CENTRAL NERVOUS SYSTEM

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- ○ Anatomy
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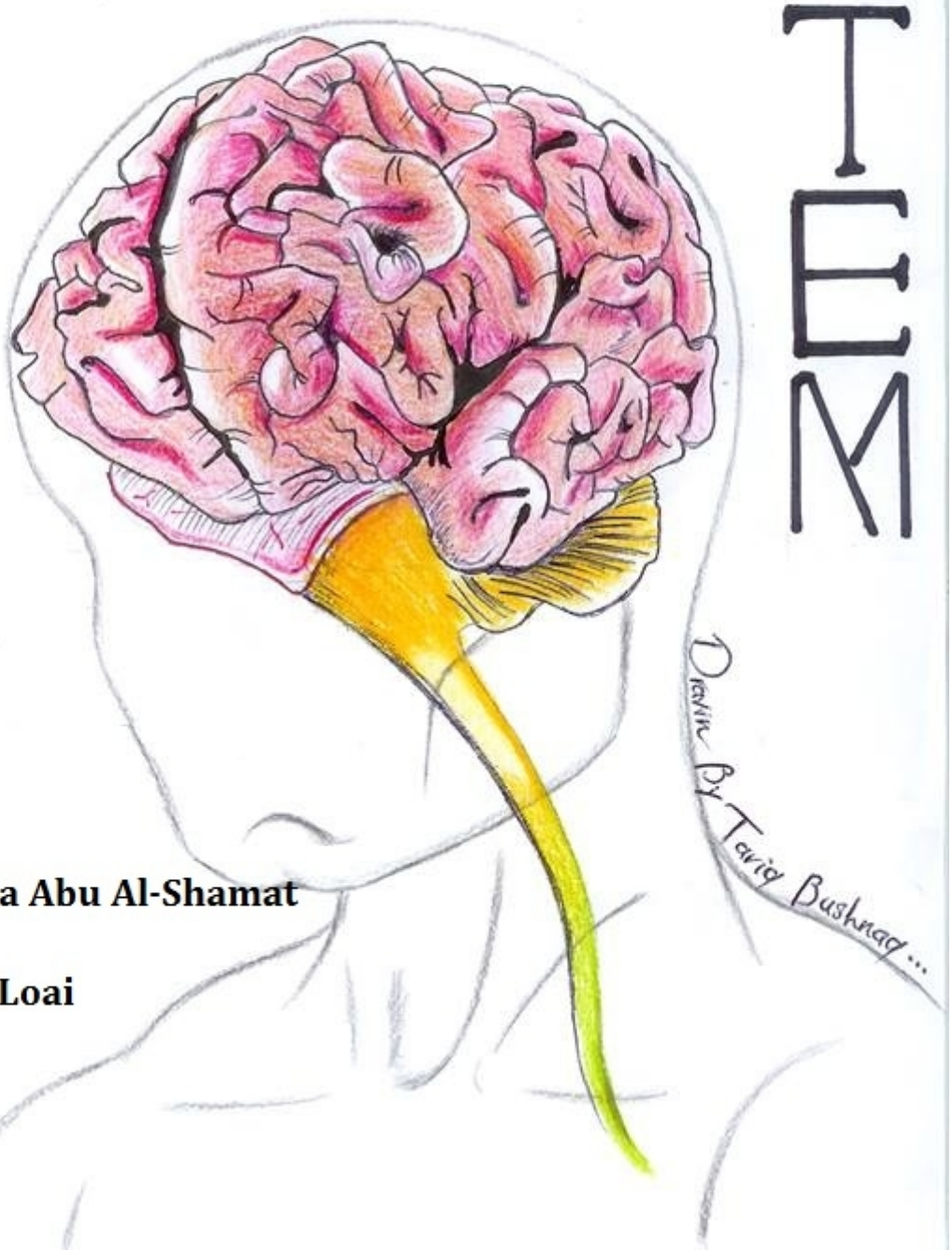

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Lec #: **11**

Hyperkinetic disorders and vestibular system

Last time we stopped at discussing the ways of managing Parkinson's disease which were:

1- **L-dopa** that crosses Blood Brain Barrier and then gets converted to dopamine.
2- **Deep brain stimulation** : Either activate the direct pathway by activating the substantia nigra to increase the dopamine release Or we can suppress the indirect pathway by inhibiting the subthalamic nucleus and globus pallidus.
3- **Novel treatment**: Depending on the balance of neurotransmitters:

Dopamine inhibits basal ganglia and excites the cortex (according to dr. Faraj : dopamine activates the striatum which inhibits the globus pallidus internus = inhibition to basal ganglia and the net effect of inhibiting the globus pallidus is activating the cortex).

