New Developments in Migraine

-or-

(Why do humans get so many headaches?)

Stasha Gominak, M.D.
East Texas Medical Center Neurologic Institute
700 Olympic Plaza, Suite 912
Tyler, Texas

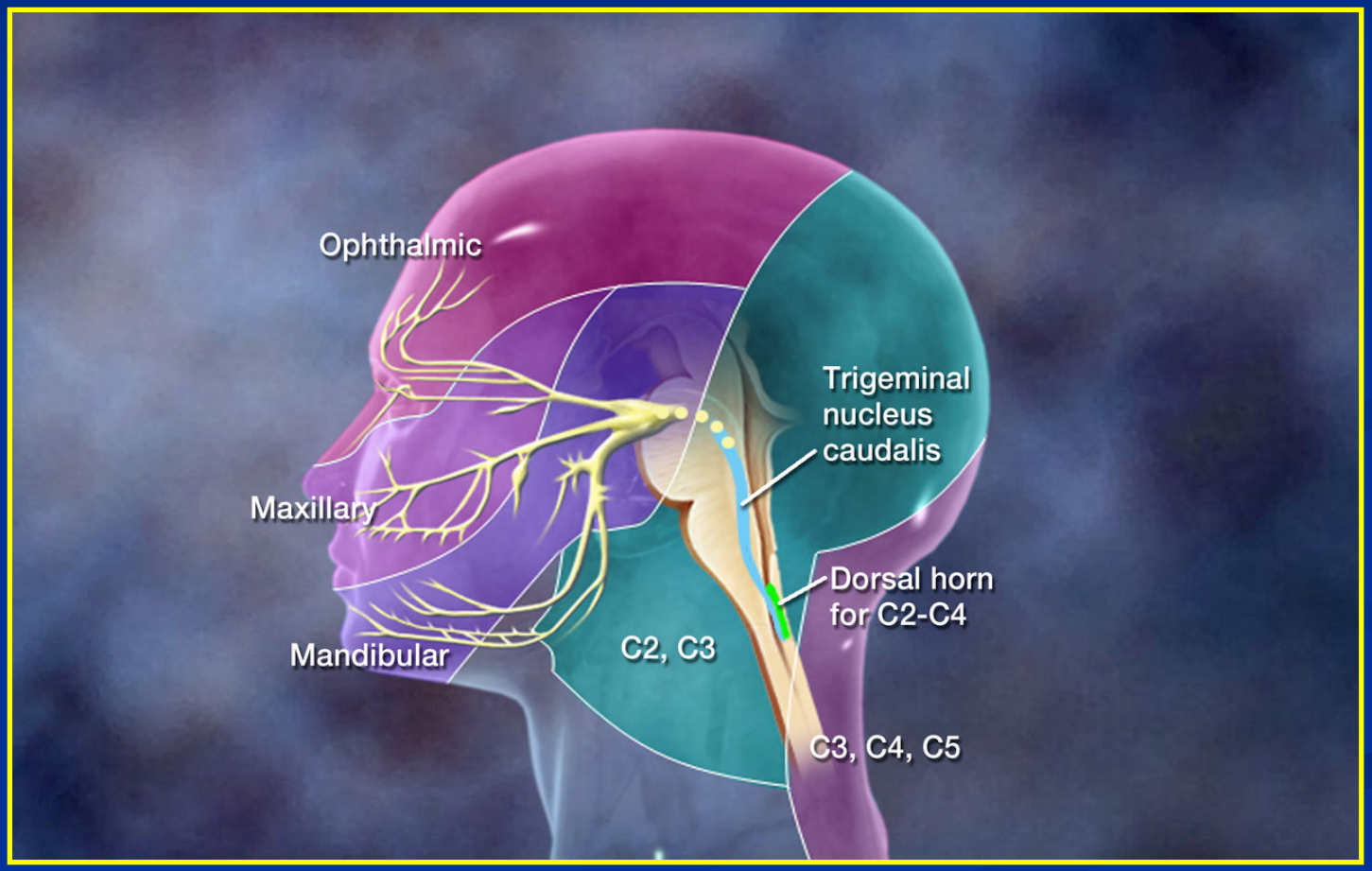
Despite what we were all taught, migraine is not a vascular disorder

I believe that migraine is a disorder of electrical hyper excitability of the head pain system coming from a brainstem "migraine generator"

I believe that all humans with normal head anatomy who have spontaneous head pain have "migraine". It comes in different sizes but all with the same mechanism.

Trigeminal Nucleus Caudalis **perceives pain for the face and the front 2/ 3 of the head.**

Dorsal Horn C2-C4 **perceives pain for the back 1/ 3 of the head and the neck.**



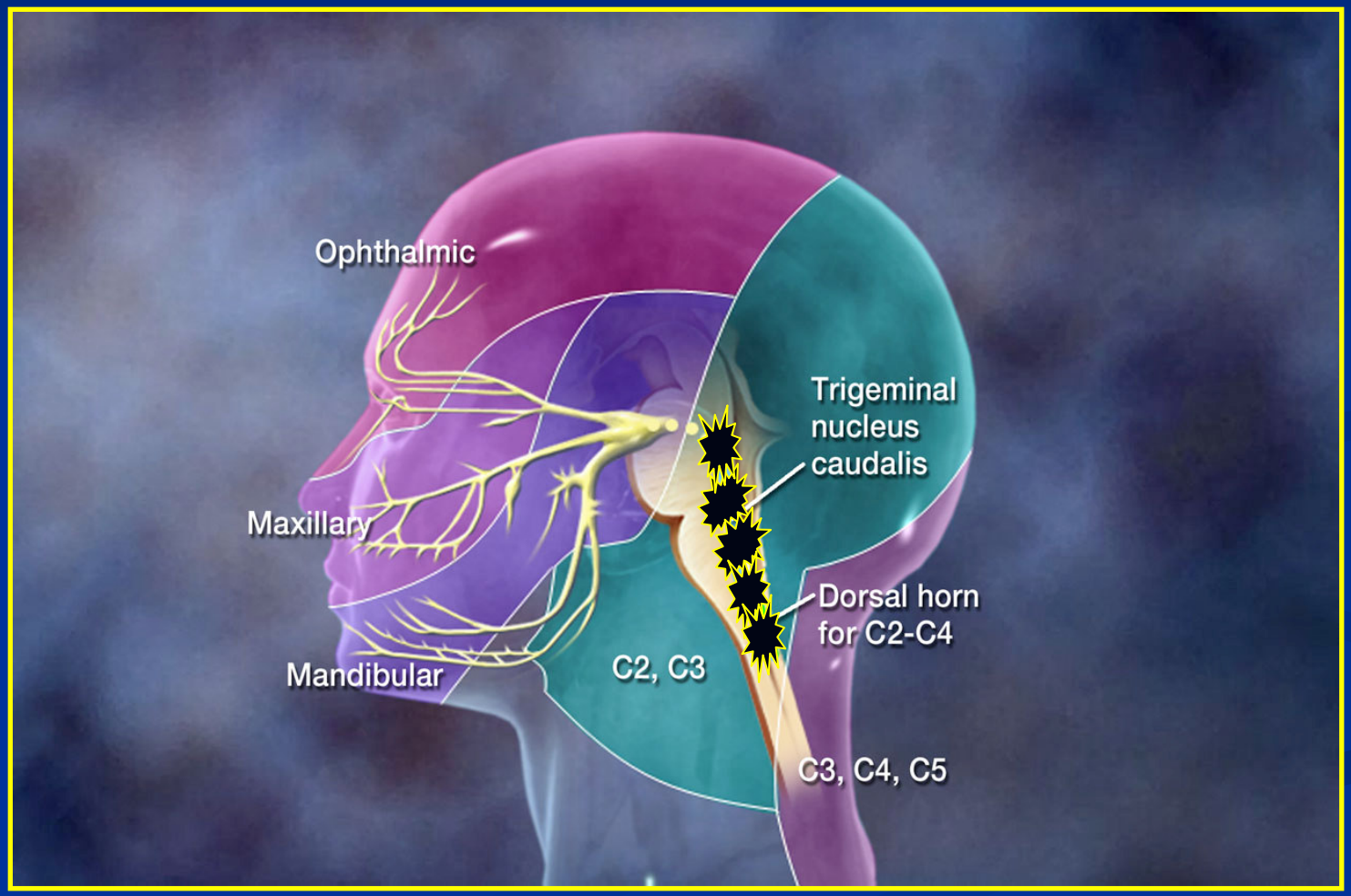
The Head Pain System

The pain system of the head was put there to tell us not to bang our heads.

