Advanced Neuroimaging of Migraine (Part I)

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Introduction

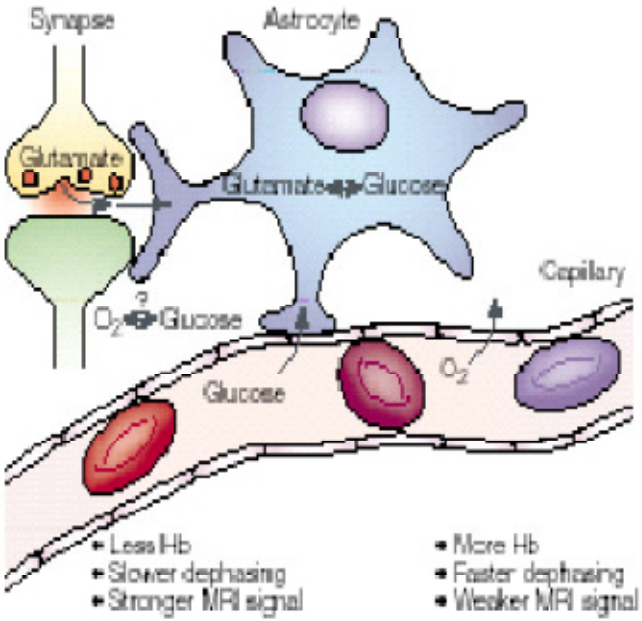
- Advanced neuroimaging has help to increase our knowledge about migraine pathophysiology. Our perception of migraine has transformed from **a vascular, to a neurovascular, and most recently, to a CNS disorder.**
- Functional imaging has confirmed the importance of cortical spreading depression (CSD) as the pathophysiological mechanism of migraine aura in human beings, where novel animal studies are unraveling the mechanistic underpinnings of CSD.

Introduction

- Altered cerebral blood flow and neurotransmitter systems have been identified during and between headaches in migraine with and without aura. **Advanced neuroimaging has identified mechanisms involved in the transformation of migraine from an episodic disorder to one with near continuous symptomatology.**
- New imaging techniques could lead to novel diagnostic and therapeutic interventions that will help to improve the lives of millions of patients with migraine.

Imaging of Migraine

- Imaging during spontaneous migraine has proven difficult. Some investigators have exposed migraine patients to attack triggers, such as photic stimulation, physical exertion, or nitroglycerine to initiate migraine.
- A few investigators have captured the onset of a migraine headache, whereas other have obtained images just after the headache began. The overall number of studies that have captured images of the migraine attack itself is small.



Neuronal activity results in:

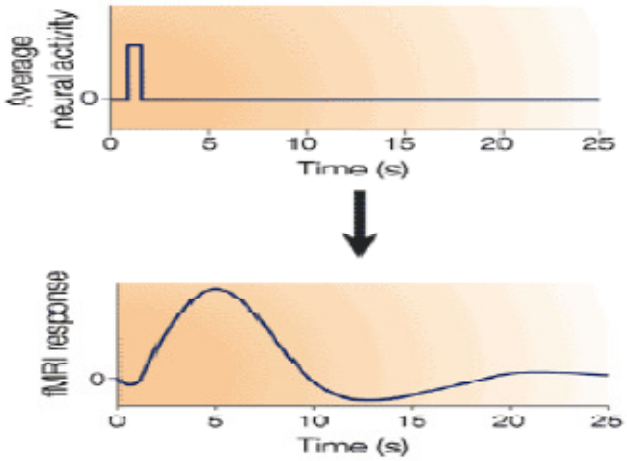
1. *An initial increase in oxygen consumption owing to increased metabolic demand.*

2. *After a delay of ~2 secs, a large increase in local blood flow. which overcompensates for the amount of oxygen being extracted*

3. *Local increase in cerebral blood volume*

The increase in blood oxyhaemoglobin is what we measure in fMRI
This is called the BOLD (Blood Oxygen Level Dependent) response. (Ogawa et al. 1990)

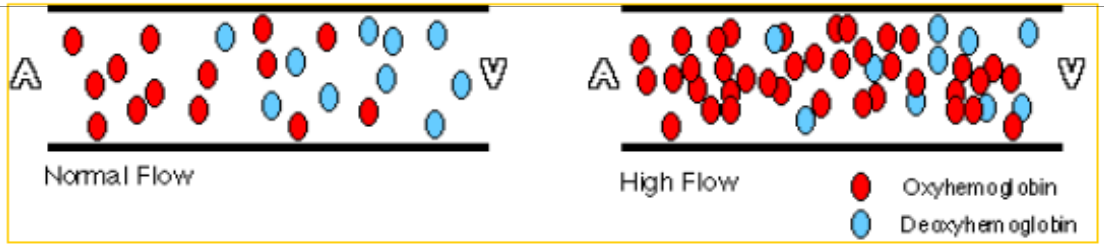
Dr. Seiji Ogawa



BOLD (Blood Oxygen Level Dependent) contrast

- Takes advantage of the different magnetic properties of oxyhemoglobin (HbO) and deoxyhemoglobin (Hb)

  Hb is *paramagnetic* and introduces an inhomogeneity into the nearby magnetic field, whereas HbO is weakly *diamagnetic* and has little effect.



Neuronal activity → local blood flow increases **overcompensating** for oxygen consumption → oxygen level in venous blood is elevated → larger MR signal.