Acetylcholine activates the basal ganglia and inhibits the cortex (makes the opposite).

The problem in Parkinson is excitation of the basal ganglia by the loss of dopamine (means as Dr. Faraj said: over active GPi), so we need to increase the dopamine and reduce acetylcholine = give **anti-cholinergic.**

Other drugs target other modulators like **a2 receptors,** which are receptors for adenosine and it have important roles in the regulation of glutamate and dopamine release.

Or reduce the excitation of glutamate by giving **anti- AMPA.**

According to the book: different areas of striatal complex are affected by the balance of dopamine, GABA, and glutamate. And this affects the complexity of how L-dopa works.

The use of MAO inhibitors slows the progression of Parkinson's and increases the level of dopamine.

Hyperkinetic disorders:

Loss of function of basal ganglia, the direct pathways is over stimulated and the indirect is not working, thus the cortex is more active. This makes motor syndromes like

1. Huntington's chorea
2. Dystonia
3. Tardive dyskinesia
4. DOPA-induced dyskinesia
5. Hemiballismus
6. Tourette's syndrome

Some of them are mainly genetics, some are environmental, and some are due to drugs like Tardive dyskinesia and DOPA-induced dyskinesia.

There are involuntary movements in chorea, ballismus, athetosis and dystonia.

Differ is in the way of movement

Rapid or slow?

Sudden or not?

Proximal or distal muscles?

Trunk or limb? Differ dystonia from rest.

Different areas lost from basal ganglia give different movement, we don't lose the same type of the neuron, and we don't get the same effect, so there are different symptoms.

-Symptoms:

Chorea: Involuntary dance like movement usually in the distal part of the limb.

Ballismus if very rapid is similar to chorea, but mainly in the proximal muscles.

Athetosis: rotation movement in hand

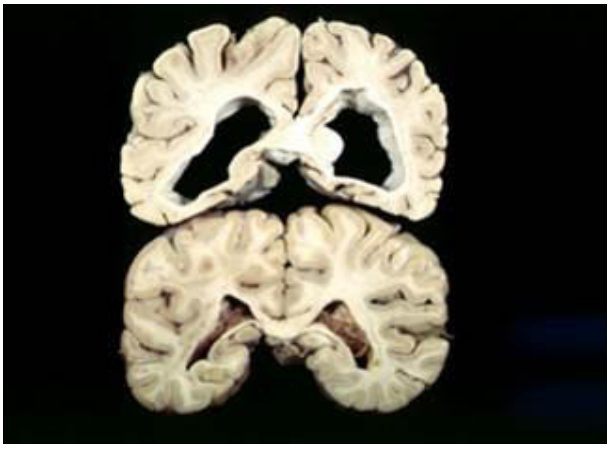
Dystonia in arm.

Huntington's disease

Genetic disorder, characterized by repeats on chromosome 4 (wiki: (CAG)—repeated multiple times), and causes atrophy of striatum, usually affects the rostral and medial part of the striatum then continues to the lateral and caudal parts.

So Rostral striatum lost first, thus prefrontal and frontal cortex is lost first, and psychiatric changes appear before motor changes, like depression, aggression and loss of good thoughts, then motor changes appear like chorea that worsens with time.

this is a cut section showing the difference between normal brain and huntington's degeneration.



dystonia:

can be due to genetics or environment or infections.

Mainly in the trunk and neck, and one of the commonest treatments if it was localized in the neck is botulinum toxin which will kill the nerve fibers.

According to wiki and the slides:

cervical dystonia (spasmodic torticollis) which affects the muscles of the neck causes the head to rotate to one side, to pull it down towards the chest, or back, or a combination of these postures and botulinum toxin causes temporary paralysis of these muscles in order to stop these repetitive movements and twitches.