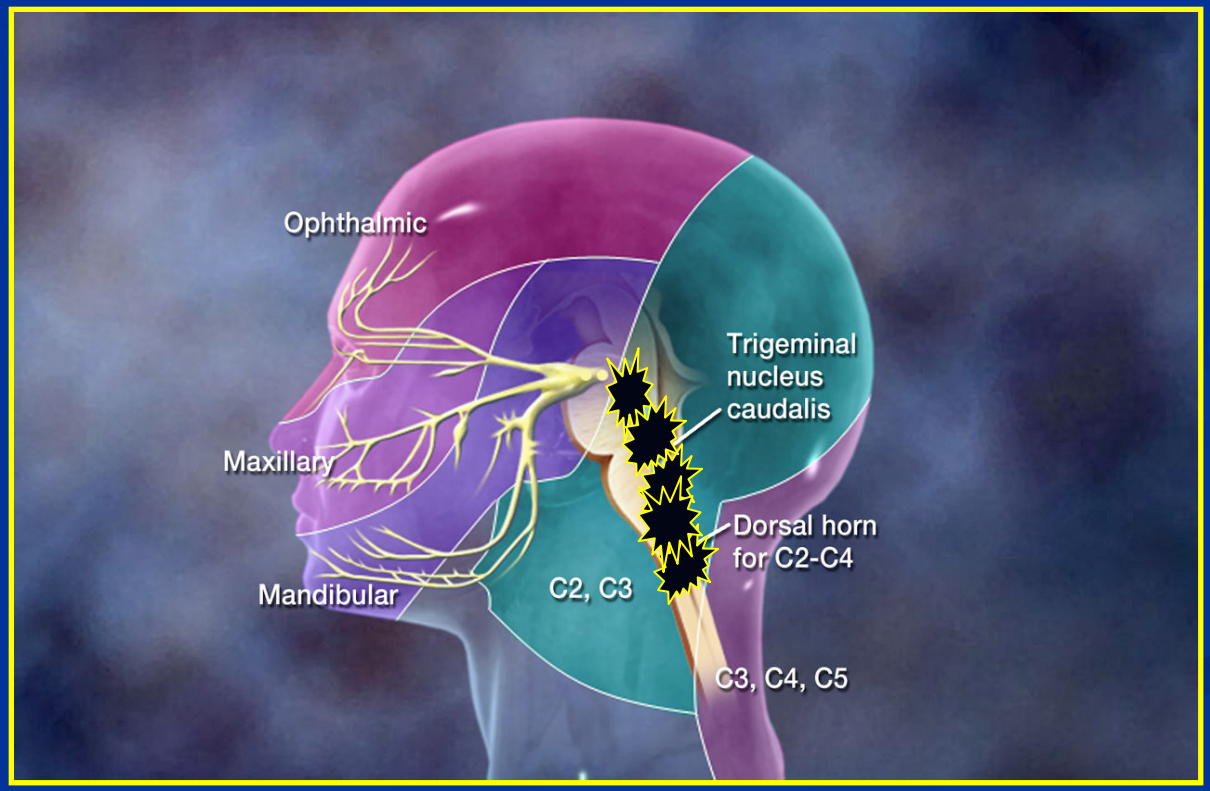
PET Scans in Migraine Patients

show that the posterior brain stem is hyper metabolic

Weiller C, May A, Limmroth V, et al. Nature Med 1995;1:658-660



The migraine sufferer has a normal wiring diagram but inherits a gene that allows the pain wires to turn “on” without a blow to the head.

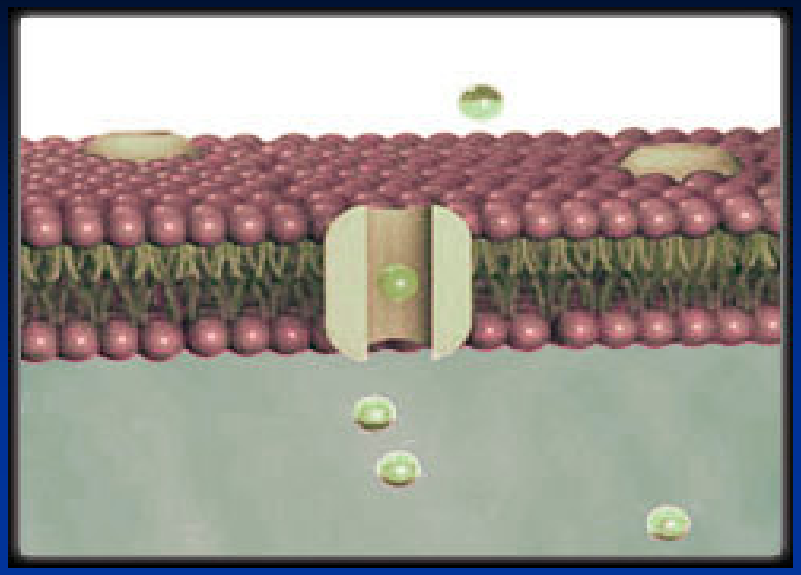


The Gene Mutations that Cause Migraine

Genes that cause migraine affect the electrical excitability of brain cells

- There are now about 40 genes that are linked to migraine
- All of these genes are mutations in the cellular apparatus that allows us to turn our cells on and off: Channel Mutations.
- About half the genes are Ca++ channel mutations the other half are Na+ channel mutations.

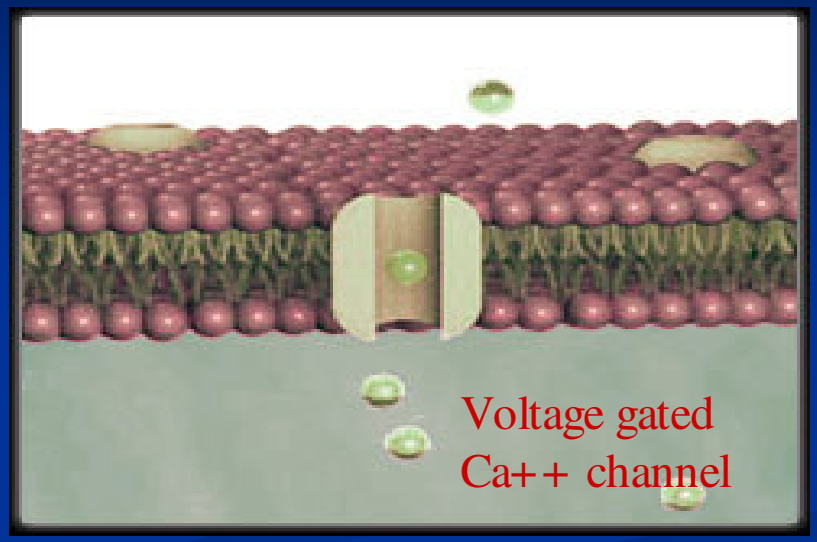
Ca++ channel in a membrane



- Our cellular electricity is more like a car battery, charges floating in water our brain uses Ca++, K+, Cl-, Na+.
- The channels move these ions in and out of our cells to turn them “on” or “off”.
- Most channels move a specific ion.
- There are now multiple Ca++ channels, K+ channels, etc., each has a specific role, or several specific roles, in our body.

Voltage gated Ca ++ channels turn cells "on" Ca++ pumps turn them "off"

- As the voltage of the cell rises the "voltage gated" Ca++ channels all open.
- Ca++ floods the cell, the cell is now very positive inside; it is "on".
- It sends it's message off down the axon.
- It's job is finished, now it is time to turn "off". To turn off it has to pump out the positive charges.



Lots of +'s cell is ON

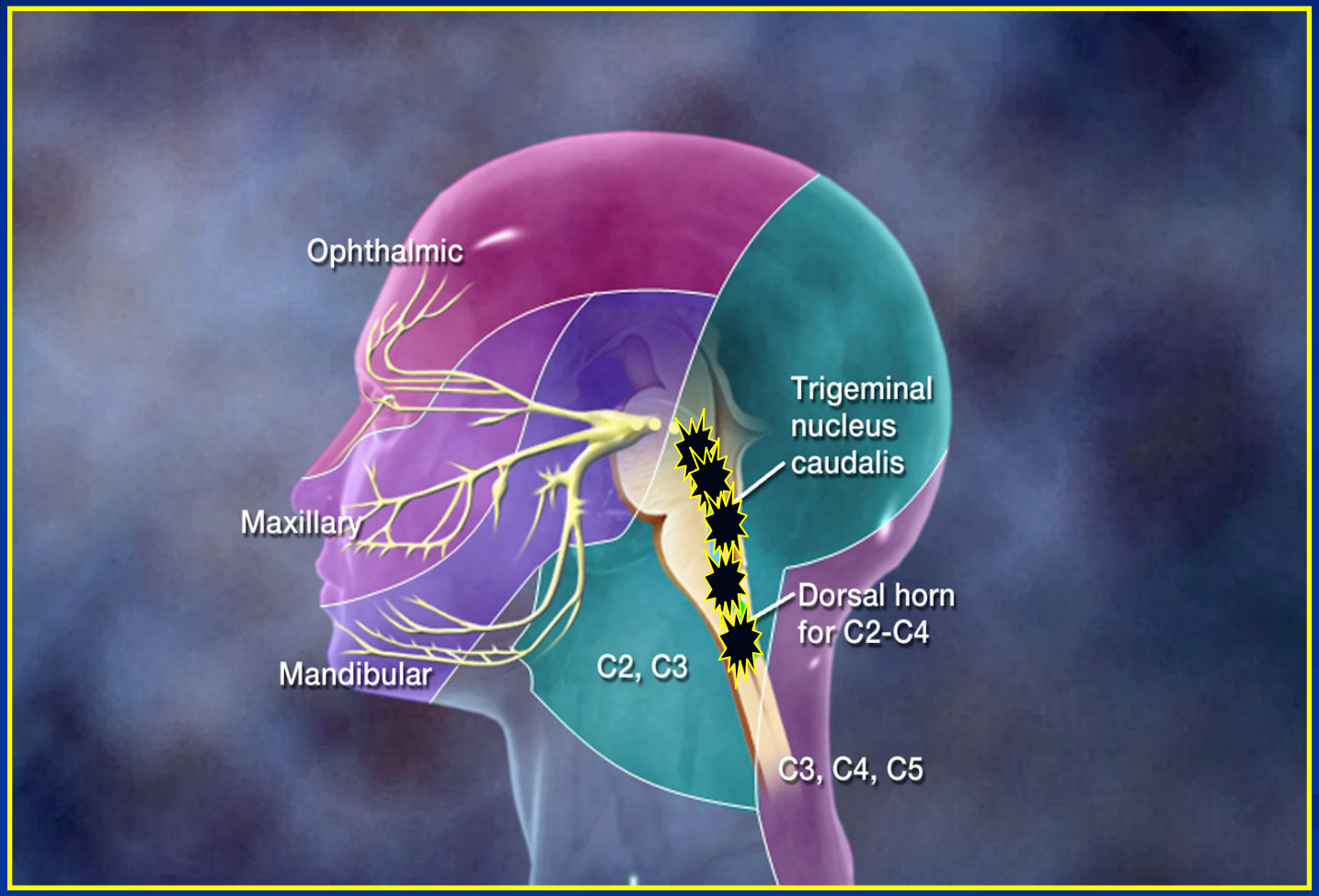
++ + +++
+
++ +
++
+ + +

Migraine is a Channel Disorder

- There are now multiple reported Ca++ channel and Na+ channel mutations that are linked to migraine.
- Also mutations of the Ca++ pumps and most recently Na-K ATPase.

