

Migraine Pathogenesis

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Migraine

- Migraine affects approximately 19.2% of females and 6.6% of males in the United States. (Patel, Bigal et al. 2004)
- ...Resulting in approximately 112 million lost work days amounting to nearly \$8 billion a year in lost productivity (Hu, Markson et al. 1999)

Migraine without Aura

Migraine without aura is described as

“Recurrent headache disorder manifesting in attacks lasting 4-72 hours. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia.”

- International Classification of Headache Disorders, Section 1.1

Migraine with Aura

Migraine with aura is described as

“Typical aura consisting of visual and/or sensory and/or speech symptoms. Gradual development, duration no longer than one hour, a mix of positive and negative features and complete reversibility characterise the aura which is associated with a headache fulfilling criteria for 1.1 Migraine without aura.”

- International Classification of Headache Disorders, Section 1.2.1

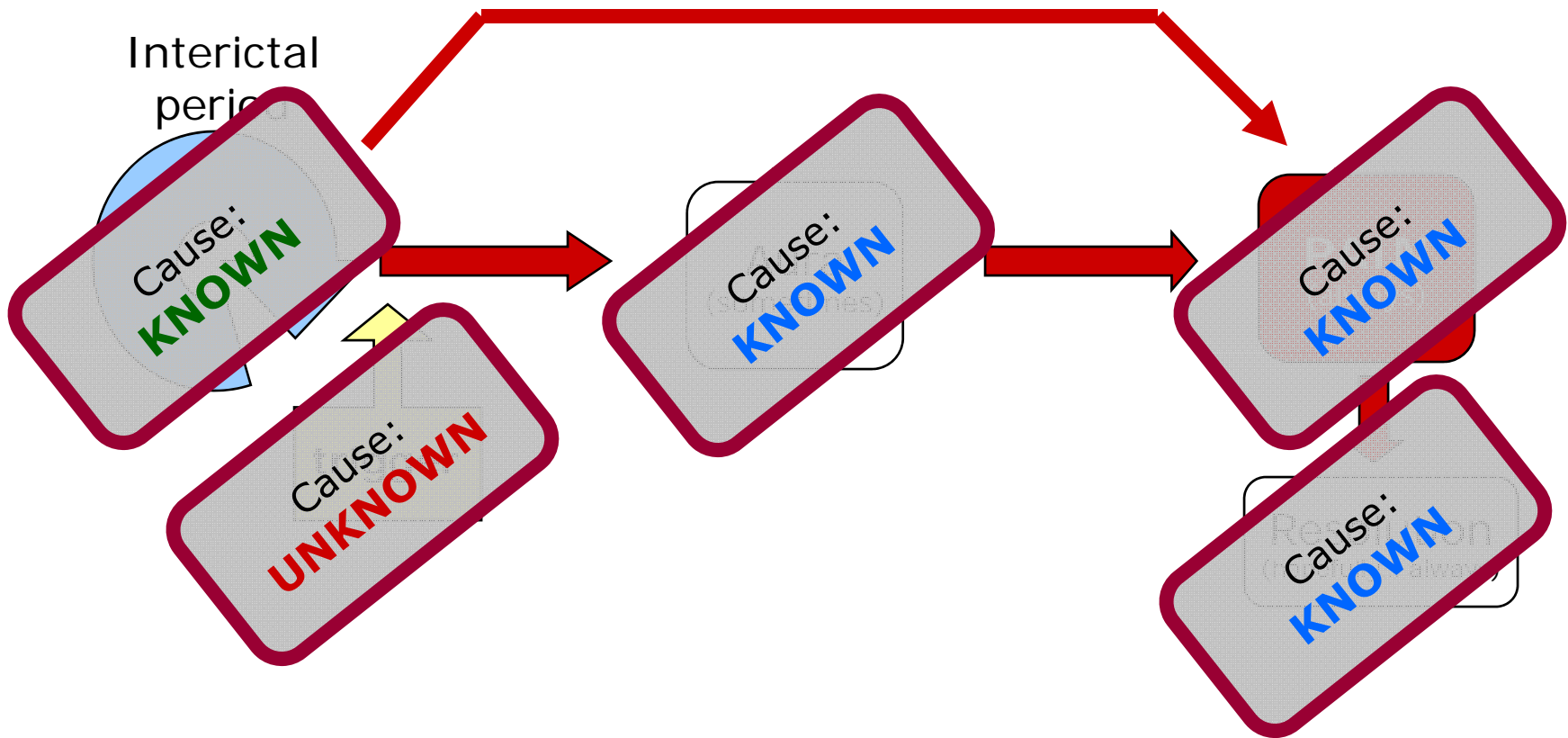
Migraine

- “Ow. My head’s been hurting while at work all day. I have migraine.”