Tardive dyskinesia:

Localized to face, mouth and tongue, associated with long term drug administration like anti-epileptic or anti- psychiatric that lower the dopamine which increases the sensitivity of dopamine receptors and get this hyperkinetic disorder.

So to treat, lower the dose of the anti- psychiatric drug, or switch to a drug that lower the use of D2 receptors.

People taking dopa, will have sensitivity of the receptor, its composition and adaptation will change, and their case will develop from Parkinson to hyperkinetic dyskinesia

From the book: Tardive dyskinesia is a basal nuclear disorder that is iatrogenic in nature, . The manifestation of this condition is uncontrolled involuntary movements, particularly of the face, mouth, and tongue, and cogwheel rigidity. These abnormalities may be temporary or permanent. The action of these neuroleptic drugs is to block dopaminergic transmission throughout the brain.

Prolonged treatment with neuroleptic drugs may lead to blockage of the D2 dopamine receptor, which causes an imbalance in the nigrostriatal influence on the basal nuclear motor loop and ultimately results in movement disorders.

Hemiballismus:

Rapid movement of the proximal part of the limb, usually it's on one side, due to stroke or damage to subthalamic nucleus.

affects one side of the body = **hemi**ballismus

Tourette's syndrome:

Hyperkinetic disorder due to genetic or environmental error, have hyper movement in face or speaking apparatus **(tics)**.

Wiki:it is characterized by multiple physical (motor) tics and at least one vocal (phonic) tic.

Tics are sudden, repetitive, nonrhythmic movements (motor tics) and utterances (phonic tics) that involve discrete muscle groups. Motor tics are movement-based tics, while phonic tics are involuntary sounds produced by moving air through the nose, mouth, or throat.

Effect of basal ganglia damage will be contralateral, because it deals with the cortex.

Note: Check these diseases with MRI images!

Wilson's disease:

Excessive copper in the body, which damages the striatum thus damages the receiving input from cortex, so cortex can't adjust the tonic inhibition from the basal ganglia, and the symptoms will be similar to parkinson's disease.

It involves the brain and the liver, so it is called hepatolenticular degeneration.

From the Book: many patients with Wilson disease will develop psychiatric symptoms, such as changes in personality, argumentative behavior, or emotional lability. However, the motor disturbances are often the most evident signs and include tremor, dysarthria, diminished dexterity, unsteady gait, and rigidity. The most common form of movement disorder in this disease is known as a wing-beating tremor; these movements are clearly different from resting and intention tremors, patients do not have a tremor at rest.

These patients may also present with a mask-like facial expression, gaping mouth,

Sydenham Chorea:

Infection in area 8, the body will react to bacterial toxin by defense mechanisms like fever that could affect kill GABA cells, so this will cause overactivity of the cortex, and will have chorea like movement.

Although the cause is different than Huntigton disease but the symptoms and movements are almost alike.

This could be transient especially in children, because the brain is still developing and plasticity occurs, so killed cells will be compensated, but sometimes the damage is too severe or it occurs at an older age so the symptoms will not get any better, as well they will never worsen with time, so there is NO cognitive decline (unlike Huntigton's) .

From the book: This is a childhood autoimmune disease that is infrequently seen. It is a consequence of rheumatic fever. The disease is self-limited and is rarely fatal. Patients present with rapid, irregular, aimless movements of the limbs, face, and trunk. These movements are more flowing and "restless" than those in Huntington disease patients. In addition, patients with Sydenham chorea have some muscle weakness and hypotonia

Vestibular system:

Sensory system in the inner ear to sense body movement and position.

We have two shell-like apparatus: cochlea which we will take about in hearing and labyrinth which is the sensory apparatus of the vestibular system

((First I'll explain myself according to guyton and grays anatomy some points to make the upcoming info clearer:

The inner ear consists of bony cavities called the bony labyrinth which is located in the temporal bone, and it consists of the vestibule, three semicircular canals, and the cochlea.