Refs 1-6

This may be why the brain stem nuclei are inappropriately "on" in migraine patients

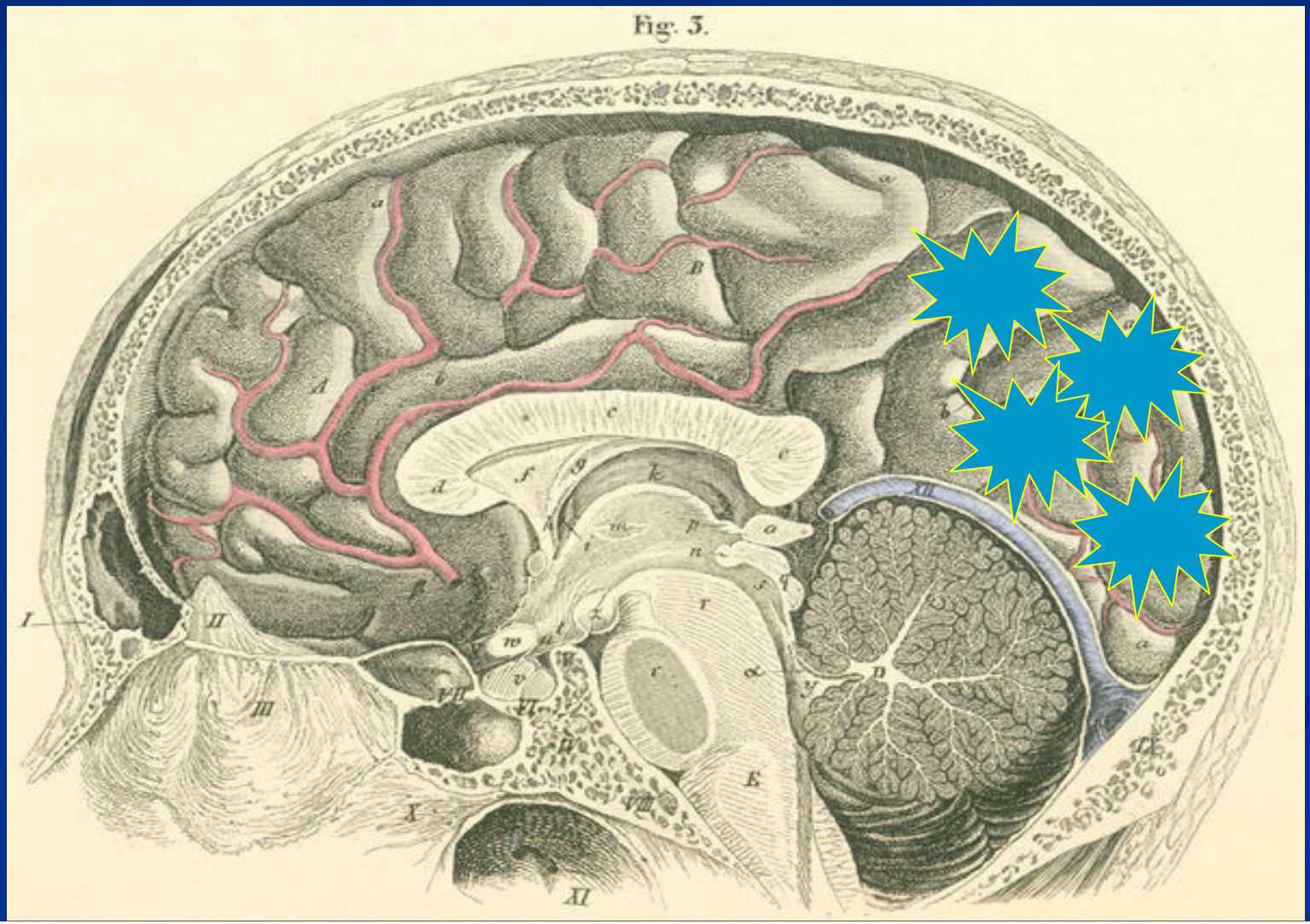


Any migraine sufferer will tell you, (if you ask), that they go to bed not just because their head hurts but because they also "can't think right"

Migraine is not just a disorder of head pain.
Any theory about migraine has to explain this global change in brain functioning.

1960's Magnetic Field Studies

Starting with the visual aura they observed electrical suppression, starting in the back during visual aura, moving slowly forward taking 15 minutes to go from back to front



Magnetic Field Studies

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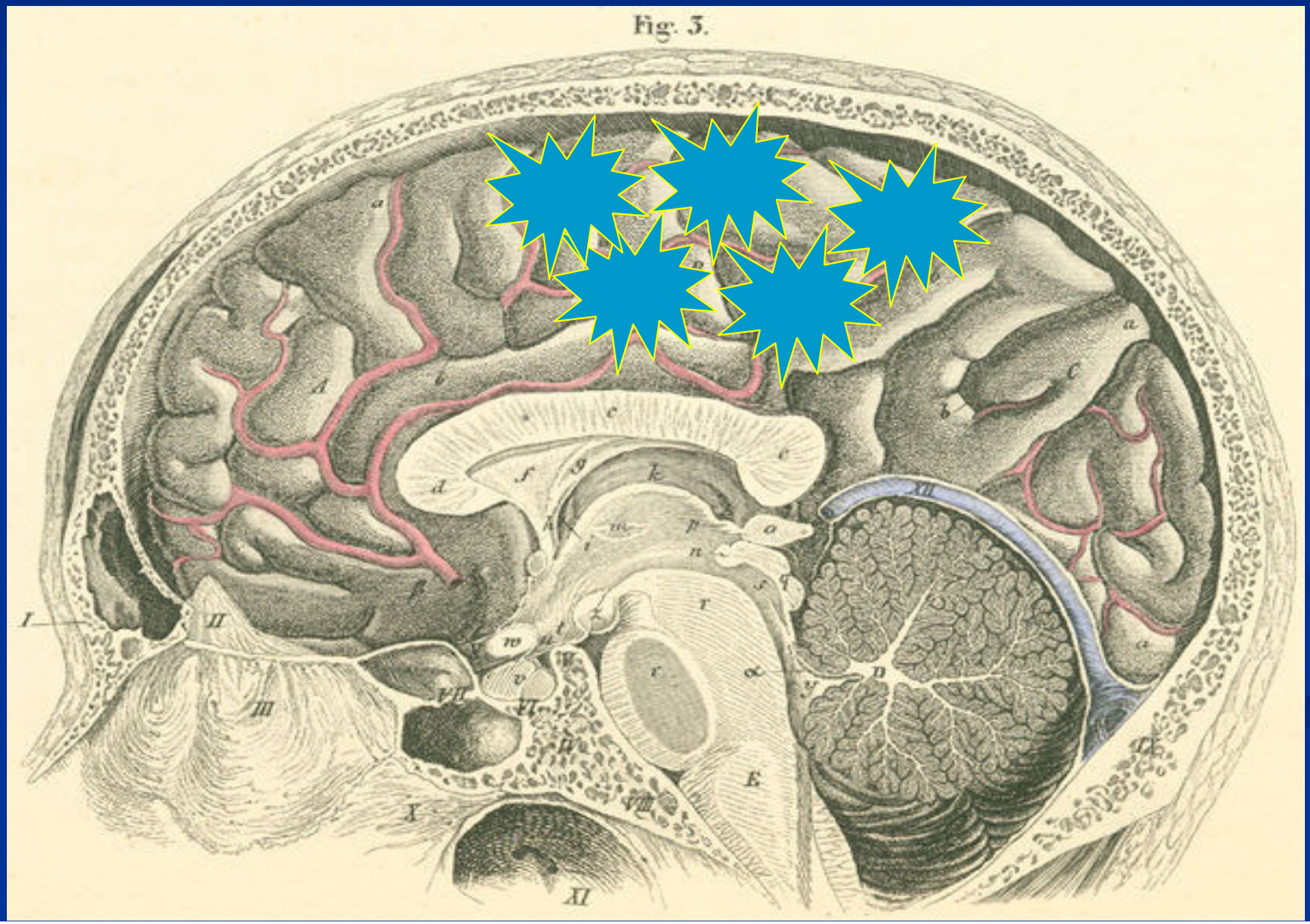