Probably not...



Migraine Progression



Migraine Triggers

- Flashing lights
- Loud sounds
- Strong odors (perfume, etc)
- Aged cheese (tyramine)
- Caffeine
- Chocolate
- Alcohol
- Sleep changes
- Stress
- MSG
- Nitrates
- Artificial sweeteners
- Tension headache
- Stress letdown
- Menstruation
- Pregnancy
- Menopause
- Birth control pills
- Acid reflux
- Not eating
- Smoking
- Changes in barometric pressure
- High humidity

- And the unknown triggers...

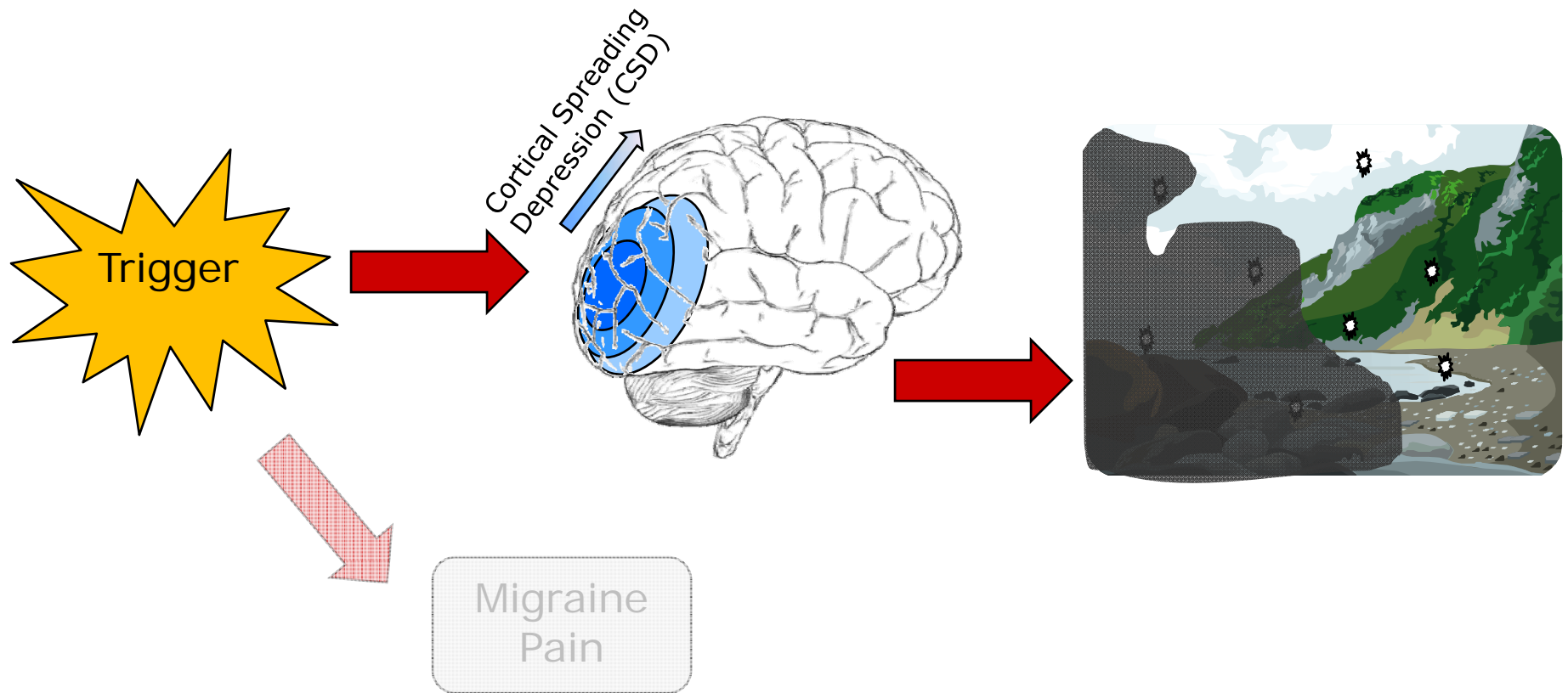
Migraine Symptoms

- Aura
 - can include sensory hallucinations
- Migraine pain
 - Stabbing pain “Like a knife is being twisted in my head”