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- **Brain**

(1). Cao and colleagues did a set of blood oxygen level dependent (BLOD) function MRI (fMRI) studies of spontaneous migraine after recurrent checkerboard visual stimulation: most patients who developed migraine had **signal intensity increase in the region on the red nucleus and substantia nigra.** This followed by increases in occipital cortex signals and then by the onset of visually triggered symptoms. (Cao Y et al. Neurology 2002; 59:72-8, Welch KM et al. Neurology 1998; 51:1465-69)

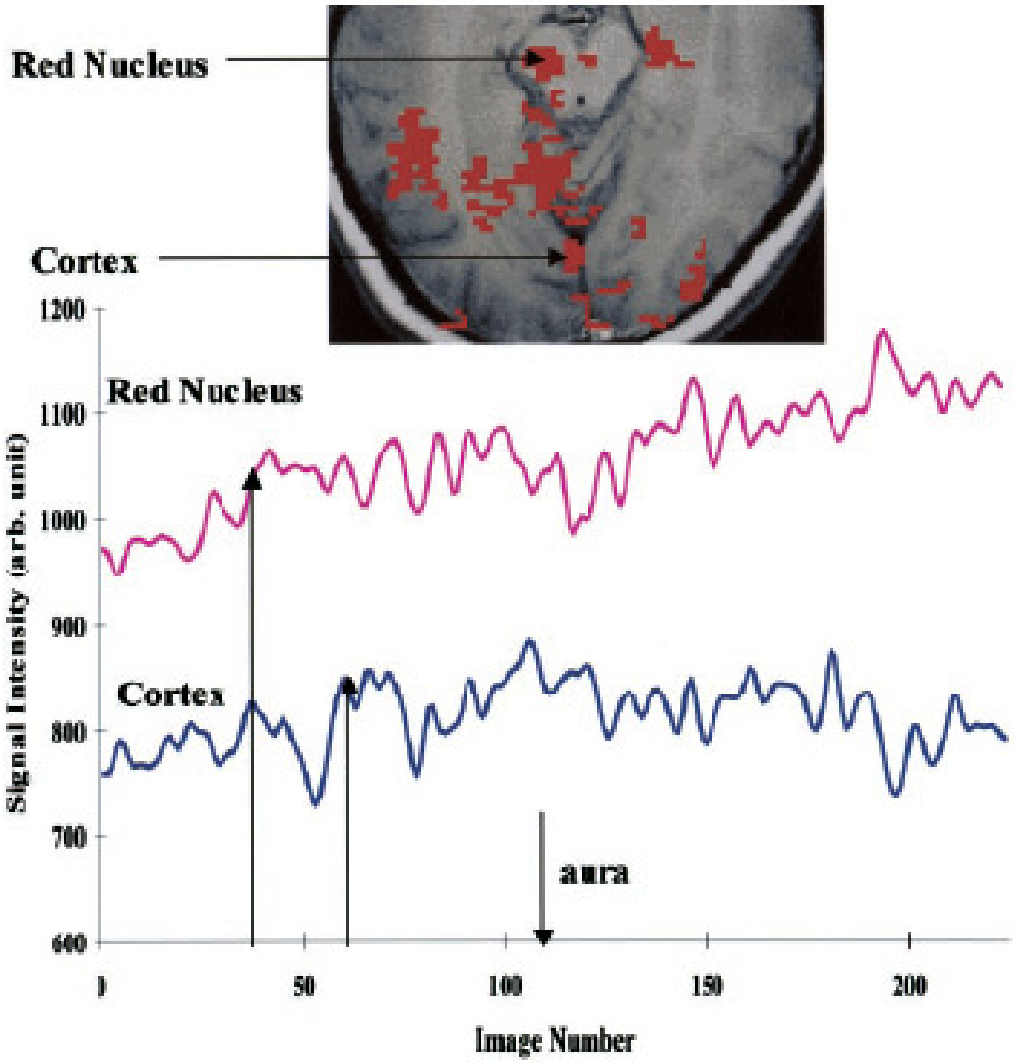

Figure 4. Increases in baseline signal intensities of the occipital lobe, red nuclei, and substantia nigra in Patient 3. (Top panel) Red depicts the increased mean signal intensity from image numbers 100 to 224, compared with the mean signal intensity of the first 56 images (Student t-test, $p < 0.001$). (Bottom panel) Time courses of signal intensities at the right red nucleus and right occipital cortex are plotted. Arrows indicate the onset of the signal increase in the right red nucleus, the onset of the signal increase in the right occipital cortex, and the onset of triggered visual aura reported by the patient. Note that the signal increase in the red nucleus occurred before the increase in the signal intensity in the occipital cortex, which occurred before the onset of aura reported by the patient.

(Cao Y et al. Neurology 2002; 59:72-8)

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(2). Less consistently, patients were found to have signal increases in other regions of the brainstem, including the **cerebral peduncle, locus coeruleus, periaqueducal grey, medial longitudinal fasciculus, basilar pons, medial lemniscus, pontine tagmentum, and central midbrain.**

(3) Afridi and colleagues in PET studies: 3 migraine without aura (M-) and 2 migraine with aura (M+): revealed **significant activation in the dorsal pons during migraine. Activation was also detected in the anterior and posterior cingulate, cerebellum, thalamus, insula, prefrontal cortex, and temporal lobes.** (Afridi SK et al. Arch Neurol 2005; 62:1270-75)

