

Why do humans have so many headaches?

Stasha Gominak, M.D.

East Texas Medical Center Neurologic Institute
700 Olympic Plaza, Suite 912 Tyler, Texas 75701

April 25 , 2014

Headache is described in
every human society
throughout written history

Why would it be so common?

Headache is a genetic disorder

Why would we want to pass on these horrible headaches to our kids?



We think that genes providing a survival advantage get spread throughout the population

What would be the survival advantage of having a headache?

Could the genes for headache convey some other thing that might improve survival?



Why have we taught each other that “normal headache” and migraine are two different things?

What if headache and migraine
are the same?

What if “migraine” and “normal
headache” occur by the same
mechanism?

Why do my patients use the phrase “normal headaches”?

- Why do we think it is “normal” for the head to hurt without injury?
- Why haven’t we fixed our most common neurologic problem?
- Are we thinking about it the wrong way?



What is the evidence that migraine and headache are on a continuum?

- All migraine sufferers also have “normal headaches”.
- When the triptans became available (triptans are migraine medications; sumatriptan, rizatriptan, naratriptan...etc.) we told our patients ”save these for your migraines”
- Their response: “if I take the medicine soon enough it works.”
- The patients found that triptans worked for their milder, “normal headaches” before they grew into a “migraine”.

The triptans work for “normal headaches” too

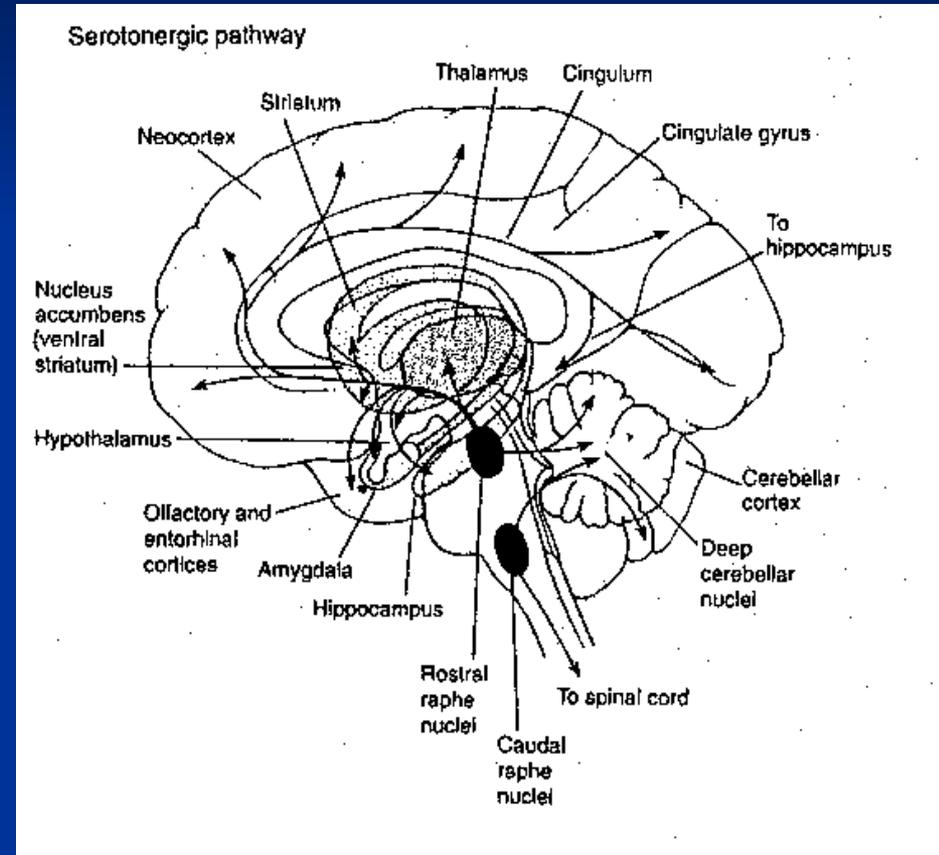
- We may not prescribe triptans for normal headaches because they're very expensive, but they **do** work well.
- That probably means serotonin plays a role in “normal headache” as well as migraine
- Baby migraine, which is “just a headache”, may grow into a bigger headache that acquires other features which make it recognizably “migraine”.

What do we know about the mechanism of the triptans?

- Triptans work on 1B and 1D serotonin receptors
- 1B and 1D receptors are feedback inhibitors; they decrease serotonin release.
- Does that mean that the mechanism of action has to do with the blood vessels? (Which is what we've been taught.)..... Not necessarily.
- Serotonin appears in many areas of the brain.

Serotonin Release

- Most of the serotonin measured in the brain originates from the raphe nuclei in the posterior brainstem.
- Serotonin acts like a neurotransmitter as well as a hormone. It is released along the axon as well as at the nerve terminals bathing the entire brain in “happy juice” every few seconds



Sleep and Serotonin

- REM sleep and triptans have something in common: They both drop serotonin levels. In order to enter REM sleep we must have low serotonin.
- Serotonin is high when we are awake but low when we enter deep sleep.
- Your brain wants to be very, very sure that you are indeed sleeping before you start to dream. Because REM and awake are similar states the serotonin level helps the brain know which state you're in .

Migraine and Sleep

- If our patients have told us for the last 100 years that getting into deep sleep is how they “break” the headache, why are there so few articles showing us what the sleep looks like in migraine sufferers?
- Why have we been told that sleep disorders only happen in fat, old men?

Migraine and Sleep

- I became interested in sleep 10 years ago when one of my young, normal weight patients insisted that I send her for a sleep study. Her husband said she “snored like a train”.
- She had been on four preventative medicines over a period of two years and still had daily headache.
- She had severe sleep apnea and 6 weeks of sleeping with CPAP mask completely cleared her headaches.
- For the following 5 years I ordered sleep studies on all of my daily headache patients. They were all abnormal.

Migraine and Sleep

- Ten years later there are still few studies looking at the results of sleep studies in migraine sufferers. Why?
- Academic neurologists who are sleep specialists do not usually study migraine?
- Those who are migraine specialists do not study sleep?
- Those who study astrocyte anatomy do not see patients?
- Most physicians feel more comfortable going along with the currently accepted medical theories.
- But what if the theories don't explain what the patient feels?

“Explanations” of headache are theories

- What the patient experiences is the only “truth”.
- Headache patients are, by definition “normal” ; normal scan, normal neuroanatomy. They don’t die from headache so there are no autopsy studies.
- Every one of our explanations is made up; it’s a theory.
- There is no user’s manual that confirms which is the real “truth”.
- But my explanation of cause *will* direct my search for how to fix it.

Sleep study results in migraineurs

- Many of my migraine patients don't sleep normally. They have various forms of insomnia, "light sleeper", "not a morning person".
- All of them had abnormal sleep studies, just not necessarily apnea.
- The most common sleep study results in my young, healthy migraine patients were delayed onset of REM, decreased REM and REM related apnea. Some slept for 10 hours and had no REM.
- We have not been treating migraine by treating sleep because we haven't known how.
- The sleep medications we have do not produce normal sleep.
- But if you know how to fix the sleep, fixing the sleep does indeed fix the headaches.

Are we the only ones?



I hope to convince you of the following:

- Migraine does not occur in the cerebral blood vessels.
- Sleep and migraine are intertwined.
- Migraine is a genetic disorder that leads to hyper-excitability of the posterior brainstem and occipital lobe.
- The posterior brainstem sleep nuclei are designed to *turn on and off spontaneously*.
- That spontaneous “on” signal can accidentally “leak” into the surrounding nuclei causing them to accidentally turn on also, even though they’re not “supposed to”.

The trigemino-vascular theory of migraine is the old theory

- This theory, which has been the most popular explanation for migraine, grew out of the fact that there are **no pain fibers in the brain itself**.
- The pain fibers are only on the meninges, (the linings that cover the brain), and on the cerebral blood vessels.
- As they are the only pain receptors in the brain the trigemino-vascular theory suggests that the pain is **experienced** in these receptors.
- It proposes that “inflammatory” signals generated in the trigeminal fibers at the meninges and the blood vessels cause the head pain.

Is there a minority opinion?

- Dr. Michael Welch and Dr. Peter Goadsby have been the major proponents of an alternative view which suggests that the trigeminal caudal nucleus and the occipital lobe are hyper-excitable in migraine patients.
- The pain is **experienced in the brain stem** not in the blood vessels.

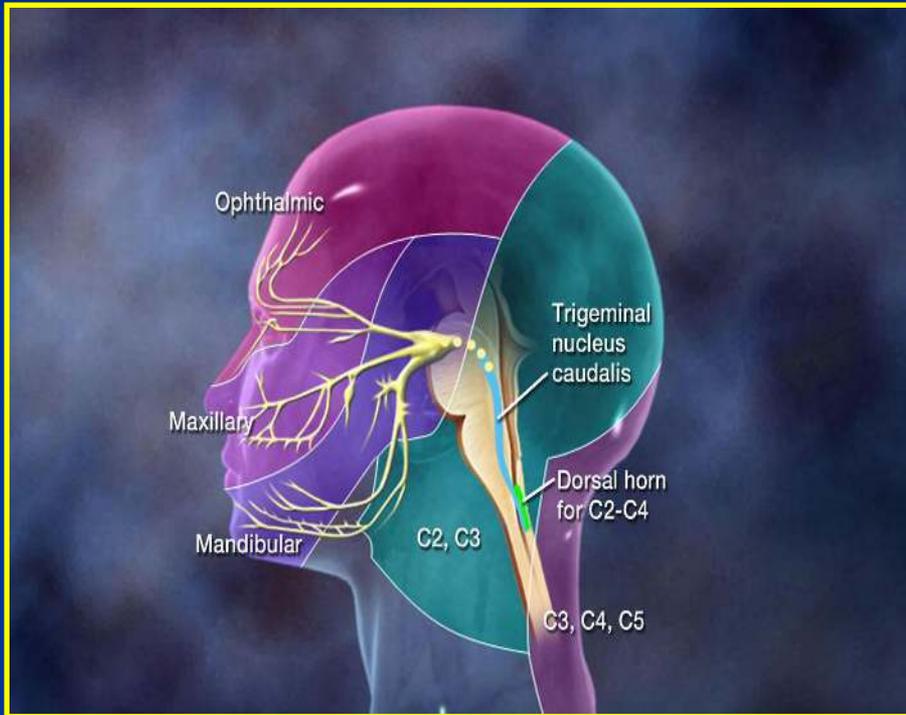
Some of Dr. Welch's articles establishing hyperexcitability of the brainstem in migraine patients

- Brain hyperexcitability: the basis for antiepileptic drugs in migraine prevention. Welch KM. Headache. 2005 Apr; 45 Suppl 1:S25-32. Review.
- Contemporary concepts of migraine pathogenesis. Welch KM. Neurology. 2003 Oct 28;61(8 Suppl 4):S2-8. Review.
- Functional MRI-BOLD of brainstem structures during visually triggered migraine. Cao Y, Aurora SK, Nagesh V, Patel SC, Welch KM. Neurology. 2002 Jul 9;59(1):72-8.
- Cortical spreading depression and gene regulation: relevance to migraine. Choudhuri R, Cui L, Yong C, Bowyer S, Klein RM, Welch KM, Berman NE. Ann Neurol. 2002 Apr;51(4):499-506.
- Magnetoencephalographic fields from patients with spontaneous and induced migraine aura. Bowyer SM, Aurora KS, Moran JE, Tepley N, Welch KM. Ann Neurol. 2001 Nov;50(5):582-7.
- Periaqueductal gray matter dysfunction in migraine: cause or the burden of illness? Welch KM, Nagesh V, Aurora SK, Gelman N. Headache. 2001 Jul-Aug;41(7):629-37.
- The occipital cortex is hyperexcitable in migraine: experimental evidence. Aurora SK, Cao Y, Bowyer SM, Welch KM. Headache. 1999 Jul-Aug;39(7):469-76.
- MRI of the occipital cortex, red nucleus, and substantia nigra during visual aura of migraine. Welch KM, Cao Y, Aurora S, Wiggins G, Vikingstad EM. Neurology. 1998 Nov;51(5):1465-9.
- Transcranial magnetic stimulation confirms hyperexcitability of occipital cortex in migraine. Aurora SK, Ahmad BK, Welch KM, Bhardhwaj P, Ramadan NM. Neurology. 1998 Apr;50(4):1111-4.
- Brain excitability in migraine: evidence from transcranial magnetic stimulation studies. Aurora SK, Welch KM. Curr Opin Neurol. 1998 Jun;11(3):205-9. Review.

Dr. Goadsby's articles regarding hyper-excitability of the brainstem in migraineurs

- Brain activations in the premonitory phase of nitroglycerin-triggered migraine attacks. Maniyar FH, Sprenger T, Monteith T, Schankin C, Goadsby PJ. *Brain*. 2014 Jan;137(Pt 1):232-41.
- Diencephalic and brainstem mechanisms in migraine. Akerman S, Holland PR, Goadsby PJ. *Nat Rev Neurosci*. 2011 Sep 20;12(10):570-84.
- Pathophysiology of migraine. Goadsby PJ. *Neurol Clin*. 2009 May;27(2):335-60.
- Trigemino-cervical complex responses after lesioning dopaminergic A11 nucleus are modified by dopamine and serotonin mechanisms. Charbit AR, Akerman S, Goadsby PJ. *Pain* 2011 Oct;152(10):2365-76.
- The vascular theory of migraine—a great story wrecked by the facts. Goadsby PJ. *Brain* 2009 Jan; 132(Pt 1):6-7.
- Functional neuroimaging of primary headache disorders. Cohen AS, Goadsby PJ. *Curr Pain Headache Rep*. 2005 Apr;9(2):141-6.
- A PET study exploring the laterality of brainstem activation in migraine using glyceryl trinitrate. Afridi SK, Matharu MS, Lee L, Kaube H, Friston KJ, Frackowiak RS, Goadsby PJ. *Brain* 2005 Apr;128(Pt 4):932-9.
- Activation of 5-HT(1B/1D) receptor in the periaqueductal gray inhibits nociception. Bartsch T, Knight YE, Goadsby PJ. *Ann Neurol*. 2004 Sep;56(3):371-81

The Minority Opinion:



- Is that migraine is not experienced at the endings of the nerves but is instead experienced in the nucleus where the wires send their messages ; the **Trigeminal Nucleus Caudalis**.
- Unfortunately Dr. Welch, who originated this viewpoint, has been effectively drummed out of the headache meetings because his ideas are different.

