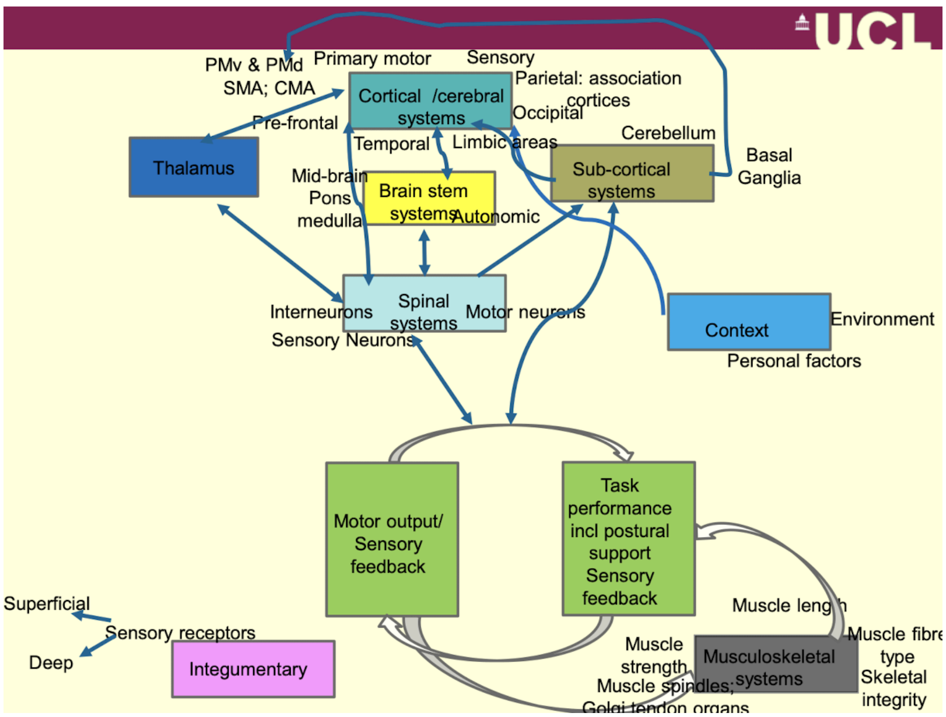
Introduction

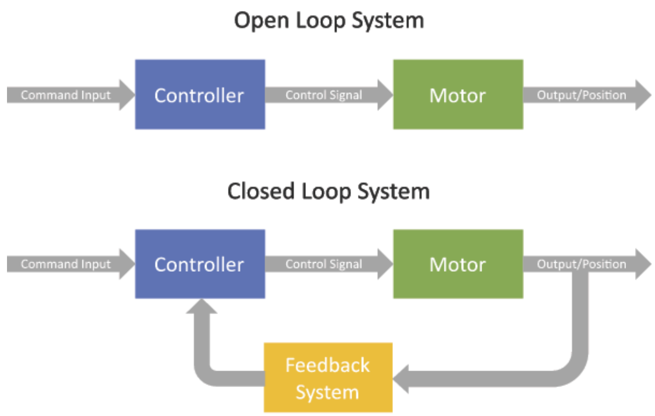
- Systems neuroscience studies how neurons work together in complex networks to give rise to integrative functions such as vision, audition, and actions.
- A major goal of systems neuroscience is to understand how neuronal circuits function to produce sensation, emotion, action and other complex behaviors.
- It deals with the functions of neural assemblies and various subsystems that compose the CNS of an organism.
- Systems integrate to produce correct motor commands → All systems are connected
  - Feedback refines action



- Motor control is the ability to regulate or direct mechanisms essential to movement
  - How the CNS can organise many different muscles and joints
  - How sensory info is used in the selection and control of movement
- Motor learning/adaptation is the neuronal changes that occur to allow an individual to accomplish a new motor task, to perform a task better, fast, or more accurately than before.
  - Adaptation can be advantageous or considered to be maladaptive
  - We can only control what we sense, thus motor learning requires sensorimotor experience of the task
- Motor abilities are innate and depend on CNS development and experience
  - Abilities deteriorate with aging → sensory systems less acute, loss of motor unit and loss of muscle size & strength
  - Abilities improve with experience as actions are refined

- Movement Categories
    - Reflex → involuntary, automatic, reproducible response to a given stimulus
        - Integration of reflex circuitry with descending motor command may be involved in modulating reflexes
    - Rhythmical → pattern generators for walking / breathing, spinal cord involved
    - Voluntary → goal-directed, maybe automatic though not reflexive, sensory feedback is integrated with central command

