

Cerebellum and Basal Ganglia

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The cerebellum (Latin, little brain) makes up about 10% of the total brain volume, and contains approximately half the neurons. It influences behavior via interactions with other brain structures. Different cerebellar regions play an integral role in the control of various behaviors including voluntary limb movements, eye movements, balance, locomotion, and now even higher brain (cognitive) functions. This view is based on the anatomy of cerebellar afferent and efferent connections, neural recording, and lesion studies. It is also clear that the cerebellum exerts control over the flexibility of these behaviors; cerebellar integrity is critical for trial-and-error adaptation (motor learning) of motor behaviors to new contexts.

General architecture

The **cerebellar cortex** has many folds (folia- Latin, leaves) and is composed of 3 layers (deep → superficial: granule cell, Purkinje cell, and molecular layers). Deep in each cerebellar hemisphere are **cerebellar nuclei (medial → lateral: fastigius, globose/emboliform (*interpositus in monkey*), and dentate)**. All output from the cerebellum is via the deep cerebellar nuclei.

Grossly, the cerebellum can be divided into an **anterior**, **posterior**, and **flocculonodular lobe** (Figure 1). It can also be divided into **longitudinal subdivisions** (Figure 2), which are more useful when considering cerebellar function and lesion effects. The **vermis** is the midline portion of the cerebellum, the **intermediate zones (paravermis)** are just lateral to each side of the vermis, and the **lateral hemispheres** are the largest and most lateral regions.

Cerebellar peduncles—axons projecting into and out of the cerebellum do so through the 3 cerebellar peduncles. **Inferior cerebellar peduncle (restiform body)** afferent: dorsal spinocerebellar, vestibulocerebellar, reticulocerebellar, & olivocerebellar efferent: cerebellar-vestibular and cerebellar reticular. **Middle cerebellar peduncle (brachium pontis)** afferent only: pontocerebellar. **Superior cerebellar peduncle (brachium conjunctivum)** afferent: small amount from the ventral spinocerebellar efferent: info goes to the contralateral thalamus (then to cortex) and to the contralateral red nucleus.

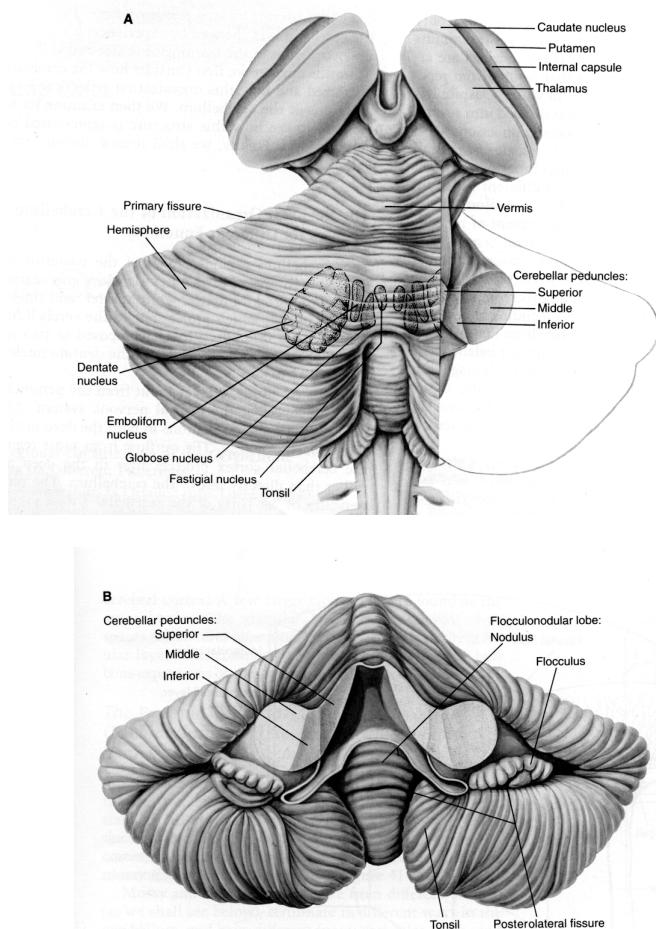


Figure 1. Dorsal (top) and ventral (bottom) views of the cerebellum. From Kandel, Schwartz and Jessell. 3rd Ed.

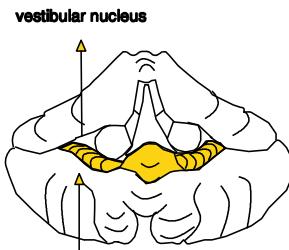
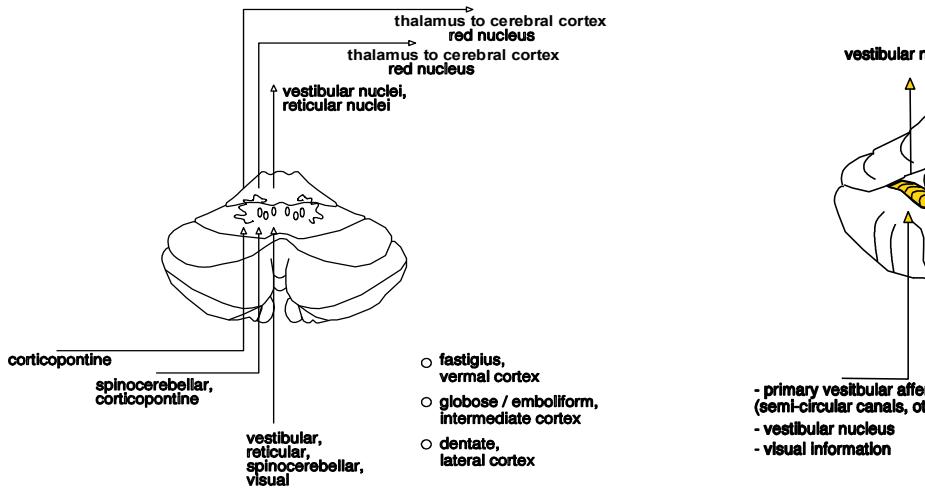


Figure 2
longitudinal
cerebellar zones.

Vermis (spinocerebellum). Input: dorsal spinocerebellar tract (proprioception), ventral spinocerebellar tract (state of spinal interneurons), brainstem nuclei (vestibular and reticular nuclei), visual signals (pontine nuclei). Output: via fastigius nuclei to bilateral vestibular and reticular nuclei, sparse spinal projections, sparse projections to contralateral cerebral motor areas (via contralateral thalamus). The vermis is important for control of some types of eye movements, postural stability, and locomotion.