Aura

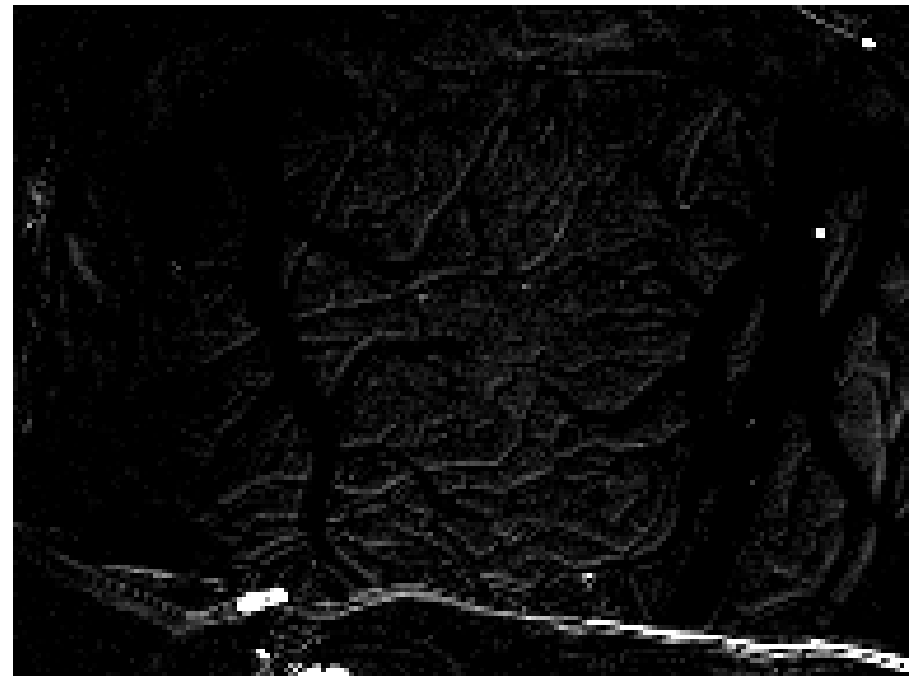
- Occurs in only 18-36% of migraineurs (Davidoff 2002)
- Mostly visual aura; scintillating lights and scotoma
- Sometimes
 - Auditory
 - Olfactory
 - gustatory hallucinations.
- Rare aura:
 - Vertigo
 - Aphasia
 - Hemiparesis
 - Delerium
 - Alice in Wonderland phenomena

Aura Pathophysiology



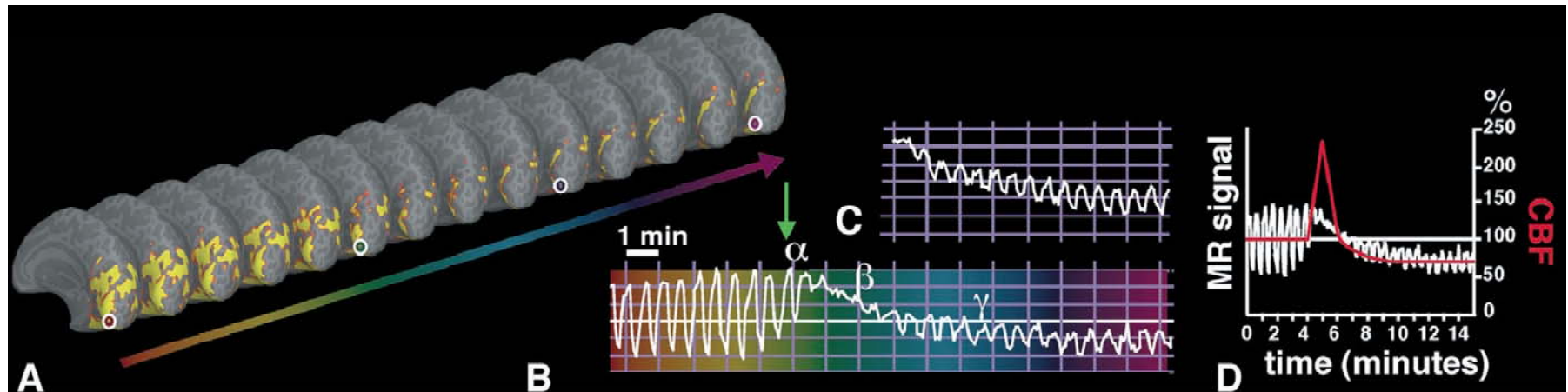
Cortical Spreading Depression

- Quick neuronal **depolarization** followed by long lasting neural suppression.
- Slow progression across the cortex (2-3mm/min)
- Quick increase in regional cerebral blood flow (rCBF) [thin dark band]
- ... followed by sustained decrease in rCBF [wide white band]
- Leao et al (1944) was first to call it 'spreading depression'.



(http://charleslab.medsch.ucla.edu/charleslab/cellular_mechanisms_of_migraine.htm)

Previous CSD Studies



Flashing checkerboards, 16s on, 16s off. A) Progression of activation during scan of basketball subject. B) BOLD signal at point indicated by circle. Green arrow indicates onset of visual aura. C) spontaneous attack from separate subject. D) rCBF from rat superimposed on basketball subject.