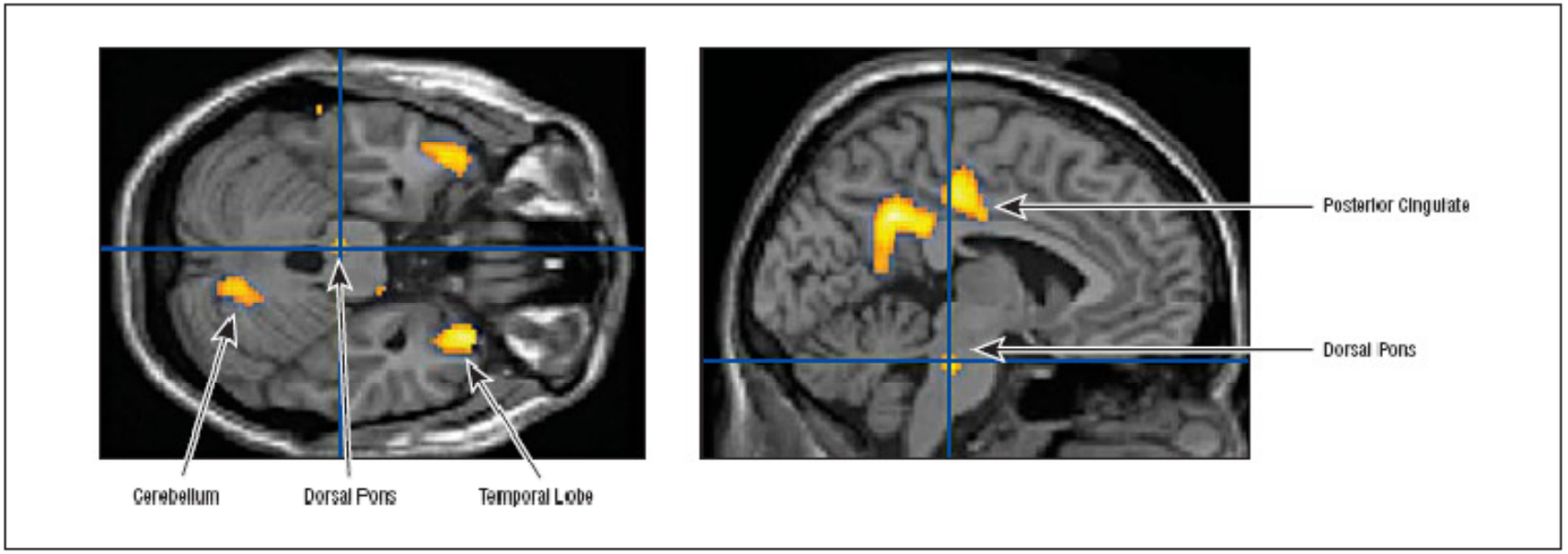

Figure 1. Activation in the dorsal pons in the migraine state compared with the interictal state.

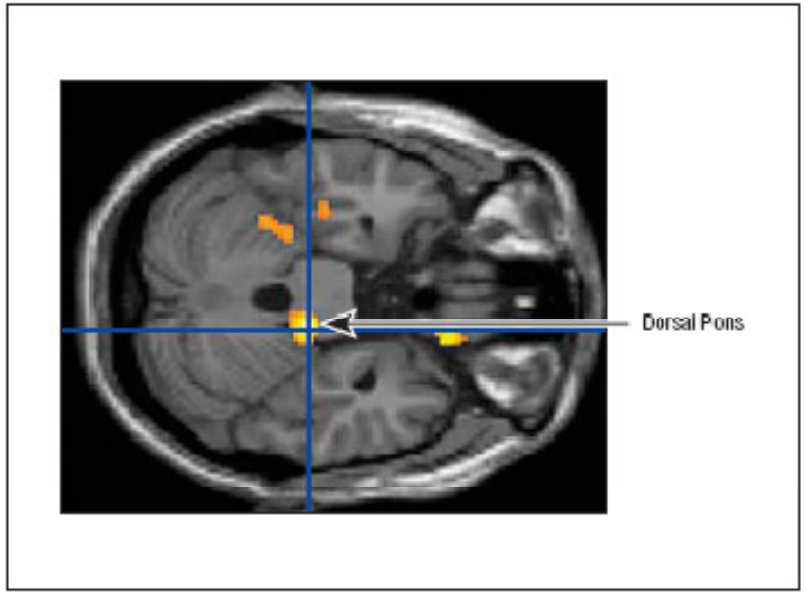

Figure 2. Activation in the thalamus and insula in the migraine state.

(Afridi SK et al. Arch Neurol 2005; 62:1270-75)

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(4). These studies identified **activation of brainstem structure during migraine.** However, one of the main challenges in interpretation of these results is to differentiate findings consistent with the general pain response from those that might be specific to migraine.

(5). PET study of 24 individuals with nitroglycerine-induced migraines: significant brainstem activation was noted during migraine in the **dorsal pons and rostral medulla. Other areas of activation included the anterior cingulate, insula, cerebellar hemispheres, prefrontal cortex, and putamen**.

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After treatment of the migraine with sumatriptan, the dorsal pons remained activated.

(Afridi SK et al. Brain 2005; 128:932-39, Bahra A et al. Lancet 2001; 357:1016-17, Weiller C et al. Nat Med 1995: 1:658-60)

(6). Matharu and colleagues: 8 chronic migraine patients treated with occipital nerve stimulation underwent PET: significant changes in regional cerebral blood flow, which correlated with migraine pain, were found in the region of **dorsal rostral pons, anterior cingulate cortex and cuneus,** whereas changes in the **anterior cingulate cortex and pulvinar** correlated with parathesias.

