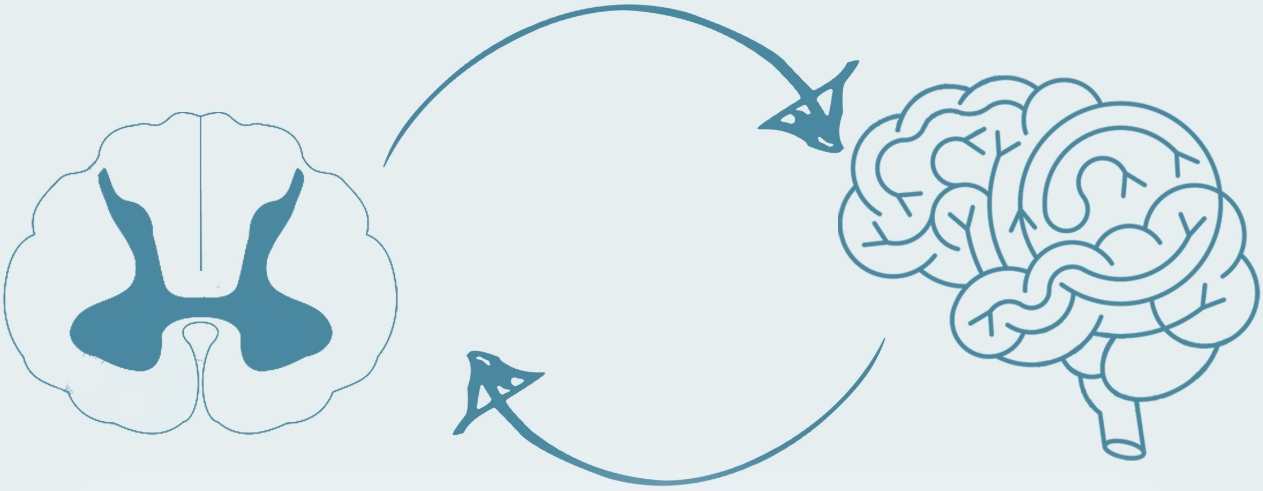

CNS

physiology

slides sheets

number	22
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Correction	--
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Sleep and Dreams

In the reticular activating system of the cortex there is Ach, norepinephrine (NE), serotonin, dopamine and histamine. Those neurotransmitters are responsible for waking the cortex up and start processing. On the other hand, we need **GABA** to turn the cortex off. During REM sleep, those should be active.

During REM sleep, the cortex is active. When the cortex is active when you are sleeping, you have dreams. This happens mainly in stage3 of sleep. In this stage, only certain areas of the cortex are active but the rest is not. While in the REM sleep the cortex is active again. If the vision area gets activated, you will have visual dreams. If the association cortex gets activated, then the dreams will be related to this area. So, we have **2 types of dreaming**; one in the REM sleep and another in the non-REM sleep.

As we said last time, when someone sleeps for 8 hours, he will have 4 cycles of REM sleep and the cortex is active in each one of these cycles. That's why on average, you have 3-4 REM dreams each time you sleep. You will also enter stage3 3-4 times in an 8-hour sleep and in each you will have a non-REM dream. In total, you dream 5-7 times each night on average (in an 8-hour sleep). But how come we don't remember all those dreams? Memory of dreams is related to oxygen and blood supply, if you woke up during the dream or not and if it was converted into a memory or not.

1. **NREM dreaming:**
   In the non-REM sleep, the cortex was turning off except for certain areas which are sending orders received as dreams. Usually, this activity is the same as the normal activity of the cortex and that's why those dreams are usually realistic (something you experienced or close to it) and just like thinking. These dreams are short because we are turning certain areas off and activating others fast.

2. **REM dreaming:**
   In REM sleep, the cortex is active for most of the REM cycle (which could last for 20-30min). During this stage, the cortex is trying new connections, removing connections and reconsolidating memories. That's why these dreams are unrealistic and long (e.g. you have the wings of a hawk and the body of a lion). If the dream was pleasant we call it a vivid pleasant fantasy. But when it is bad we call it a nightmare. Nightmares

exclusively happen in REM sleep. Some people say that nightmares can happen in NREM sleep but this only happens if your life and all your thinking is bad (*remember*: NREM dreams are realistic :')).