- Hadjikhani (2001) scanned a migraine patient with extremely predictable aura and migraine. Always gets migraine after playing basketball. Shows definite spreading depression across the occipital lobe.

Migraine 'generator' theories

1. CSD (in migraine **w/aura**) causes the migraine to begin (Bolay 2002).
2. A 'silent' CSD in migraine **w/out aura** gives rise to migraine attack.
3. Migraine triggers activate brainstem structures (dorsal raphe nucleus, periaqueductal grey, locus coeruleus) and begin the migraine attack. (*my favorite)

(summary from Sanchez 2004)

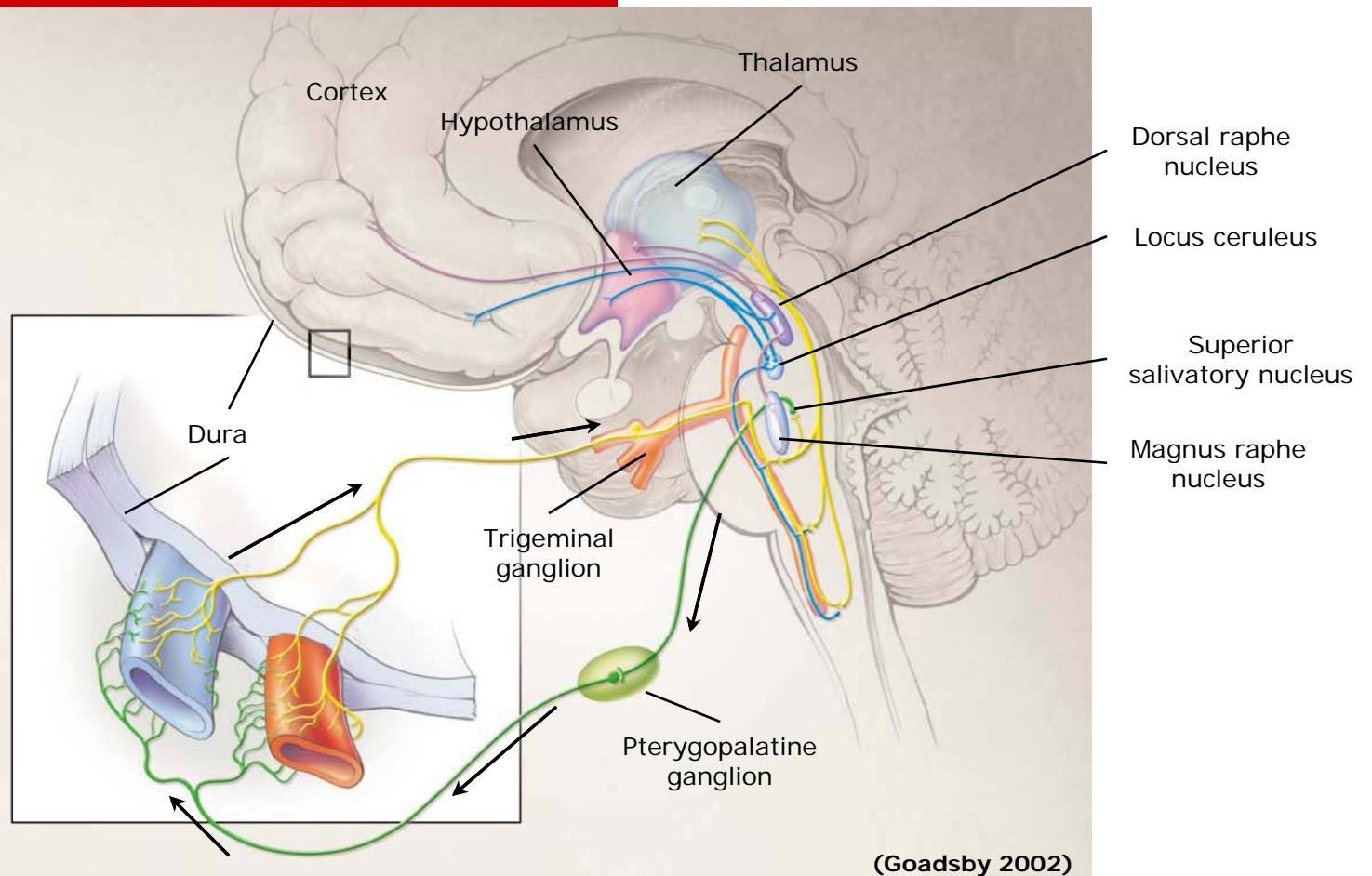
Migraine Pain

Ouch.