Intermediate zone (spinocerebellum). Input: dorsal and ventral spinocerebellar tracts (proprioception, state of spinal interneurons, respectively). Corticopontine input (cerebral cortex → pontine nuclei → cerebellum), carrying somatosensory and motor information. Output: via globose and emboliform nuclei to the contralateral red nucleus and cerebral motor areas (via thalamus). The intermediate zone of the cerebellum therefore receives information about motor commands and sensory consequences of movement. One idea is that it acts as a comparator (actual vs. intended movement) and makes the appropriate corrections during movements. Another idea is that it can alter muscle spindle sensitivity by changing gamma motor neuron drive, which would alter reflex gains. Damage could impair this control and ultimately result in tremor.

Lateral zone (pontocerebellum). Input: corticopontine input from higher order cerebral cortical areas (e.g. premotor, visual, sensory, prefrontal). Output: via dentate nucleus to the contralateral red nucleus and cerebral motor and non-motor areas (via thalamus). The lateral zone of the cerebellum communicates with classical motor areas of cortex, but also non-motor regions such as the prefrontal and parietal cortex.

Vestibulocerebellum. Input: primary afferents from the vestibular ganglion (driven by stimulation of the vestibular apparatus), other vestibular inputs from second-order neurons in the vestibular nuclei, visual input via the pontine nuclei. Output: via vestibular nuclei, 1) medial vestibular nuclei to control head and eye movements and 2) lateral vestibular nuclei to control axial musculature and extensor muscles for postural control against gravity (upright stance).

Deep Nuclei

Somatotopy. Each deep cerebellar nucleus appears to have a separate somatotopic representation of the body (Figure 3). The

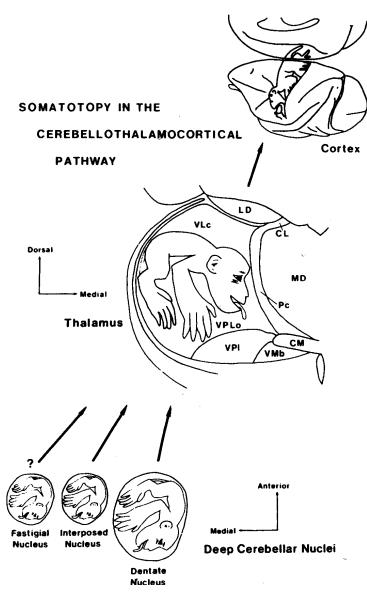


Figure 3. Somatotopy in the deep cerebellar nuclei, from Thach et al. 1992.

head is represented caudal, tail rostral, trunk lateral, and extremities medial.

Physiology. In the absence of movement, DCN fire at high, maintained rates (40-50 Hz). During movement, firing rates increase and decrease above and below their baseline. Through this activity, the cerebellum modulates its target structures, presumably to help maintain optimum sensitivity to their other inputs. In addition, increases in cerebellar nuclear firing rate precede and help to increase the discharge frequency in its target structures, thus helping to initiate movement. There is also evidence that the cerebellum combines the functions resident in the “downstream” motor structures into new or novel combinations.

Single unit recordings done in the **fastigius** relate to eye movements, control of head orientation and control of musculature activity during stance and gait. Fastigius activity modulates with the step cycle during walking. Cerebellar damage can disrupt how brainstem structures (vestibular and reticular nuclei) modulate during walking.

Single unit recordings done in the intermediate zone of cerebellar cortex and **interpositus** nucleus have shown firing in relation to the antagonist muscle group being used. When a holding position is suddenly perturbed, there is a reflex movement that returns the perturbed part to the hold position. Neurons in the interpositus fire when the holding position is perturbed, and in doing so appear to control the antagonist muscle that ‘checks’ the return movement to the prior hold position. Interpositus neurons have also been shown to modulate in relation to sensory feedback including that from tremor accompanying movement

Activity in the **dentate** nucleus precedes the onset of movement and may also precede motor cortex cell activity (Figure 4). Dentate cells preferentially fire at the onset of movements that are triggered by mental associations with either visual or auditory stimuli.

Both **dentate** and **interpositus** activity are relate more to movements involving multiple joints than movements involving single joints. Neither the dentate nor the interpositus codes exclusively for any specific parameter (velocity, amplitude, duration). The dentate plays a role in initiating movements requiring a mental interpretation of the visual or auditory signal, and both the dentate and interpositus are more active during multi-jointed movements.

Cerebellar cortical circuitry

Cell types. There are 5 cell types in the cortex (granule (+), Golgi (-), Purkinje (-), stellate (-), basket (-)).

Afferents. Cerebellar inputs from different brain and spinal cord structures are called **mossy fibers**. They

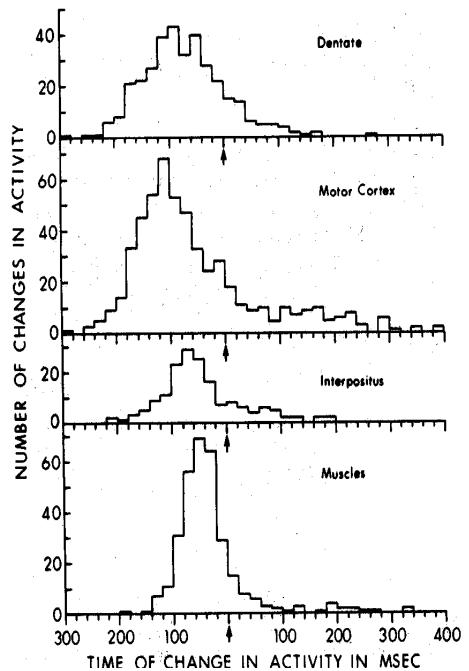
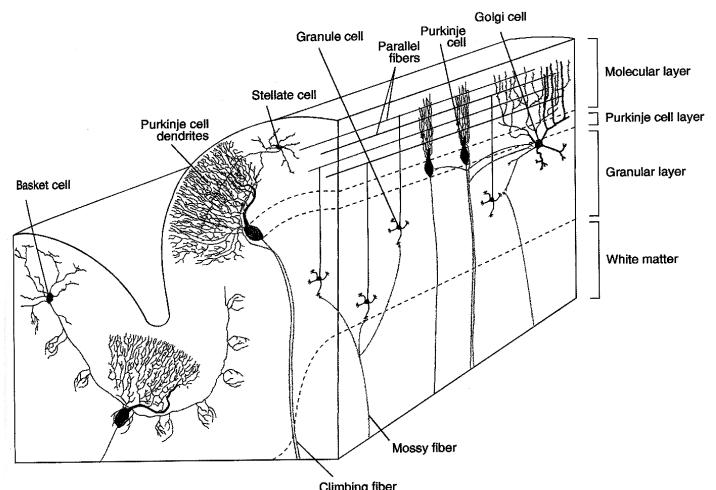


Figure 4. Time of change of activity relative to a light triggering stimuli. From Thach 1978.



excite the deep nuclei and also granule cells (which, in turn, excite Purkinje cells). **Climbing fibers** originate from a brainstem structure called the inferior olive. They excite the deep nuclei, and also make multiple contacts on Purkinje cells. Each Purkinje cell receives only one climbing fiber input. Each climbing fiber branches to innervate ~ 10 Purkinje cells.