If the blood vessels are the only part of
the brain with pain fibers it seems
perfectly logical to blame them for the
headache

And, by the way, why *doesn't* the brain have pain
fibers?

The brain and the spinal cord don't have pain fibers in the pinkish- grey gooey stuff because they don't need them

The brain and the spinal cord are the only parts with the skeleton on the outside

The skull protects the brain from penetrating objects



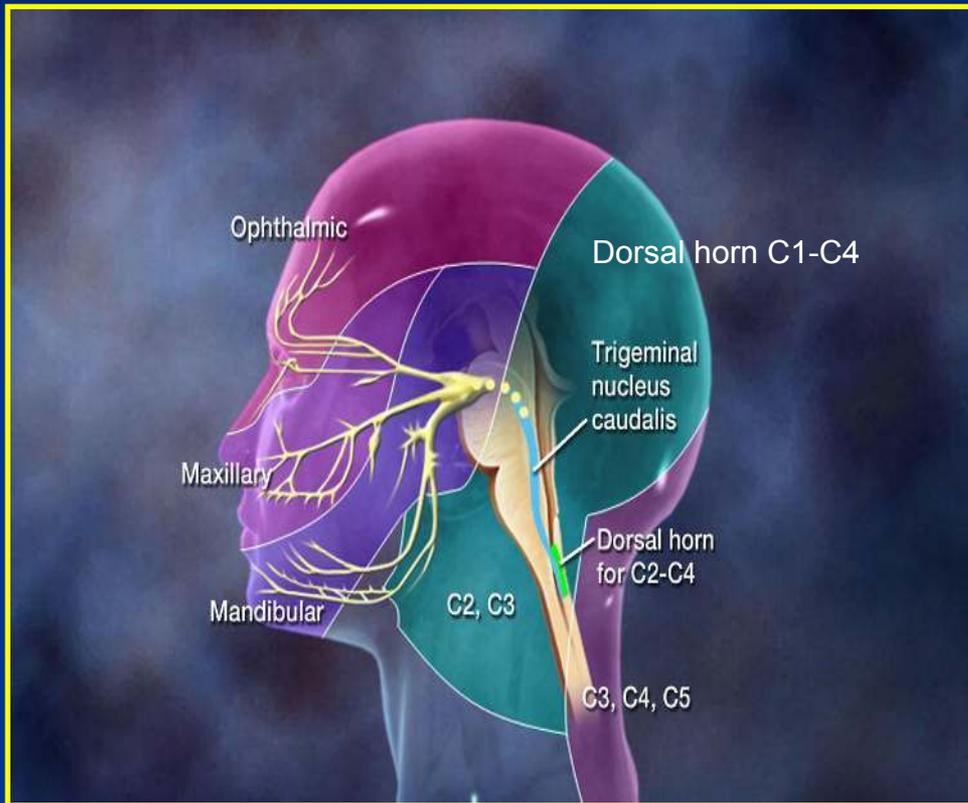
- But the skull does not keep the soft, fragile brain from banging against the inside of the skull when shaken
- The pain fibers are on the vessels and the meninges to tell us not to bang our heads.

This still doesn't tell me why it's
“normal” to have a headache

(when it's not normal for any other part of our
body to start hurting for no reason.)

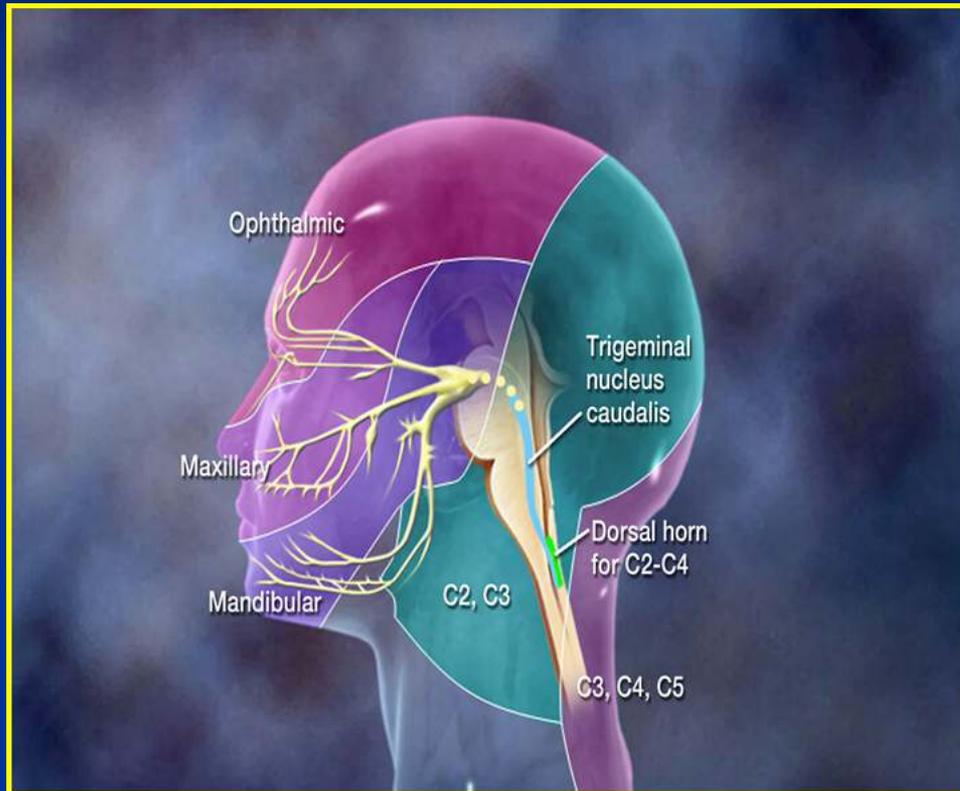
Is there something different about the pain system of the brain that would make it more likely to turn on spontaneously?

The head pain system is in two parts



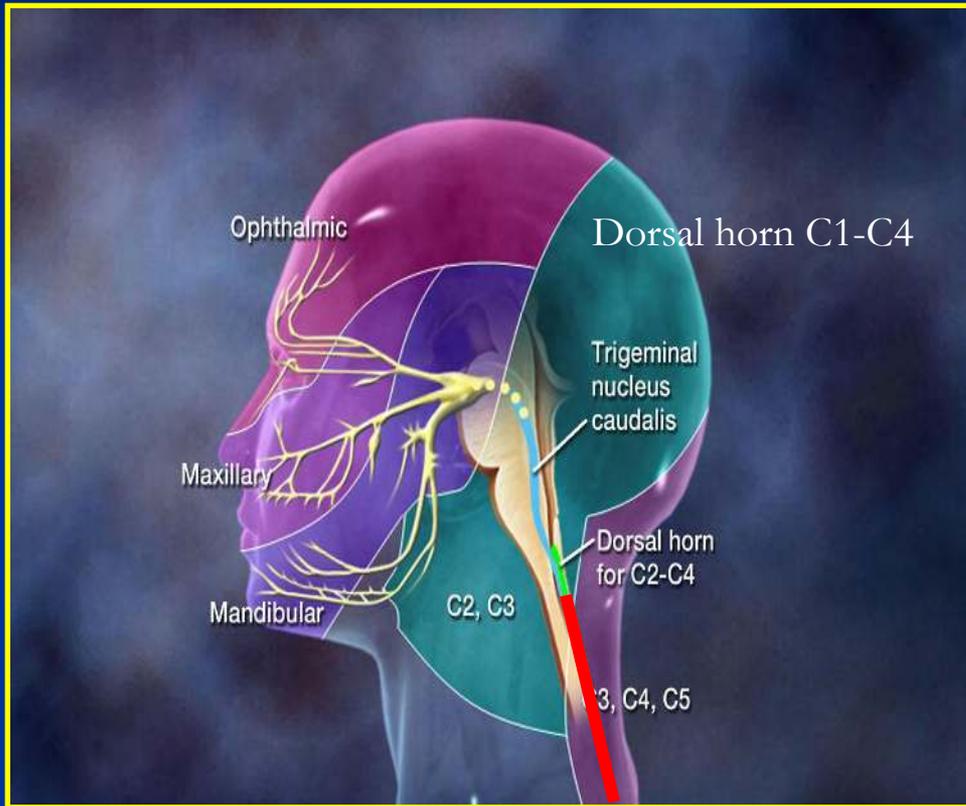
- The *Trigeminal Nucleus Caudalis* : in blue perceives pain for the face and the front of the scalp shown in pink and lavender
- The dorsal horn of C 1- C4 shown in green perceives pain for the back of the head and upper neck.

Headaches happen in head and in the neck



- Headaches start just as commonly in the neck as in the head, even though the neck is not really “in” the head.
- Why do they both turn on spontaneously?
- Why those two and not other nuclei?

Pain system extends down the spinal cord but does not just “turn on”

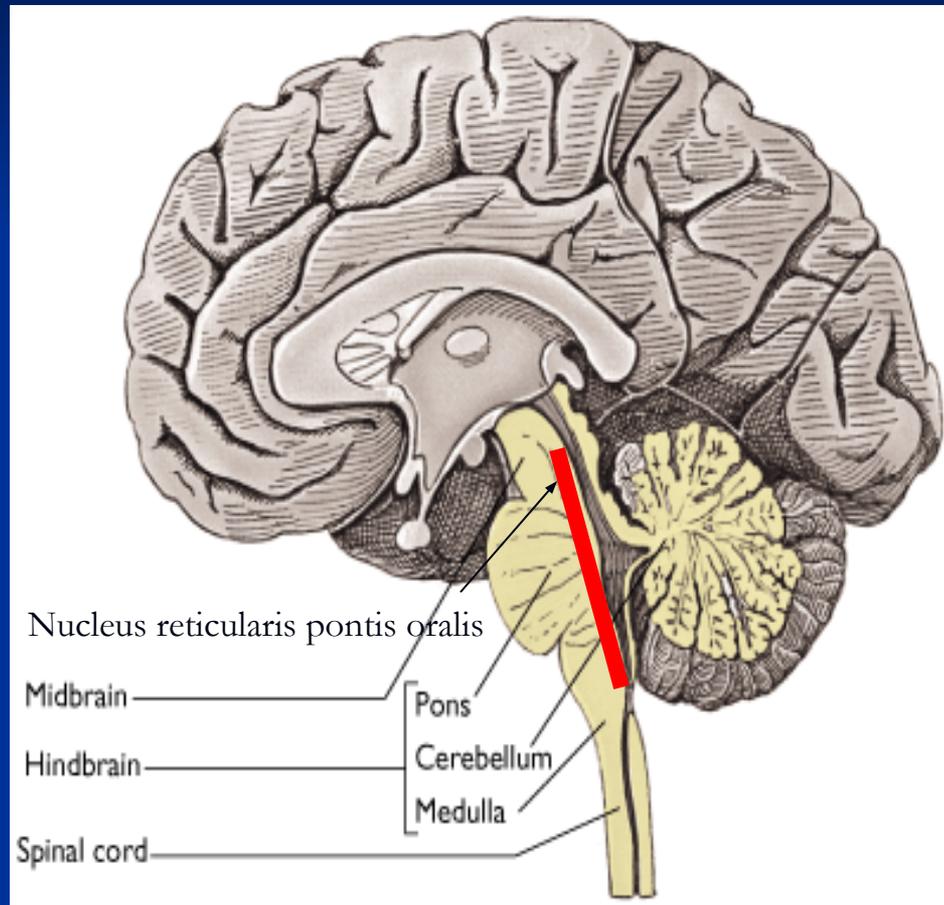


- There are analogous cells all the way down the spinal cord perceiving pain from the rest of the body called the dorsal horn of C4-C8, the dorsal horn of T1-T12...
- Why don't they turn on spontaneously too?
- What's the difference between dorsal horn C1-C4 and those below?

Why just the trigeminal nucleus and upper cervical roots and not the rest?

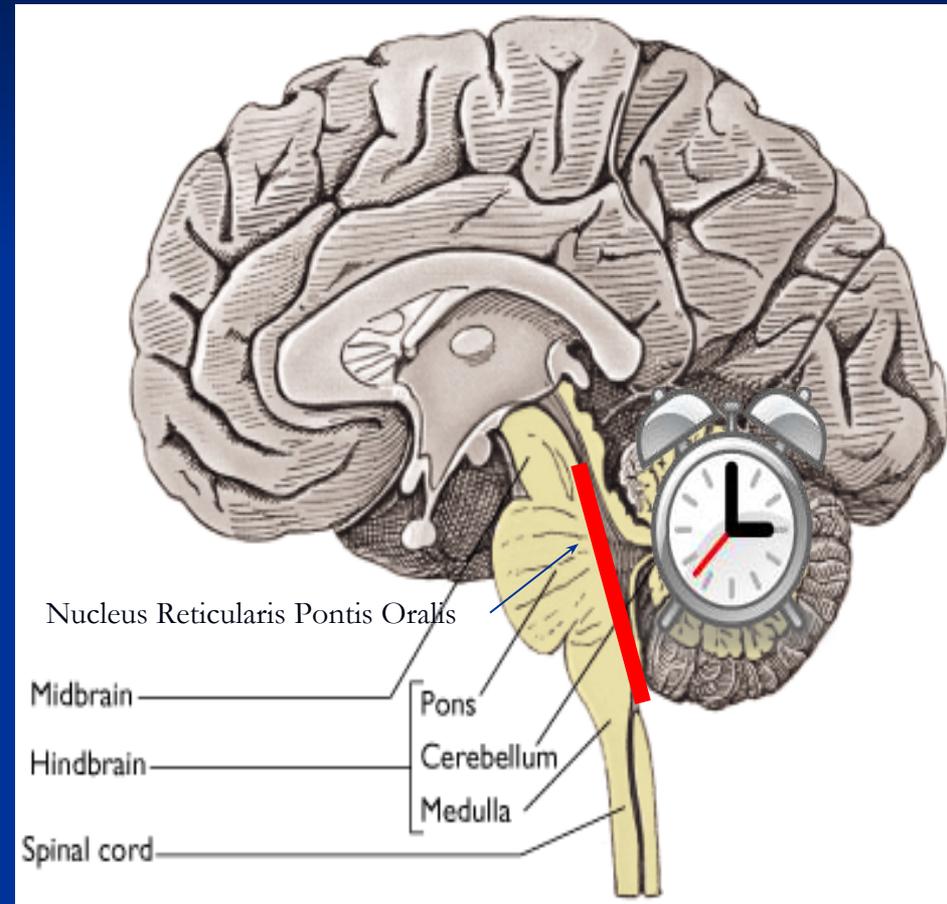
- Could the top two; the trigeminal nucleus and the top part of the dorsal horn *have something nearby that affects only them*, that doesn't extend down into the spinal cord?
- What about the periaquiductal grey nuclei that govern sleep, including the raphe serotonergic nuclei?