Trigeminovascular Mechanism

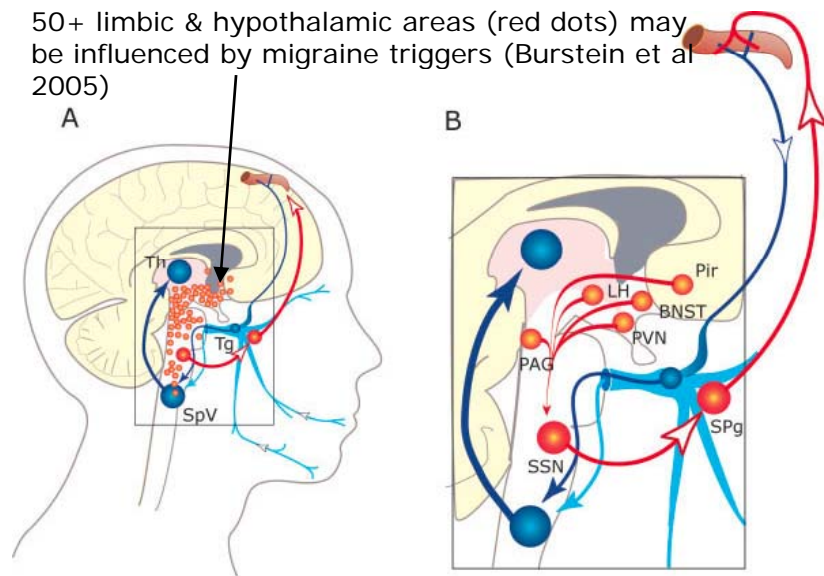
- This trigeminal–autonomic reflex is present in normal persons (Goadsby 2002). And regulation may be abnormal in migraine attacks (Giffin 2003).

- Imaging studies suggest that modulation of the trigeminovascular nociceptive input comes from the **dorsal raphe nucleus, locus ceruleus, and nucleus raphe magnus** (Goadsby 2003)



Parasympathetic activation of menengial nociceptors

- Burstein and Jakubowski (2005) state the areas (hypothalamic, limbic, cortical) that project to the **superior salivatory nucleus** also receive afferent connections from the trigeminovascular pathway.
- So... the **trigeminovascular pathway can activate the same brain areas that have triggered its own activity** in the first place.
- Therefore, Burstein proposes that this loop invalidates “migraine generator areas” found in fMRI studies because they are likely driven by the migraine pain itself



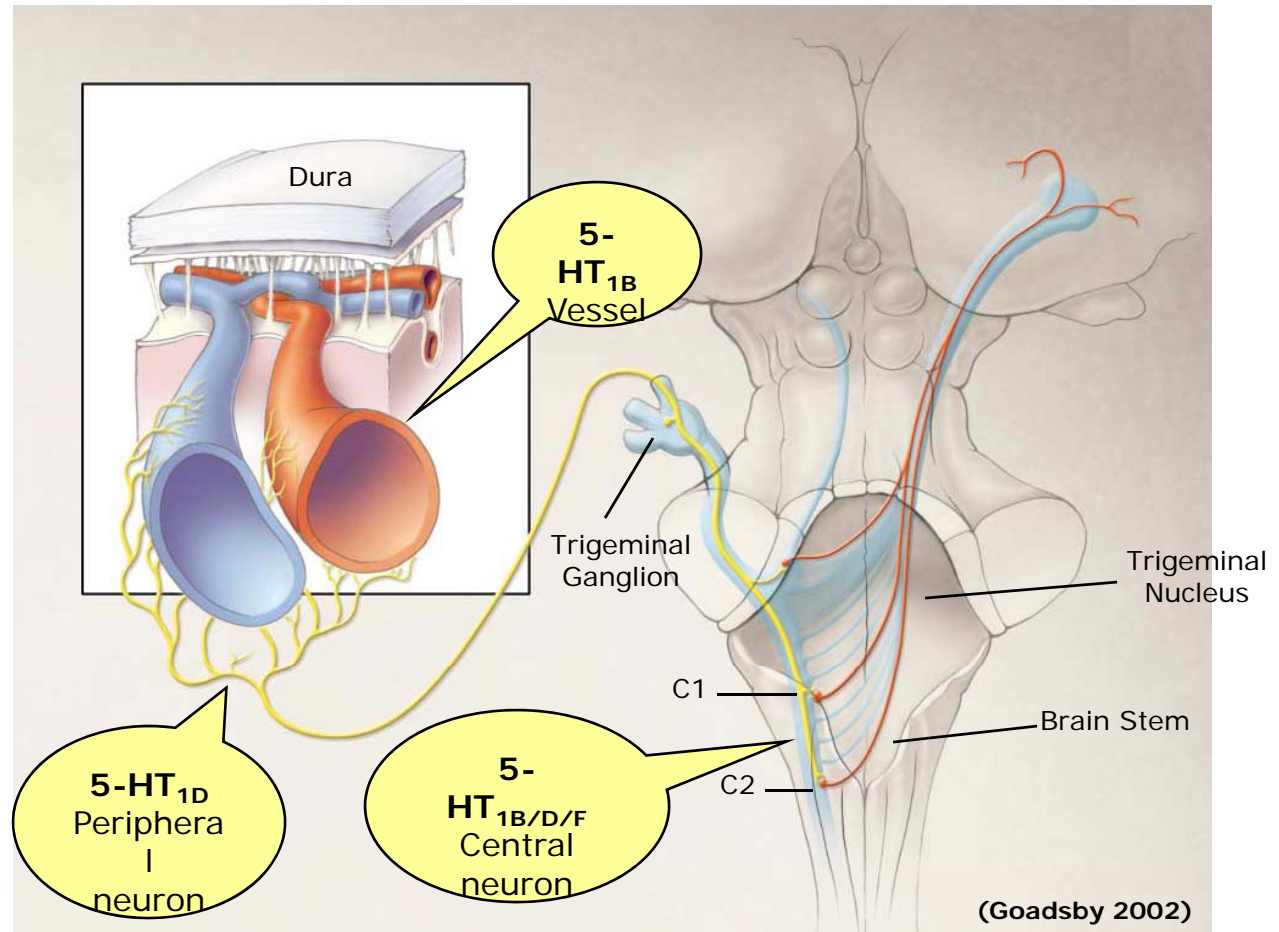
SSN – superior salivatory nucleus
SPG – sphenopalatine ganglion
BNST – bed nucleus stria terminalis
LH – lateral hypothalamus
PAG – periaqueductal gray
Pir – piriform cortex
PVN – paraventricular hypothalamic nucleus