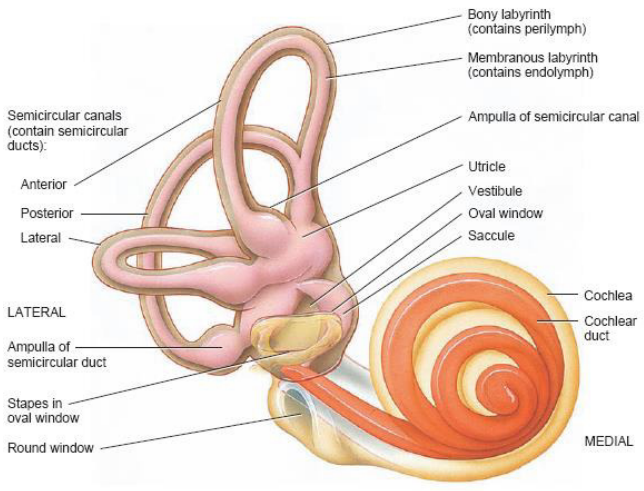
Inside the bony part, there is a membranous labyrinth which has two sacs called the utricle and the saccule, and three semicircular canal and they form the vestibular apparatus which is responsible for balance.

Between these two parts, there is a fluid called perilymph.

Inside the membranous part there is a fluid called endolymph.

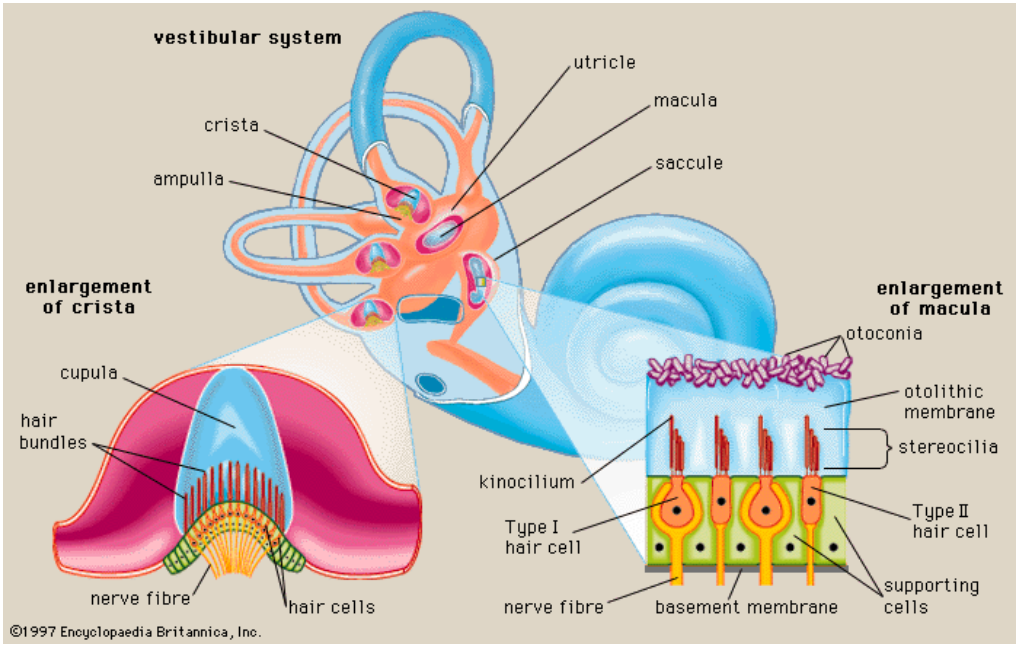
Three semicircular canals are situated in three axises: posterior, anterior, lateral (horizontal), which contribute to the axises of head movement, nodding (up and down), going to right and left (like saying no), and tilting your head to your shoulder.

At the end of each hemi circle there is a dilation called the ampulla which is attached to a part called utricle.



Sensory receptors are found in each part of the vestibular apparatus, in the utricle it is called the macula of utricle that is responsible for vertical accleration and plays an important role in determining the orientation of the head when it's upright, and the other one is the macula of saccule which is responsible for linear acceleration accleration and plays an important role in determining the orientation of the head when the person is lying down , and for the three hemicircles, respond to movement in any direction.

Flow of the fluid inside the hemi circles and the ampulla excites the sensory organs inside the ampulla which is the crista. On top of it, there is a gelatinous mass called the cupula, as the head bend, the fluid passes through the ducts and the ampulla, and this bend the cupula.