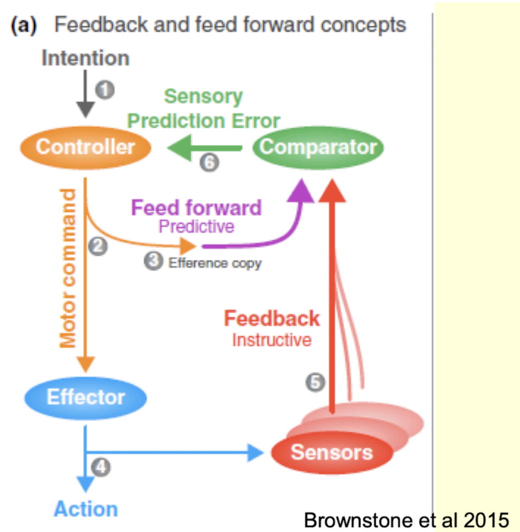
Feedforward vs Feedback



Forward model	Feedback model

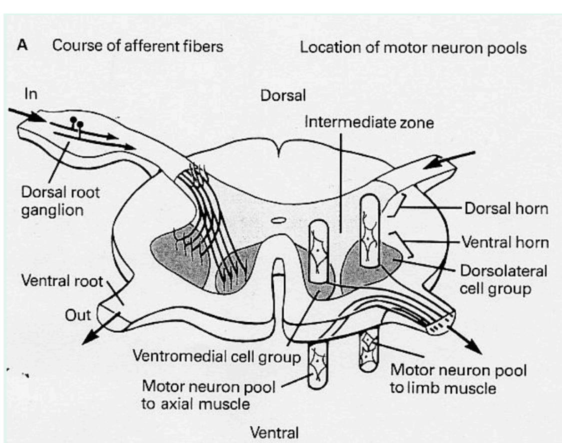
• Open loop
• Accuracy problems
  ○ Produces best estimate
• Fast
• Useful for well-known asks
• Updated through <u>learning</u> (feedback model)
• **Predictive**
  ○ In advance of activity occurring
  ○ No need for sensory input
	• Closed-loop
	• Accurate
	• Delay
	  ○ 50 - 100ms
	  ○ Timing of sensory feedback: at least 50ms to get to sensorimotor areas of brain and back to the spinal cord & muscle to adjust output for hand
	• Useful for novel tasks
	• Enables learning
	  ○ Success of ongoing actions and adaptation of sensorimotor plans for future
	• **Reactive**
	• Event movement generates sensory feedback processed at all levels of CNS

Mechanism: Integration of Feedforward and Feedback



1. CNS predicts what is needed to achieve goal (makes a predicted plan)
    a. Require an internal model for creating this predictive plan
2. Sends motor command (**feedforward model**)
3. Motor command activates motor neurons in spinal cord which innervate muscles required to execute task
4. Movement initiated without the use of sensory feedback
5. The resultant movement generate sensory feedback (reactive control)
6. Sensory feedback is used to correct errors in the predicted plan or counteract unexpected deviations both at the level of the spinal cord and in supraspinal areas (**online use of feedback**)
7. Predicted plan for future performance (feedforward model) is updated if needed (**offline use of feedback)**

Spinal Cord

- Spinal cord structure overview:
    - 

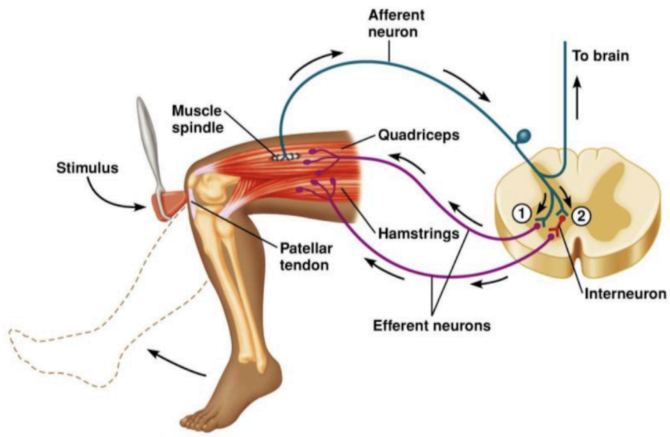
    - White matter (axons) in columns
        - Dorsal → ascending sensory afferents to brain
        - Ventral → descending motor efferents from brain
        - Lateral → sensory, motor + autonomic
    - Grey matter (cell bodies) divided into 10 layers
        - 3 major zones:
            - Dorsal (I-VI)
            - Ventral (VIII-IX)
            - Intermediate (VII)
- Spinal cord connects with the periphery through afferent and efferent axons in spinal roots
- Communicates with the brain by ascending and descending pathways
    - Tracts in spinal white matter
- Have spinal circuits and reflexes predetermined by neuronal circuits
    - Reflex
        - Stretch reflex → Muscle spindle (receptor)
        - Golgi tendon organ reflex → Golgi tendon organ (receptor)
    - Circuit (not reflex)
        - Central pattern generator for locomotion
- **Alpha (α) motorneurons** are the final output neurons from the spinal cord
    - Signals converge from the brain, periphery, and other sources onto the alpha motor neuron
- Enables activation of muscles in patterns directed by the brain
    - May be dependent on proprioceptive input
        - Muscle length and tension inform CNS about body position and muscular effort (movement)