Sleep happens here too. Could it affect the nearby trigeminal and dorsal column nuclei?



The Periaquiductal Gray runs the timing and paralysis of sleep

- The **pacemaker cells** in the periaquiductal grey pictured in red, beat all day all night.
- They are the brain clock that determines when we sleep
- The paralysis switch is here also, Nucleus Reticularis Pontis Oralis.
- The two are heavily intertwined to be sure that we only get paralyzed while we are deeply asleep.



Why would areas of the
brainstem that are next to each
other affect each other?

(That seems rather sloppy)

Genetic mutations that cause migraine

(Or, how your hyperactive neighbor in
the brainstem might just make you
cranky too.)



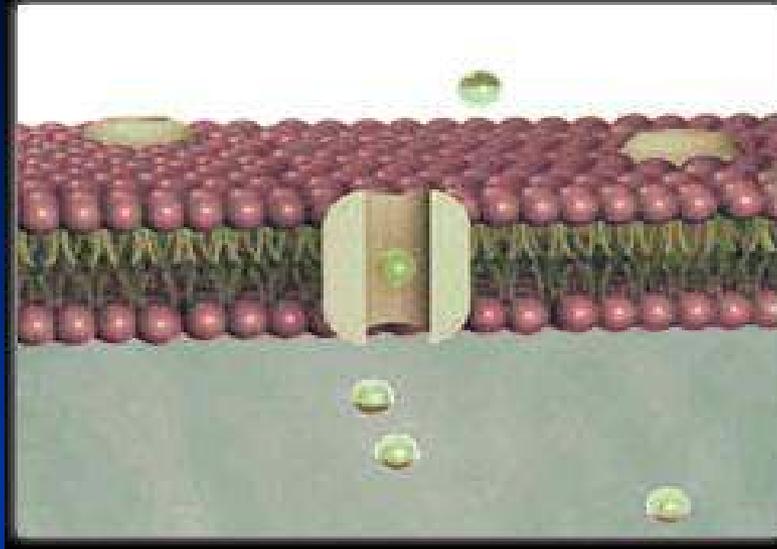
Bar



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:
- Ion Channel Mutations.

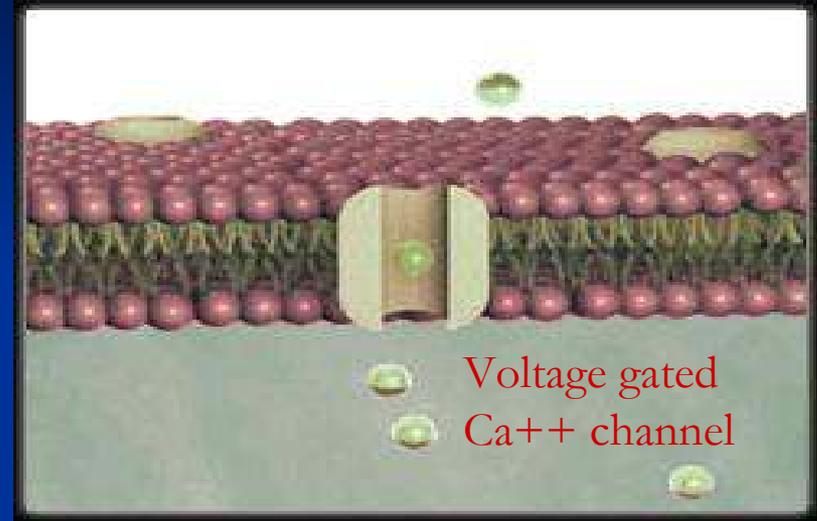
Ca⁺⁺ channel in a membrane



- Our cellular electricity is like a car battery; we use ions 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”.
- We have multiple Ca⁺⁺ channels, K⁺ channels, etc., each has a specific role, or several specific roles, in our body.

Ca⁺⁺ channels turn cells “on” Ca⁺⁺ pumps turn them “off”

- To turn the cell “on” Ca⁺⁺ channels open.
- The cell is now very positive inside; it is “on”.
- To turn “off” it pumps out the positive charges.
- The mutation leads to a malfunctioning channel; the cell goes “on” but can’t turn “off” again.



Lots of +’s cell is
++ +ON+++
 +
 ++ +
++ + + +

Migraine is a Channel Disorder

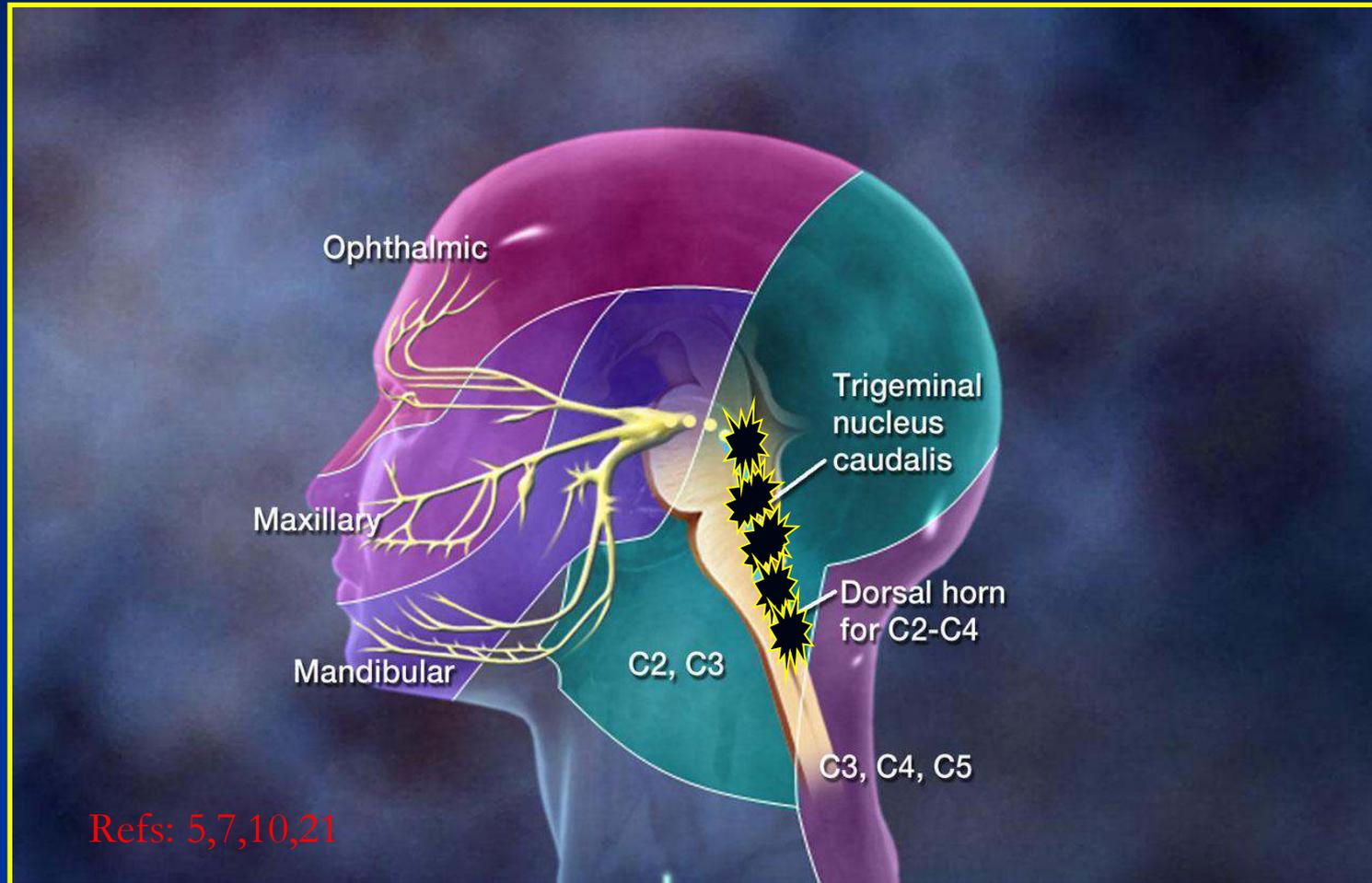
- There are now multiple Ca^{++} and Na^{+} channel mutations linked to migraine.
- Also mutations of Ca^{++} pumps and most recently Na-K ATPase.
- But which cell type has these mutated channels and how does a malfunctioning channel produce headache?

Is their proof that the
posterior brainstem is too
“on” in migraine?

PET Scans in Migraine Patients

show that the posterior brain stem is too “on”

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



How do the channel mutations result in brainstem and occipital lobe hyper-excitability?

Which brain cell has the mutant channels? Is it the neurons or some other cell in the brain?

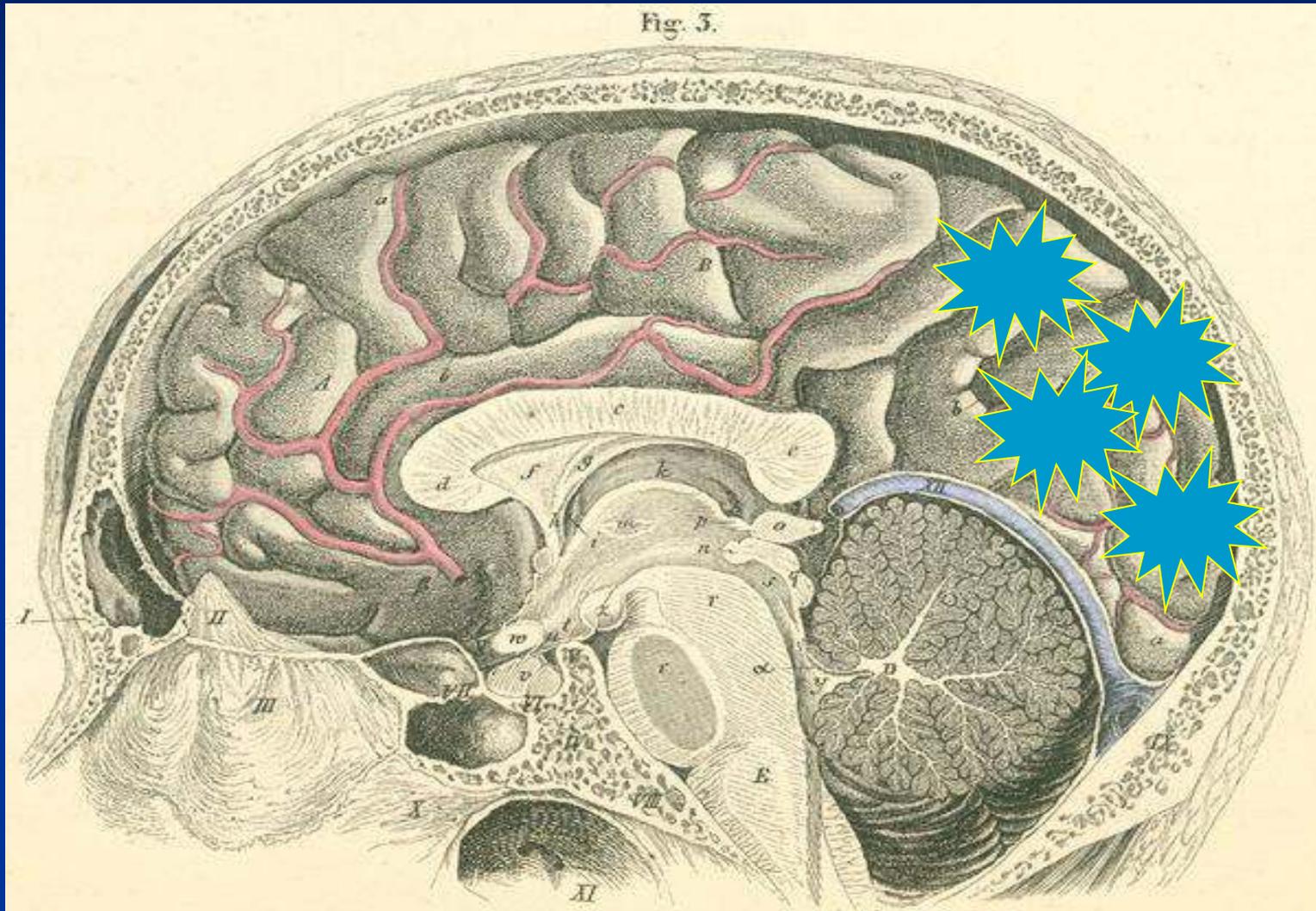
Are there other imaging procedures that show what happens in the brain during a migraine?

1960's Experiments: "Spreading Depression"

- Enrolled migraine patients who had a warning, a visual aura, telling them the headache was about to happen
- They rushed them into a magnetic field as they were experiencing the visual symptoms to measure the electrical events during and after the visual aura.