Simple and complex spikes. Purkinje cell **simple spike** activity occurs at high spontaneous rates, even if an animal is at rest. Simple spike activity is driven by mossy fiber inputs to granule cells. This activity sets the moment-to-moment firing rate of Purkinje cells important for control of movement. Purkinje cell **complex spike** activity occurs at very low rates (1-3 Hz), and is driven by climbing fibers.

Physiology. Purkinje cell **simple spike** firing in the **vermis** modulates with the step cycle during walking. Simple spike firing in the **intermediate zone** can be related to the pattern of muscle activity. Activity in the **intermediate and lateral zones** has been shown to relate to movement direction and velocity. Tuning of simple spike activity in cerebellar Purkinje cells for direction is much more variable than that in motor cortex.

Complex spike firing rates are thought to be too slow to convey ongoing information about specific movement parameters. Instead, they are thought to be important for motor learning, serving as a teaching (Marr 1969) or error (Albus 1971) signal that adjusts Purkinje cell responsiveness to parallel fiber inputs via long term depression (Ito 1989, 2001; Hansel et al. 2001). Studies in monkeys have shown complex spike activity during limb movements to be related to errors in resisting a perturbation (Gilbert and Thach, 1977), reach endpoint error (Kitazawa et al. 1998), and errors in velocity of an arm movement (Ojakangas and Ebner 1994).

Cerebellar cortex: motor learning.

The cerebellum is considered to be one of the more ‘plastic’ structures in the brain. In cerebellar cortex, Purkinje cells undergo long-term depression (LTD) in response to paired parallel fiber-climbing fiber inputs. The simple circuit in Figure 7 shows the important cellular components for LTD: Purkinje cells, climbing fibers and granule cell parallel fibers. Paired activation of climbing fibers and parallel fibers causes LTD of the parallel fiber-Purkinje cell synapse. This results in decreased firing of the Purkinje cell, causing increased firing of the deep cerebellar nuclei (DCN) cells.

How could this account for learning of a new movement? An example linking this mechanism to behavior is the study of eye-blink conditioning. Eye-blink conditioning is a form of associative learning where animals are exposed to a conditioned



Figure 6. Recording of simple and complex spikes from a Purkinje cell. Thach, 1968.

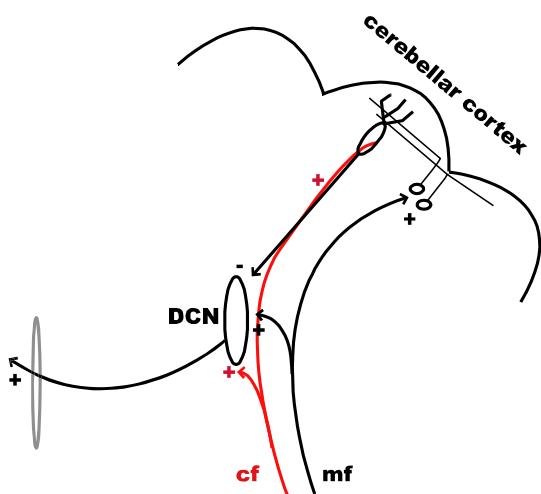


Figure 7. Simple circuit

stimulus (e.g. a tone) followed by an unconditioned stimulus (e.g. small shock to the eye, causing it to blink). Initially, animals blink with the stimulus. However, with repeated exposure, animals start to blink when the tone sounds (this is the conditioned response).

In the cerebellar cortex, mossy fibers carry information about the conditioned stimulus (tone) and climbing fibers are activated by the unconditioned stimulus (shock). Climbing fiber activity causes LTD of the parallel fiber synapses carrying information from the tone. This reduces Purkinje cell output (inhibitory) to the deep cerebellar nuclei, and the eye-blink is then driven by the tone. Importantly, inactivation of the interpositus nucleus (via muscimol, a GABA A receptor agonist) disrupts this conditioning.

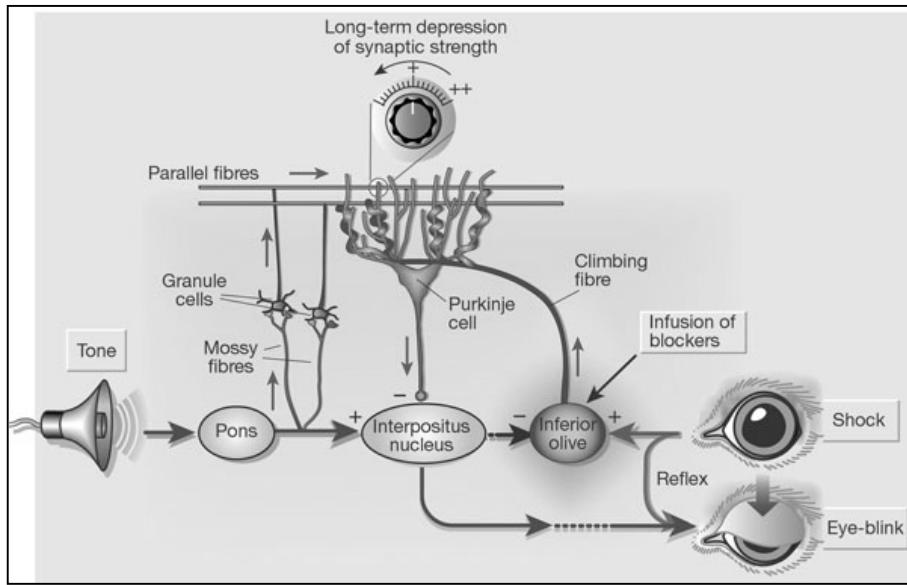


Figure 8. Schematic of cerebellar circuitry involved in eye-blink conditioning.
From Kitazawa, 2002.

Lesion / inactivation studies.

Vermis/fastigius. Ablations done in the nucleus fastigius in cat and monkey have been shown to dramatically impair movements requiring control of equilibrium, like unsupported sitting, stance and gait. Animals with acute lesions tend to fall to the side of the damage. Longitudinal splitting of the cerebellum at midline also gives rise to very significant and long lasting disturbances of equilibrium. In humans, it has been shown that lesions in the vermal and intermediate zones of the anterior lobe preferentially impair movements requiring equilibrium control. These data suggest that fastigius may be preferentially involved in movements like gait and stance.



Figure 9. Deficits observed after inactivation of the fastigius (left), interpositus (middle), and dentate (right). From Thach et al. 1992.