RECAP

REM dreaming	**NREM dreaming**
"Vivid and exciting"	"Just thinking"
~3 per night	Shorter, less active
Longer, more detailed	Logical, realistic
Fantasy world, nightmares	

Sleep Disorders

- insomnia
- sleep walking, talking, and eating
- nightmares and night terrors
- narcolepsy
- sleep apnea

We talked previously about these disorders except nightmares and night terrors. Nightmares and night terrors happen as a result of disturbance in the sleep cycle.

What wakes cortex up is the RAS system (reticular activating system) and what turns it off is GABA. The cortex is active in REM sleep so we need RAS during REM sleep. What actually happens is that the cortex turns off then the RAS system is activated to turn it on (most importantly Ach, NE and serotonin and DA and histamine for a lesser degree). Their **functions** are similar to their function during the day where:

- Serotonin is involved in processing associated with emotion.
- NE: selection of attention
- Ach: sustaining of attention

That's why when I need to active a certain area and process certain things **NE** helps in choosing and activating it during the first REM cycle. We also want to sustain the activation of the cortex during the whole cycle so we need **Ach** to do this job. So, NE has a role in starting and ending REM cycle whereas Ach is active through the whole cycle.

When there is a disturbance in these NTs the sleep cycle will be disturbed and this will cause nightmares and night terrors. They also happen when REM is longer or when you

wake up in the middle of it (because of disturbance in starting or ending REM). That's why they are common in people with problems in NE like ADHD patients. Also when you give a drug that affects those neurotransmitters it will affect the sleep cycle and cause what we call ***parasomnia*** (disturbances in sleep cycle). All the disturbances in sleep cycle are collectively called parasomnia.*

*Parasomnias are a category of sleep disorders that involve abnormal movements, behaviors, emotions, perceptions, and dreams that occur while falling asleep, sleeping, between sleep stages, or during arousal from sleep. Most parasomnias are dissociated sleep states which are partial arousals during the transitions between wakefulness and NREM sleep, or wakefulness and REM sleep. *Wikipedia*

Examples on parasomnia:

- Disturbance in waking up
- Vivid nightmare dreaming
- Disturbance in when to shut the output of the cortex so you experience a lot of movements. *Remember*: In REM sleep there is complete paralysis.

00:00-10:00

One of the side effects of **β-blockers** is nightmares. Drugs used in ADHD like Amphetamine or Desipramine cause nightmares as a side effect.

Increase in the activating system (which causes wakefulness or insomnia-very common) or disturbance in the cycle and resultant nightmares are common when using **SSRIs** (selective serotonin reuptake inhibitors). SSRIs are used in depression but the problem is that they cause more severe insomnia in depressed people (who already have insomnia). Subtypes which do not cause complete insomnia are associated with nightmares or parasomnia.

Coma & Brain death

Coma is caused by inactivation of the cortex where the cortex stays asleep for long periods. This is because there is a disturbance in the RAS system most importantly in Ach and the nuclei in the pontine-midbrain junction. This causes the cortex to stay inactive and nonresponsive. EEG shows some waves or simple flat waves because of absence of rhythmic activity or it might have rhythmic activity similar to sleep.

Ach has 2 pathways (ventral and dorsal), both are important in waking up. Sometimes if one of the pathways gets cut the patient falls into a long coma until there is up-activation of the other pathway to activate the cortex again and the person gets out of it.

Whereas when cell in the cortex have died they will never be active again and there will be no EEG response. In this case, the cortex itself is dead. This is called **brain death**.

The motor regulators

CNS has a lot of motor functions. The spinal cord, subcortical structures and brain stem each have motor output. The cortex has several motor areas. All these will work together to do the motor functions. In addition to all these tracts, there are certain parts of the brain related to the motor function in that they **regulate** the function of these structures without giving direct orders to lower/α motor neurons. Those are called ***motor regulators***.

We have 2 important motor regulators: **Basal ganglia** and **cerebellum**.

Basal ganglia

Basal ganglia include many subcortical structures; they are divided into neostriatum and paleostriatum. BG structures are also divided according to location into dorsal and ventral (each has neo and paleo structures).

There are interactions between neostriatum and paleostriatum, some are **inhibitory** and some are **excitatory**. The function of BG, just like the cortex, depends on the balance between excitation and inhibition. Outside the BG there are modulators that either increase excitation or increase inhibition and vice versa.