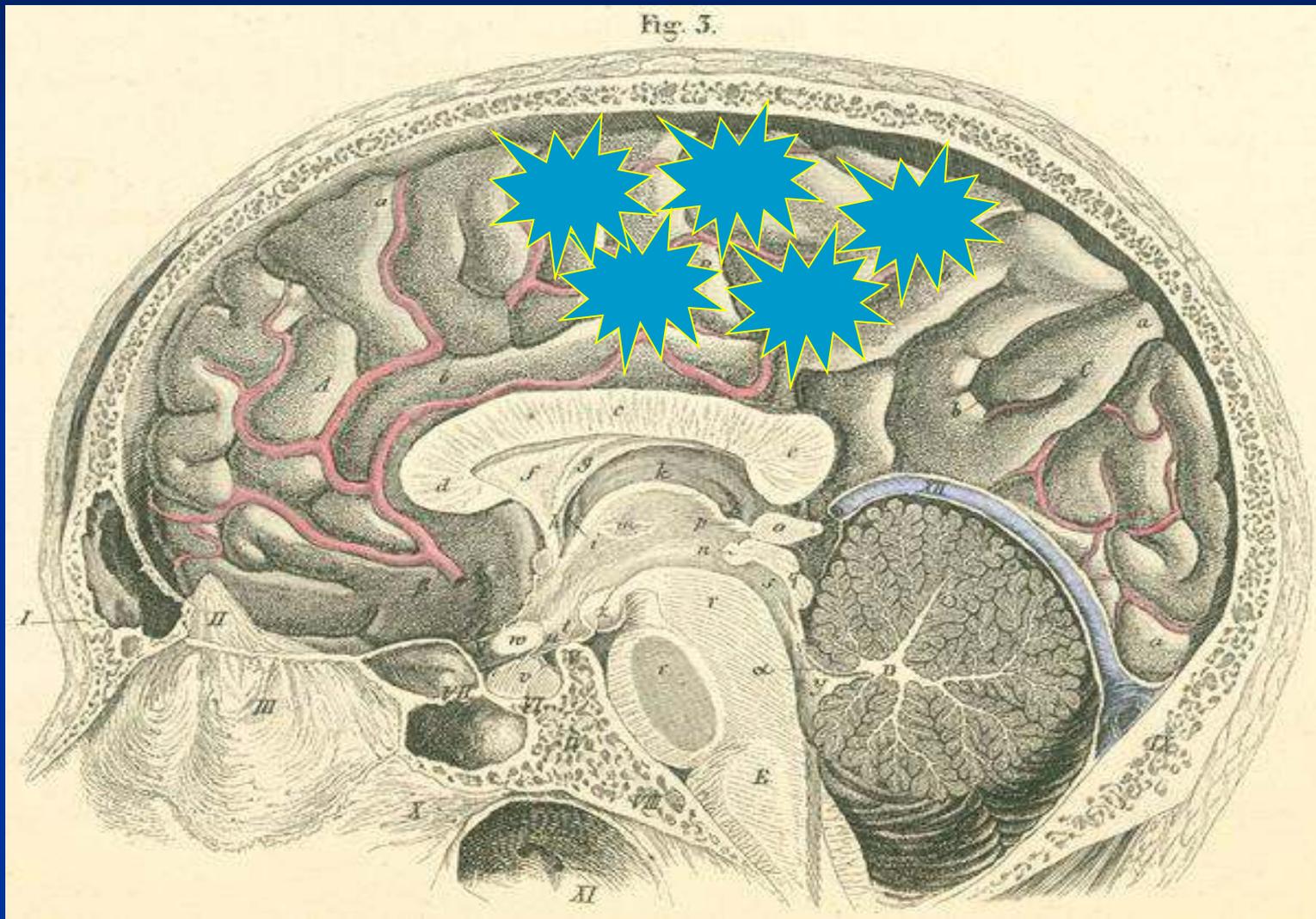
Magnetic Field Studies

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



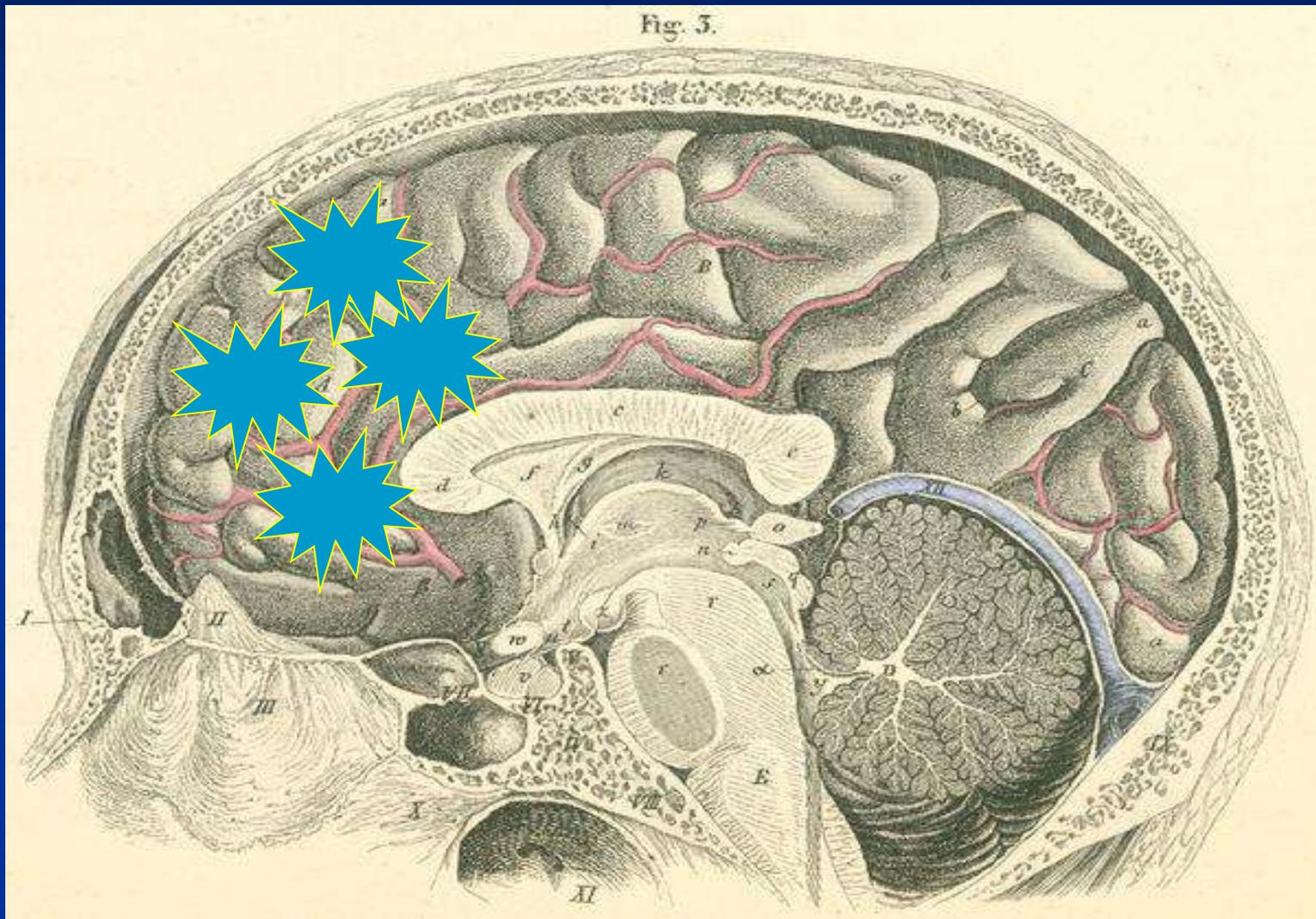
Magnetic Field Studies

electrical suppression, starting in the back during visual aura, moving slowly forward, 15 minutes to go from back to front



Magnetic Field Studies

electrical suppression, starting in the back during visual aura, moving slowly forward, 15 minutes to go from back to front



But what did it mean?

- Why was it moving so slowly, about 3mm/min?
- Why was it moving in a wave spreading outward like a ripple in water instead of jumping from one place to another like neurons transmit messages?
- What did it have to do with the headache?
- What cell in the brain produced this wave?

Spreading Depression of Dr. Leao

observed in rabbit brain slices



Spread of the visual aura was
at the same speed as the

Spreading wave in the brain



- Stimulating the brain electrically caused a slowly spreading electrical wave.
- Traveling 3mm/min, contiguously, taking about 15 minutes to cross the brain
- **Why is it so slow?** What moves at this rate in the brain? It's too slow for neurons.
- Is it related to migraine in humans?

I always get a headache
when I have to ride in
the car.

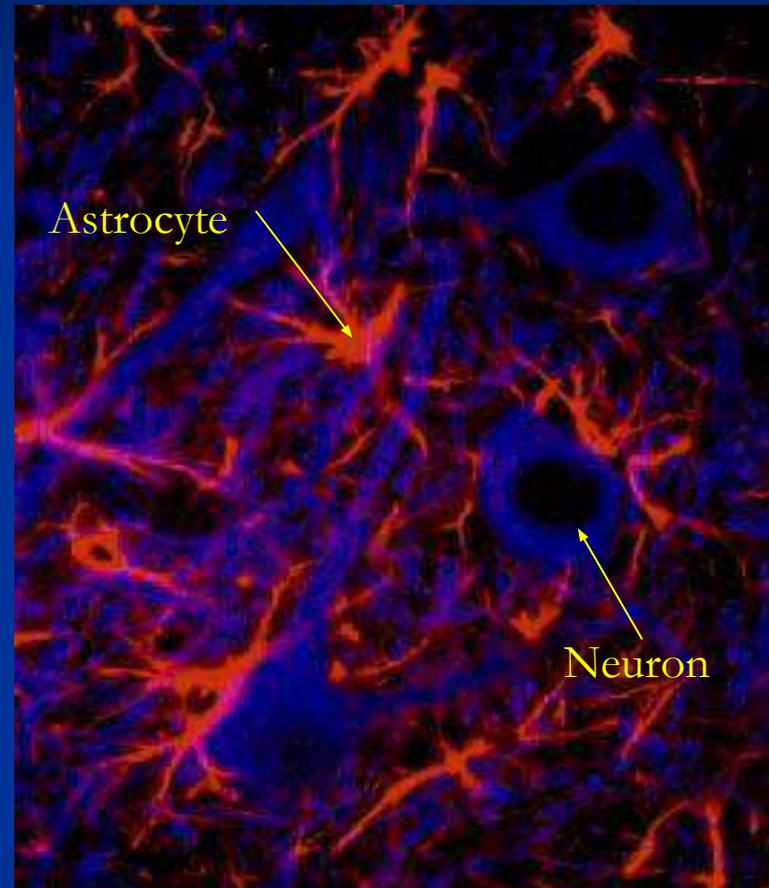


Bella can't tell us if she has a headache and sometimes she looks a little depressed about it

Astrocytes to the Rescue!

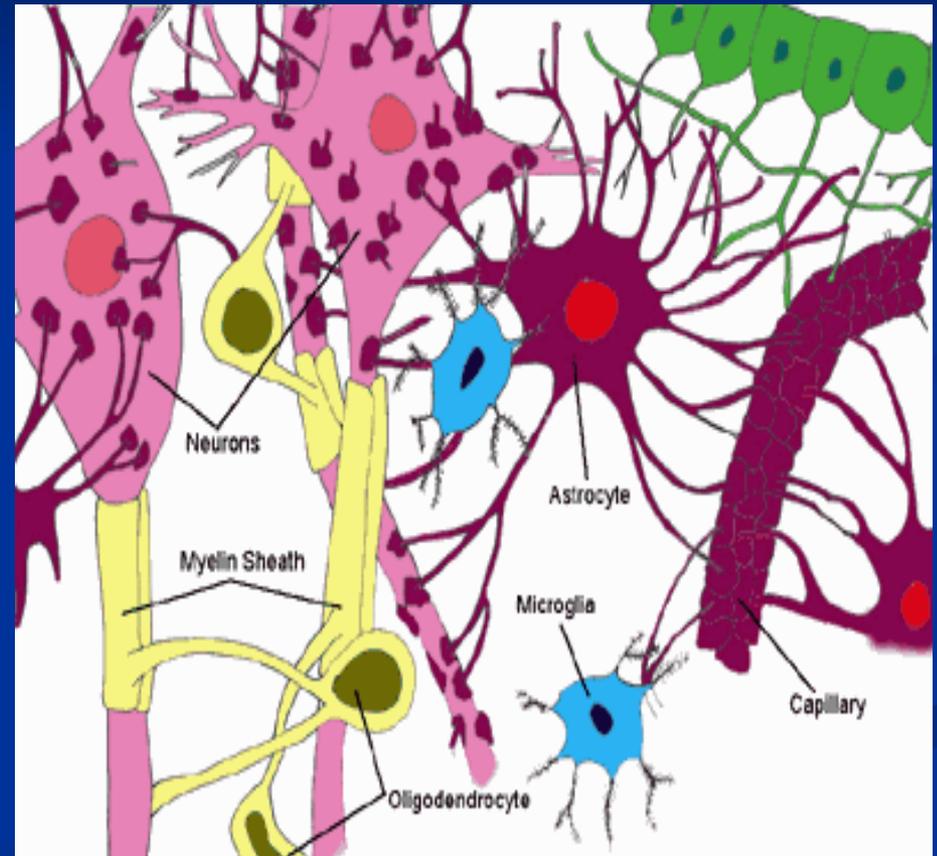
Astrocytes may explain “spreading depression”

- Confocal microscopes show us brain cells in 3 dimensions.
- We thought these little “star-like” cells were the skeletal system of the brain as they had many processes spreading out like a star.



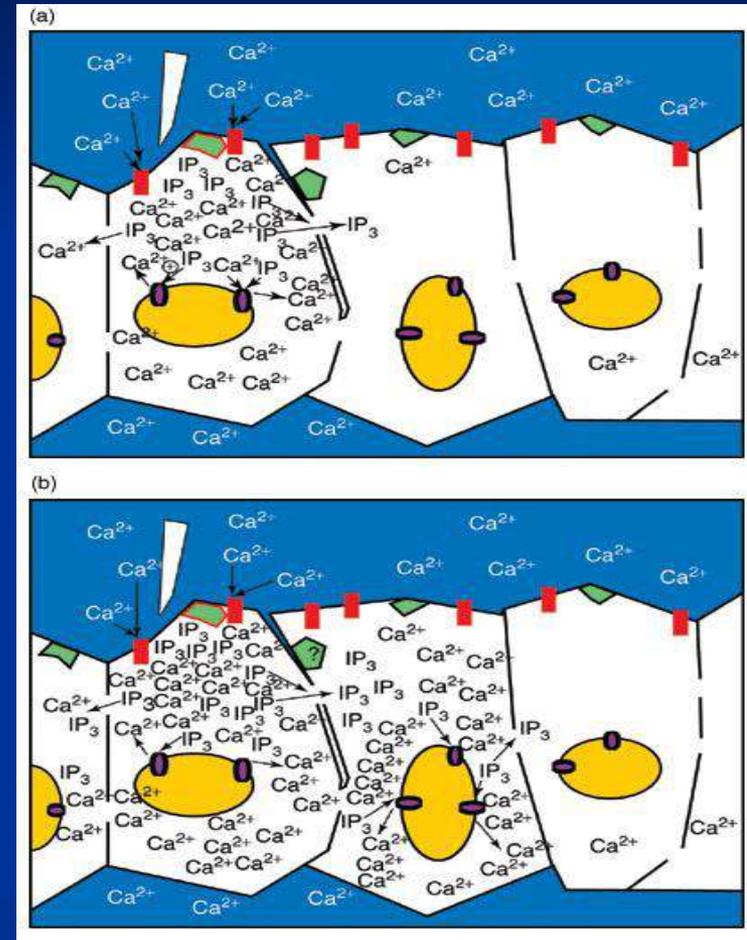
Astrocytes are more influential than previously imagined

- 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.