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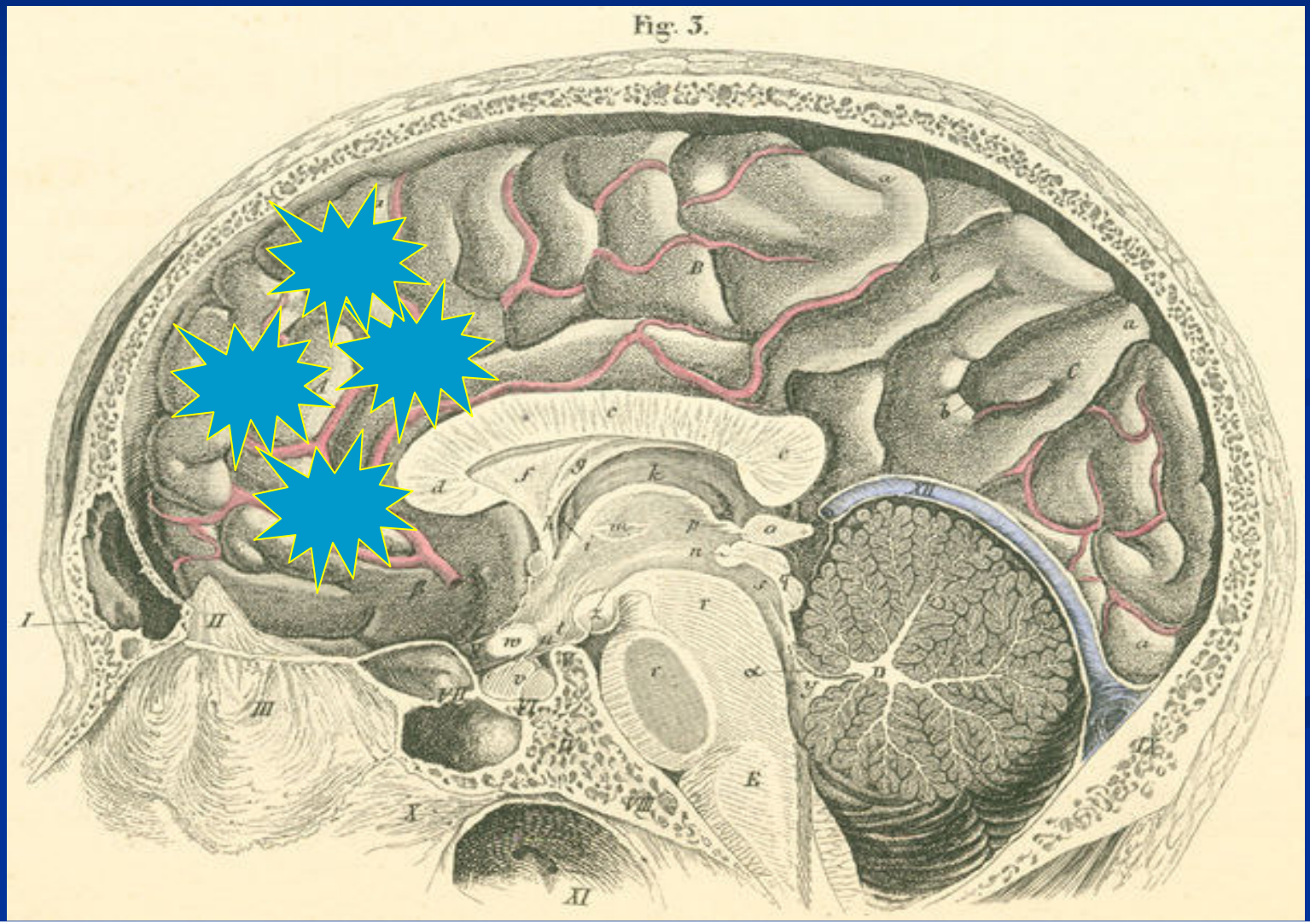
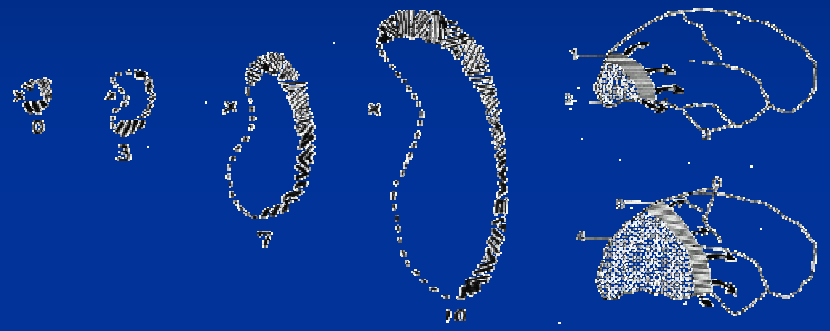


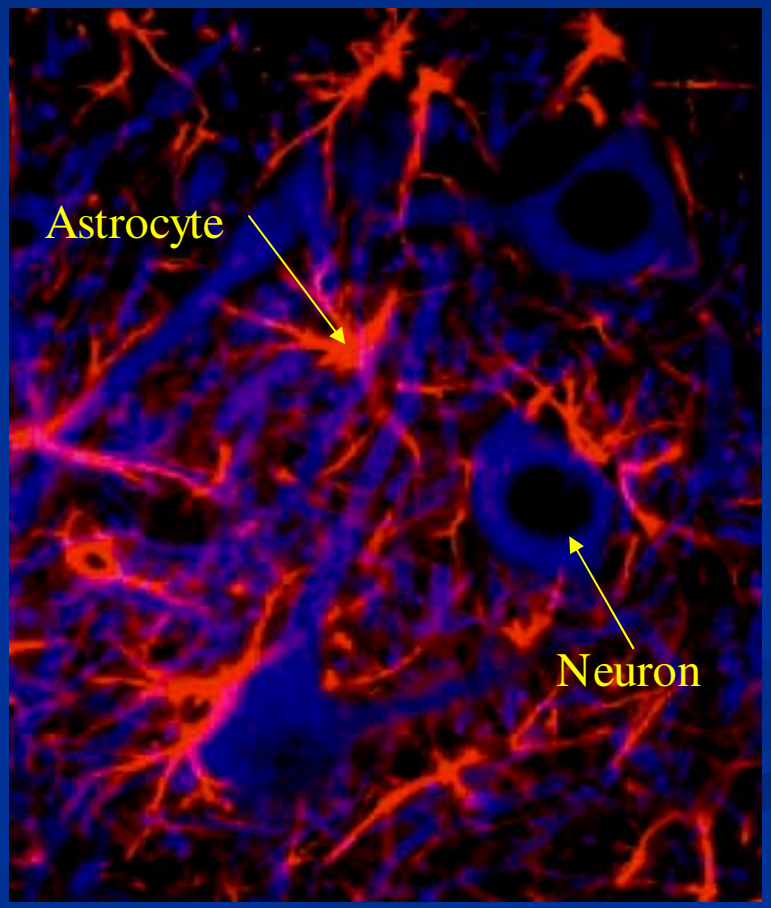
Spreading Depression of Dr. Leao



- Observed in animal brain slices: Stimulating the brain electrically causes a slowly spreading electrical wave.
- Travels 3mm/ min, contiguously, taking about 15 minutes to cross the brain
- What conveys this slowly moving wave? Is it directly related to migraine in humans? Why is it so slow?

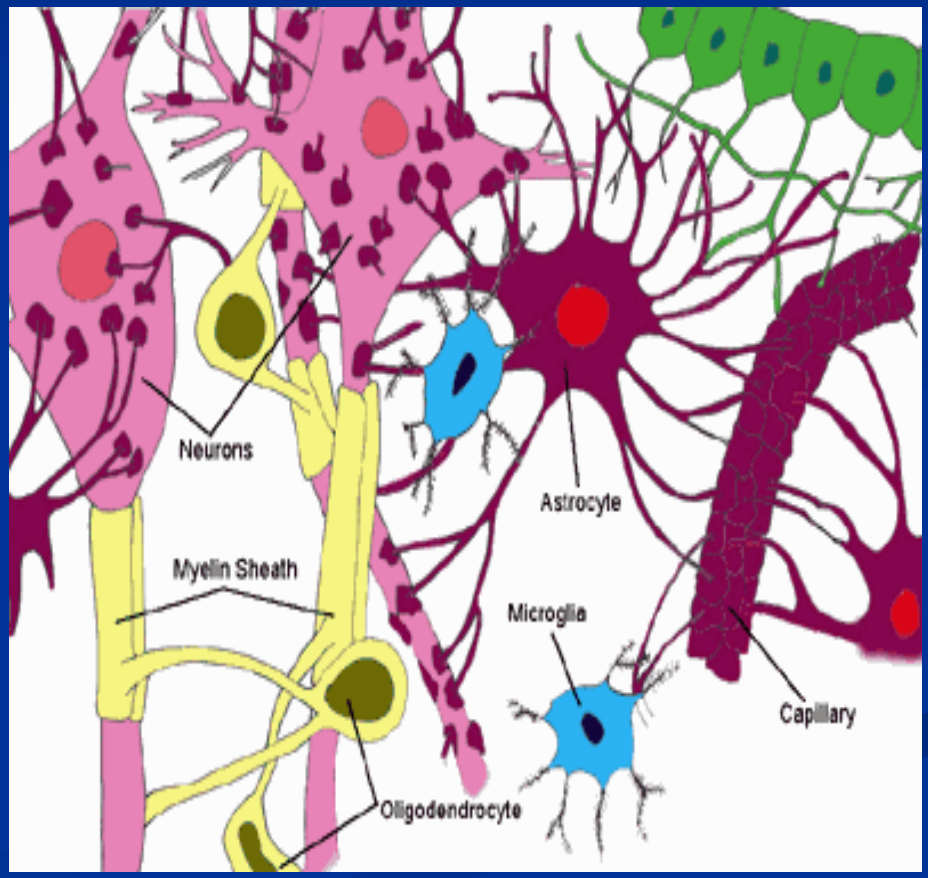
Newest Brain Discoveries that Explain Spreading Depression

- Confocal microscopes show us brain cells in 3 dimensions.



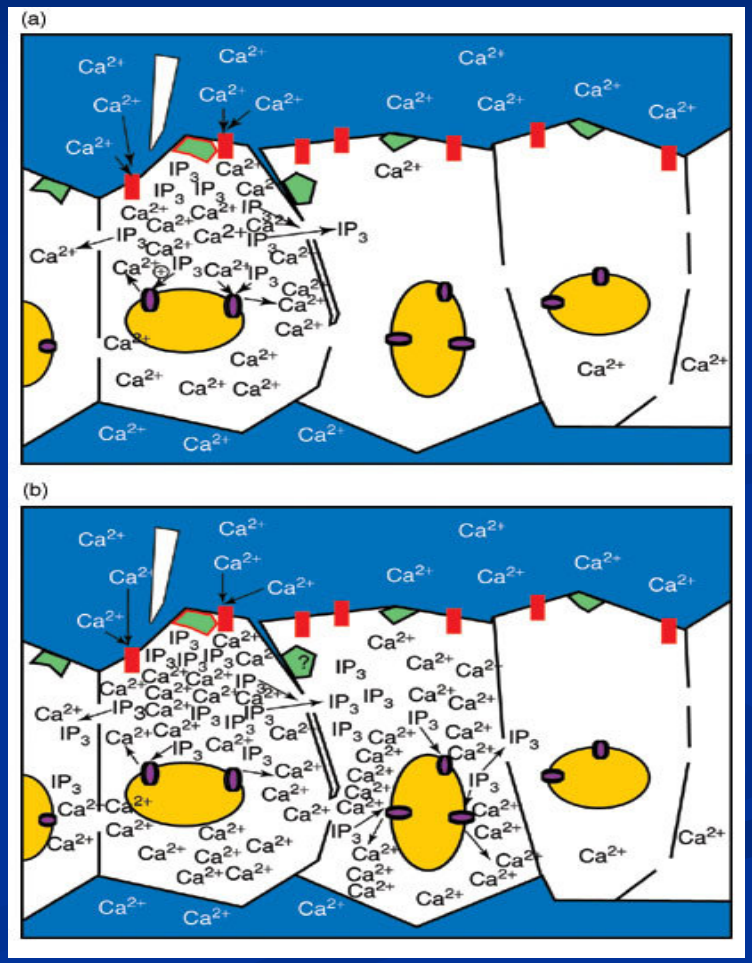
Astrocytes are more influential than previously imagined

- Astrocytes are electrically active cells that can talk to one another and other brain cells.
- Their dendrites wrap around 20-30 neurons with multiple endings on the surface of the neurons giving excitatory or inhibitory input to the neurons.
- Each astrocyte is assigned several neurons and a blood vessel.