Now for the pain...

- Migraine pain is of a pulsing quality.
- Worse during normal pressure-causing activities such as touch, coughing, and pulsing arterial blood pressure.
- Burstein (2001) states that it may be caused by meningeal primary afferent neurons that have become hyperexcited
 - ... and the neurons of the trigeminal ganglion have become hyperexcited

Resolution

Effects of Triptans



The study

Inclusion Criteria:

- Female, age 18-45
- Current menstrual migraine as defined by ICHD-II
- No history of head injury, epilepsy, or status migrainosis; no current Axis 1 disorder; no previous treatment of migraine with opiates

Subjects:

- 6 Migraine w/aura; 6 Migraine w/out aura; 6 healthy controls

The study

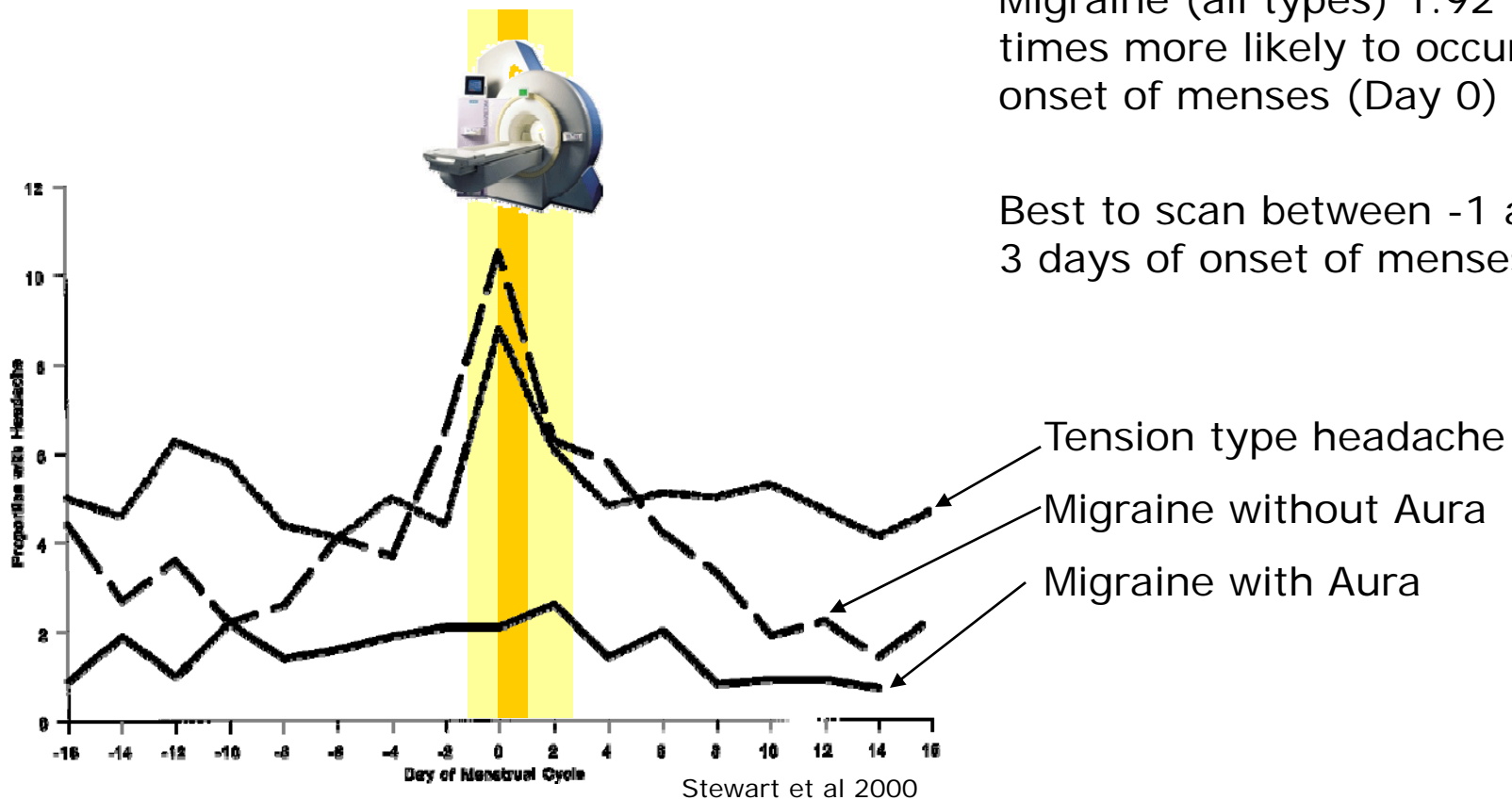
Objective:

- Find CSD or changes in vessel diameter
- Use ICA to find areas of activation during a migraine

Tasks:

- Two 15 minute runs of 16s flashing checkerboards (2Hz) and 16s fixation