Spinal Circuits and Reflexes

- Reflexes are flexible
- Integrated by centrally generated motor commands into complex adaptive movements
    - Circuit underlying reflex are utilsied by descending commands to produce complex movements
- Sensory stimuli for spinal reflexes arise from muscles, joints and skin
    - Multiple inputs
- Neural circuitry is within the spinal cord → provides basis for patterns of muscle activity
- Neural signalling is adjusted to task
- Supraspinal areas play important role in modlulation and adapting spinal reflexes

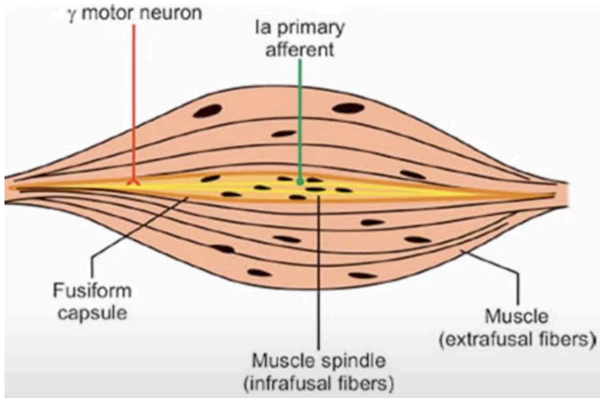
Stretch Reflex

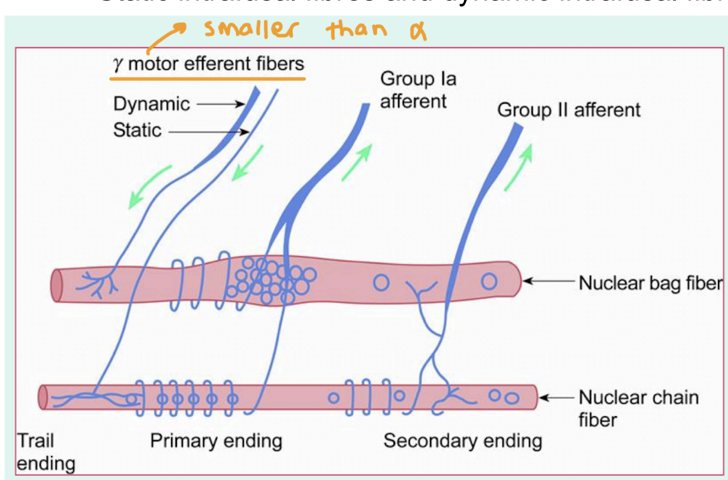
- Modulated by descending pathways and other inputs
- Cicuitry innervates both agonist and antagonist muscles
- 2 components

- Short latency: Spinal Porcessing
    - 

    - 1a afferent neuron send signals to spinal cord
    - 1a afferent neuron synapses directly onto alpha motor neuron innervating agonist muscle
    - 1a afferent neuron synapses onto 1a inhibitory interneuron which synapses onto alpha motor neuron to antagonist
        - Stimulation of agonist muscle → contraction
        - Inhibtion of antagonist muscle → relaxation to facilitate agonist muscle → knee-jerk
- Long latency: 2 responses
    - Transcortical Processing:
        - EMG recordings of upper limb EMG in participants with unilateral descending pathway and bilarteral descending pathways
            - Unilateral: Short latency and long latency response (EMG recordings) in the ipsilateral limb, none in contralateral
            - Bilateral: short latency only in ipsilateral, but long latency in ipsilateral and contralateral limb → signal travels up to the cortex, and then output comes down form cortex via descending pathway to both limbs, resulting in response for both
                - Long latency response is processed in cortex
    - Cutaneous Receptor Stimulation:
        - Descending pathway important for regulation of reflex
        - Disturbance in descending pathway led to disturbance in reflex
        - Stroke patients show continuous, overactive stretch reflex activity at all levels by cutaneous receptor stimulation
            - Stimulation by a motor (which the arm is placed into), however, healthy participants show reflex responses only at high velocities and there is alterations in reflex gain as larger response to stretch led to high reflex gain
        - Important for upper limb stability
            - Long latency response seen during the flexion of arm (Kurtzer et al., 2008)