Intermediate cortex/interpositus. Ablations of the nucleus interpositus in monkeys causes tremor. Thus the interpositus in monkeys might be most concerned with the balance of agonist-antagonist muscle activity of the limb as it moves. It has been speculated that the interpositus normally uses abundant afferent input from the periphery and to send predictive signals that will decrease alternating stretch reflexes that cause limb oscillation. Others have proposed that the interpositus plays also plays a more prominent role in the coordination of forelimb movements. Inactivations in the anterior versus posterior the interpositus differentially disrupt grasping and reaching movements, respectively (Mason et al. 1998). They propose that the anterior and posterior interpositus are involved in coordinating distal and proximal musculature together.

Dentate. Lesions of dentate produce a slight delay in reaction time of the movement when triggered by light or sound. In single jointed movements, dentate ablation has been reported to cause monkeys to overshoot very slightly (Thach et al. 1992) or moderately (Flament and Hore 1986). In studies of monkeys making unconstrained multijointed movements, dentate inactivation resulted in profoundly impaired reaching patterns with abnormally increased angulation of the shoulder and elbow and excessive overshoot of the target (Thach et al. 1992b). Dentate inactivation also caused poor finger dexterity. In sum, dentate ablation profoundly impairs movements requiring coordination of multiple joints to a greater extent than deficits observed in single jointed movements. Further, inactivation of the dentate nucleus also causes slight impairment of the initiation of movements that are triggered by vision or mental percepts. The dentate may facilitate motor cortical cells, particularly for movements triggered teleceptively.

Humans: Cerebellar signs.

In the early 1900's, Gordon Holmes made some of the most detailed descriptions of the movement deficits associated with discrete cerebellar lesions caused by gunshot wounds. These descriptions are still considered to be the fundamental basis for our understanding of clinical cerebellar syndromes. Based on Holmes's work, the clinical manifestations of cerebellar disease can be divided into basic deficits. All of these deficits may be reliably attributed to cerebellar disease if and only if there is normal strength and somesthesia. This is because similar symptoms may arise from damage to peripheral nerves, corticospinal motor and lemniscal-thalamo-cortical sensory systems.

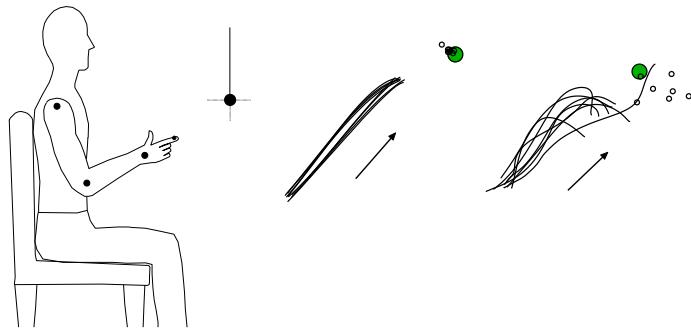
1) Ataxia is term that globally incorporates any incoordination between movements of body parts in cerebellar disease. Ataxia is often used in reference to gait or movement of a specific body part (ie ataxic arm movements).

2) Dysmetria refers to the inability to make a movement of the appropriate distance. **Hypometria** consists of undershooting a target and **hypermetria** consists of overshooting a target. People with cerebellar damage tend to make hypermetric movements when they move rapidly and hypometric movements when they move more slowly and wish to be accurate.

3) Dysdiadochokinesia is an inability to make rapid, alternation movements of a limb, and appears to reflect abnormal agonist-antagonist control.

4) Asynergia refers to an inability to combine the movements of individual limb segments into a coordinated multi-segmental movement.

Recall from physiology that cells in the interpositus and dentate sometimes relate better to more natural multi-jointed movements as compared to instrumented single jointed movements (e.g. flex the wrist). Inactivation of the dentate also causes greatest ataxia in multi-jointed movements, with smaller deficits in single jointed movements. Why are these movement types different? Multi-jointed movements are mechanically more complicated than single jointed movements. When multiple joints are moved together, there are additional forces called interaction torques that must be predicted and adjusted for, in order to generate a normal movement. Interaction torques are generated at one joint when there is movement of a segment linked to it. Cerebellar patients have an inability to compensate for interactive torques generated during multijointed movements. Because of this, their movements can become dominated by the interaction torques and will appear ataxic and inaccurate. Thus it has been proposed that a major function of the lateral cerebellum is to generate predictive and feedback based corrections that are used to compensate for extraneous forces generated by one's own body movements.



5) Hypotonia or abnormally decreased muscle tone manifests as a decreased resistance to passive movement, so that a limb swings freely upon external perturbation. Often, hypotonia is either present only during the acute phase of cerebellar disease or not present at all.

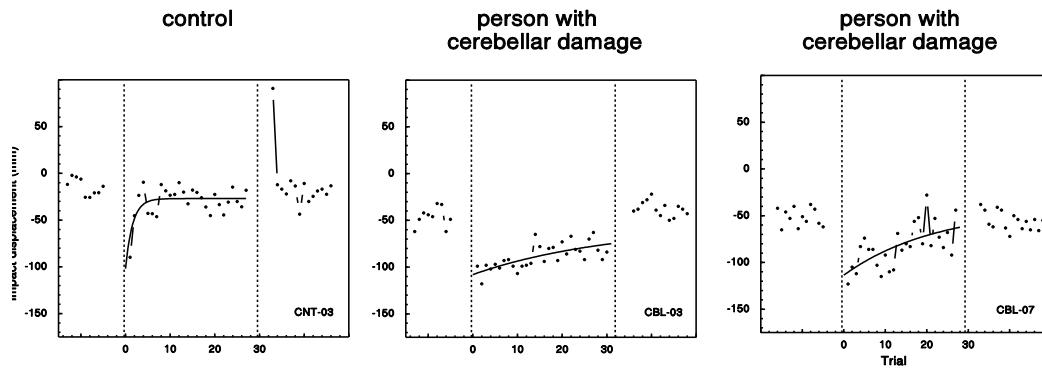
6) Nystagmus is an involuntary and rhythmic eye movement that usually consists of a slow and fast phase. In a unilateral cerebellar lesion, the fast phase of nystagmus is towards the side of the lesion.

7) Action or intention tremor is an involuntary oscillation that occurs **during movement** and disappears when the limb is at rest. Cerebellar action tremor is generally high amplitude and low frequency (3-5 Hz). **Titubation** refers to tremor of the entire trunk during stance and gait. Finally, lesions of cerebellar target structures (red nucleus, thalamus) often result in **cerebellar outflow tremor** or **postural tremor**. Postural tremor is most prominent when the limb is actively held in a static posture, attenuates during movement, and disappears when the limb is at rest.

Motor learning in humans with cerebellar damage.