- Subject indicates pain level when the level changes.

Menstrual Migraine



Imaging Migraine

fMRI	128x128x32 BOLD images; TR=2.5s 3 Runs; 10 minutes each	Induce migraine. Observe cortical BOLD signal changes
MRA	320x256x90 TOF 3D	Image cranial vessels to observe changes in arterial diameter before and after BOLD

Results

Recruitment goal:

- 6 Migraine w/aura; 6 Migraine w/out aura; 6 healthy controls

Actual recruitment:

- 4 Migraine w/aura; 5 Migraine w/out aura; 3 healthy controls

Actual subjects scanned:

- 1 Migraine w/aura; 3 Migraine w/out aura; 3 healthy controls

Successful scans:

- 1 Migraine w/out aura; 2 non-migraine

Subjects

#1 – Migraine w/out aura

- 24 year old female
- Monthly menstrual migraines since age 12
- Takes Zomig as rescue medication

#2 – No migraine

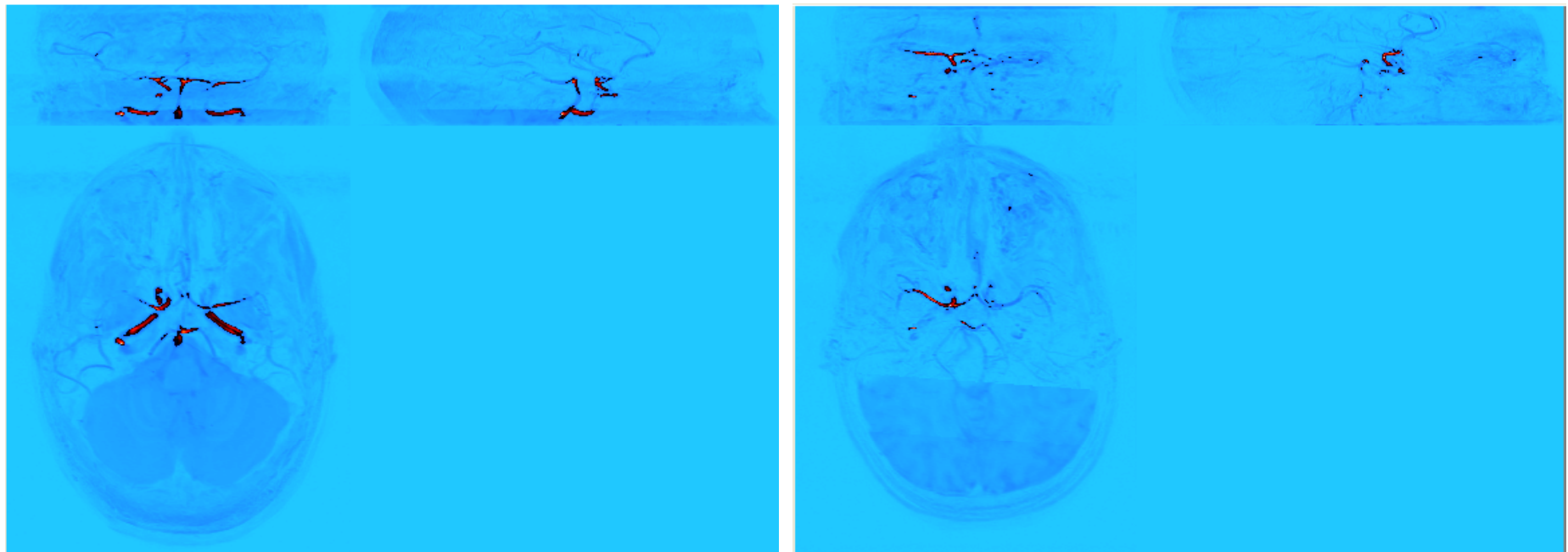
- 49 year old female
- Scored 2 on MIDAS. Would not diagnose as having migraine