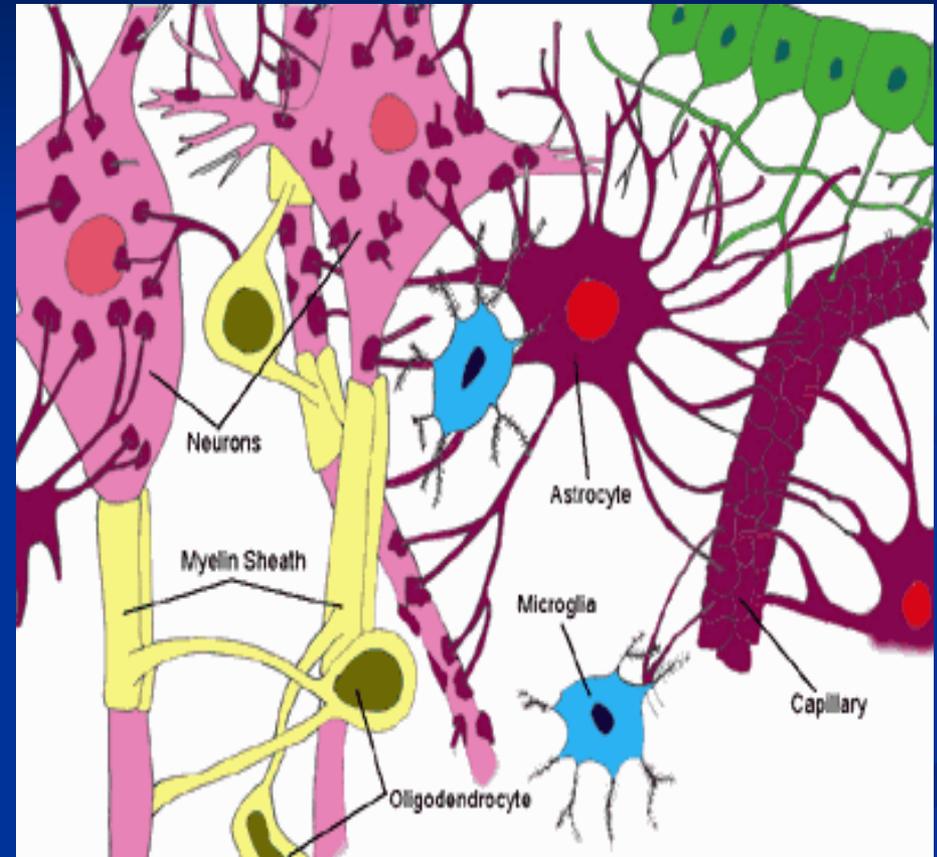
Spreading Depression of Leao is an inter cellular calcium wave

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



The Astrocyte Neurovascular Unit

- A single astrocyte and its neurons are called “**astrocyte neurovascular unit**”
- A chemical blood signal can be received by the astrocyte, then sent to the neurons amplifying the message
- Thus, spreading depression has a similar arterial vasoconstrictive wave that accompanies it.
- The change in mental status and paralysis is the **neuronal effect not the vascular effect**.



What have we suggested so far?

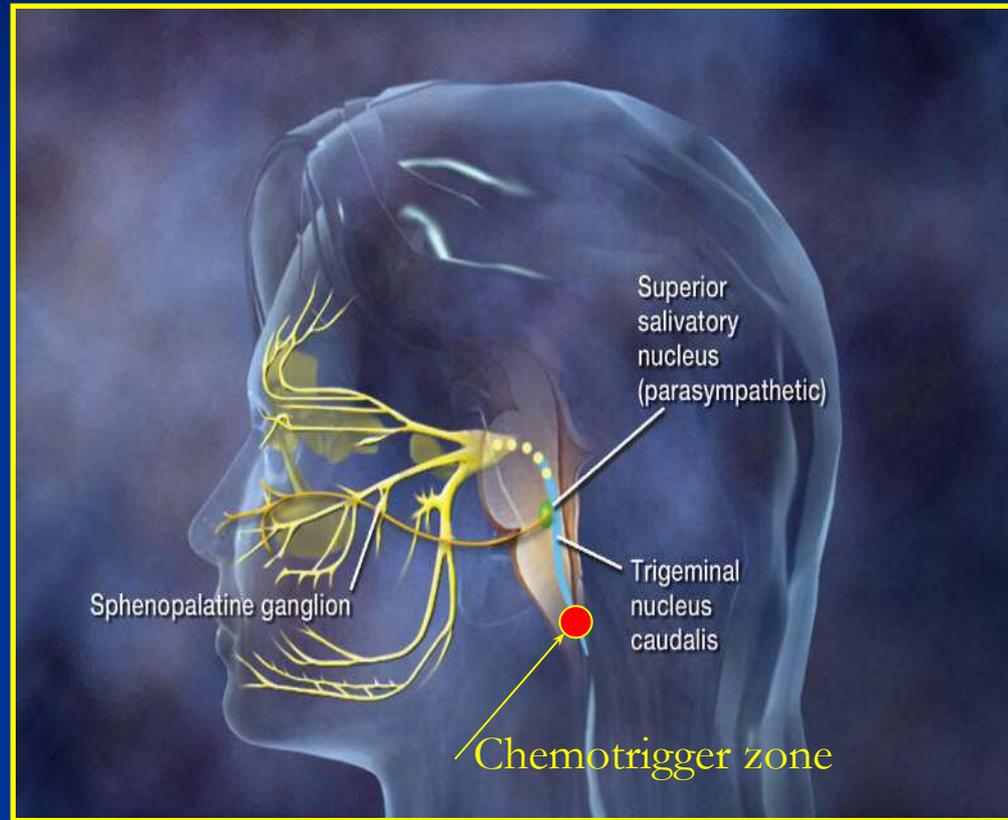
- Headaches happen equally in the neck and head
- Small headaches may grow into big migraine
- Brain stem hyper-excitability has been observed in various types of studies.
- Astrocyte physiology seems to explain spreading depression
- The astrocytes probably carry the channel mutations and are the “hyper- excitable “ cells

Are there other migraine symptoms that must be explained by our theory?

- Dizziness
- Hypersensitivity to light sound and smell
- Ringing or buzzing in the ears
- Visual aura
- Nausea
- Nasal congestion
- Sleepiness
- Stroke like episodes; weakness, aphasia

What about the other migraine symptoms? They're not in the trigeminal caudal nucleus but they're right nearby

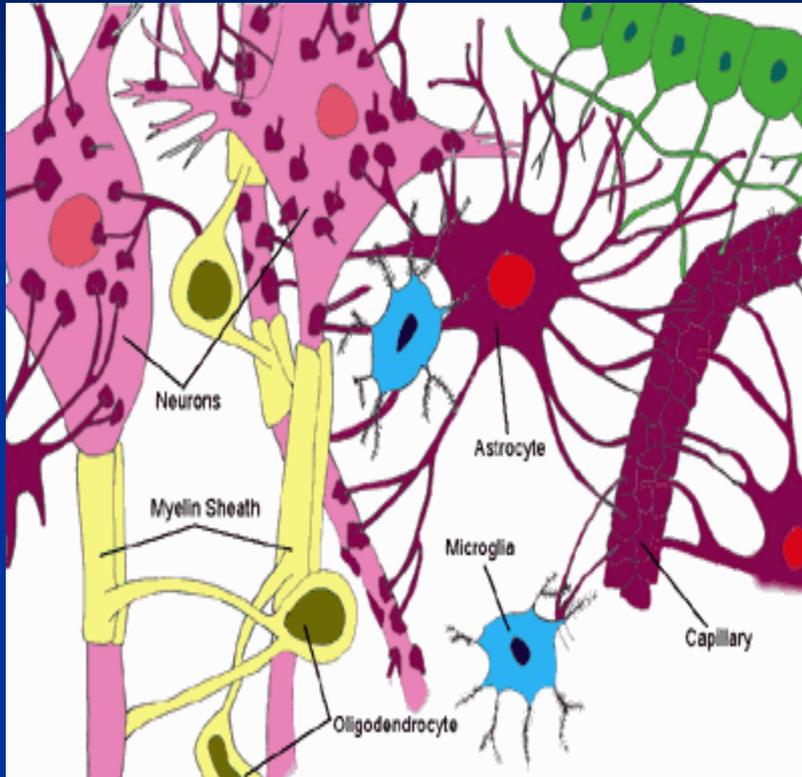
- Nausea from the **Chemotrigger Zone**
- Facial congestion from the **Salivatory Nucleus** which innervates the mucosa of the sinus cavities .
- **Several, nearby brainstem nuclei are being excited together.**



Can this theory explain the accompanying symptoms of migraine?

- Dizziness - brain stem cerebellar nuclei
- Hypersensitivity to light sound and smell-lat and med. geniculate
- Tinnitus - VIIIth nerve nucleus
- Visual aura - occipital lobe
- Nausea - chemotrigger zone
- Nasal congestion - salivatory nucleus
- Sleepiness - raphe nuclei
- Stroke like episodes; weakness, aphasia- brain stem or cortex

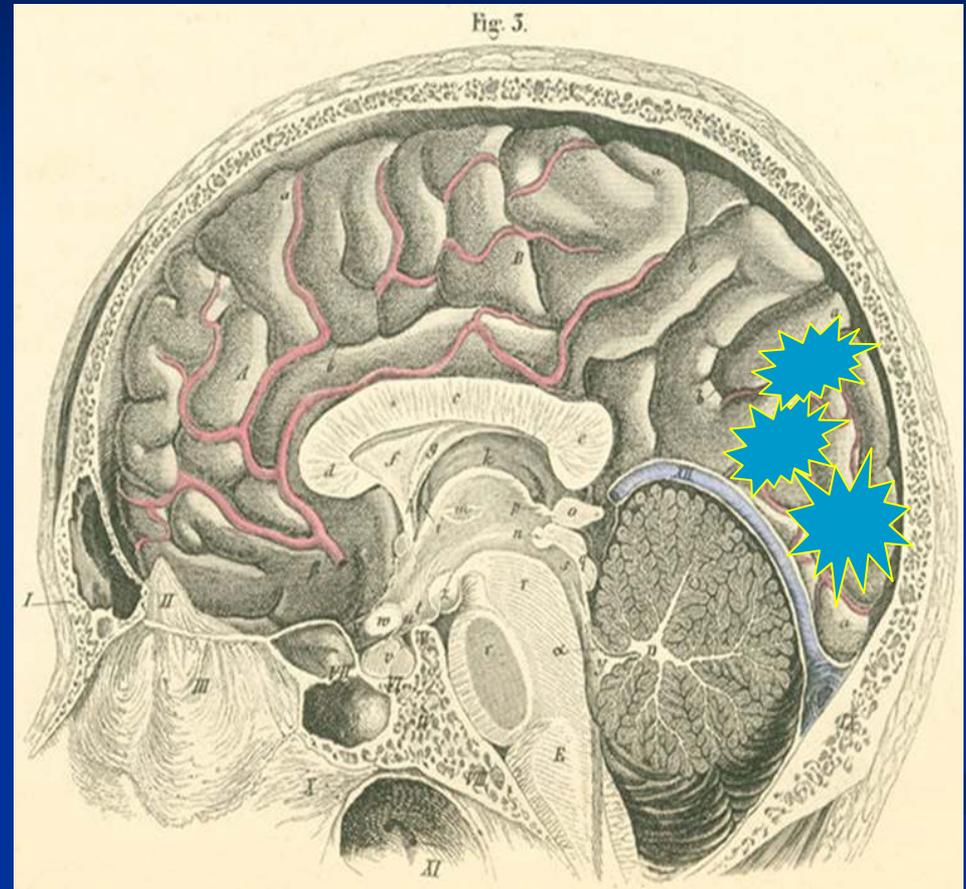
Astrocyte anatomy is regional



- Astrocytes do not follow neuronal anatomy, they overlap adjoining nuclei supplying **regions** of the brain.
- There may be regional differences in astrocyte physiology.

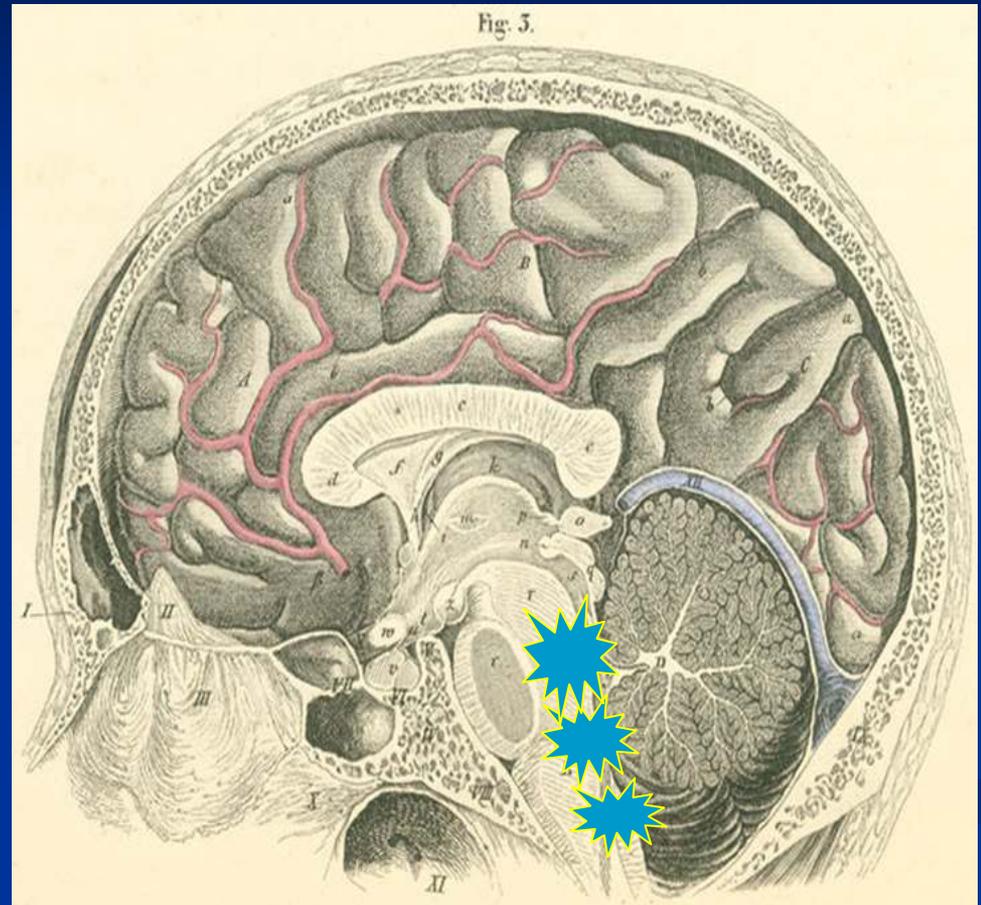
What about the visual “aura” of migraine