Physiology suggests that the cerebellum might be important for learning movement through trial-and-error practice. If this is true, then people with cerebellar damage should have difficulty learning / adapting movements with practice. Many studies have shown that this is the case—**cerebellar patients are slow to adapt movement to novel contexts and often do not store the**

effect of short-term training. Examples of tasks that cerebellar patients have been shown to have difficulty learning include: visuomotor adaptation to prism glasses, adaptation to novel forces or loads with the arms, adaptation to perturbations during standing, eye-blink conditioning, adaptation of the vestibulo-ocular reflex, and adaptation during walking to novel situations (rotating treadmill, split belt treadmill). All of these paradigms require practice dependent (error based) learning, information from multiple segments or parts of the body, and use of sensory inputs from one or more modality (vision, vestibular, somatosensory). Clearly, if patients have difficulty learning movements through practice, then this might complicate attempts to improve their movement via rehabilitation training. However, no studies have addressed whether long-term training of a specific movement can alter performance in people with cerebellar damage.



Is the cerebellum involved in cognitive processes?

Until recently, the cerebellum was thought to contribute only to generation of movement. This belief was predominant because 1) cerebellar projections had only been traced to motor areas and 2) cerebellar lesions in humans seemed to cause only motor and no cognitive deficits. This view of the cerebellum has recently changed. Evidence for cerebellar contributions to cognition has been acquired through sophisticated anatomical techniques, human brain imaging, and lesion studies.

Initial suggestions that the human cerebellum participates in cognition were based on anatomic connections thought to exist due to the parallel expansions of the frontal lobe, the lateral cerebellum, and the dentate nucleus. It is now known that the lateral cerebellum receives input from not only motor and premotor areas, but from parietal, temporal and prefrontal cortex. It is now also known that the dentate nucleus projects to non-motor areas of the brain such as the prefrontal and parietal cortex.

Studies done using functional neuroimaging have provided evidence that the cerebellum participates in some types of cognitive functions. For example, right lateral cerebellar activations occur during practice of a language task where subjects were asked to generate appropriate verbs for visually presented nouns. The cerebellum was not activated when the nouns were simply read, indicating that cerebellum somehow contributed to the generation of the appropriate verb. Interestingly, once the verb generation task was well practiced, cerebellar activation diminished.

During a pegboard puzzle, the dentate was activated bilaterally and this activation was three to four times greater than during the simple peg movements. These studies illustrate the fact that the lateral cerebellum and dentate nucleus can contribute to complex tasks above the levels that would be expected to account for movement alone.

Behavioral studies of humans with cerebellar damage also suggest that the cerebellum participates in aspects of cognition. Cerebellar patients have largely been found to have normal IQs, but show other abnormalities on specific tasks, including a verb generation language task as well as a timing perception and production task. They can show abnormal planning, set-shifting, verbal fluency, abstract reasoning and working memory. Cerebellar patients may also have difficulty with spatial cognition including visual-spatial organization and memory. Some have been reported to have personality change with blunting of affect or disinhibited and inappropriate behaviour.

Basal Ganglia

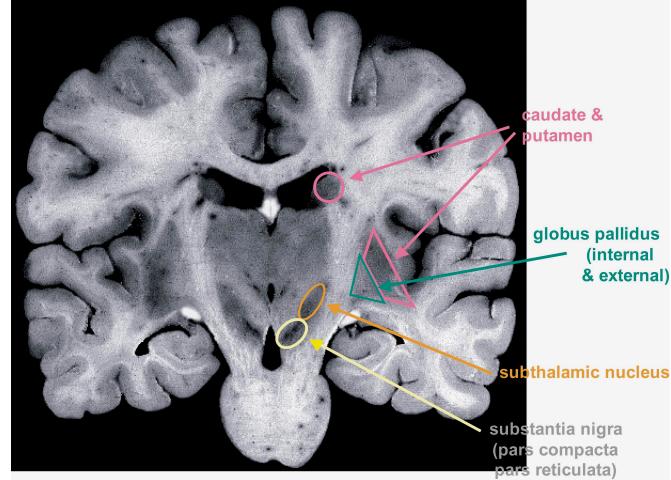
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The basal ganglia are composed of masses of neurons (nuclei) located base of the cerebrum. These nuclei receive excitatory input from the thalamus and from the cerebral cortex. **Output of the basal ganglia is inhibitory (GABA). The basal ganglia have no direct spinal projections- they influence movement control through projections back to cerebral cortex.**

Basic Anatomy of the Basal Ganglia

Five nuclei comprise the basal ganglia. The **caudate** and **putamen** developed from the same telencephalic structures and are composed of identical cell types. Functionally they are the same structure, though separated by the internal capsule. They are often referred collectively as the striatum and are the input nuclei of the basal ganglia. The caudate receives input related to eye movements and cognitive processes. The putamen receives input related to body movements. There are neurochemically

specialized compartments of the striatum called **striasomes** and **matrix**. Limbic projections terminate in the striasomes, and striasomes project to the SNpc dopameric cells. Cortical projections concerned with sensation and movement terminate in the matrix. The matrix projects to the pallidum and to the SNpr and is thought to mediate information critical for motor and cognitive behavior.



The **globus pallidus** is a structure that has two distinct subdivisions. It lies medial to the putamen and lateral to the internal capsule. The **internal segment (GPi)** is an output structure for the basal ganglia circuit. The **external segment (GPe)** is not an output structure, but is part of the basal ganglia circuit

The **subthalamic nucleus (STN)** lies below the thalamus at the junction with the midbrain. It acts as an input structure (receiving information from cortex) and other basal ganglia nuclei.

The **substantia nigra** lies in the midbrain and is divided into two zones. The **pars reticulata (SNpr)** is the ventral pale zone that cytologically resembles the globus pallidus. SNpr (like GPi) is an output nucleus of the basal ganglia, though more concerned with eye and face movements (whereas GPi is more concerned with body movements). SNpr and GPi can be considered functionally the same structure. The **pars compacta (SNpc)** is the dorsal darkly pigmented zone that contains dopameric cells whose bodies contain neuromelanin. The SNpc exerts a modulating influence (via dopamine) on the striatum.

The **general input-output structure of the basal ganglia** is as follows: cortical information (from all regions of cerebral cortex, except primary visual and auditory cortex) is sent to the striatum. Processing is done in the basal ganglia circuit and then output is sent via the GPi and/or SNpr back to the cortex (via thalamus).