#3 – No migraine

- 23 year old healthy female

MRA results

Post > Pre

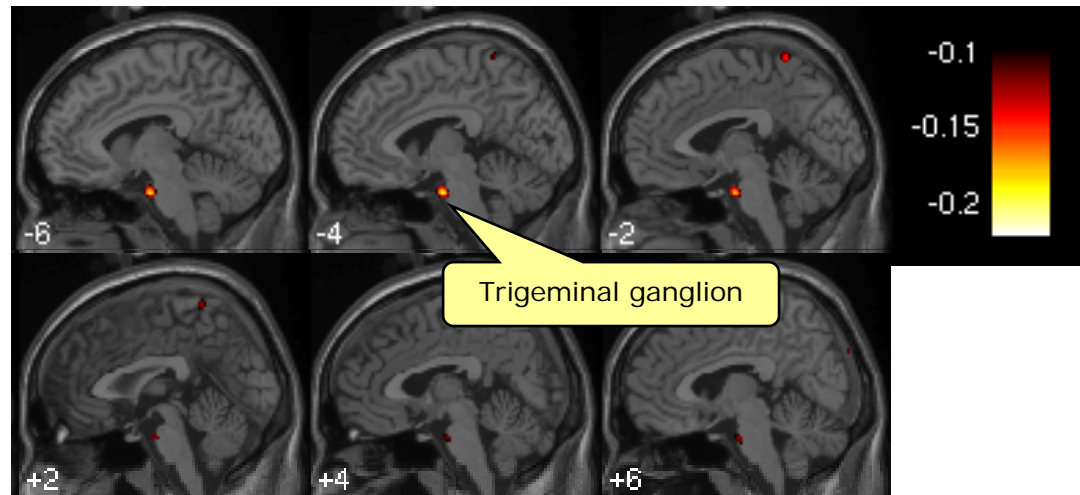


Migraine w/out aura (#1)

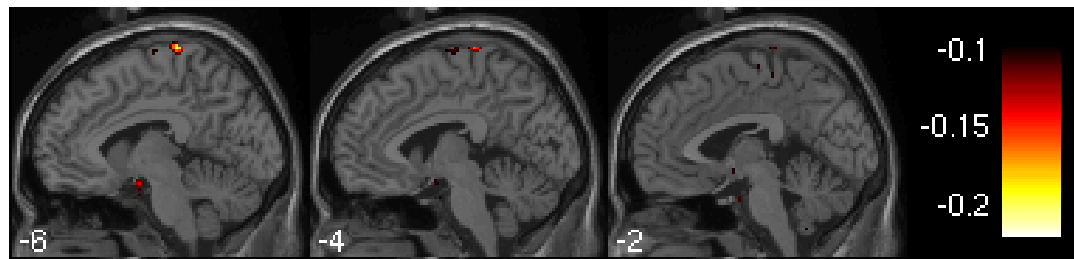
Healthy control (#2)

fMRI results using ICA

Migraine w/out aura (#1)
Results similar to Borsook et al (2004)



No migraine (#2)



Difficulties

- Inducing a true and lasting migraine
- Observing the true beginning of the migraine
- Subject willingness

Study Improvements

- Use ASL sequence instead of BOLD to observe cortical spreading depression
- Recruit more subjects

Acknowledgements

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