- Muscle spindle = receptors
    - Proprioceptors for muscle length changes

- Intrafusal muscle fibres are attached at the end of extrafusal muscle fibres (that envelope it) and lie in parallel with muscle fibres
    - 

- Contains dynamic (bag) and static fibres (bag and chain)
    - Signal phasic and tonic aspects of muscle stretch
- Primary afferents = Ia
    - Large diameter
    - Arise from all intrafusal fibre types
- Secondary afferents = type II
    - Medium diameter
    - From **static** fibres
- Muscle spindle sensitivity is controlled by gamma efferent system
    - Smaller diameter than alpha motor efferent neurons
    - Corticomotor neurons (from somatosensory cortex) communicate with gamma neurons
    - Alpha-gamma coactivation allows the intrafusal fibres to contract along with the extrafusal fibres (which contracted due to alpha input) → muscle spindle stay taut and can continue to detect stretch
        - Static intrafusal fibres and dynamic intrafusal fibres both contract
    - 

Inverse Myotactic Reflex

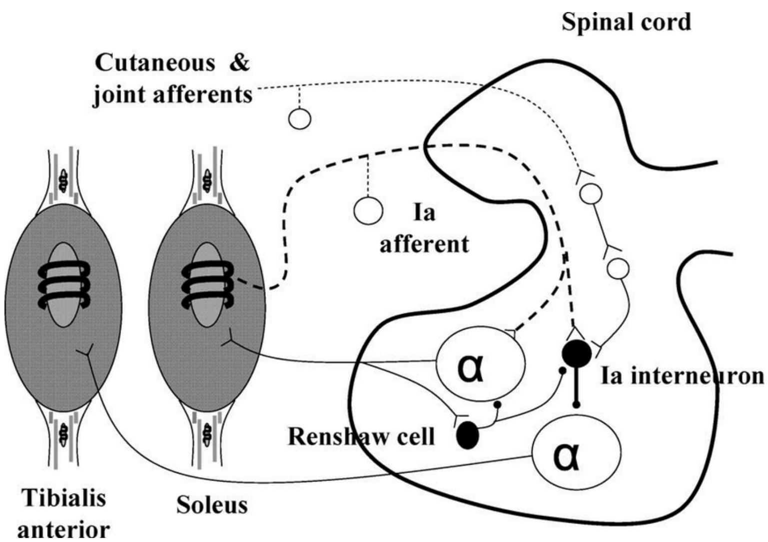
- Golgi tendon Organ (GTO) = receptors
  - Proprioceptors for tension
    - Signals variations in contractile force
    - Mechanoreceptors → stretch/tension → opening of ion channels and generation of AP
  - Encapsulated receptors which lie at junction between musclefibres and tendons (musculo-tendinous junction) → lie in series in the muscle
  - Primary afferents = 1b
    - Synapse onto 1 group of 1b interneurons that are inhibitory to homonymous, agonist (at least disynaptic) muscles that the afferent fibre arises from, which then synapse onto alpha motor neurons
    - Synapse onto other interneurons which are excitatory to antagonist muscles (disynaptic or trisynaptic)
      - Reciprocal excitation
  - Firing rate of 1b neuron is related to whole muscle force
    - Discharge rate signals force in a muscle
  - No mechanism to modulate sensitivity to tension unlike 1a afferent of muscle acitivity
  - **Activity of GTO is task dependent**
    - Nervous system can reverse the effect → reflex reversal
      - GTO becomes excitatory rather than inhibitory when it senses increased tension in the agonist muscle
        - Important for wa;lomg
    - During locomotion, action of 1b fibres on extensor motor neurons (which are homonymous/agonist muscles in this case) reversed from inhibition to excitation
      - During resting, stimualtion of 1b afferent fibres from ankle extensor muscles inhibits ankle extensor motor neurons through connection with inhibitory interneuon
      - During walking, 1b afferent send signals facilitated by descending signals to interneurons, opening a 1b excitatory pathway from GTO to extensor motor neurons, depressing inhibitory interneuron activity
- Mechanism
  - High levels of tension, 1b inhibitory interneuron drive (which suppresses agonist) becomes high enough to inhibit motor neurons
  - Agonist muscle relax