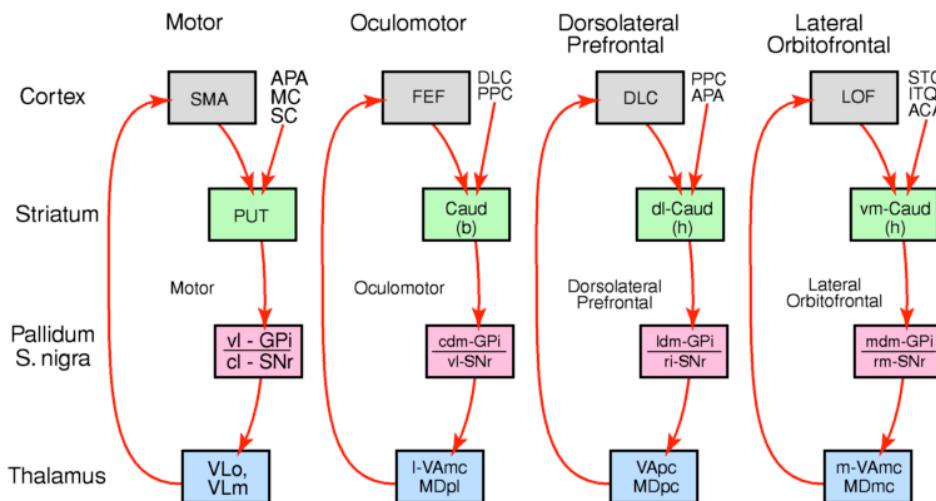
Based on anatomical studies, we now know that there are separate circuits or loops that go through the basal ganglia:

For the **motor circuit**, sensorimotor areas (e.g. SMA, premotor cortex, primary motor cortex, sensory cortex) project to the putamen. Output is primarily via GPi back to those motor areas.

For the **oculomotor circuit**, frontal eye fields project to the body of the caudate. Output is primarily via the SNpr, which then projects to the superior colliculus and the frontal eye fields via thalamus. This is involved in the control of saccades.

For the **dorsolateral prefrontal circuit**, the dorsolateral prefrontal cortex (and other association areas) project to the dorsolateral head of the caudate. Output is via GPi and SNpr, which project back to the dorsolateral prefrontal cortex via thalamus. This might be involved in aspects of memory concerned with orientation in space.

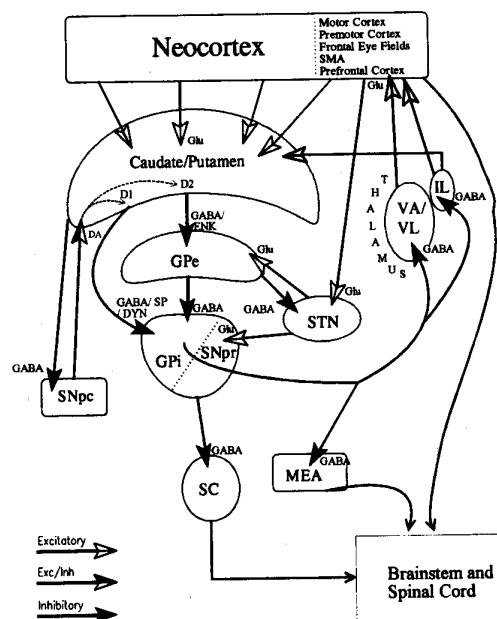
The **lateral orbitofrontal circuit** links lateral orbitofrontal cortex with the ventromedial caudate. It is thought to mediate changes in behavioral set.



We will focus on the motor and oculomotor circuits in this lecture.

Direct and indirect pathways through the basal ganglia.

A schematic of all of the basal ganglia projections is shown to the right. However, we will consider a simple circuit depicted below. Black arrows are inhibitory and white arrows are excitatory. The dopaminergic projection from SNpc to the striatum is excitatory or



inhibitory depending upon the dopamine receptor type in the striatum.

The **direct pathway** is the pathway from cerebral cortex → striatum → GPi/SNpr → thalamus → cerebral cortex. The direct pathway acts to inhibit the basal ganglia output nuclei (GPi/SNpr). This results in disinhibition of the thalamus.

The **indirect pathway** is a sort of side loop from cerebral cortex → striatum → GPe → STN → GPi/SNpr → thalamus → cerebral cortex. The indirect pathway acts to excite the basal ganglia output nuclei (GPi/SNpr). This results in inhibition of the thalamus.

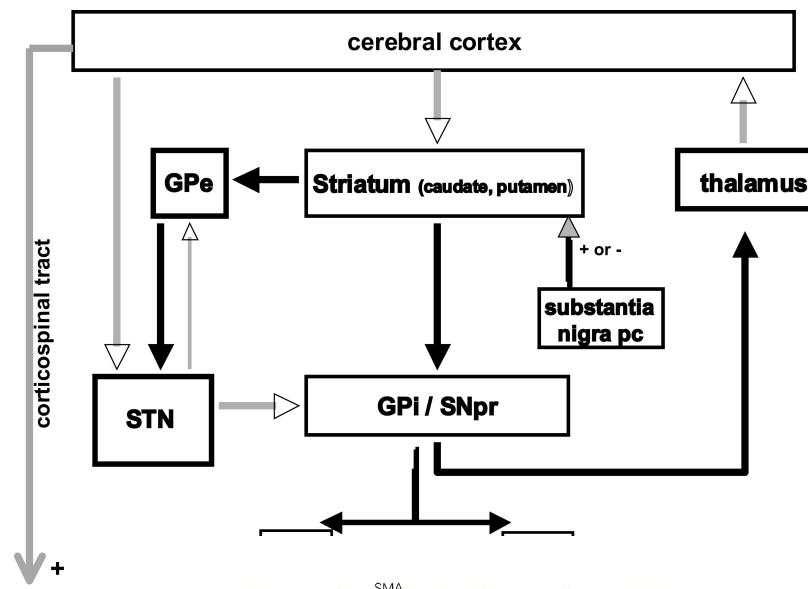
Note: there is also a direct projection from cerebral cortex → STN → GPi/SNpr. However, when people refer to the 'direct pathway', they mean that which goes through the striatum.

The action of dopamine on neurons in the striatum appears to be modulatory. Medium spiny neurons in the striatum (cells that receive dopamine inputs) can have different types of dopamine receptors (D1 & D2—note that there are more receptor subtypes, but we will consider only these two for simplicity). Dopamine excites striatal neurons with D1 receptors- these striatal neurons tend to project along the direct pathway. Dopamine inhibits striatal neurons with D2 receptors- these striatal neurons tend to project along the indirect pathway.