- The visual warning of migraine is thought to be a spontaneous electrical discharge of the occipital lobe as seen in the spreading depression experiments.
- We know that some migraines start there and not in the brainstem, **what would link the brainstem to the occipital lobe making both hyper-excitable?**



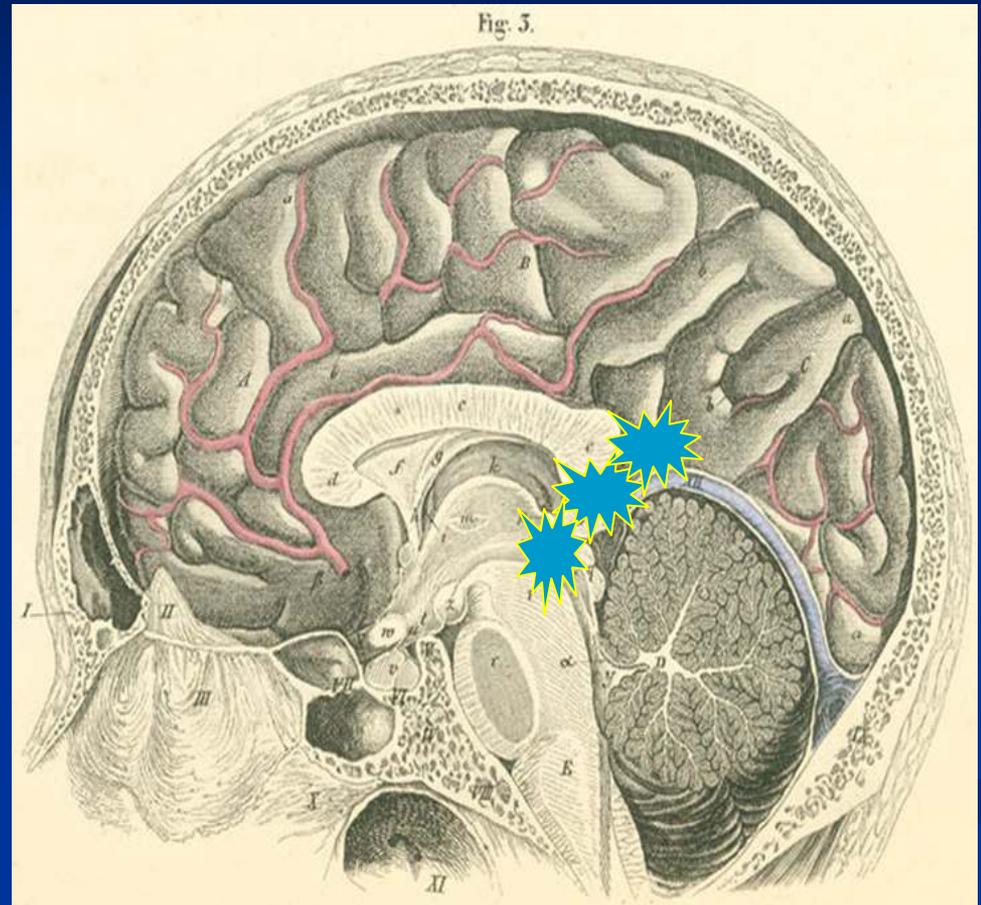
PGO waves

- Pons Geniculate Occipital Lobe
PGO Waves
- Waves that go back and forth between the brainstem and the occipital lobe at the rate of REM eye movements. (Even while we're awake.)
- These waves may suggest a special population of astrocytes linking the posterior brainstem to the occipital lobe (and probably hypothalamus geniculate ganglia and thalamus).
- Ref: 33, 34



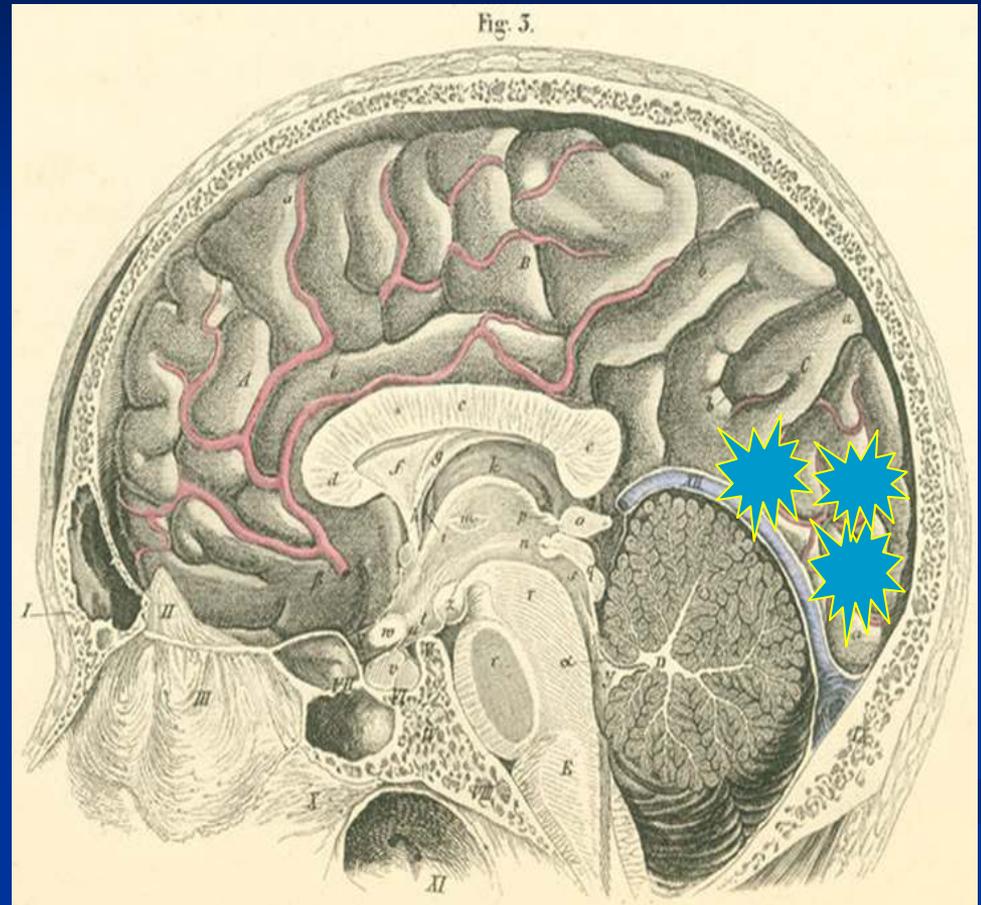
PGO waves

- Pons Geniculate Occipital Lobe
PGO Waves
- Waves that go back and forth between the brainstem and the occipital lobe at the rate of REM eye movements. (Even while we're awake.)
- These waves may suggest a special population of astrocytes linking the posterior brainstem to the occipital lobe (and probably hypothalamus geniculate ganglia and thalamus).



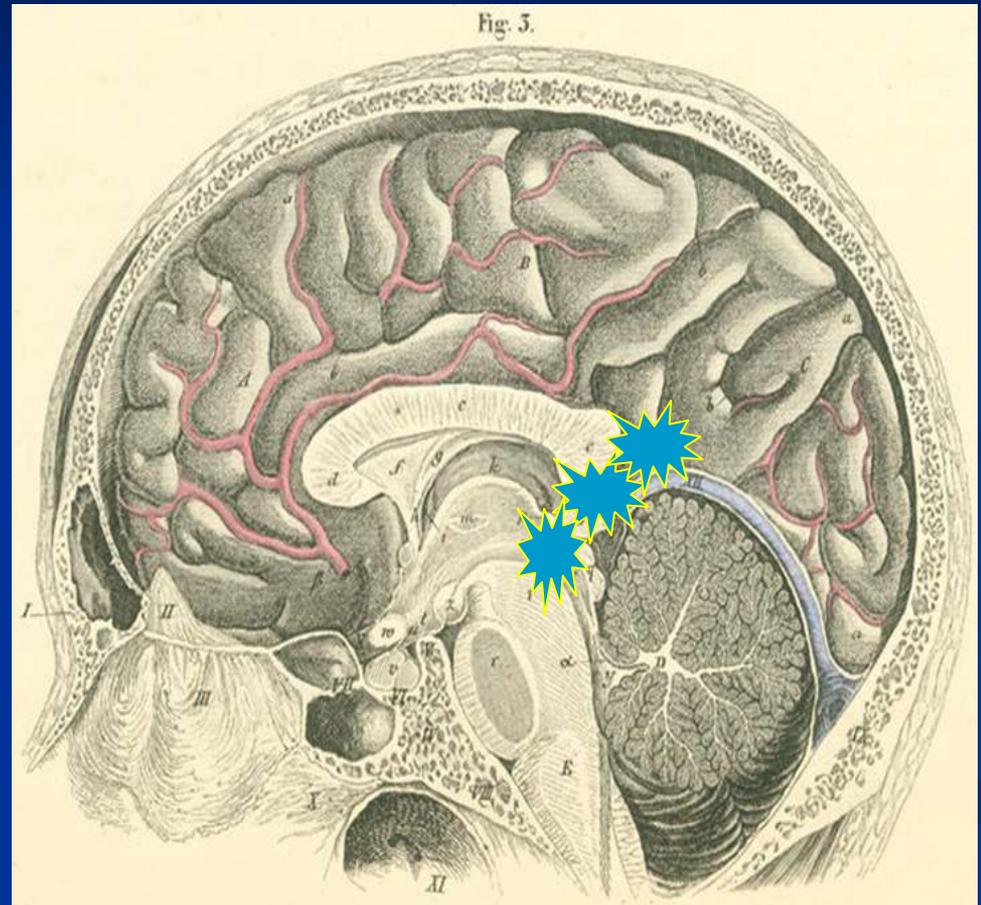
PGO waves

- Pons Geniculate Occipital Lobe
PGO Waves
- Waves that go back and forth between the brainstem and the occipital lobe at the rate of REM eye movements. (Even while we're awake.)
- These waves may suggest a special population of astrocytes linking the posterior brainstem to the occipital lobe (and probably hypothalamus geniculate ganglia and thalamus).



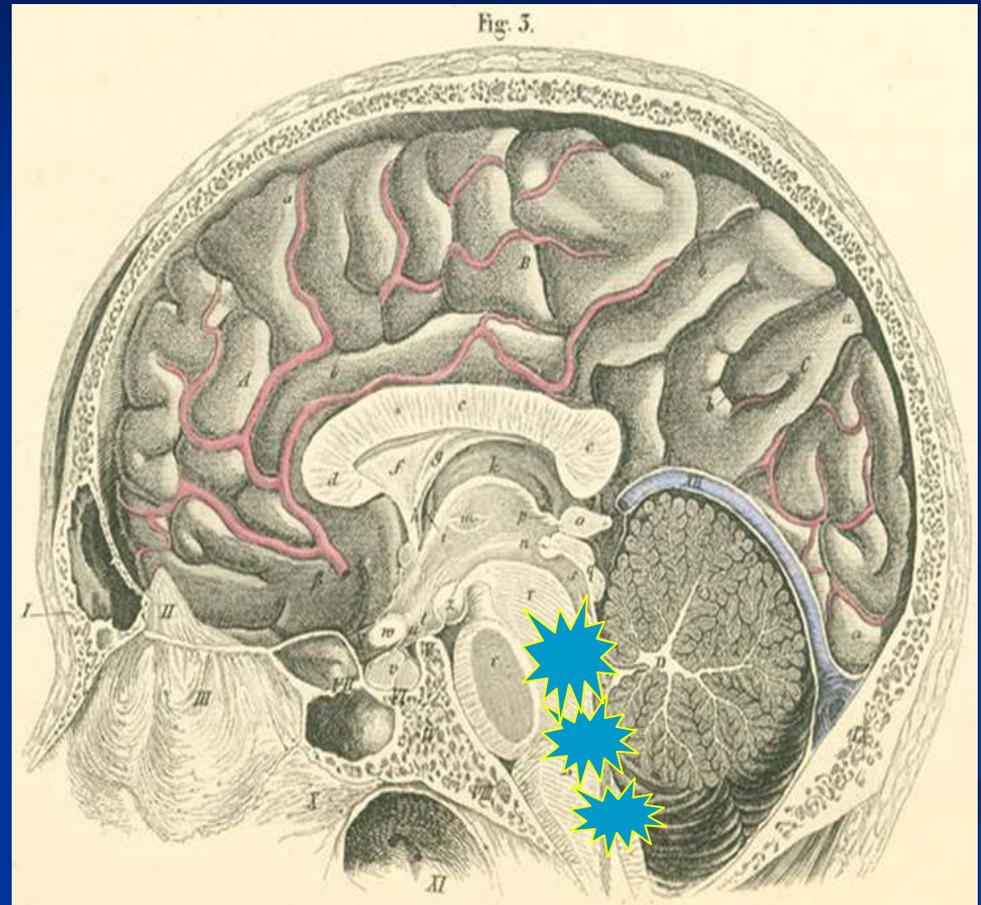
PGO waves

- Pons Geniculate Occipital Lobe
PGO Waves
- Waves that go back and forth between the brainstem and the occipital lobe at the rate of REM eye movements. (Even while we're awake.)
- These waves may suggest a special population of astrocytes linking the posterior brainstem to the occipital lobe (and probably hypothalamus geniculate ganglia and thalamus).