Flexion- Withdrawal and Crossed-Extensor Reflex

- Cutaenous receptors = receptors
- Polysynaptic
  - Takes longer to process input
- Crossed pathway = pathway corsses in spinal cord to opposite limb

- Mechanism of flexion withdrawal and crossed-extensor (when standing) reflex
    - Stimulated leg:
        - Excites motor neurons that innervate flexor muscle
            - Activation of flexor muscles = contraction
            - Pulling away
        - Inhibits motor neurons that innervates limb extensor
    - Other leg:
        - Inhibition of flexor muscle
        - Activation of extensor muscles
            - Counteracts the increased load caused by the stimulated leg pulling away
- Can be modulated according to posture and have been shown to be adaptable
    - Reflexes can be overridden voluntarily
        - Such as if the leg stepping on the noxious stimulus is holding the weight

Renshaw Circuit



- Inputs:
    - Excited by collaterals (side branches) of axons of alpha motor neurons
    - Receives input from descending pathways
- Outputs:
    - 1a inhbitory interneurons that synapse onto alpha motor neurons
        - Descending inputs adjust excitability of all motor neurons that contorl movement around a joint
    - Can inhibit motor neurons (including the motor neurons that excite them)
        - Influences the sensitivity of alpha motor neurons
        - **Negative feedback system**

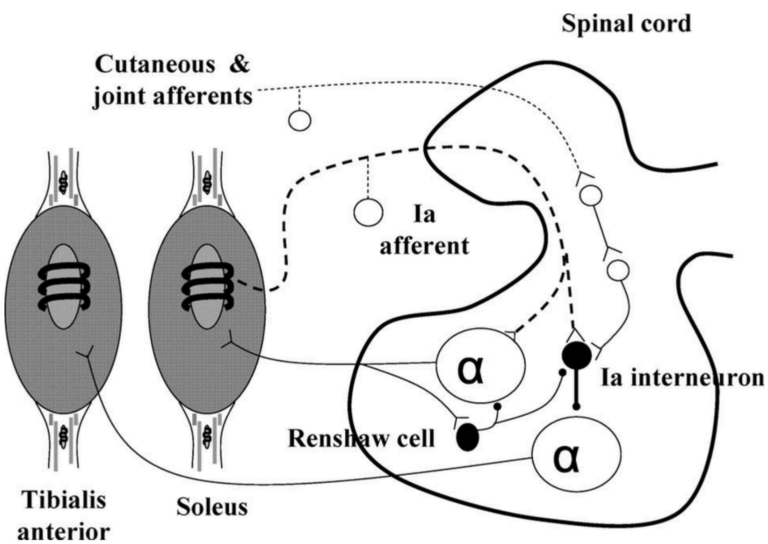
Help to stabilise motor neuron firing

Central Pattern Generators

Neural network in lumbar spinal cord
Modulated by descending commands from various supraspinal areas (e.g. from motor cortex)
Studies in cats prove their existence

Voluntary commands modulate reflex

Reciprocal Inhibition & Co-contraction



(Tiabialis = antagonist muscle in this case)

- Reciprocal inhibition is when the contraction of 1 muscles inhibits contraction in another
  - For example, in stretch reflex, the activation of agonist muscle will inhibit the contraction of the antagonistic muscle
  - By modulating the amount recirpocal inhitbion, both agonist and antagonist muscles can contract together = co-contraction
- 1a inhibitory interneuons regulates contraction in antagonist muscles in stretch reflex
- 1a inhibtiory interneurons receive descending inputs which can be both exitatory and inhibtiory
- Supraspinal centers modulate reciprocal inhibition of muscles and enable co-contraction by changing the balance of excitatory and inhibitory inputs onto the 1a inhibitory interneurons
  - Co-contraction of both agonist and antagonist muscles stiffens the joint and is useful for precision and joint stabilisation
    - For example: The elbow immediately before catching a ball
  - Controls relative amount of joint stiffness to meet requirements of motor act

Ascending Pathway

Dorsal column system

- Large diameter afferents → fast conduction velocity
- Light touch, vibration, proprioception and 2 point discrimination
- High degree of discrimination
    - No precision without dorsal column
- Crosses at brainstem level → ascend ipsilaterally until reaching brainstem

Spinothalamic System

- Smaller diameter afferents → slower conduction velocity
- Touch and pressure but less precise
    - Poor stimulus discrimination
- Temperature and noxious information
    - Lateral spinothalamic tract
        - Painful and thermal stimuli
    - Anterior spinothalamic tract
        - Crude touch and pressure changes
- Corss at level of spinal cord