One idea is that the firing rate of the GPi/SNpr is the critical variable that explains abnormalities in movement associated with basal ganglia pathology. Thus, there must be some ideal/appropriate balance of excitation from the indirect pathway and inhibition from the direct pathway. **However, there are some significant inconsistencies in this theory. We will consider those in a later section.**

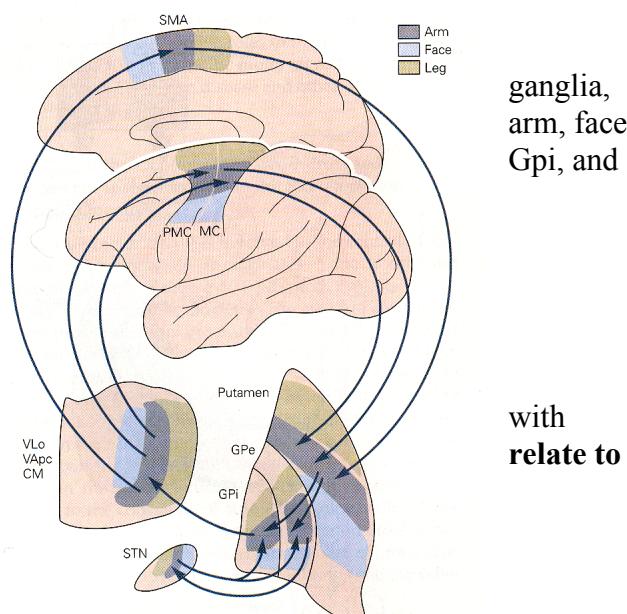
Mapping in the basal ganglia.

There is a rough somatotopic map in the basal ganglia with separate areas of representation for the arm and leg. This is true of the putamen, GPe, and STN.

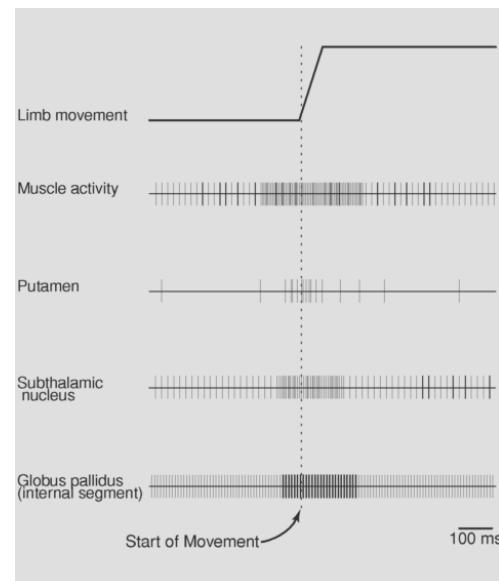


Some physiology

Neuron activity in the basal ganglia modulates movement, though it **does not systematically**



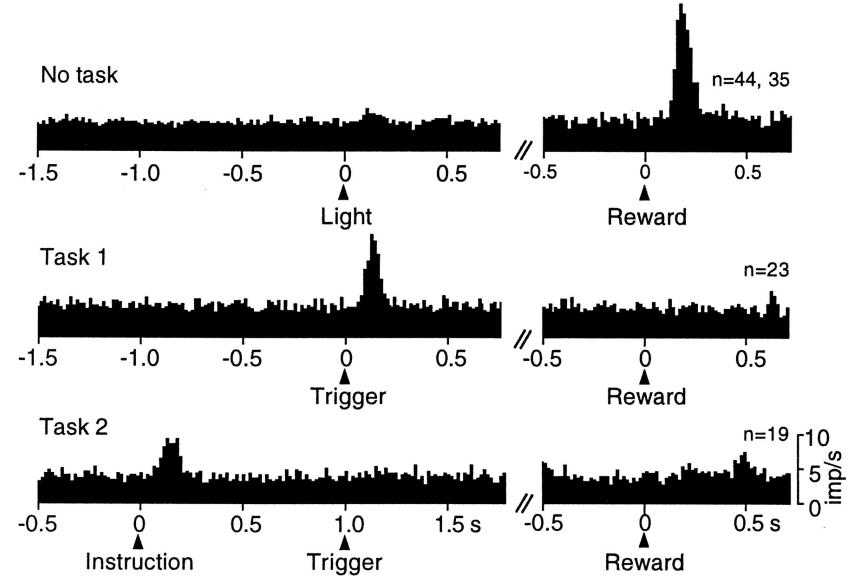
a single movement parameter (e.g. direction, force). Also, **activity in the basal ganglia (e.g. GPi) often occurs late (i.e. after the onset of muscle activity).** This suggests that the role of the basal ganglia is not in initiating movement, but may be involved in something else. One suggestion has been that, **since basal ganglia output is inhibitory and since it occurs late, then it could be acting to inhibit unwanted muscle activity that could oppose the desired movement.** This function would be of great importance during sequences of movement (where. It is known that neurons in the globus pallidus show activity related to specific portions of a sequence (Mushiake and Strick 1995). They speculated that an ensemble of GP neurons with phase-specific responses could be used to encode the detailed spatio-temporal characteristics of a sequential movement.



Neurons in the SNpc (that use dopamine as their neurotransmitter) normally fire at a very low rate (2 Hz). They don't appear to signal movement parameters and have no apparent somatotopy. **These neurons may signal behavioral relevance and reward—may help “learn associations.”** **SNpc activity also can change the sensitivity of striatal neurons to cortical inputs for a specific behavioral context.**

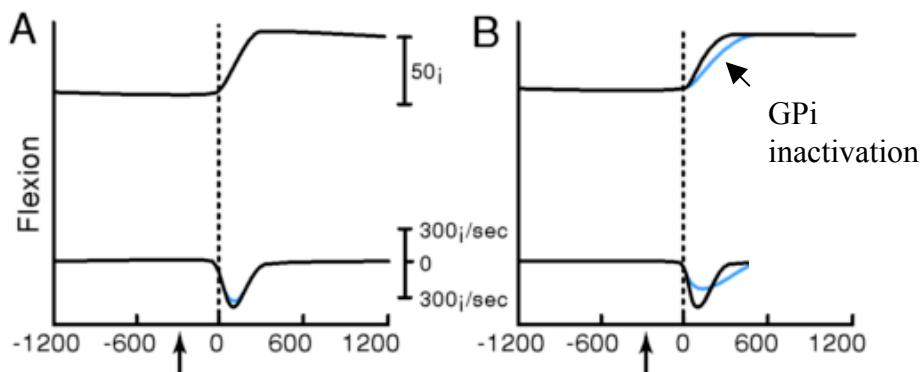
In a study from Schulz et al. (1995), it was found that **SNpc neurons fire in relation to reward and stimuli that predict the availability of reward.** The following figure shows the average discharge of multiple SNpc neurons. No task refers to the task before training (reach out and get a food reward)—SNpc neurons respond to the delivery of the reward. In Task 1 (after training), SCpc neurons respond to a trigger stimulus that tells the monkey that it can reach into a well for food. Task 2 is another trained task.

SNpc neurons respond to an instruction that tells the monkey to move when the trigger stimulus occurs. Thus, SNpc neurons respond to the earliest cue that predicts that the monkey will get a reward.