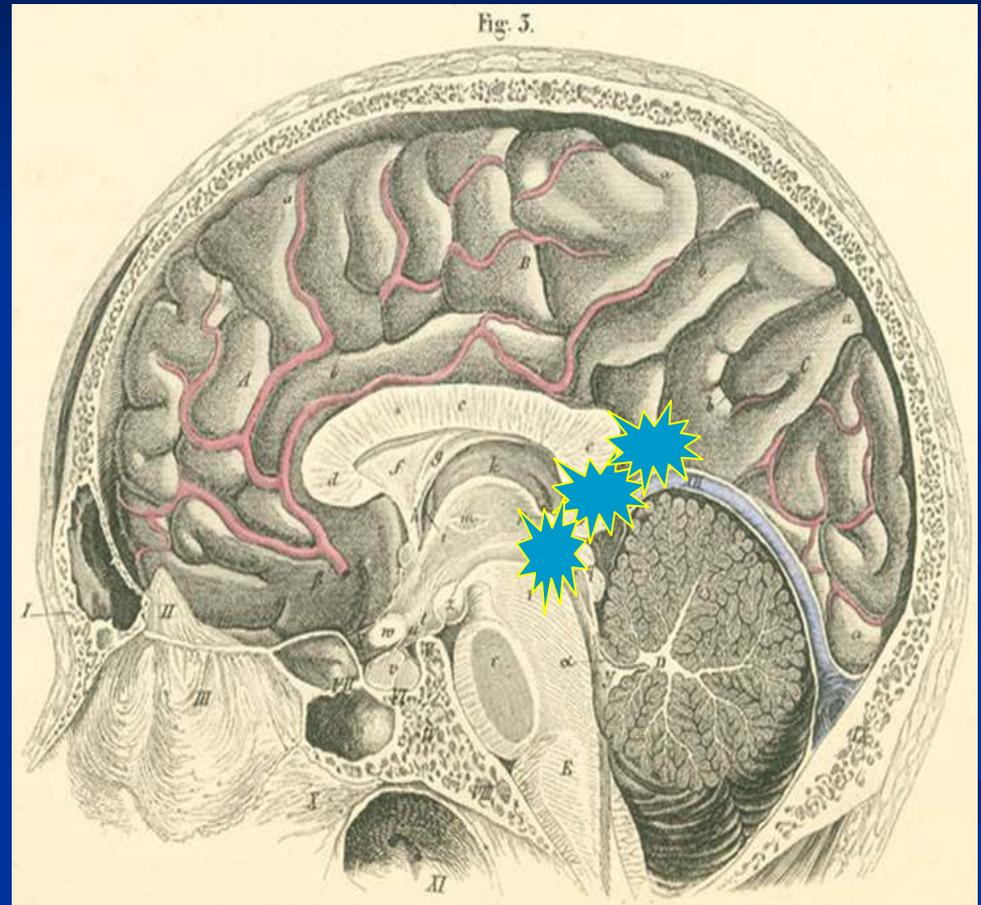
PGO waves

- Pons Geniculate Occipital Lobe
PGO Waves
- Waves that go back and forth between the brainstem and the occipital lobe at the rate of REM eye movements. (Even while we're awake.)
- These waves may suggest a special population of astrocytes linking the posterior brainstem to the occipital lobe (and probably hypothalamus geniculate ganglia and thalamus).



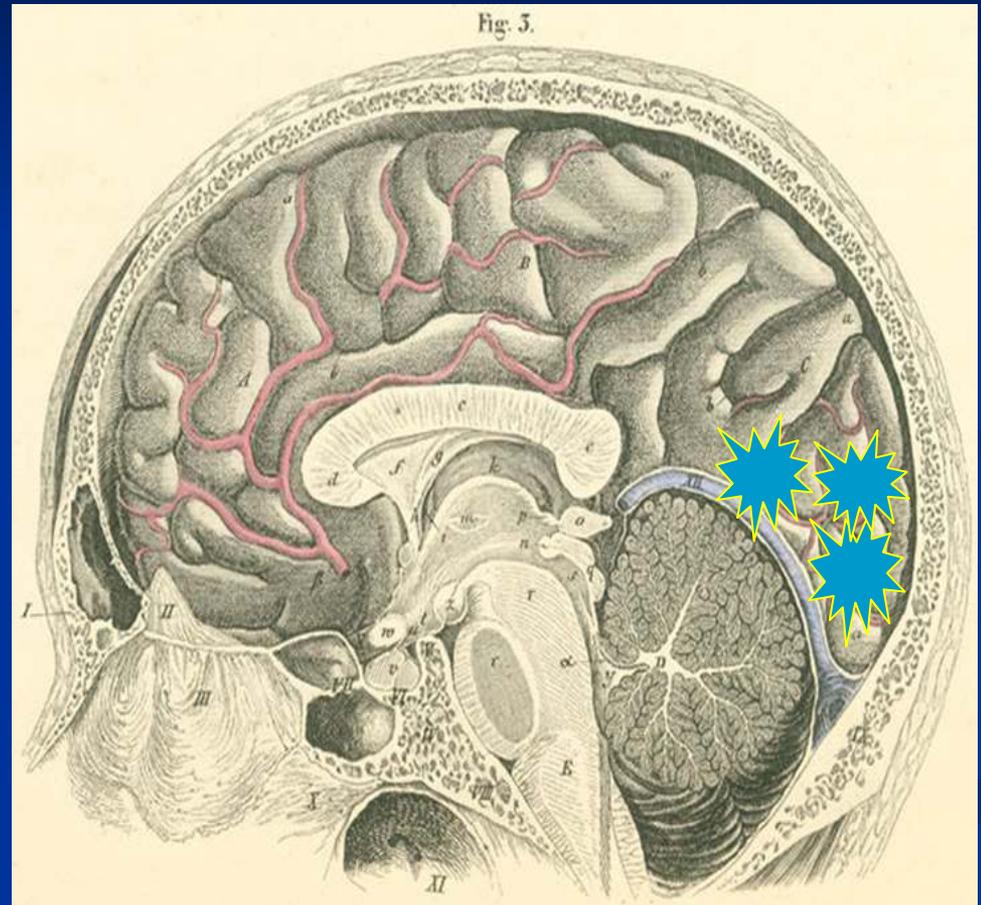
PGO waves

- Pons Geniculate Occipital Lobe
PGO Waves
- Waves that go back and forth between the brainstem and the occipital lobe at the rate of REM eye movements. (Even while we're awake.)
- These waves may suggest a special population of astrocytes linking the posterior brainstem to the occipital lobe (and probably hypothalamus geniculate ganglia and thalamus).



PGO waves

- Pons Geniculate Occipital Lobe
PGO Waves
- Waves that go back and forth between the brainstem and the occipital lobe at the rate of REM eye movements. (Even while we're awake.)
- These waves may suggest a **special population of astrocytes linking the posterior brainstem to the occipital lobe** (and probably hypothalamus geniculate ganglia and thalamus).



Why are all these waves
and excitable
astrocytes important?

The channel mutations probably didn't arise to cause headaches

- The same astrocyte population which affects the “excitability” of the sleep switches also affects the whole posterior brainstem.
- Since sleep is the most important thing we do every day, mutations that improve sleep (make it “switch on” easily) might convey a survival advantage and become common in humans.

Key Points of Brainstem Hyper excitability

- Activation observed in the posterior brain stem on PET scans in migraine patients.
- 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 Salivatory Nucleus can lead to sinus congestion, nausea from the chemotrigger zone, hypersensitivity to light sound and smell from connections to the geniculate ganglia.
- Dizziness, tinnitus, double vision, all brain stem nuclei



How do we fix the headaches?

If I've had this "mutation" since I was born why is it only showing up now?

Fix the sleep fix the headaches

- We have to fix the hyper excitability of the brain stem nuclei, make them go back to “off” .
- The pills we’ve used for prevention of migraine (even before the mutations were described) are **calcium channel blockers** like verapamil, and **sodium channel stabilizers** like topiramate.
- They work by stabilizing cranky, easily excitable cells that are turning “on “ too easily.

Most people only get an occasional mild headache

They have the mechanism to make a headache but it doesn't act up all the time and make their life miserable.

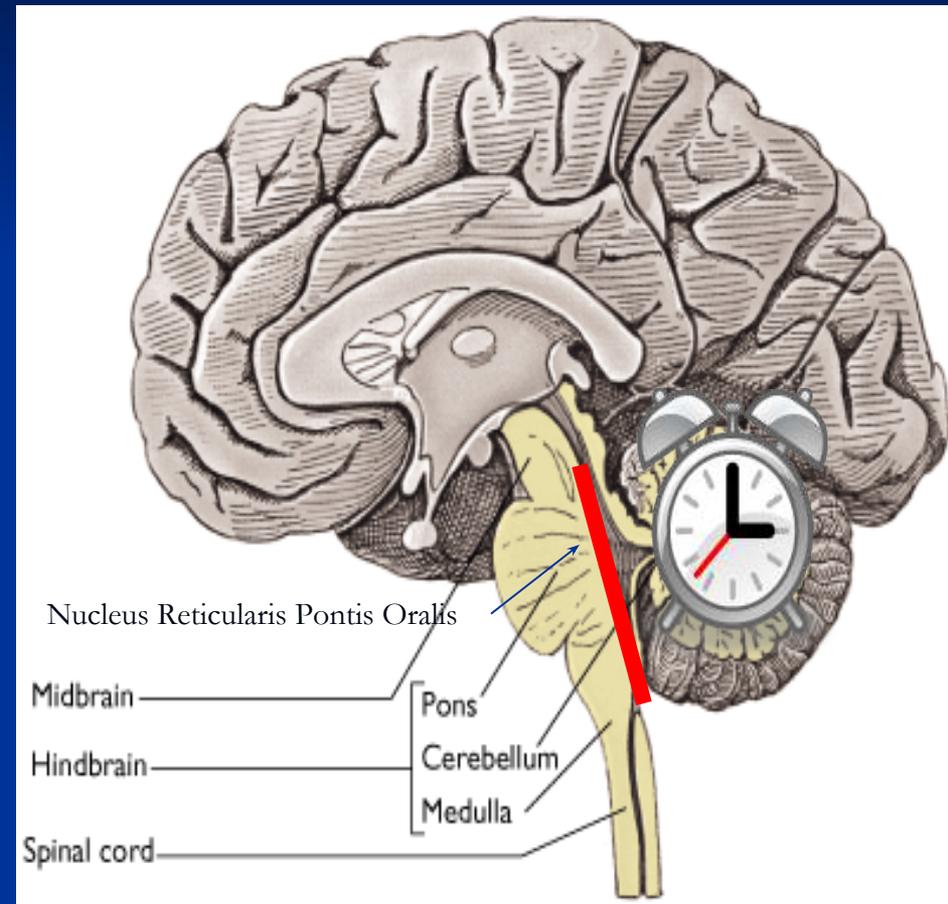
How do I get back to
being one of those
people?

What I learned from sleep apnea masks

- Why did the CPAP mask make my patient's headaches better?
- The masks are not about getting oxygen to the brain, that's what the blood does.
- We all get **paralyzed** in deep sleep and we have to be paralyzed to repair
- Apnea occurs when the paralysis system gets goofed up and we get too paralyzed in deep sleep
- The mask blows air in to allow the brain to stay in deep sleep long enough to get work done.

The Periaquiductal Gray runs the timing and paralysis of sleep

- The **pacemaker cells** in the periaquiductal grey pictured in red, beat all day all night.
- They are the brain clock that determines when we sleep
- The paralysis switch is here also, Nucleus Reticularis Pontis Oralis.
- The two are heavily intertwined to be sure that we only get paralyzed while we are deeply asleep.



What I learned from CPAP masks

- My patients returned and said not only were their headaches gone but they were on fewer blood pressure meds and they were off their diabetes pills.
- Their knee pain was gone they could think more clearly and they didn't feel depressed any more,
- And oh, yeah, I think my memory is better too.
- Does that mean we repair everything in sleep , do we make insulin in sleep, do we make our serotonin in sleep?

Sleep is not just being unconscious

- We all know what it feels like to wake tired
- Sleep is not a passive process
- There are specific stages of sleep in which we get paralyzed and get the “work” of sleep done
- I believe that we all make enough chemicals in sleep to last about 16 hours, then we run out and we have to go back to sleep to make more.
- I believe all repair of all systems only happens while we're sleeping

Apnea is not the only sleep disorder

- My 18 year old patient with daily headache slept for 10 hours during her sleep study but had no deep sleep at all, no apnea, but also no deep sleep.
- Most of my headache patients have reduced or no REM sleep.
- They all say the same thing: “I have a headache every day, I can’t remember anything and I’m in a bad mood.”
- The chemicals that prevent headache are made in deep sleep, memories are made in deep sleep serotonin to make us happy is made in deep sleep.

How do we get the REM back?

- Why is there no REM ?
- Apnea is the end stage terrible disease before we die, none of us want to get even close to that.
- Why does everyone who comes to see me, regardless of the problem; headache, vertigo, tremor, burning in the feet, balance difficulty, parkinson's, seizure, tics, stroke, all have an abnormal sleep study? Even little 8 year olds?
- This is an epidemic that began in the early 1980's as did fibromyalgia and chronic fatigue

Why do I want my REM sleep back?

- While we're sleeping we make millions of chemicals that allow our bodies to run normally.
- If you've always had the migraine gene mutation but didn't always have a headache then you made modifications in other chemicals that allowed your cells to run normally, to stay "off" until.
- You stopped sleeping in deep sleep long enough every night to make those chemicals that "shored up" your weakness.
- Each of us have genetic weaknesses we're born with.

Give me back my REM sleep

- Could it be that each drug that helps migraine is really just duplicating a chemical the brain ran out of?
- And my brain knows how to make my chemical, which exactly fits the gene mutation I have, but I only make that chemical in REM sleep.
- 40 different channel mutations may explain why I have only partial success with the medicines I use, and they “wear off”, the headaches get better, then they’re back again.
- Your brain knows exactly which chemical to make for you, it’s been doing it since you were born.

Sleep Disorders

- There are many types of abnormal sleep, one is “I sleep all night but wake with a headache”.
- If you wake up every morning with mild neck pain or facial pain your sleep is not “normal”
- If you sleep all night, wake feeling “fantastic” and have no pain and no medical problems, then your sleep is normal.
- That is common now in my practice but not common in the developed world today.

Vitamins are Dangerous

- Fixing the sleep is not just a matter of taking vitamins, they are chemicals that have to stay in a specific range for sleep to occur normally, use them carefully.
- But humans and all other animals lived here on this planet for millions of years before doctors arrived.
- They missed those “well rounded diet” lectures, most of the squirrels still don’t get those lectures.
- That means the things our bodies can’t make were actually partly from the intestinal bacteria and partly from the food.