Spinocerebellar tract (spinal cord to cerebellum)

- Proprioception
- Light and strong touch
- Ventral spinocerebellar tract decussates twice, terminate in ipsilateral cerebellum
- Others do not decussate and terminal in ipsilateral cerebellum

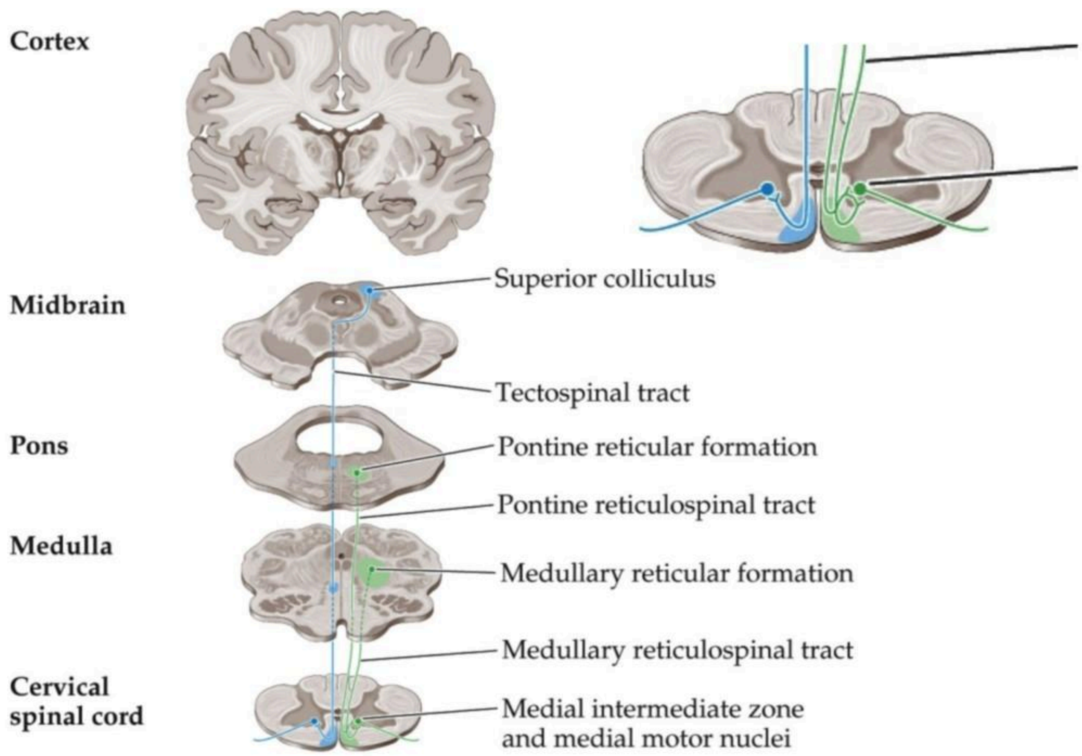
Desending Tracts

Brainstem tracts

Group A → ventomedial brainstem pathways Bilateral projections to the ventromedial part of intermediate zone of the spinal cord ● Reticulospinal ○ Extensive inputs from primary and premotor areas of both hemispheres, reticular formation nuclei and spinal afferents ○ Important for the recovery after lesions ■ (Lemon et al., 2019)	Group B → dorsolateral brainstem pathways Project contralaterally in the dorsolateral region of the intermediate zone of the spinal lcord ● Rubrospinal ○ Originates in red nucleus ○ Influences ongoing movements ○ Modulating flexor muscle tone

■ Considerably higher levels of reticulospinal excitation of forelimb flexor and hand motor neurons 6 months after unilateral pyramidal lesion ○ Ventral Retiulospinal tract ■ Arises from pontine reticular formation ■ Ipsilateral ■ Excitatory connections with extensors more than for flexors ■ Maintain posture ■ Less under direct cortical control although inputs from ipsilateral SMA/pre-motor vortex ■ Travels in ventromedial cord alongside the VST ○ Dorsal Reticulospinal Tract ■ Arises from medullary reticular formation ■ Greater amount of inhibitory input to spinal motorneurons/interneurons ■ Initiate locomotion via CPG ■ Travels in the dorsolateral funiculus of cord alongside CST ● Vestibulospinal ○ Medial VST ■ Arises from rostral part of descending vestibular nuclei ■ Bilateral to cervical levels especially upper body/neck ■ Stabilises head on body ■ Synapses both directly and via interneurons onto extensor motor neurons of axial muscles ● Activates extensor muscles ■ Can be slower than lateral VST	