Into the cupula are projected hundreds of cilia from hair cells, all oriented in the same direction, bending toward it will cause depolarization, and bending to the opposite site will cause hyperpolarization.

Innervation: from 8th cranial nerve, vestibulocochlear, which divides to form the cochlear and the vestibular nerves. The vestibular nerve enlarges to form a ganglion, then divide to a superior and inferior parts.))

Now again to what the doctor said:

Labyrinth has 5 sensory parts:

The first three ones are semi-circular canals, and at the end there is a bulge called the ampulla.

One is vertical, one is horizontal and the last is lateral, so they cover all planes of axis (all directions of movement). ((however according to guyton this is wrong as lateral is the same as horizontal))

They mainly send rotational movement, because it accelerates the fluid inside them, however any movement against the gravity like nodding, jumping, tilting, will not make enough force for rotation, and will not make the fluid accelerate in them.

Inside the ampula there is a gelatinous membrane called cupula, any acceleration will bend this gelatinous membrane to one side, and underneath it we have the receptors (hair cells) because they are cells with hairy like extentions.

They are mechano-ion channel receptos, upon bending to one side, the ion channel opens and ions leak in, and upon bending to the other side the channel will close and ions leaking will be less.

The ion that enters is potassium.

The fluid inside the cochlea and the labriynth (which is called the endolymph) has high concentration of K+ and low concentration of Na+, so when the ion channel opens, K+ will enter to the cell moving from high concentration to low concentration, meaning positive ions are entering so depolarization will happen.

Remember these receptor cells will not make action potential, instead they will make graded potential, and the amount of K+ that enters will determine the amount of depolarization, which along with amount of opening voltage gated calcium channels and amount of Neurotransmitter release will determine the frequency of action potential of the first order neuron.

At rest, half opening of the channels.

Tilting to one side, more K+ entering, more frequency of action potential.

Tilting to other side, closure of the channels and less K+ entering, and less frequency of action potential.

Upon rotation from right to left, the fluid will move in both ears, we have vestibular system in each ear, but the lining of the hair cells of each one is opposite to the other.

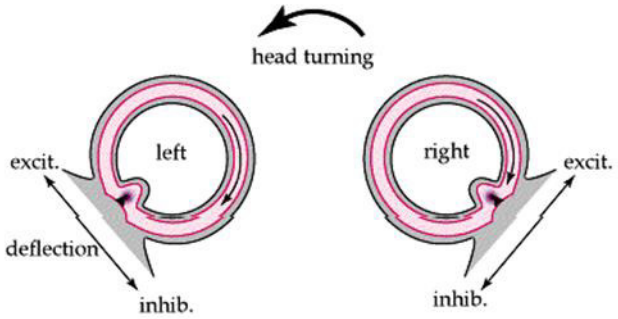
So for example, the superior circle of one is opposite the posterior circle of the other vetibular system (at the same plane).

They work in pairs, so in the left ear, the cupula will bend toward the direction of excitation and causes depolarization, while the right cupula will bend to the opposite direction and causes hyperpolarization.

So we know that we are rotating and to which direction.

When there is a difference between the two of them, and the left is higher than the right, the brain will interpret that we are rotating toward the left side, and the amount of difference will be interpreted as the velocity or the power of rotating,

and the direction is determined by which one has the activity going on.



The other type of movement is tilting up and down, here there is no rotating, and the brain has to know this information that is called movement against gravity and this includes nodding, acceleration, deceleration (like when I'm in a car and pressing on the brakes), so we need two other apparatuses in the vestibular systems to detect these movements directed to the gravity which are the saccule and the utricle.