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(7). Increased activity in the dorsal rostral pons during migraine and when pain free versus the intermediate state suggests **a persistent dysfunction of this structure in these chronic migraine patients.** (Matharu MS et al. Brain 2004; 127: 220-30)

(8). These studies suggest that a migraine generator exists in the brainstem, probably the **dorsal rostral pons. Persistent activation of the dorsal pons after sumatriptan therapy and suboccipital stimulator therapy implies that this region is specific to migraine.**

	Findings
Functional MRI[47]	Activation in dorsal rostral pons, periaqueductal grey, red nucleus, substantia nigra, anterior cingulate, posterior cingulate, cerebellum, thalamus, insula, prefrontal cortex, temporal lobes, cerebral peduncle, locus coeruleus
PET[8–12]	Activation in dorsal pons, rostral medulla, anterior cingulate, insula, cerebellar hemispheres, prefrontal cortex, putamen, cuneus

Table 1: Functional brain events during migraine headache identified by modern imaging techniques

(Schwedt TJ et al. Lancet Neurol 2009; 8: 560-68)

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■ Cerebrovasculature

(1). The vascular and neurovascular theories of migraine had assumed that dilation of cerebral and meningeal arteries is essential for the production of migraine pain.

(2). A recent 3 T magnetic resonance angiography study has questioned the importance of the cerebral vasculature in the pathophysiological of migraine. Investigations of 20 attacks of migraine without aura provoked by nitroglycerine identified **no significant changes in cerebral artery diameters or cerebral blood flow during migraine.**

(Schoonman GG et al. Brain 2008; 131: 2190-200)

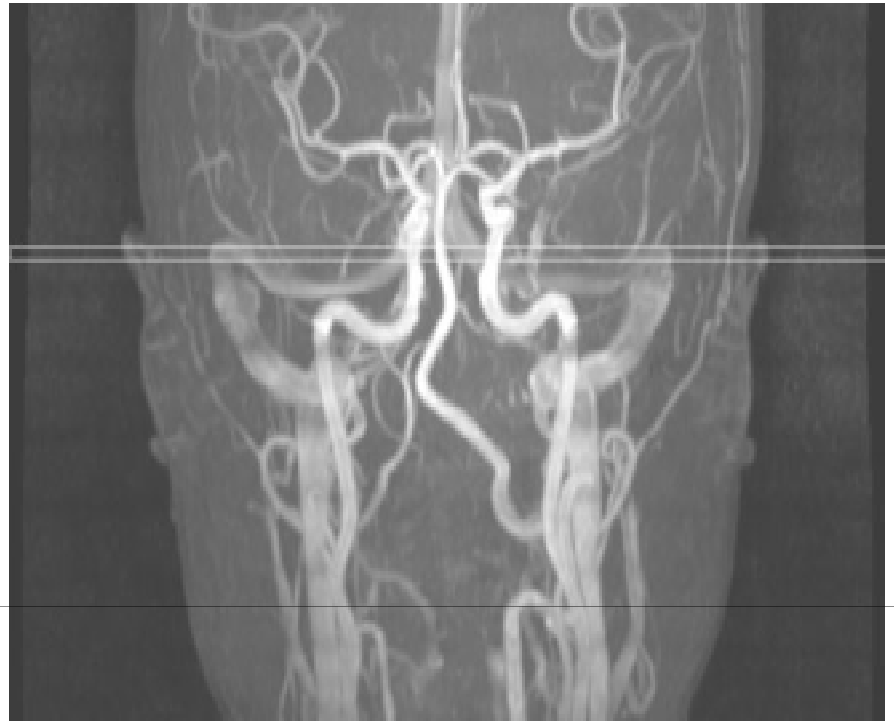

Fig. 1 MRA, coronal maximum intensity projection. Horizontal line indicates the positioning of the 2D phase contrast section through the ICA and the BA.

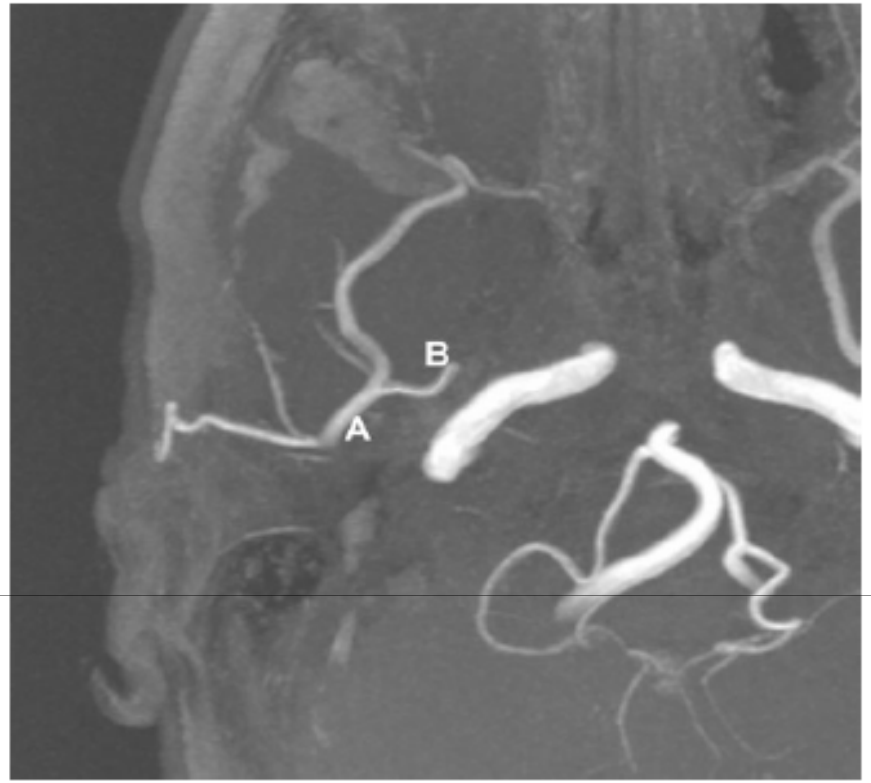

Fig. 2 MRA of the MMA region and position of the measured segment: (A) maxillary artery, (B) MMA.