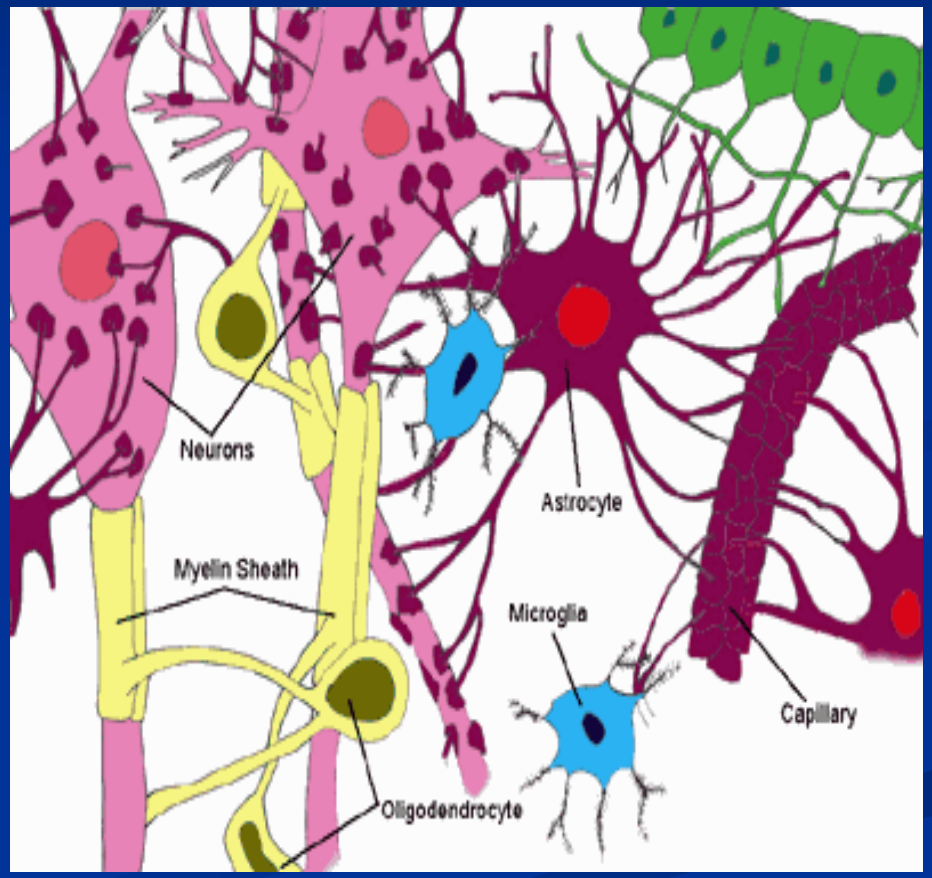
Spreading Depression of Leao is an inter cellular calcium wave

- Astrocytes have gap junctions that open between adjoining cells allowing them to directly share their ionic environments.
- **Spreading depression is a spreading inter cellular calcium wave traveling through the astrocyte population through these gap junctions**
- The wave travels slowly, 3mm/ min, and contiguously, because it is **transmitted by the astrocytes, not the neurons**



Astrocytes link blood signals to neuronal signals

- A single astrocyte and it's neurons are called "**astrocyte neurovascular unit**"
- A chemical blood signal is received by the astrocyte, then sent to the neurons amplifying the message
- Thus spreading depression has a similar arterial vasoconstrictive wave that accompanies it.
- But I believe the change in mental status is the neuronal effect not the vascular effect.



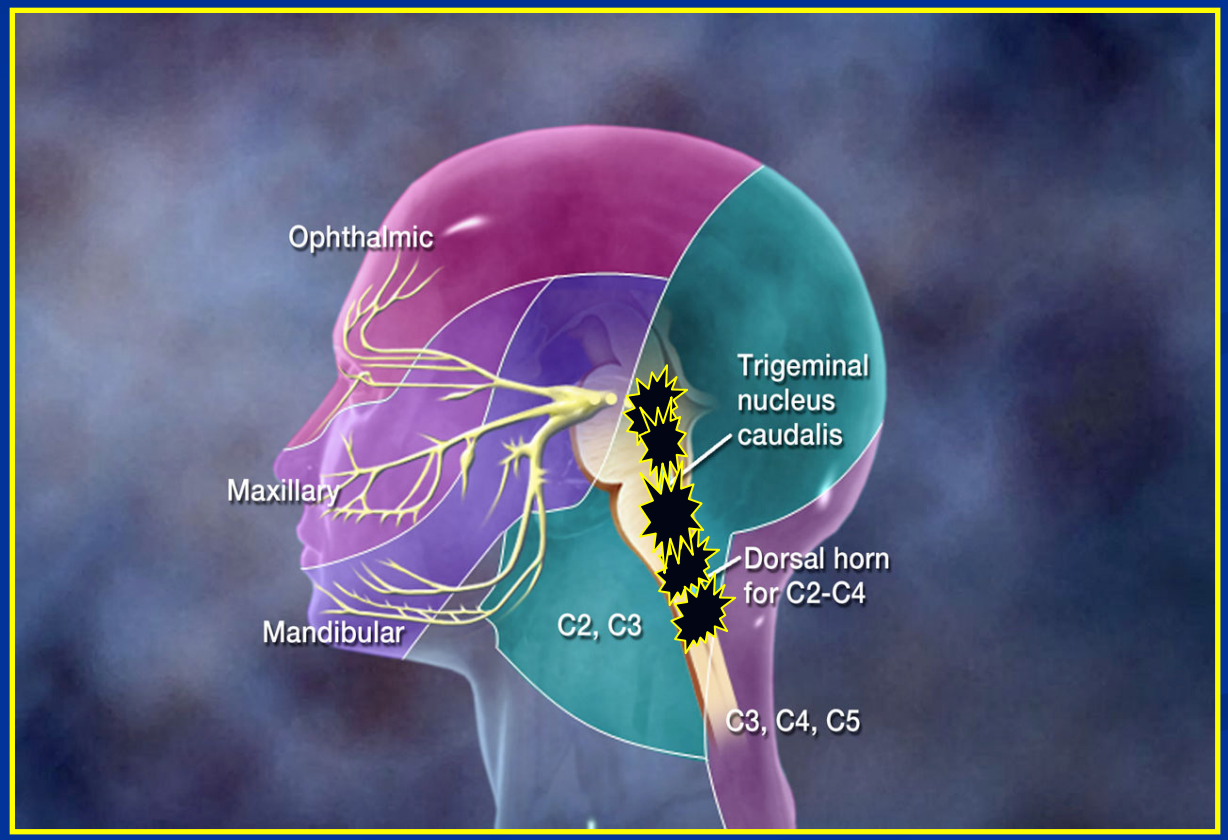
Most headaches are "migraine"

- I believe that all the headaches that most of us have are "migraine" meaning a ***genetically inherited tendency to turn on the head pain system without a blow to the head.***
- This excludes people who have headache because of brain infection, a blow to the head, a brain tumor, or a stroke. All of those people have head pain because of irritated nerve endings.
- **Always have a scan. The headache of a brain tumor is no different than daily headache from migraine**.

- Why do humans think headaches are "normal"? It is the only pain syndrome we think is "normal".

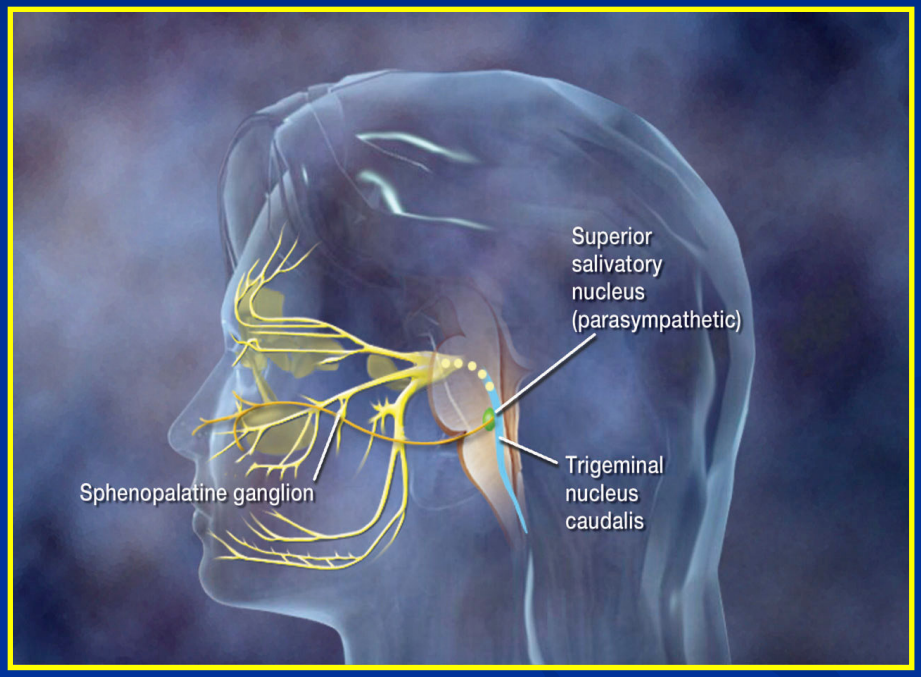
What is unique about the head pain system that makes it turn on spontaneously?