○ Lateral VST ■ Arises from lateral vestibular nuclei ■ Highly branched innervation mostly via interneurons to motor neurons in cervical and lumbo-sacral levels ■ Excitatory to extensor muscles ■ Inhibitory to flexor muscles	



(E) **Tectospinal tract and reticulospinal tract**

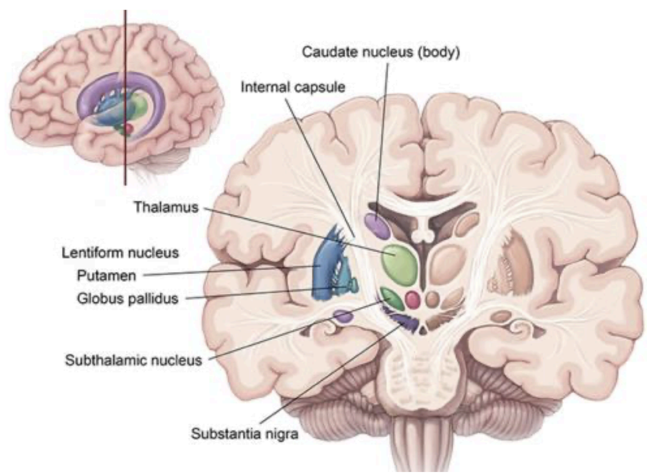
Corticospinal pathway

Propriospinal pathway → Connections between different levels of the spinal cord

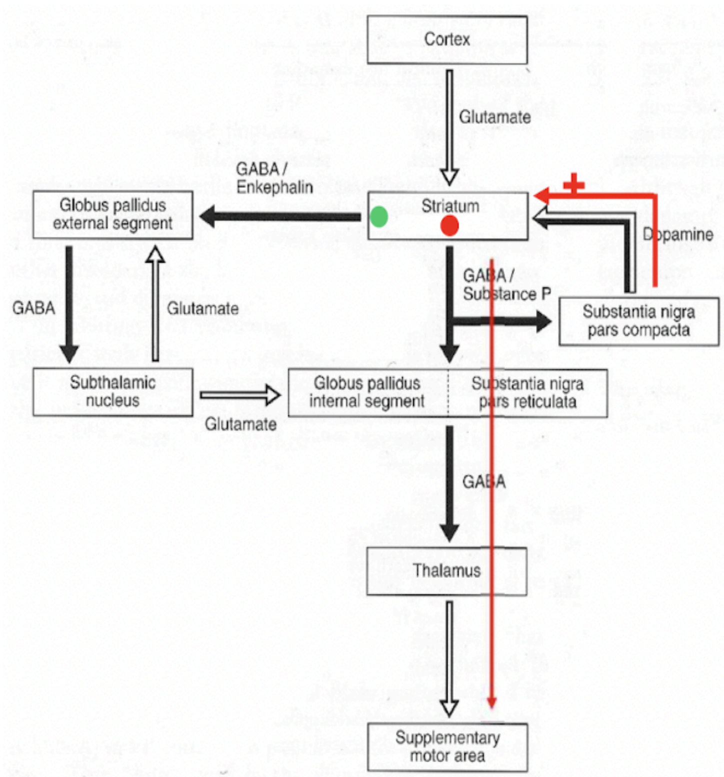
Basal Ganglia & Cerebellum

<u>Basal Ganglia</u>

- Basal Ganglia is comprised of:
  - Caudate nucleus
  - Lentiform nucleus
    - Putamen
    - Globus pallidus
      - Internal
      - External
  - Subthalamic nucleus (STN)
  - Substantia nigra (SN)
    - Pars compacta
    - Pars reticulata
- In rat/mouse the striatum is equivalent to caudate nucleus and putamen
  - Striatum: Caudate + Putamen