Humans lived before doctors

- Most died of infectious diseases that we have eliminated to large extent
- What remains is slow death by organ failure; diabetes, heart attack, stroke, parkinsons, alzheimers, cancer.
- All of these diseases result from incomplete healing during sleep and can be partially or fully reversed by sleeping normally.
- Headache can be cured by sleeping normally

D and B vitamins

- The epidemic of low vitamin D in the developed world started with computer, television and air conditioning in the late 70s early 80's when we all went indoors.
- Since there are no drugs to bring back REM what we're left with is trying new things.
- Go to the vitamin D lecture to see the connection in detail but vitamin D deficiency is the cause.
- Get the D to 60-80 ng/ml and fix the secondary effects of low D (intestinal bacterial change) so the B's get made daily in the right amounts
- And the REM comes back and the headaches go away

Why sleeping pills are valuable

- 16 year olds with their first bout of daily headache are easy to fix with vitamins
- 52 year olds with daily headache for the last 30 years are not easy to fix with just vitamins
- Every night the brain tries to fix the sleep switches but doesn't have the time in deep sleep to succeed.
- Daily headache for 30 years means that patient has old, rusty, poorly functioning sleep switches and even when those cells get the raw materials they've needed, (the vitamins) they don't just snap to it and work perfectly.

Long standing sleep disorders usually require sleeping pills

- If you give a sleeping pill but don't fix what's wrong in the background they may work for a little while but then they "wear off" and they need more and they "get addicted"
- They can't sleep without the medication, but they couldn't sleep in the first place.
- The medications aren't bad they just aren't the whole answer.
- Fix what's wrong in the background and use the sleep meds as a bandaid to help while the brain is repairing

It is sleep, not vitamins that cures the headaches

- Sleep is the cure for headache, if the sleep is not normal the headaches won't resolve.
- Be patient. If the sleep has been abnormal for 30 years it doesn't get fixed over night.
- Find the sleeping pill that is right for you.
- Fall asleep stay asleep and wake feeling great means that medication is what the brain has been needing to get into the right phases
- They won't work alone but they are helpful

CPAP is still helpful

- Anyone with apnea will still get better faster with the mask on.
- Many people who have apnea will not get fixed unless they are able to wear the mask and sleep
- Listen to your body, if you sleep better in the recliner stay in the recliner.
- People end up sleeping on the couch because they sleep better there than in the bed. The couch keeps them in a position where their apnea is less.

Listen to your body

- *As you get better, the drugs I have used to help you will start to have different effects*
- *The sleep medicine that used to help you now makes you dopey in the morning*
- *Just like taking away the blood pressure meds when the blood pressure normalizes you need to take away sleep meds as the sleep gets better*
- *Always wait until your body tells you it doesn't want them, they make you feel funny now instead of better*

Listen to your body

- Once the sleep gets better and the headaches go away you have to learn what to watch for so they don't come back
- The vitamin D is hard to keep in range. Every person needs a different dose depending on their skin color, where they live, how much they're in the sun in the summer and how long they were sick
- This means the D dose usually goes down over the first 2-3 years as we get better, we have to have a way to tell when to get the level checked and catch it before our sleep falls apart again and the headaches come back.

Little headaches are important

- If you learn that those little “normal headaches” are warning you that your head pain switch is getting cranky again and you do something about it right away, like check the D level, you’ll fix your sleep before you’ve spent another six months not sleeping and the headaches are out of control again.
- Each time your sleep gets goofed up for more than a brief period the headaches will return until you’ve had months on end of normal sleep.

Headache meds are still important

- The preventatives such as verapamil and topiramate are still necessary for many patients. There's nothing wrong with using them but the improvement won't last if the sleep remains abnormal.
- The triptans are very important.
- The warnings per the FDA are not correct. The receptors that they work on do not increase serotonin, they decrease serotonin, and they do indeed cause chest and joint aching but they are generally very safe.
- They do not work in the daily headache sufferers because they work best when the headache is in the earliest stages.
- Even if they failed when the headaches were daily, they will usually work later when the headaches are once a week.

Always have a CT scan

- Any patient with headaches bad enough to talk to their doctor or watch this lecture needs a CT of the head at least once.
- There is no difference between the headache of a brain tumor and “normal headache” at the beginning. Always confirm that the anatomy is normal before assuming that it’s migraine.









References

1. Why does serotonergic activity drastically decrease during REM sleep? Sato K . Med Hypotheses. 2013 Oct;81(4):734-7.
2. Serotonin control of sleep-wake behavior. Monti JM Sleep Med Rev. 2011 Aug;15(4):269-81
3. Brain hyperexcitability: the basis for antiepileptic drugs in migraine prevention. Welch KM. Headache. 2005 Apr;45 Suppl 1:S25-32. Review.
4. Contemporary concepts of migraine pathogenesis. Welch KM. Neurology. 2003 Oct 28;61(8 Suppl 4):S2-8. Review.
5. Functional MRI-BOLD of brainstem structures during visually triggered migraine. Cao Y, Aurora SK, Nagesh V, Patel SC, Welch KM. Neurology. 2002 Jul 9;59(1):72-8.
6. Cortical spreading depression and gene regulation: relevance to migraine. Choudhuri R, Cui L, Yong C, Bowyer S, Klein RM, Welch KM, Berman NE. Ann Neurol. 2002 Apr;51(4):499-506.
7. Magnetoencephalographic fields from patients with spontaneous and induced migraine aura. Bowyer SM, Aurora KS, Moran JE, Tepley N, Welch KM. Ann Neurol. 2001 Nov;50(5):582-7.

References

8. Periaqueductal gray matter dysfunction in migraine: cause or the burden of illness? Welch KM, Nagesh V, Aurora SK, Gelman N. *Headache*. 2001 Jul-Aug; 41(7):629-37.
9. The occipital cortex is hyperexcitable in migraine: experimental evidence. Aurora SK, Cao Y, Bowyer SM, Welch KM. *Headache*. 1999 Jul-Aug;39(7):469-76.
10. MRI of the occipital cortex, red nucleus, and substantia nigra during visual aura of migraine. Welch KM, Cao Y, Aurora S, Wiggins G, Vikingstad EM. *Neurology*. 1998 Nov;51(5):1465-9.
11. Transcranial magnetic stimulation confirms hyperexcitability of occipital cortex in migraine. Aurora SK, Ahmad BK, Welch KM, Bhardhwaj P, Ramadan NM. *Neurology*. 1998 Apr;50(4):1111-4.
12. Brain excitability in migraine: evidence from transcranial magnetic stimulation studies. Aurora SK, Welch KM. *Curr Opin Neurol*. 1998 Jun;11(3):205-9.

References

13. Brain activations in the premonitory phase of nitroglycerin-triggered migraine attacks. Maniyar FH, Sprenger T, Monteith T, Schankin C, Goadsby PJ. *Brain*. 2014 Jan;137(Pt 1):232-41.
14. Diencephalic and brainstem mechanisms in migraine. Akerman S, Holland PR, Goadsby PJ. *Nat Rev Neurosci*. 2011 Sep 20;12(10):570-84.
15. Pathophysiology of migraine. Goadsby PJ. *Neurol Clin*. 2009 May;27(2):335-60.
16. Trigemino-cervical complex responses after lesioning dopaminergic A11 nucleus are modified by dopamine and serotonin mechanisms. Charbit AR, Akerman S, Goadsby PJ. *Pain* 2011 Oct;152 (10):2365-76.
17. The vascular theory of migraine--a great story wrecked by the facts. Goadsby PJ. *Brain* 2009 Jan;132(Pt 1):6-7.
18. Functional neuroimaging of primary headache disorders. Cohen AS, Goadsby PJ. *Curr Pain Headache Rep*. 2005 Apr;9(2):141-6.

References

19. A PET study exploring the laterality of brainstem activation in migraine using glyceryl trinitrate. Afridi SK, Matharu MS, Lee L, Kaube H, Friston KJ, Frackowiak RS, Goadsby PJ. *Brain* 2005 Apr;128(Pt 4):932-9.
20. Activation of 5-HT(1B/1D) receptor in the periaqueductal gray inhibits nociception. Bartsch T, Knight YE, Goadsby PJ. *Ann Neurol*. 2004 Sep;56(3):371-81
21. Brain stem activation in spontaneous human migraine attacks. Weiller C, May A, Limmroth V, et al. *Nat Med*. 1995 Jul;1(7):658-60.
22. Joutel A, Bousser MG, Biouesse V, et al. A gene for familial hemiplegic migraine maps to chromosome 19. *Nat Genet* 1993;5:40-45.]
23. Joutel A, Ducros A, Vahedi K, et al. Genetic heterogeneity of familial hemiplegic migraine. *Am J Hum Genet* 1994;55:1166-1172.
24. Ophoff RA, Terwindt GM, Vergouwe MN, et al. Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca²⁺ channel gene CACNL1A4. *Cell* 1996;87:543-552.
25. Terwindt GM, Ophoff RA, Haan J, et al. Variable clinical expression of mutations in the P/Q-type calcium channel gene in familial hemiplegic migraine. *Neurology* 1998;50: 1105-1110.

References

26. Ophoff RA, van Eijk R, Sandkuijl LA, et al. Genetic heterogeneity of familial hemiplegic migraine. *Genomics* 1994;22:21-26.
27. Ducros A, Joutel A, Vahedi K, et al. Mapping of a second locus for familial hemiplegic migraine to 1q21-q23 and evidence of further heterogeneity. *Ann Neurol* 1997; 42:885-890.
28. Hans M, Luvisetto S, Williams ME, et al. Functional consequences of mutations in the human $\alpha 1A$ calcium channel subunit linked to familial hemiplegic migraine. *J Neurosci* 1999;19:1610-1619
29. Jurkat-Rott, K., Freilinger, T., Dreier, J. P., Herzog, J., Gobel, H., Petzold, G. C., Montagna, P., Gasser, T., Lehmann-Horn, F., Dichgans, M. (2004). Variability of familial hemiplegic migraine with novel $A1A2 Na^+/K^+-ATPase$ variants. *Neurology* 62: 1857-1861
30. Elliott MA, Peroutka SJ, Welch S, May EF. Familial hemiplegic migraine, nystagmus, and cerebellar atrophy. *Ann Neurol* 1996;39:100-106.
31. van den Maagdenberg AM, Pietrobon D, Pizzorusso T, Kaja S, Broos LA, Cesetti T, van de Ven RC, Tottene A, van der Kaa J, Plomp JJ, Frants RR, Ferrari MD. A *Cacna1a* knockin migraine mouse model with increased susceptibility to cortical spreading depression. *Neuron*. 2004 Mar 4;41(5):701-10.
32. Knight YE, Bartsch T, Kaube H, Goadsby PJ. P/Q Type Calcium-channel blockade in the periaqueductal gray facilitates trigeminal nociception: A functional genetic link for migraine? *Jour Neurosci* 2002 ;22: RC213 1-6.

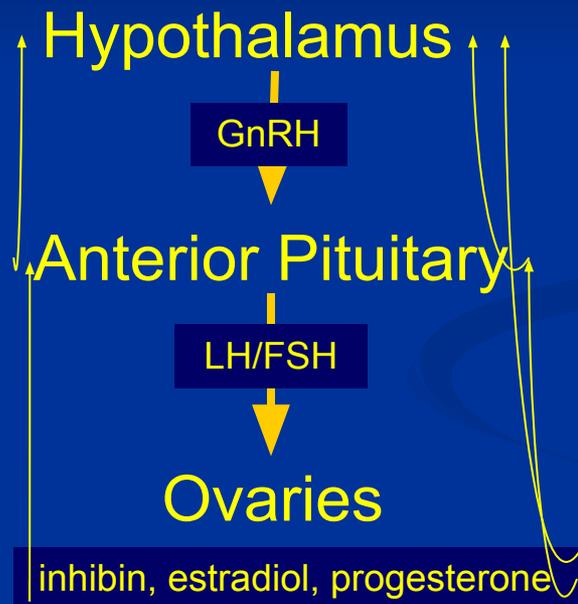
References

33. Pontogeniculooccipital waves: spontaneous visual system activity during rapid eye movement sleep. Callaway CW1, Lydic R, Baghdoyan HA, Hobson JA .Cell Mol Neurobiol. 1987 Jun;7(2):105-49.
34. Waking and dreaming consciousness: neurobiological and functional considerations. Hobson JA1, Friston KJ. Prog Neurobiol. 2012 Jul;98(1):82-98.

Hormones and Migraine

The background of the slide is a solid dark blue. In the bottom right quadrant, there are several overlapping, wavy, light blue lines that create a sense of movement or depth, resembling stylized waves or a decorative graphic element.

Menstruation and Releasing Hormones



Gonadotropin Releasing Hormones

- The releasing hormones (GnRH) boss the ovaries and the testicles. GnRH starts to spike in boys and girls at puberty.
- GnRH is also a **neurotransmitter**. There are GnRH receptors in the brainstem. GnRH levels affect sleep and brainstem excitability.
- After age 18 the boys have a constant daily testosterone level, (their GnRH levels stay steady), but their sisters have monthly GnRH spikes at ovulation and menstruation.
- At menopause ovaries are out of eggs, estrogen goes down and so GnRH levels go up. Low doses of estrogen replacement may not be enough to inhibit GnRH completely. Women in menopause can't stay asleep when their vitamin D is low and GnRH is high.
- 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.

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

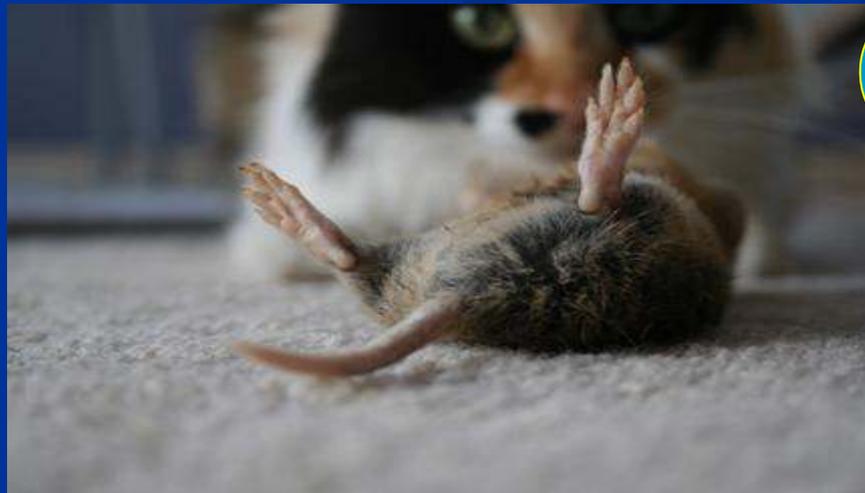
- One of the Ca^{++} channel mutations that causes migraine is found in mice.
- Unfortunately the mice can not tell us if they have a headache
- They do have staggering episodes and occasionally, epilepsy.
- There are also **inherited epilepsy syndromes and vertigo syndromes** that are caused by Ca^{++}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

Boy do I
have a
Headache
!



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”