The other, analogous pain areas of the rest of the spinal cord don't just switch on when ever they feel like it.

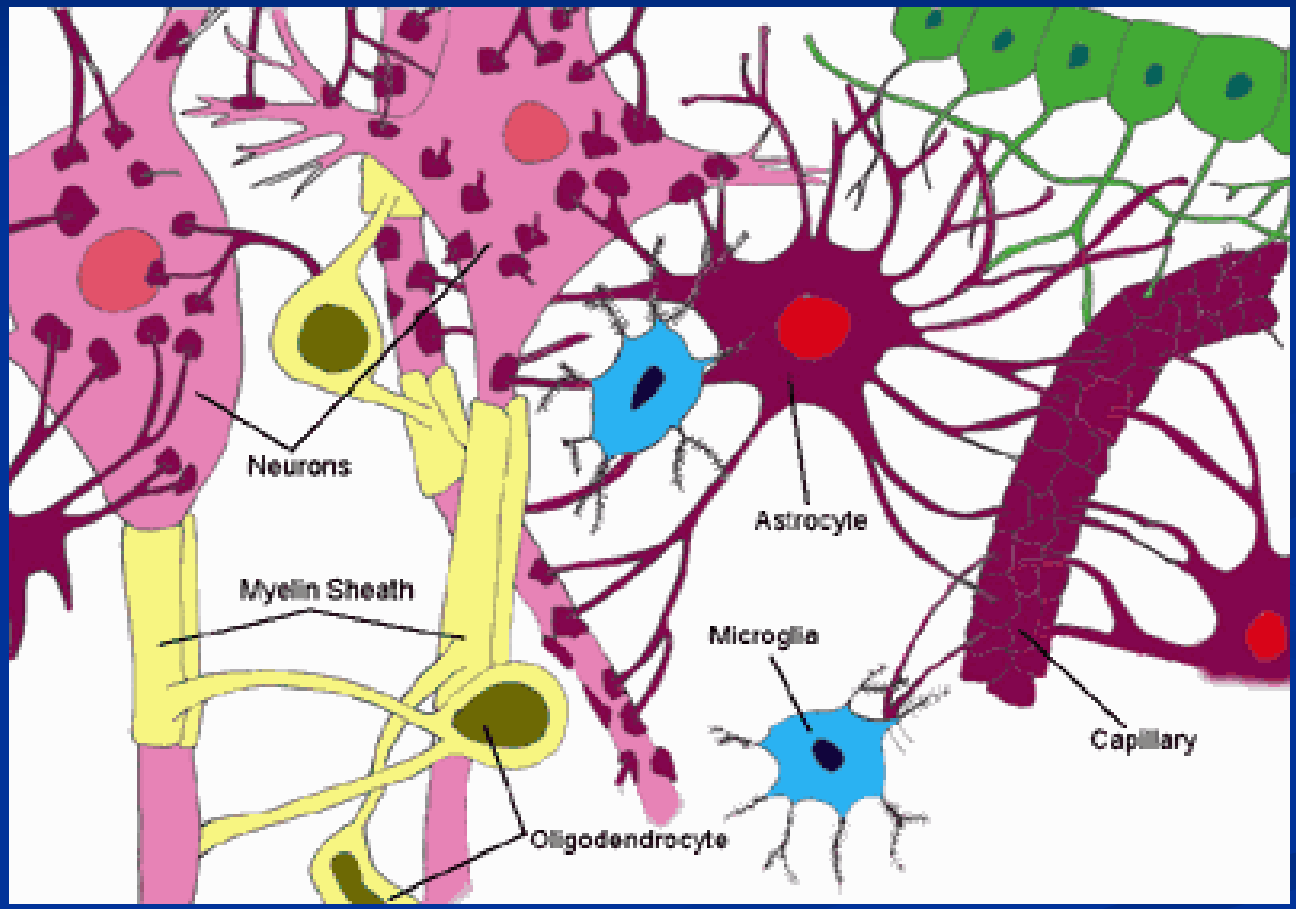


What about the other migraine symptoms? They're not in the trigeminal caudal nucleus

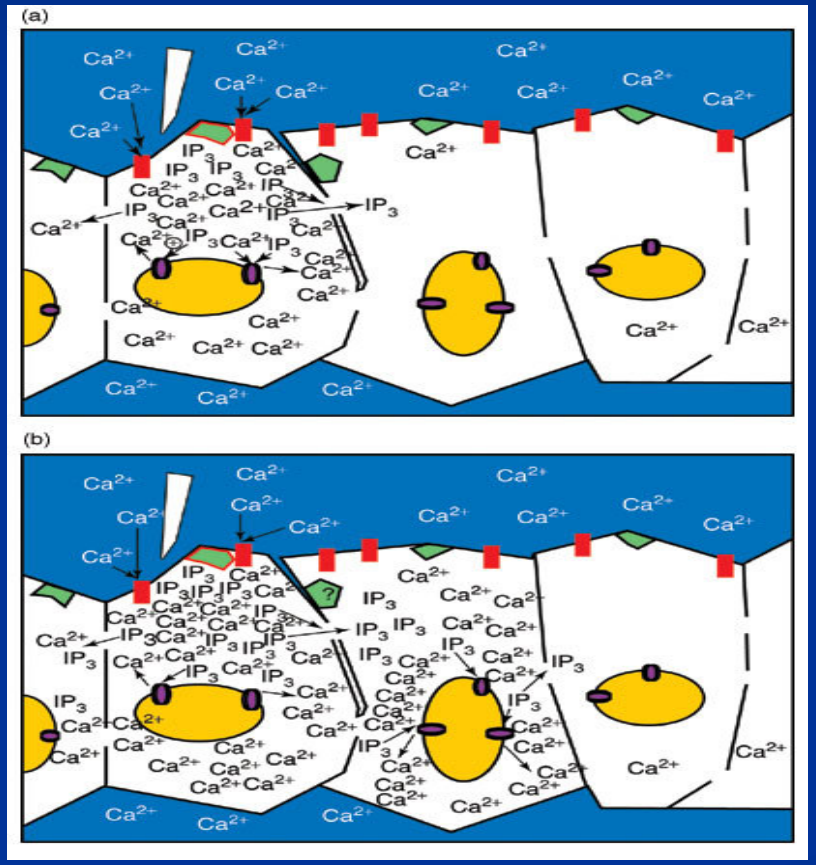
- Nausea from the Chemotrigger Zone
- Facial congestion from the Salivatory Nucleus which innervates the mucosa of the sinus cavities .
- Several brainstem nuclei are being excited together.

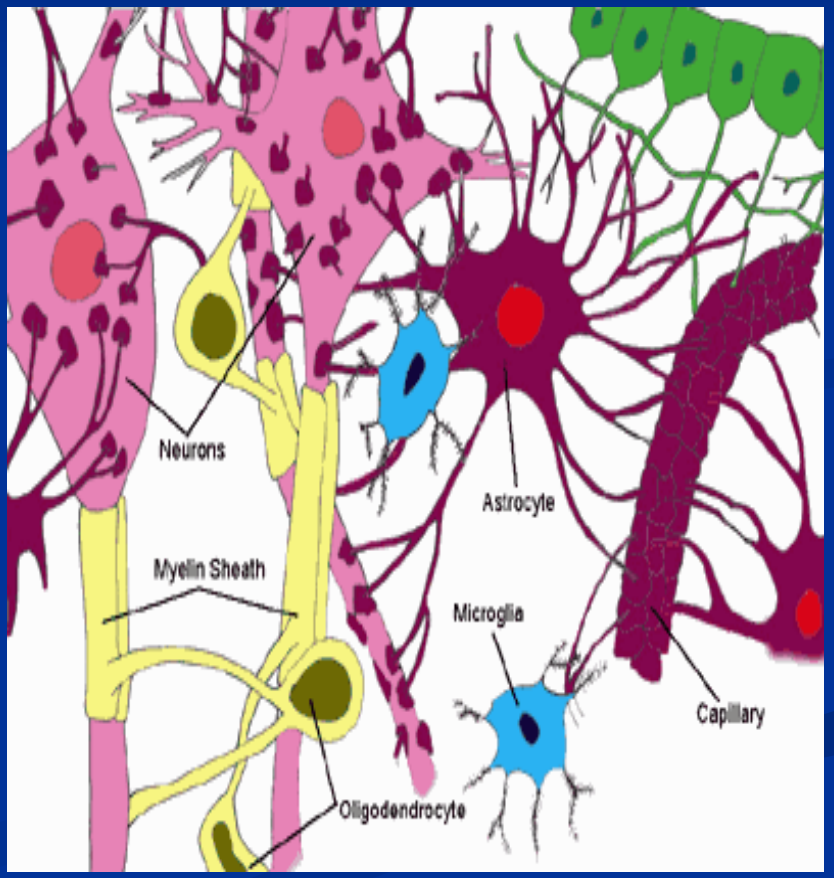


What causes this excitation? Remember our friend the astrocyte?