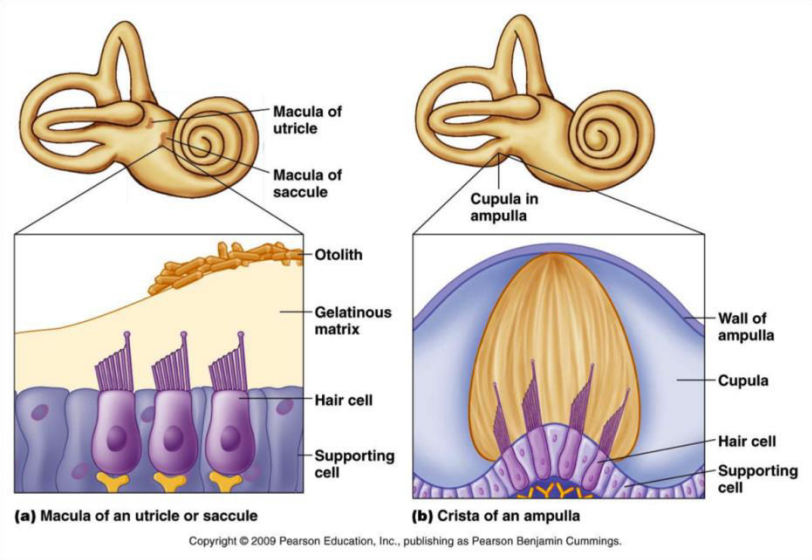
The utricle is almost horizontal, so more sensitive to the nodding, acceleration, deceleration, in the horizontal plane.

The saccule is almost vertical, so more sensitive to vertical movements like jumping and falling.

Note : inside the utricle and saccule there is a fluid called endolymph.

Inside them there is another gelatinous membrane, and to make sure that this gel will move, it has more weight on it, which is calcium deposits called the otolith membrane, and here is only unidirectional, so in each ear we have distinct direction of the hair cells of the otolith membrane.

So when you move your head to the left the fluid will move to the right and when you move your head to the right the fluid will move to the left ,so upon moving the head to the right the right side will be stimulated and the left side will be inhibited and vice versa.



According to gutyon: hair cells are oriented in a different direction so some are stimulated when the head bends forward, others are stimulated when the head bends backwards and so forth, so there is different pattern of excitation for each orientation in the gravitational field.

From the vestibular, first order neurons will take the signal and deliver it to the brain stem through the vestibulocochlear nerve which synapses on the vestibular nuclei there, and from there will go to the:

1- Cortex passing through the thalamus, particularly to the parietal lobe.
2- To make reflexes, and to move the head, will go to the accessory nuclei which supply the trapezius and sternochledomastoid muscles that move the head.
3- Vestibulospinal tract that goes to the trunk,and lower limb to ensure balance and not falling down.
4- Cerebellum that takes all sensation to ensure balance.
5- Vision field, the eyes move in an opposite direction of the head movement, as a reflex, so when I'm turning to the right, my eyes will look to the left to preserve my vision feild, and as I move I go up and down, and when I go up my eyes will look down and vice versa..
   And when you drive a car and moving forward you can fix your eyes on a poster to the right to read it for couple of minutes.

Eyes movements happen through three nuclei which are: occulomotor, trochlear, and abducent (3, 4, 6).

At rest, both ears have the same frequency of firing, and the brain will understand it as no rotation.

During rotation to the left, the left one is excited, the right one is inhibited, and the brain will detect this difference, and understand it as rotating to the left.

In case of damage to the labrynth, or infection of the vestibulocochlear nerve, damage to the nuclei, or imbalance pressure inside the labyrinth when the patient is at rest and he is straight and due to this damage the firing of the damaged ear will be less, and the other ear is still firing at its baseline, and this makes a difference between the two ears, which will be interpreted in the brain as rotating to the healthy side, and this what is called VERTIGO.

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Maybe associated with nausea or not, it will affect also all the reflexes, the patient will fall easier, because the reflexes are not oriented, and some muscles have more tone and stretched more than the other, and the postural reflexes are weak.

Also there is a reflex in the eye, the patient is standing still and his eyes are moving, so if the damaged area is the left, the brain will interpret the tilt is toward the right, and eye will move to the left.

If the difference in the frequency is small, the eye movement will not be a complete nystagmus, it will just go once and return back.

If the difference is big, it will go to the end of the eye and then return back to the center as nystagmus.

This is the principle of the caloric test, which depends on the fact that at rest both ears are firing at same frequency, and this can be modulated by temperature.

If we increase the temperature we increase the kinetic movement of ions through ion channels which induces excitiation and increases the firing, and this creates a difference between the two ears if one is warmer than the other.

By this way we examine the vestibular system of comatose patient, by placing warmth in one ear which creates a difference and the eye will go to the opposite direction.

I tried to make this understandable as possible.

Sorry for any mistake and good luck ☺