Function of BG

BG are connected to the cortex which either has real activity or non-real activity (will be explained in a bit). The cortex has neurons and those neurons have rhythmic activity (baseline firing). They could get excited by a stimulus but we don't want them to be excited so we need to remove it. For example, areaA gets active but an adjacent area

(areaB) gets also activated because of current leakage. We want areaA to be active but not B. That's why activity of the cortex could be real (purposive, intentional activity) or non-real activity. The function of the **prefrontal cortex** is to determine if the activity is real (wanted) or non-real (not wanted). To make this decision easier we go back to the **motor cortex**. Sometimes the motor cortex is active due to intentional movement and it gives voluntary movement. In other times and due to rhythmic activity (baseline firing) in one of the neurons in the motor cortex (non-purposive activity) it gives involuntary movement (not intentional activity from cortex, we don't want this movement). The **function of the BG** is to see if this movement is real (wanted) or not wanted before sending out these activities to muscles.

How does the BG do this?
In the neostriatal part there are **big spiny neurons** (they are called spiny because they have a lot of spines on the dendrites, they are related to memory). Those spines will get activity from the cortex and calculate if this movement is real or not. They have excitatory and inhibitory pathways and the balance between those pathways is what determines if this activity is real (and activate the cortex) or not (and inhibit the cortex).

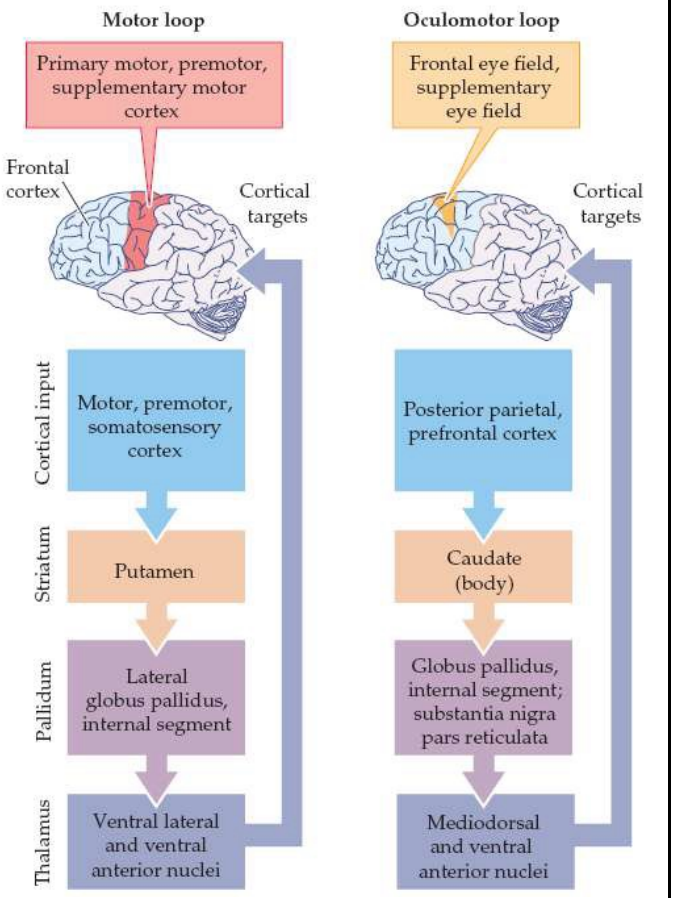
In addition to these connections, there are a lot of modulators (associated nuclei); some of the most important are those from inside or outside BG which give Ach. Other modulators are those that come from substantia nigra and give dopamine.

Connections and circuits

There are excitatory and inhibitory connections between the components of the BG to determine if the activity is real (we want to activate it) or not (we want to inhibit it). The BG does that for the whole cortex and has connections with all parts of cortex *except* the primary sensory cortexes (primary visual, auditory, gustatory and olfactory); those are the only cortical areas that are not connected with the BG.
We said there are anterior parts and posterior parts and both (ant. And post.) have neostriatal and paleostriatal segments because both are needed for the function of the BG.