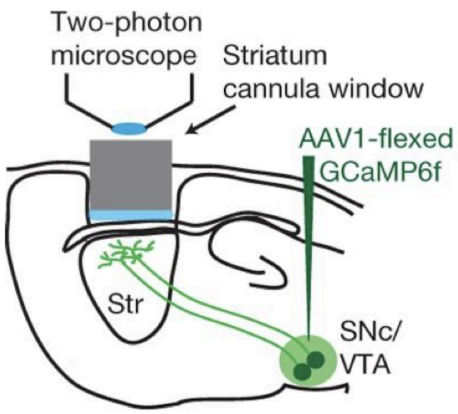


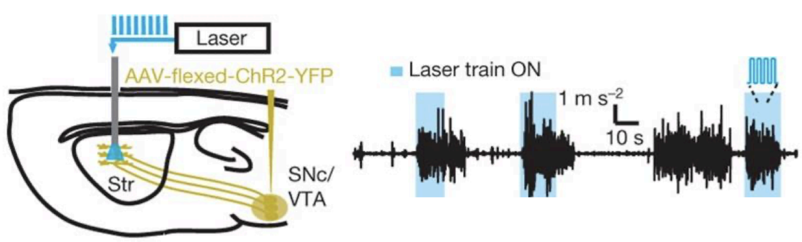
- Motor commands are sent from the cortex to the striatum
  - 90% of cortex motor commands sent to striatum (caudate + putamen)
  - Striaum is the main input structure of the basal ganglia
- Pathways
  - The primary output of the basal ganglia to the motor output areas is inhibitory
  - Main motor output areas = thalamus + cortex
  - Many neurons in the striatum respond to initiation and termination of motor programmes as cortex sends commands to striatum

- 

- Direct pathway → medium spiny neurons, inhibitory (GABA)
  - Inhibition of inhibitory control in SNr / GPi (Inhibition of inhibition = excitation)
  - Less inhibition to motor output areas
- Indirect pathway → medium spiny neurons, inhibitory (GABA)
  - Inhibition of GPe, resulting in less inhibition of STN which sends excitatory glutamatergic drive to SNr and GPi
  - More inhibition to motor output areas
- Hyperdirect pathway
  - Cortex input directly to STN
  - Stimulates STN (which sends excitatory glutamate output) leading to increased excitation of SNr / Gpi, hence more inhibition on motor output areas

- Dopaminergic neurons of SNc target striatum
  - DA is released to the striatum serve to promote movement and some in response to rewards
  - DA release from the SNc to the striatum promotes motor activity
  - Experiment (Howe and Domeback, 2016):
    - Virus selectively express genetically encoded calcium indicators target dopaminergic neurons in the SNc which sends its projection to the striatum
      - Calcium is very useful as a proxy for activity → can uses fluorescence to tell the level of activity
    - Remove cortex over striatum and put microscope over it to see what is going on in the striatum

        - Saw dopaminergic axons in striatum and can see when they are releasing dopamine into striatum
        - Bright light flashes when high levels of activity as calcium influx during high activity of neurons (indicating release of NT)
    - 

    - Association between movement and DA input (don't know causation)
    - Second part of experiment:
        - Channel rhodopsin 2 (light sensitive channel) is an optogenetics tool
            - Channel rhodopsin 2 is a cation channel, thus opening of channel rhodopsin 2 causes the neuron to depolarise and generate an action potential
                - Light shines → channel opens → cell fires
            - Optogenetics is a way of controlling activity of cell using light
        - Make dopaminergic neurons in the SNc expressed channel rhodopsin 2
        - When light turns on and the dopaminergic neurons fire, huge running activity observed from mouse
        - Dopamine important in driving movement
        - 

        - Laser shines light on channel rhodopsin 2 → channel opens, → movement recorded (activity shown on the right-hand side of the diagram)
- DA binds to D1 (excitatory, direct) or D2 receptors (inhibitory, indirect) on medium spiny neurons in the striatum
- Action selection
    - Direct pathway promotes movement
    - Indirect and hyper-direct suppress movements
    - Initiation of motor function is associated with **increased activity in both direct and indirect pathways** in the basal ganglia

- Action selection → promote appropriate actions (direct pathway) and suppress inappropriate actions (indirect and hyperdirect pathways) when motor function is needed
- Experiment (Cui et al., 2013)
  - Expressed calcium markers in D1 (direct pathway) or A2A receptor (indirect pathway)
  - Record activity in both pathway
  - Made mice to lever presses
  - Big increase in fluorescent in direct and indirect pathway when mouse goes to press lever

- Chunking
  - Basal ganglia involved in linking movements together
    - Allow for sequencing
  - Sequences of actions can become associated with each other forming routines
  - Experiment (Kalueff et al., 2016)
    - Lesions to dorsolateral striatum prevent mice from forming action sequences without disrupting individual movements
      - No complex connected set of movements, but can still perform individual movements
    - Plasticity in striatum is vital for sequence learning

Cerebellum

- Lesions to cerebellum affect balance, coordination and ability to learn new motor skills
- Major components:
  - Deep cerebellar nuclei
    - Interposed nuclei
      - Globose + eboliform
    - Dendate nucleus
    - Fastigial nucleus
    -