Astrocytes act more as a syncytium joining all of the neurons of the brain





Migraine as an astrocyte disorder

- The channel abnormalities linked to migraine are probably manifested in the **astrocytes,** not in the neurons, thus the syndrome is not a single brainstem nucleus, but a **region** of the brain that is hyper excitable.
- Snuggled right up against the migraine brainstem generator is the **sleep switch**, which is **designed to go on and off spontaneously.**

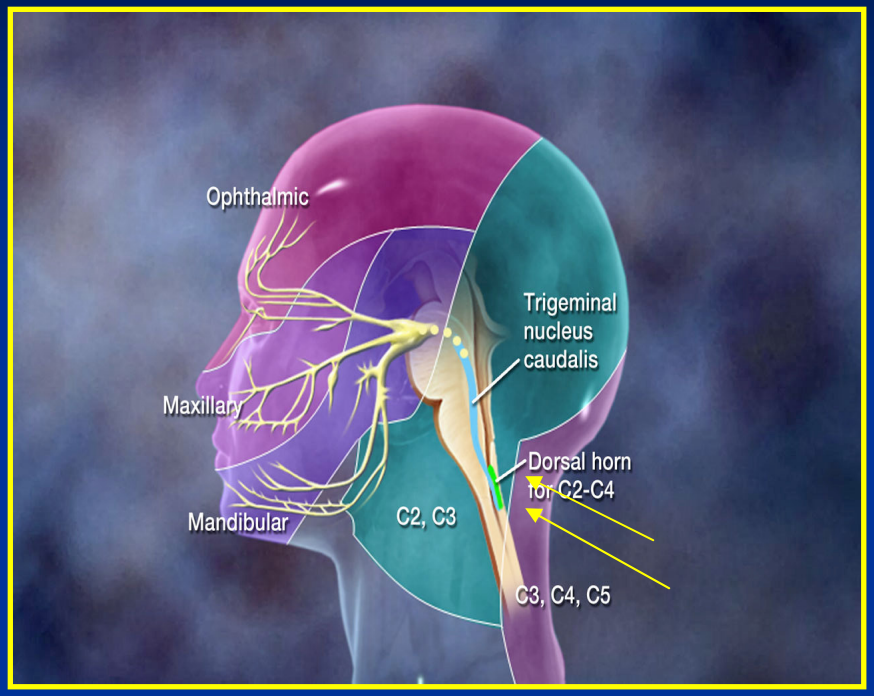
Why would humans have so many genes to give them headaches?

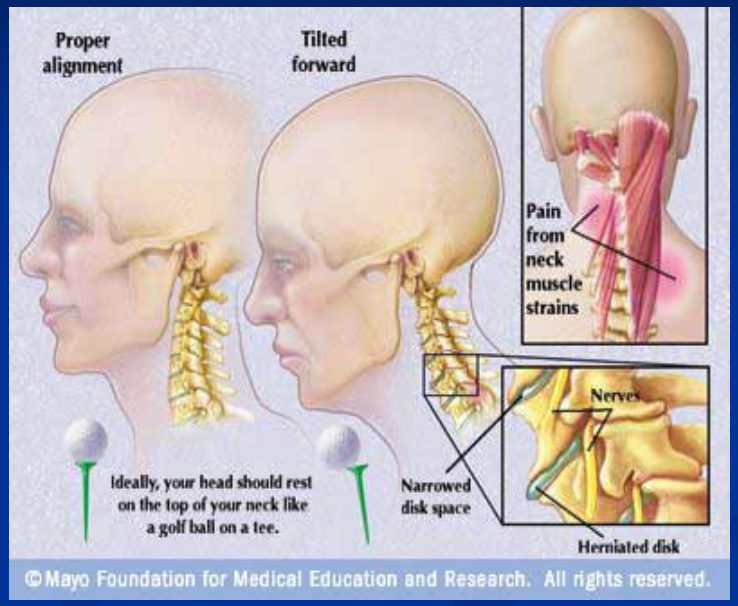
- Those 40 genes for migraine are probably not there to cause headaches, they're there to make the sleep switch work better.
- Sleep is the most important thing we do every day. If you sleep better you survive longer and have more children.

Migraine and Sleep are intertwined

- I believe that the unique aspect of the trigeminal caudal nucleus is not the nucleus itself but instead its proximity to the periaquiductal grey.
- Most daily headache sufferers have a sleep disorder underlying.
- But if you don't have a migraine gene your sleep disorder won't produce headache.
- Patients with a migraine gene often have a headache that lasts longer after mild head injury as well. They can't turn "off" their migraine generator.

What about chronic neck pain and "tension headaches"





- If mild head injury can become chronic daily headache because the pain center cannot turn off, then
- Mild irritation of cervical roots might also lead to daily headache.
- To make the neck pain resolve *we have to decrease the excitability of the brain stem center* that receives the input instead of focusing on the neck.
- The neck looks normal because it is normal.

Are daily headaches migraine too?

- What some authors are calling “transformed migraine” is just daily migraine, some days milder, some days more severe.
- Daily headache or daily “migraine” is probably one of the biggest causes of daily, non radiating neck pain.
- Sinus headaches without green or yellow snot are just migraine in the face.
- In order to assume this the **anatomy must be normal, so always scan first.**

Key Points of Brainstem Hyper excitability

- Activation observed in the posterior brain stem on PET scans is probably that whole region of the brainstem.
- Activation of the posterior brain stem can result in pain anywhere along the trigeminal-cervical network; including the head, the neck, and the face.
- Activation of the TNC can cause cross-over activation of the Salivatory Nucleus leading to sinus congestion symptoms, nausea through the chemotrigger zone, hypersensitivity to light sound and smell through connections to the thalamus.

Sleep disorders cause migraine

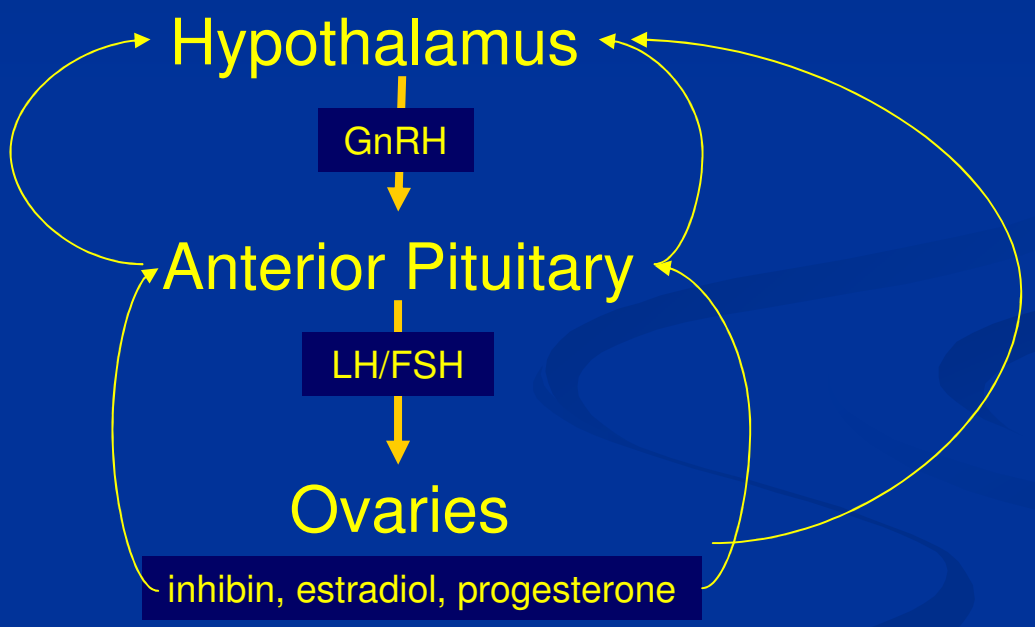
- Most patients with daily headache have a primary sleep disorder, either sleep apnea, restless leg syndrome or periodic limb movements of sleep.
- Many just don't get into the right phases of sleep.
- Most of these patients have vitamin D deficiency with or without accompanying B12 deficiency.
- Measure D 25OH, B12, iron and replace all that are low first. D 70-85 ng/ ml. B12 > 500.
- The good sleep cures the headache, not the D or B12, so if sleep is still terrible help with that also.

Hormones and Migraine

Any migraine theory has to explain:

- Why do migraines start at puberty?
- Why do they start in boys and girls around the same age but get much better in boys?
- Why are they worse around the menses?
- Why are they much worse perimenopausally?
- Why do they go away after menopause?

Menstruation and Releasing Hormones



Adapted from MacGregor EA. *Neurologic Clinics* 1997;15(1):125-141.

Gonadotropin Releasing Hormones

- The releasing hormones start to spike in boys and girls at puberty.
- GnRH is also a **neurotransmitte**r, it has receptors in the brainstem periaquiductal gray. GnRH levels affect sleep snd brainstem excitability.
- After age 18 the boys have a constant daily testosterone level, their sisters have monthly spikes.
- Perimenopause causes lack of estrogen so releasing hormone levels go sky high, low doses of estrogen replacement are not enough to inhibit GnRH completely. Women in menopause can't stay asleep.
- Fix the D/ B12 system first to get the sleep as good as possible and the headaches might go away. Estrogen/ progesterone replacement also makes sleep better.

Children Have Headaches Too

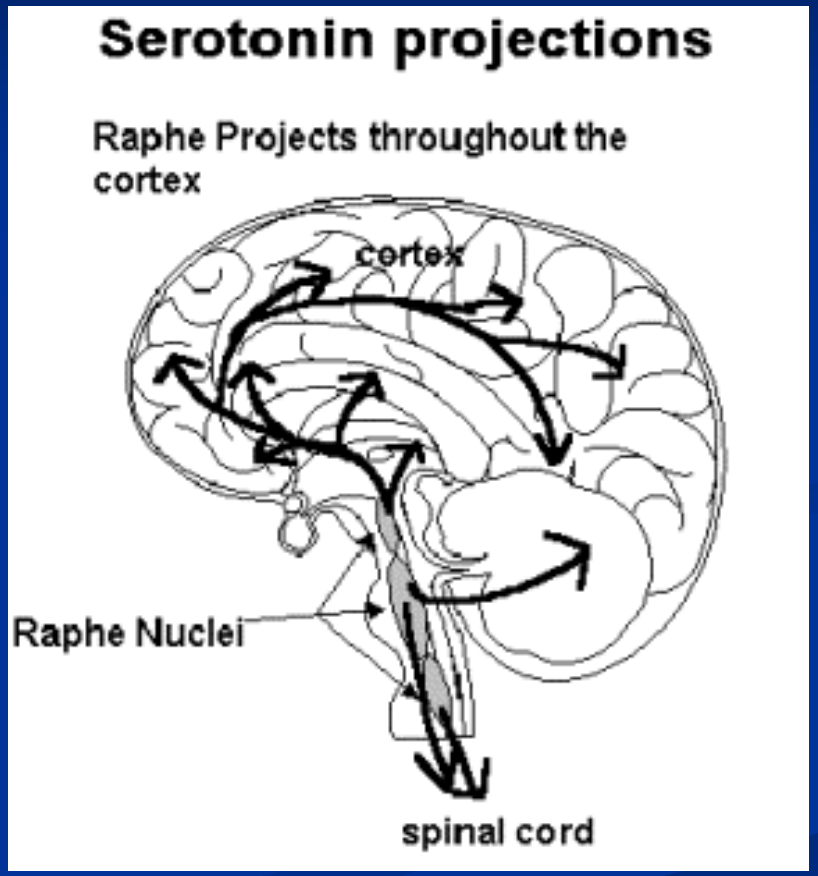
- There is absolutely no difference between adults with headache and children with headache.
- All of the children I see with headache have poor sleep and vitamin D deficiency.
- Some have leg pain from kicking in sleep which is basically, rickets.
- Children who get significant headaches before puberty all have sleep disorders and D deficiency. Fix that first. **Always have a CT scan.**

Episodic Treatment:
Triptans; sumatriptan, naratriptan, eletriptan, etc.