(Schoonman GG et al. Brain 2008; 131: 2190-200)

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(3). The findings suggest that changes in vascular diameter might not occur, or at least might not be necessary during migraine, and further support the hypothesis that migraine should be thought of as a CNS disorder.

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- **Central sensitization**

(1). Development of central sensitization results in additional pain during a migraine attack **(cutaneous allodynia)** and might contribute to the transformation from episodic migraine to chronic migraine.

(2). Cutaneous allodynia develops in **about 65%** of patients with migraine during individual headache. Patients with allodynia report painful sensitivity of the skin to normally innocuous stimuli such as light touch. Methods of blocking or reversing the development of central sensitization can reduce the pain of migraine and reduce the rate of transformation to chronic migraine.

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(3). By use of the heat/capsaicin model of sensitization, fMRI studies have identified activation in the region of the midbrain reticular formation that seems specific to central sensitization. Investigators have thus suggested that **activation occurs at the location of the nucleus cuneiformis (NCF) and rostral superior colliculi/periaqueductal grey (SC/PAG).** (Zambreanu L et al. Pain 2005; 114: 397-407, Lee MC et al. J Neurosci 2008; 28:11642-49)

(4). fMRI studies examined the modulating effect of gabapentin on brain activators after painful mechanical stimulation of normal skin and skin with capsaicin-induced

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secondary hyperalgesia. In both conditions, gabapentin reduced activations in the operculoinsular cortex. However, only in the presence of central sensitization did gabapentin reduce activations in the brainstem and suppress stimulus-induced deactivations, **indicating that gabapentin more effectively reduces painful transmission in the presence of central sensitization.**

(Iannetti GD et al. Proc Natl Acad Sci USA 2005; 102: 18195-200)

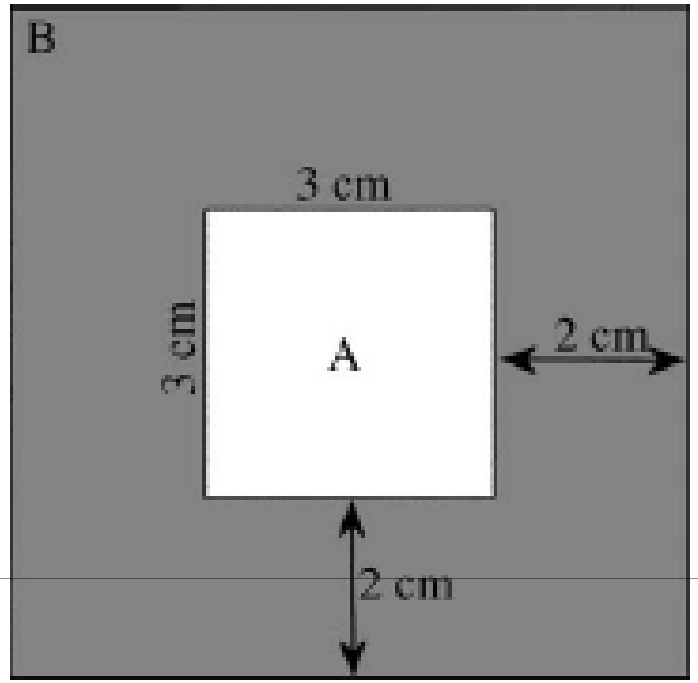

Fig. 1. Area of punctate stimulation. (A) Reference site (white area, 3×3 cm): heat/capsaicin treated in the hyperalgesia session and untreated in the control session. (B) Area of punctate stimulation (grey area, 2 cm outside the reference site in each direction): hyperalgesic following heat/capsaicin treatment and control site in the absence of treatment.

(Zambreanu L et al. Pain 2005; 114: 397-407)