a. Motor Loop

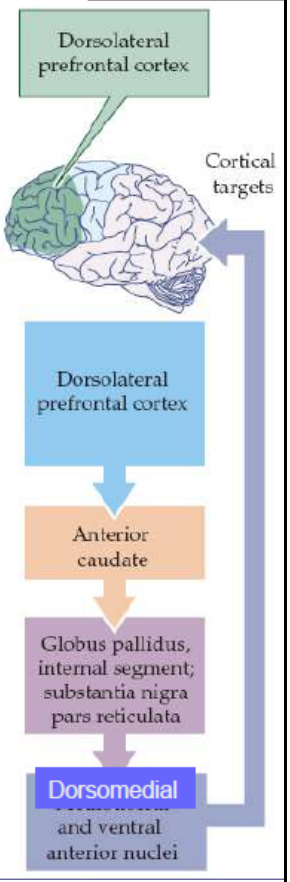
In the central area of the cortex there are the motor areas. This area will be mainly connected with the middle part of the BG which is the putamen and globus pallidus. Then the fibers will go to thalamus (ventrolateral and ventral anterior nuclei) and return to the motor cortex. This loop regulates motor areas so it's called the motor loop of BG. Disturbance in this loop will result in motor symptoms.



b. Visuomotor Loop

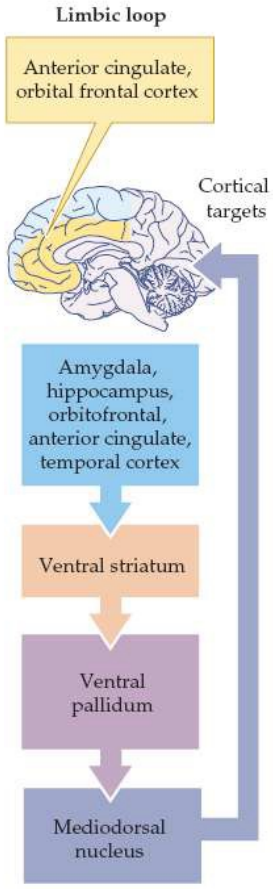
A little bit anterior/rostral to the previous area is the prefrontal area. It is connected to the anterior parts of BG (body of caudate). This loop is related to visual movement and regulation.

10:00-20:00



c. Executive Loop

The anterior part of the BG is associated with anterior part of cortex (prefrontal). It is connected with the anterior part of BG which is the head of caudate. Then it goes to the dorsomedial and ventral anterior nuclei of the thalamus and then back again to the cortex. This loop regulates prefrontal functions.



d. Motivational loop

We saw that the dorsal parts of BG are mainly associated with the dorsal parts of the cortex. Whereas, the inner parts of the cortex like insula and cingulate gyrus and the lower parts of frontal cortex will be associated with the more internal parts of BG which is the ventral basal nucleus. Those are associated with emotions (happiness and sadness), internal regulation and motivation.

We will concentrate more on the function of the motor loop because symptoms related to it are more common and it is easier to understand.

We already said that connection of the BG are either excitatory or inhibitory. The excitatory pathway is called the **direct pathway**. So whenever there is activation to this pathway, the net effect is excitation of the cortex so it tells it this activity is real so send it out.

The other pathway is the **indirect pathway**. When the activity of the cortex goes to the BG and it decides this activity is not real (not wanted), it will inhibit the cortex through this pathway. It starts with an activity in the cortex but the end result is inhibition of cortex (because this activity passes to BG first) so the cortex won't send an output.

So, we have 2 pathways: the direct pathway which ends in activating the cortex and sending an output, and the indirect pathway which ends in inhibiting the cortex and not sending an output.

Before sending its output, the activity of the cortex actually passes both pathways and the balance between the two will decide whether to send the output or not (according to which pathway dominates). This is done with the help of connections within the BG, the distribution of connections on the spine neurons and modulators from outside the BG (that modulate function by either increasing direct pathway or indirect pathway or vice versa).

If something (abnormally) caused the balance to lean toward the direct pathway (by increasing direct of decreasing indirect), the activity of the cortex will increase. When the activity of the motor cortex increases, this means there will be motor output for something that we don't want. This will lead to involuntary movements (increase in the motor activity of the cortex) which is called ***hyperkinetic disorder*** (choreatic syndromes).

When the opposite happens (the balance is toward indirect pathway), the cortex will be inactivated so there is no movement. This is called ***hypokinetic disorder***.