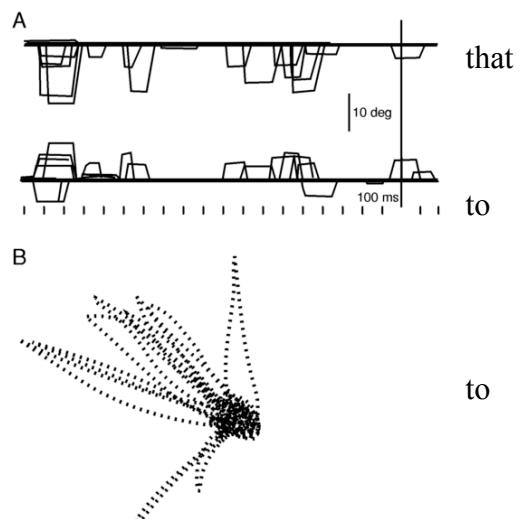


Lesion studies

Using muscimol to inactivate output nuclei of the basal ganglia causes specific deficits. Mink and Thach (1991) trained monkeys to make a wrist movement moving against a load (figure A below, requiring the monkey to turn a muscle on to make the movement) or with a load (figure B below, requiring the monkey to turn a muscle off to make the movement). When they inactivate GPi, they found that monkeys had more trouble making the movements where they had to turn off the muscle activity. This is consistent with the idea that the basal ganglia help to inhibit muscle activity.



In a classic study, Hikosaka and Wurtz (1985) showed inactivation of the SNpr (recall, this is the output nuclei concerned with eye movements) caused monkeys to be unable to maintain fixation of gaze because of involuntary contractions of the eye muscles. This is due disinhibition of the superior colliculus. The figure to the right shows (A) eye position traces (vertical and horizontal versus time) and (B) the trajectory of the involuntary eye movements in a monkey after muscimol injection in the lateral SNpr. The monkey was attempting to maintain gaze fixation on the central dot.



Short summary

Basal Ganglia function:

- contralateral control via cortex; bilateral control via brainstem.
- inhibition of unwanted movement and facilitation of desired movement.
 - selection of motor pattern.
 - switching from one movement to another.
 - dopamine reinforcement- signal reward?

Human pathology

Lesions of the basal ganglia cause hyperkinetic or hypokinetic movement disorders.

Characteristic movements:

Hyperkinetic

athetosis- slow writhing movements of the fingers and hands and feet at times.

chorea- abrupt movement of the limbs and facial muscles

ballism- violent involuntary flailing movements.

Hypokinetic

akinesia- inability to initiate mvmt, frozen.

bradykinesia- slowed movements.

rigidity- co-contraction of muscles around a joint.

postural instability- reduced postural reflexes.

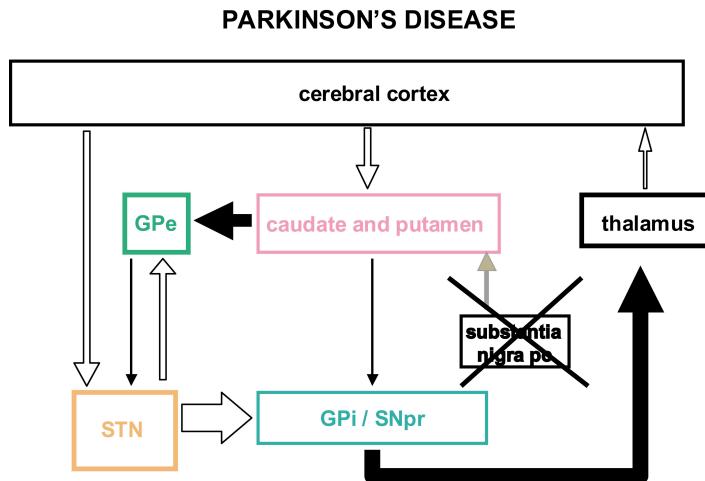
Other

dystonia- persistent posture of a body part which may distort the body.

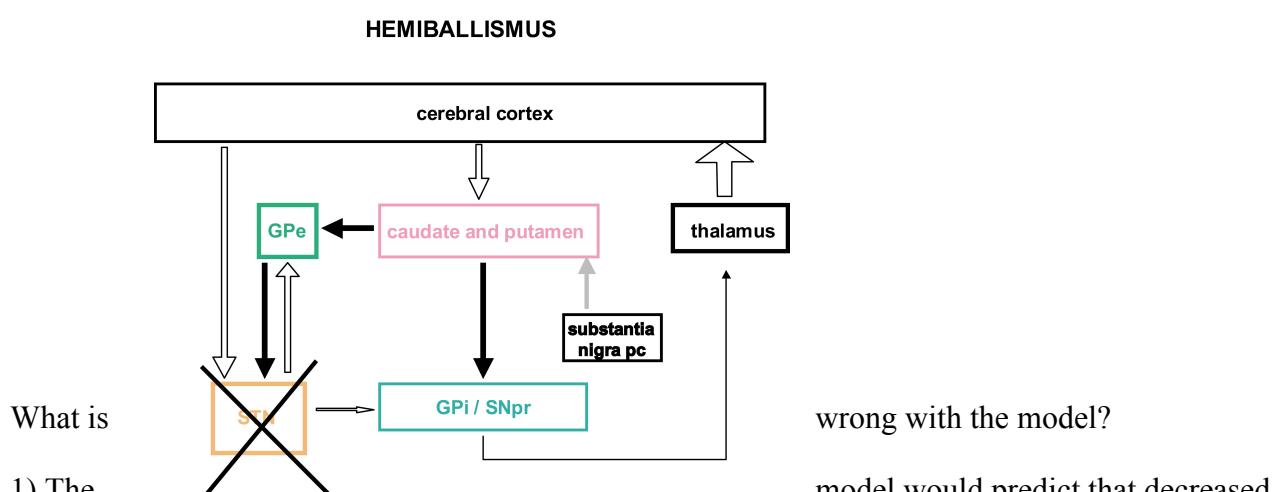
resting tremor- rhythmic, involuntary, oscillations 3-6 hz, "pill rolling" example.

Circuits and pathophysiology

People with PD can have bradykinesia, akinesia, postural instability, resting tremor, and rigidity.



Hemiballismus (violent involuntary flailing movements on one side of the body) results from damage to the STN on one side of the brain (usually from a stroke).



- 1) The model would predict that decreased output from GPi would result in involuntary movements (hyperkinesias). Yet, when the GPi is inactivated in monkeys (via muscimol), movements get slow (bradykinesia) and there are no involuntary movements.
- 2) A treatment for Parkinson's disease is STN stimulation (high frequency stimulation). This treatment is extremely effective at improving movement speed and quality. It is not clear whether stimulation activates or inhibits STN. It was initially thought that it inhibited STN (depolarization block or activating inhibitory interneurons), yet recent physiology and imaging studies have shown that it probably activates STN. If it activates STN, then the model would predict that the bradykinesia would worsen.

The answer is that the pattern of activity (rather than just the rate of firing) might be the more important feature.