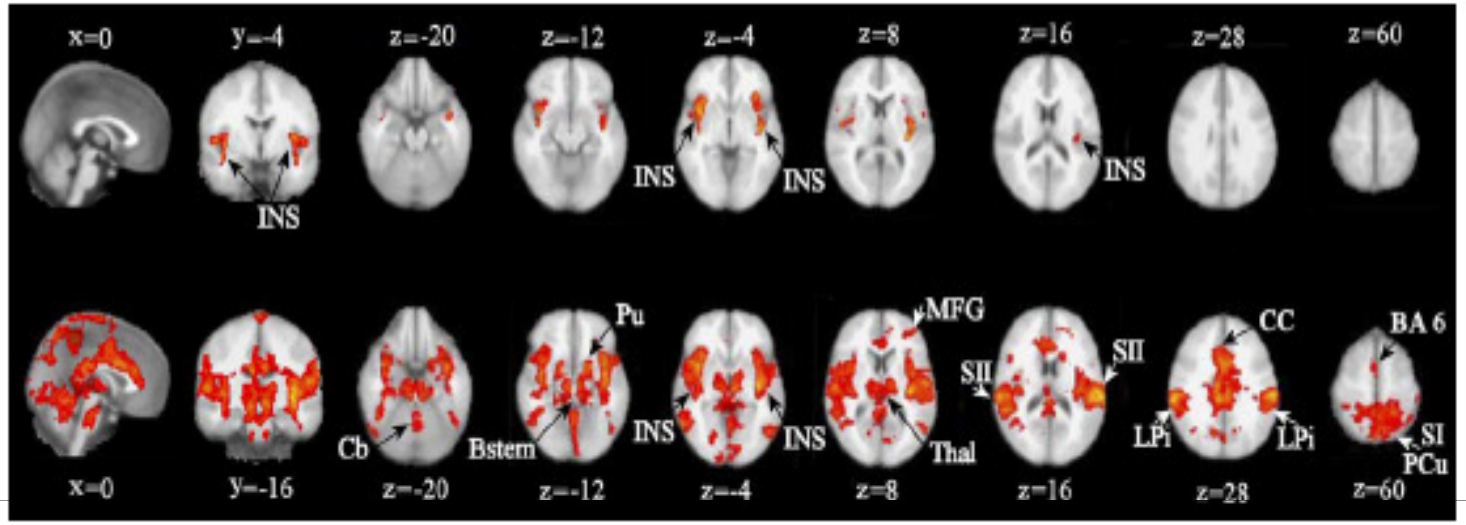

Fig. 2. Brain activation during punctate mechanical stimulation. Top row, in control skin; Bottom row, in the area of secondary hyperalgesia. Group activations registered onto the MNI standard brain in axial view, Z score >2.3, cluster corrected $P<0.01$. Both panels show a midline sagital section ($x=0$), followed to the right by a coronal section and then by a series of seven axial views in infero-superior succession. The y and z coordinates at the top and bottom of the figure indicate the antero-posterior and the superior–inferior location of the sections, respectively. INS, insula; Cb, cerebellum; Bstem, brainstem; Pu, putamen; MFG, middle frontal gyrus; Thal, thalamus; SII, secondary somatosensory cortex; LPi, inferior parietal lobule; CC, cingulate cortex; SI, primary somatosensory cortex; PCu, pre-cuneus (BA7); SMA, supplementary motor area (BA 6). Images are displayed in radiological convention.

(Zambreanu L et al. Pain 2005; 114: 397-407)

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- **Migraine medications**

(1). 18F-fluorodeoxyglucose PET was used to study patients while they experienced an analgesic-overuse headache and 3 weeks after withdrawal of the overused medications: many areas of abnormal metabolic activity were seen during the medication-overuse headache (**hypometabolism at thalamus, orbitofrontal cortex, anterior cingulate cortex, insula, and inferior parietal lobule, and hypermetabolism at cerebellar vermis**) and were normalized after the medication was withdrawn. However, **metabolic activity of the orbitfrontal**

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cortex was further reduced after medication withdrawal, suggesting a role for this structure in the predisposition to analgesic overuse.

(Fumal A et al. Brain 2006; 129: 543-50)

(2). Orbitofrontal cortex dysfunction has also been identified in many other disorders, **including substance dependence and in those with gaming addiction.**

(Tanabe J et al. Biol Psychiatry 2008; 65: 160-64, Ko CH et al. J Psychiatr Res 2009; 43: 739-47)

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(3). The rate of serotonin synthesis during migraine and after treatment with sumatriptan was recently studied by use of PET: six patients were scanned within 6 h of onset of a spontaneous migraine, 2 h after treatment with sumatriptan, and when migraine free for at least 3 days.

Pain-free state: slightly lower serotonin synthesis than did controls.

The rate of serotonin synthesis increased during a migraine attack.

Reduced to levels lower than the pain-free state by administration of sumatriptan.

(Sakai Y et al. Neurology 2008; 70: 431-39)

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(4). Reduction in the rate of serotonin synthesis were independent of changes in pain intensity, suggesting the sumatriptan exerts its effect on serotonin synthesis at a different site from its pain-relieving effects.

(5). It is thought that **action at serotonin 5-HT_{1B} receptors of the raphe nucleus is responsible for the reduction of serotonin synthesis, whereas action at 5-$HT_{1B/1D}$ receptors of the periaqueductal grey is responsible for the pain-relieving effect.**

(Bartsch T et al. Ann Neurol 2004; 56: 371-81)

Imaging of cortical spreading depression or migraine aura

- **Cortical spreading depression (CSD)** has long been thought to be the physiological substrate of migraine aura. During CSD, an initial neuronal depolarization occurs, followed by hyperpolarization, and relative neuronal silence that spreads contiguously from the occipital lobe forward. This spreads wave of neuronal depression travels slowly, at 3-5 mm/min, which coincides with the progressive visual symptoms typical of migraine aura.
- A brief decrease in blood flow is followed by hyperperfusion lasting a couple of minutes and then a prolonged hypoperfusion.

Imaging of cortical spreading depression or migraine aura

- Hadjikhani and colleagues studied three migraineurs with aura by use of fMRI (BOLD) during spontaneous attacks. All patients were studied within 20 min of attack onset and one patient who could trigger migraine by exercise was studied at the onset of episode.