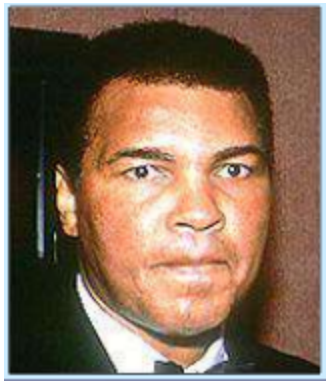
This also applies to other loops.

Basal ganglia disorders:

The key factor in stimulating the basal ganglia is dopamine whether in the direct pathway by binding to D1 receptors (excitatory) or in the indirect pathway by binding to D2 receptors (inhibitory) especially in the middle part of the basal ganglia and putamen . Disruptng the balance between direct and indirect pathways leads to hypokinesia (insufficient direct pathway output or excess indirect pathway output) or hyperkinesia (excess direct pathway output or insufficient indirect pathway output)

- D1+5 receptors→excitatory , D2+3+4→ inhibitory

Parkinson's :



Is the only hypokinesia disorder discussed in this sheet. It is caused by the degeneration of the substanstia nigra causing inhibition of the cortex thus nullifying the control over the lower motor neurons to end with rigidity expressed through tightened shoulders, curly back and resting face. Other effects of losing the substansia nigra is delayed initation of movement (bradykinesia) described as cogwheel movement, another effect is tremors at rest starting from the distal parts to the proximal parts of the body as the disease progresses.

Parkinson can cause depression as it spreads as well as dementia that hinders learning.

Treatment:

1) Using drugs: Mainly prescribing L-Dopa to replinish the dopamine storage in order to increase the direct pathway and decrease the indirect pathway. The major issue is the down regulation of direct pathway receptors after administration of L-Dopa usually during 5 years as it occurred with 50% of the Parkinson's patients taking the drug, this is called L-Dopa induced dyskinesia. L-Dopa affects the limbic system and can cause hallucinations.
   Other drugs used :- anticholinergics – works on acetylcholine
   - A2-adenosine antagonists- works on decreasing the indirect pathway (works like coffee)
   - anti AMPA - antagonist for glutamate

2) Surgery: Tonic high frequency stimulation of the subthalamic nucleus or globus pallidus interna directly instead of using L-Dopa to avoid the side effect of dyskinesia, this method works for early onset patients.

Hyperkinetic disorders:

The symptoms of these disorders are classified depending on motion, location and variation.

Definition of symptoms:

Chorea: is a dance-like movement , usually in distal parts of body

Ballismus: flinging of the limb involuntarily , usually proximal

Athetosis: writhing (twitch/jerk) movements , common in distal upper limb, slow

Dystonia: contraction of antagonist muscles simultaneously

-worth noting that any of the above terms can appear together and are named together like : choreoathetosis , athetotic dystonia

1-Huntington's:

The first hyperkinetic disorder mentioned in this sheet. A mutation increasing the CAG repeats in the DNA causing malfunction in the rostral part of the basal ganglia first and spreading posterior, this means that the first symptom will be depression and irritability as the prefrontal is affected first then the sudden falls and chorea are followed when the motor cortex is affected.

When this autosomal dominant gene is passed on to the next generation; the symptoms become apparent at an earlier age with each generation so the initiation of atrophy in the striatum leading to the loss of GABA neurons will eventually begin in the early 20's.

2-Dystonia:

A continuous contraction of opposing muscles due to genetic or idiopathic origin resulting commonly in an irregular posture in the cervix (torticollis) or axial (thoracic/lumbar) or both. Botulinum toxin is used to manage the situation.

3- tardive dyskinesia + 4-L-Dopa induced dyskinesia:

Both conditions commence from taking dopamine medications, where L-Dopa induced dyskinesia is caused by taking L-Dopa for Parkinson's as mentioned earlier whereas tardive dyskinesia is a result from taking dopamine antagonist drugs such as antipsychotic drugs and antiemetic drugs.

Tardive dyskinesia is the same repetitive movement in the limbs, mouth or lips.

5-Hemiballismus:

A unilateral flinging in the limb due to a vascular lesion in the subthalamic nucleus. If the flinging occurs in both sides, it is called ballismus. This is the only condition here caused by a vascular incident rather than a neuronal defect in the basal ganglia.