- They work on Serotonin 1B and 1D receptors that are **feedback inhibitors of Serotonin release**.
- They are not pain relievers or anti-inflammatories.
- We told our patients to "save them for your migraines", but our patients were smarter.
- "if I can get my medicine soon enough it works"
- It turned out that the triptans worked better when used earlier, on the little headaches, teaching us that all the headaches are migraine in mechanism.

Where are the Serotonin receptors ?

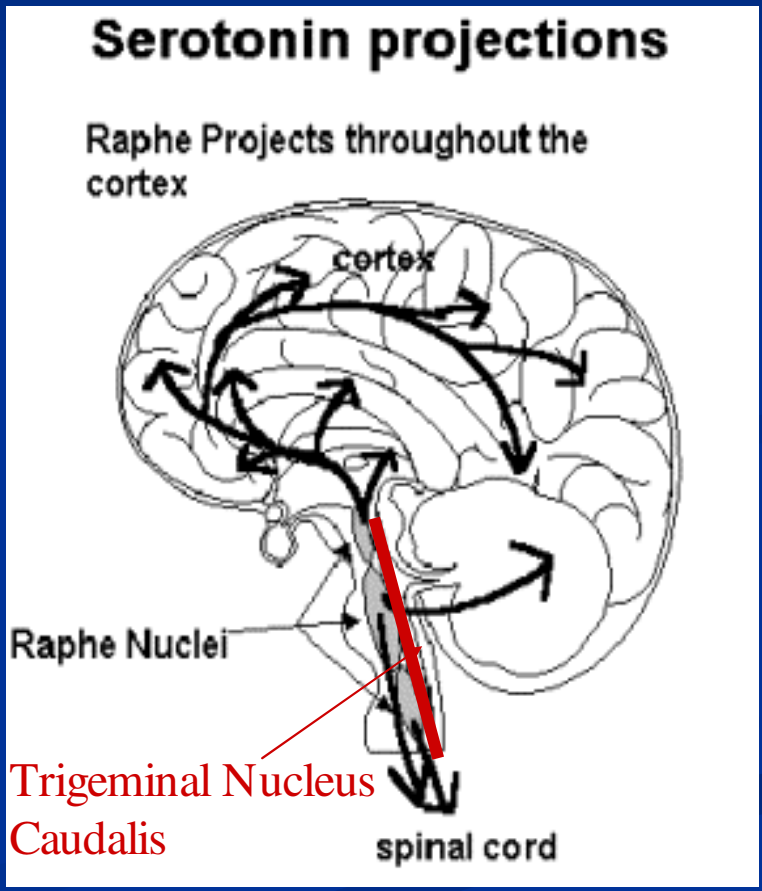
- Most of the serotonin measured throughout the brain originates from the Raphe nuclei in the brainstem.
- So they are probably not acting primarily on blood vessels in the brain they are working at the “migraine brainstem generator”.



Serotonergic cells in Raphe Nuclei of the Periaquiductal Grey

- Brain serotonin levels are directly related to the level of vigilance or alertness.
- The brainstem chemoreceptor trigger zone is in the same area, controlling nausea, (the newer anti nausea agents act on serotonergic receptors in the brainstem).
- Animal studies show that the Serotonergic Raphe Nuclei directly control the level of excitability of the TNC.

Ref 9



Treatment: Prevention

- Use the triptans early!
- Treat the sleep first if possible, before a daily preventative.
- Very severe headaches not responding to triptans may need a daily preventative.
- Once the daily headache patient gets on the right preventative medication, (correcting their genetic hyper excitability), their headaches become episodic and are no different than any other migraine.
- After the preventative medication decreases the severity and incidence of the headaches, try the triptans again.

Daily Preventatives are all Channel Stabilizers

- Verapamil SR 180 to 360 (careful in renal failure)
- Atenolol 100 mg qd (Ca++ channel active in migraine)
- Topiramate75-100mg hs
- Zonisamide 100mg -200mg BID, 300-400 qhs
- Divalproex sodium 500- 1000 qd (ER) or BID
- Gabapentin
- Cyproheptidine
- Other, newer seizure medications, Levetiracetam, Lamotragine, Oxcarbazepine, Tiagabine, Pregabalin

Are there other things like Migraine?

- Episodic vertigo is a channel disorder as well. Ca++ or Na+. (**Assumes normal anatomy so always have a scan**.)
- Ringing in the ears is a "turning on" of the central brainstem hearing system and frequently acts like migraine: i.e., comes on spontaneously for hours to days, can be daily, gets worse when the sleep is bad.
- When it's both sides, **no hearing loss,** with or without "dizzy", treat it the same way you would migraine; check the vitamin levels, get the sleep better.

Mouse models of Migraine

- One of the Ca++ channel mutations that causes migraine is found in mice.
- Unfortunately the mice can not tell us if they have a headache
- They do have staggering episodes and occasionally, epilepsy.
- There are also **inherited epilepsy syndromes and vertigo syndromes** that are caused by Ca++ channel mutations.

Epilepsy and Channels

- If you can make a mouse epileptic with a channel mutation it should not be surprising that
- Most of the inherited epilepsies are now known to be channel disorders as well, usually Na+ or Cl- channels.

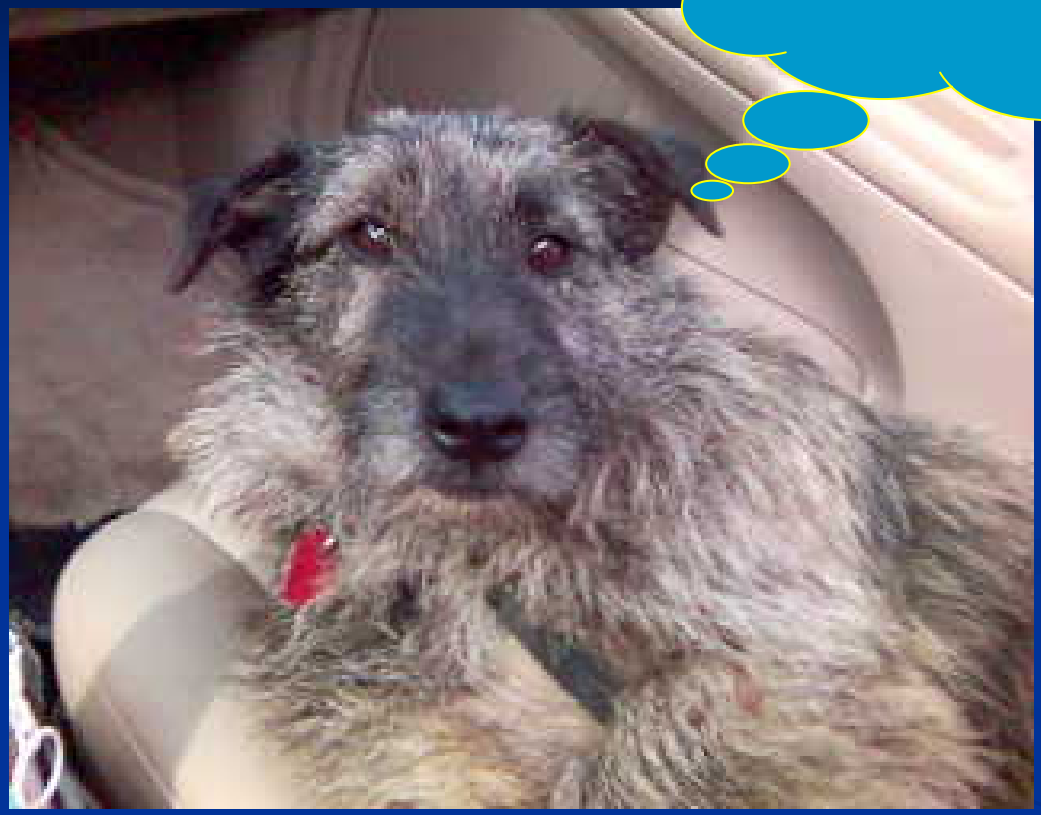
So this is what they meant by "knockout mouse"

Most epilepsy medications are "channel stabilizers". They act on malfunctioning channels to make them act more normally. Which is probably why some of them are also migraine preventatives and treat vertigo.

- Lyrica
- Neurontin
- Depakote
- Topamax
- Trileptal
- Tegretol
- Keppra
- Gabatril
- Diamox
- Zonegran
- Lamictal
- Dilantin

Can Epilepsy be like Migraine?

- If there is no abnormality of the brain anatomy it is a spontaneous “turning on” of neurons in the brain.
- It gets worse when the sleep is worse.
- We use the same medicines.
- Can be genetically linked to vertigo attacks and migraine.
- Any of the hyperexcitability disorders that we use seizure medicines for can be thought of as inappropriate “turning on” of a part of the nervous system.



Do animals have migraines?

(Bella can't tell us if she has a headache.)

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