  # An initial focal increase in BOLD signal in the extrastriate cortex.

  # BOLD changes were time locked to the onset of migraine aura.

  # BOLD changes progressed contiguously over the occipital cortex at approximately 3.5 mm/min.

  # BOLD signal then diminished after the increase.

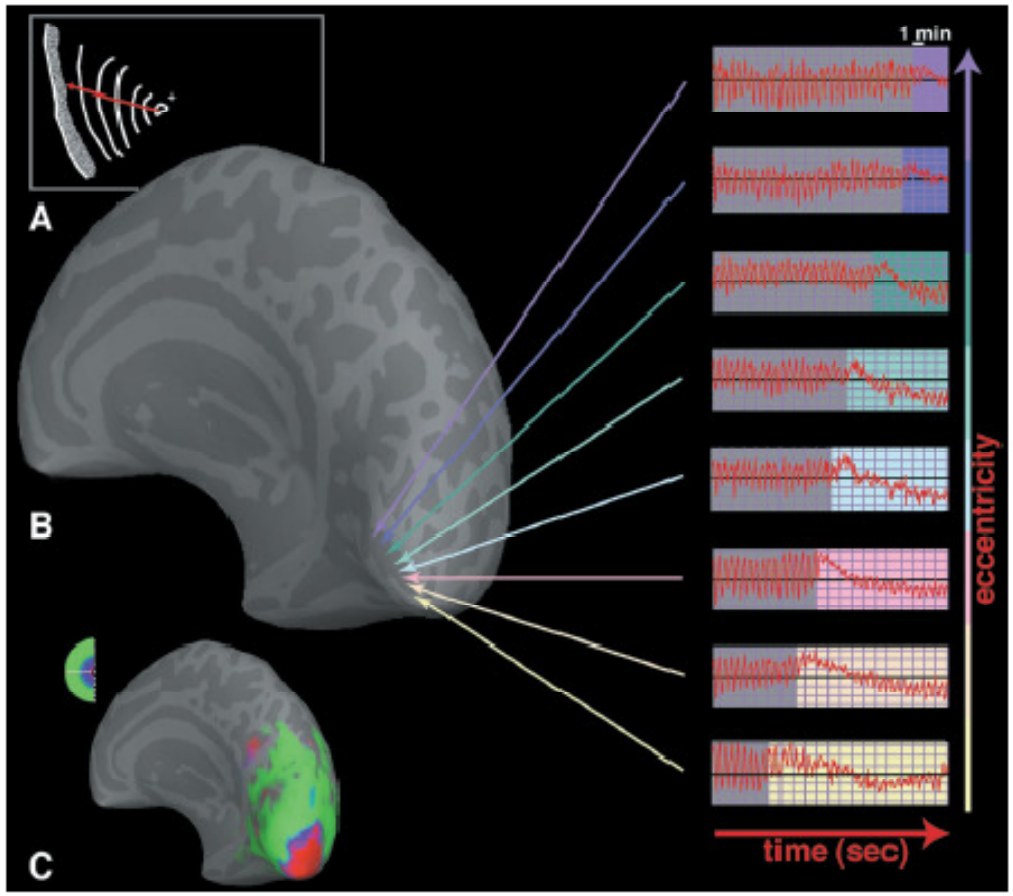

Fig. 3. Spreading suppression of cortical activation during migraine aura. (*A*) A drawing showing the progression over 20 min of the scintillations and the visual field defect affecting the left hemifield, as described by the patient (P.R.). The fixation point appears as a small white cross. The red line shows the overall direction of progression of the visual percept. The front of the scintillation at different times within the aura is indicated by a white line. (*B*) A reconstruction of the same patient's brain (P.R.), based on anatomical MR data. The posterior medial aspect of occipital lobe is shown in an inflated cortex format. In this format, the cortical sulci and gyri appear in darker and lighter gray, respectively, on a computationally inflated surface. MR signal changes over time are shown to the right. Each time course was recorded from one in a sequence of voxels that were sampled along the calcarine sulcus, in the primary visual cortex (V1), from the posterior pole to more anterior location, as indicated by arrowheads. A similar BOLD response was found within all of the extrastriate areas, differing only in the time of onset of the MR perturbation. The MR perturbations developed earlier in the foveal representation, compared with more eccentric representations of retinotopic visual cortex. This finding was consistent with the progression of the aura from central to peripheral eccentricities in the corresponding visual field (*A* and *C*). (*C*) The MR maps of retinotopic eccentricity from this same subject, acquired during interictal scans. As shown in the logo in the upper left, voxels that show retinotopically specific activation in the fovea are coded in red (centered at 1.5° eccentricity). Parafoveal eccentricities are shown in blue, and more peripheral eccentricities are shown in green (centered at 3.8° and 10.3°, respectively).

Imaging of cortical spreading depression or migraine aura

 # BOLD signal followed the retinotopic progression of the visual percept.

(Hadjikhani N et al. Proc Natl Acad Sci USA 2001; 98: 4687-92)

- Cerebral hypoperfusion with migraine aura has also been seen by use of MRI perfusion-weighted imaging. Five attacks of migraine with aura were imaged within 45 min of aura onset. Decrease in cerebral blood flow (16-53%) and blood volume (6-33%) and increase in mean transit time (10-54%) were seen in the occipital lobe.

(Cutrer FM et al. Ann Neurol 1998; 43: 25-31)

Imaging of cortical spreading depression or migraine aura

- CSD was initially assumed to be a process isolated to migraine with aura, a few studies have now provided evidence of CSD-like changes in cerebral blood flow during migraine without aura. In the study of Woods and colleagues, PET imaging detected **bilateral hypoperfusion of the occipital lobes that spread anterior to the temporal and parietal lobes in patient with spontaneous migraine without aura.**

  (Woods RP et al. N Engl J Med 1994; 331: 1689-92)

- Denuelle and colleagues did PET studies on seven individuals during spontaneous attacks of migraine without aura. Mean time from attack onset to imaging was just over 3 h.

Imaging of cortical spreading depression or migraine aura

Investigators found a relative **decrease in perfusion in the bilateral occipital, parietal, and temporal cortices during migraine compared with the headache-free state. Regional cerebral blood flow was reduced by just over 10%.**

Whether this reduction in cerebral perfusion was associated with the presence of pain or was a manifestation of CSD is not clear. (Denuelle M et al. Cephalalgia 2008; 28: 856-62, Coghill RC et al. J Cereb Blood Flow Metab 1998:18:141-47)

- Several studies have detected no change in cerebral perfusion during migraine without aura. Furthermore, demonstration of a progressive wave of hypoperfusion would be more indicative of CSD than single measurements of perfusion.