6-Tourette's Syndrome:

The etiology is still unknown but the presentation begins with the person having an urge to do a motion or be vocal (make a sound or say a certain phrase). The person is aware of this situation and can only control it slightly for they feel obliged to do the act as it "just seems right".

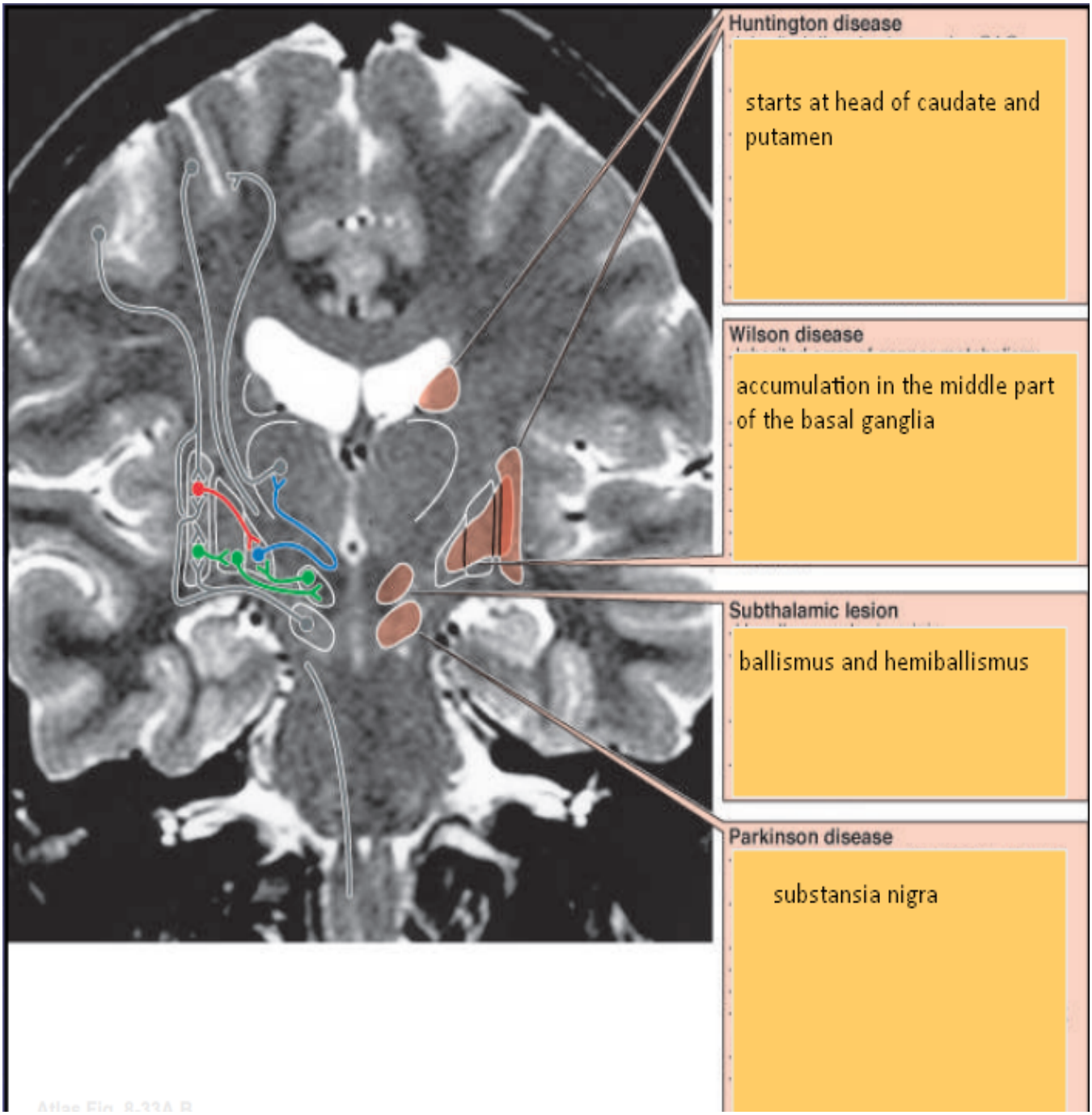
7-Sydenham Chorea:

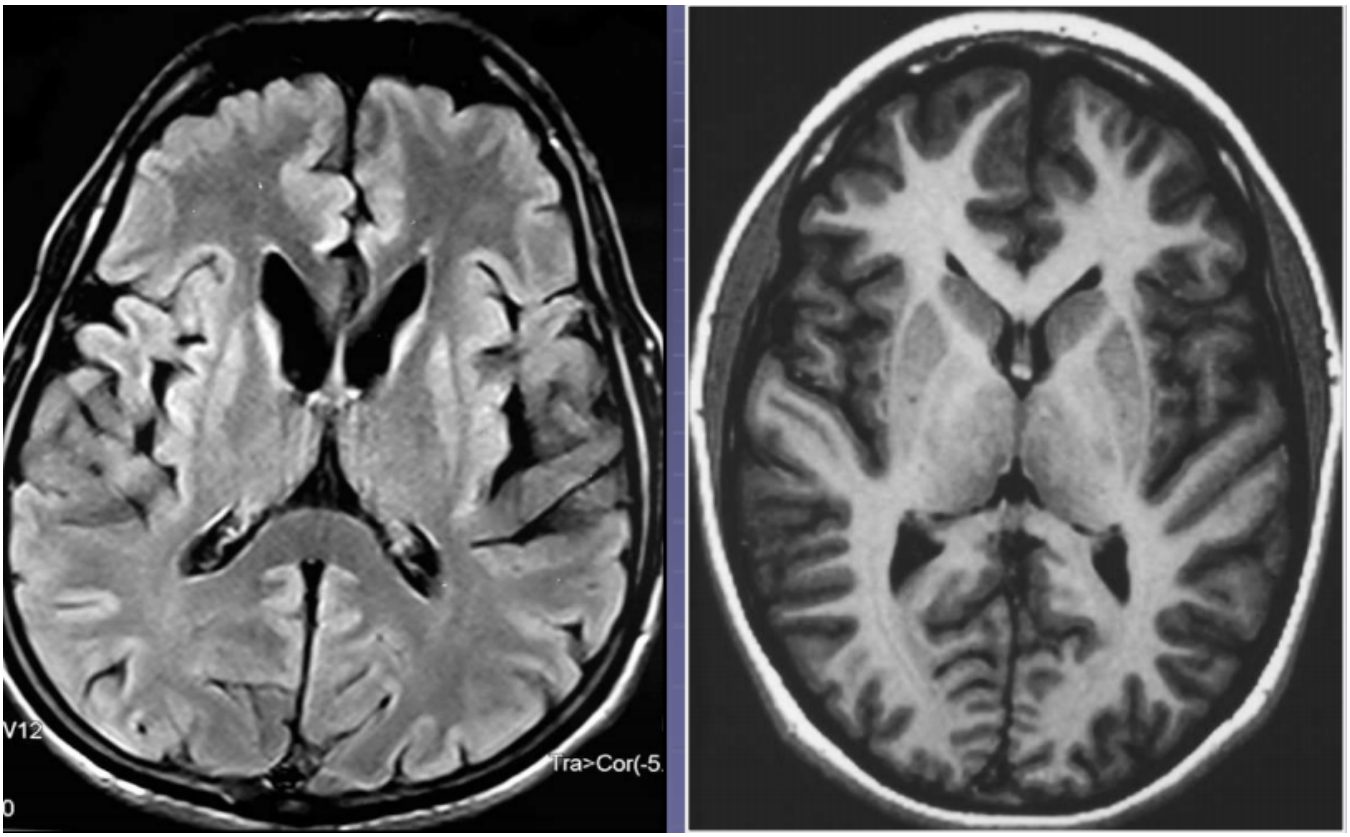
Happens mostly during childhood after an infection causes degeneration in the development of the GABA neurons through inflammation and increased body temperature. Luckily, there is no decline and the degeneration is fixed after the infection resolves.

MRI:

There are 3 MRI images discussed here.

Each disorder that begins at a specific site is mentioned in the first image to know the location defect.


Huntington disease
starts at head of caudate and putamen
Wilson disease
accumulation in the middle part of the basal ganglia
Subthalamic lesion
ballismus and hemiballismus
Parkinson disease
substansia nigra



Here the right image is of a normal person while the left image is of a person with Huntington's . As you can see, the left image has a missing head of caudate bilaterally.

The arrows point to the middle part to show accumulation of copper in the case of Wilson's disease which will cause Parkinson symptoms at first.