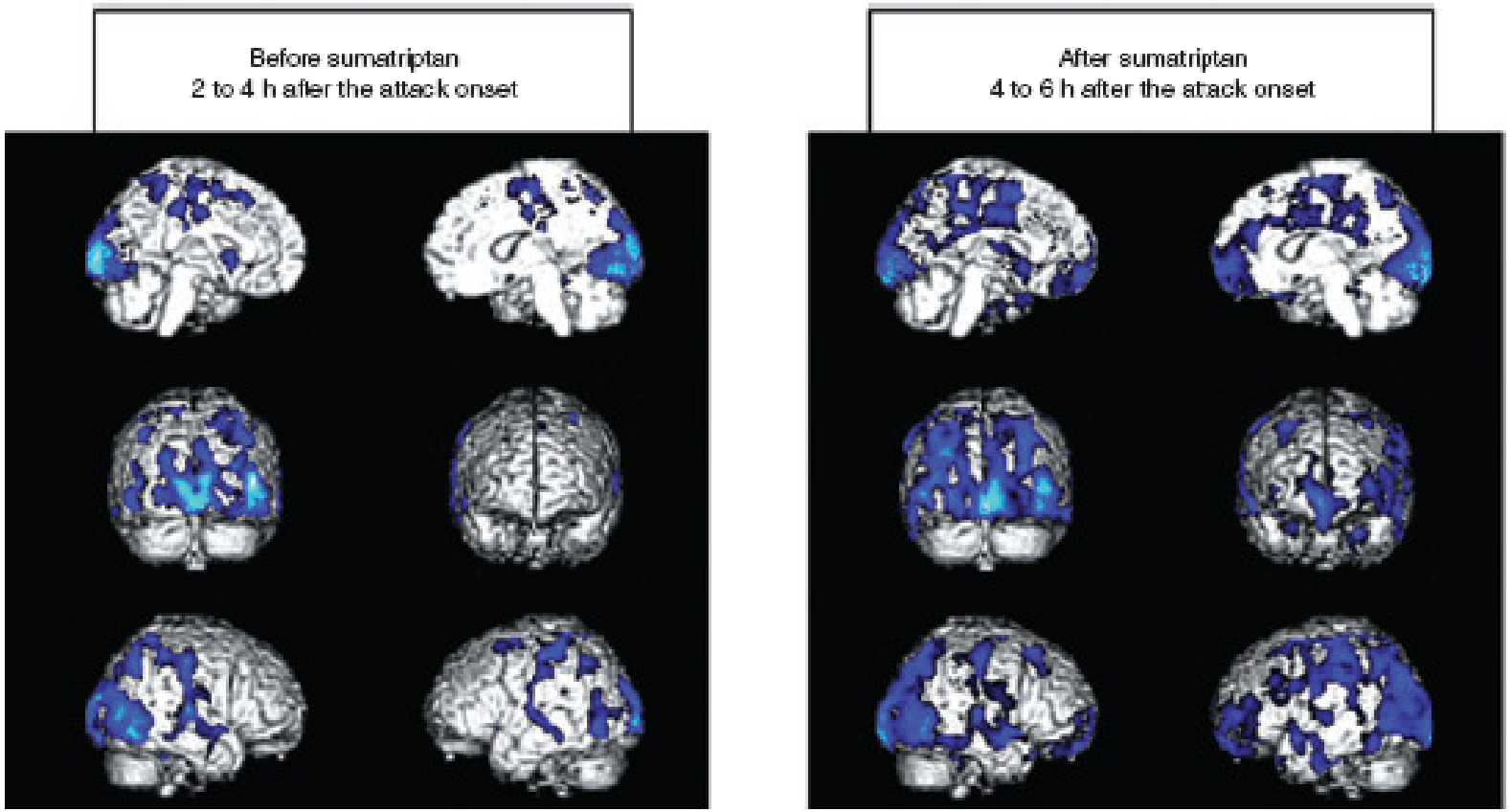

Figure 1 Hypoperfusion during migraine without aura attacks in seven patients. Statistical parametric maps showing significant regional cerebral blood flow (rC3F) decreases during migraine without aura attacks. Blue plots correspond to rCBF decrease [$P < 0.01$ false discovery rate corrected, cluster > 200 voxels] before and after sumatriptan compared with the headache-free interval. Posterior bilateral hypoperfusion can be seen.

(Denuelle M et al. Cephalalgia 2008; 28: 856-62)

Imaging of cortical spreading depression or migraine aura

- Vascular changes were previously assumed to occur concurrently or after the CSD wave and to be a product of CSD. **Optical intrinsic signal imaging** allows simultaneous investigation of CSD (parenchymal reflectance) and cortical surface arteriole diameter.
- Investigators found that arteriolar vasodilation propagates with a greater velocity than dose CSD and thus precedes CSD in its spread across the brain cortex. Furthermore, there was dissociation of vascular changes and CSD in areas distant

Imaging of cortical spreading depression or migraine aura

from the CSD propagation and with frequent repetitive CSD events. Repetitive CSD was associated with a reduced or absent vascular response.

(Brennan KC et al. J Neurophysiol 2007; 97: 4143-51)

- These findings imply that vascular changes associated with CSD have a mechanism of propagation independent from the CSD itself. Investigators also used optical intrinsic signal imaging to compare CSD in male and female mice. **Female mice had a lower threshold for triggering of CSD than**

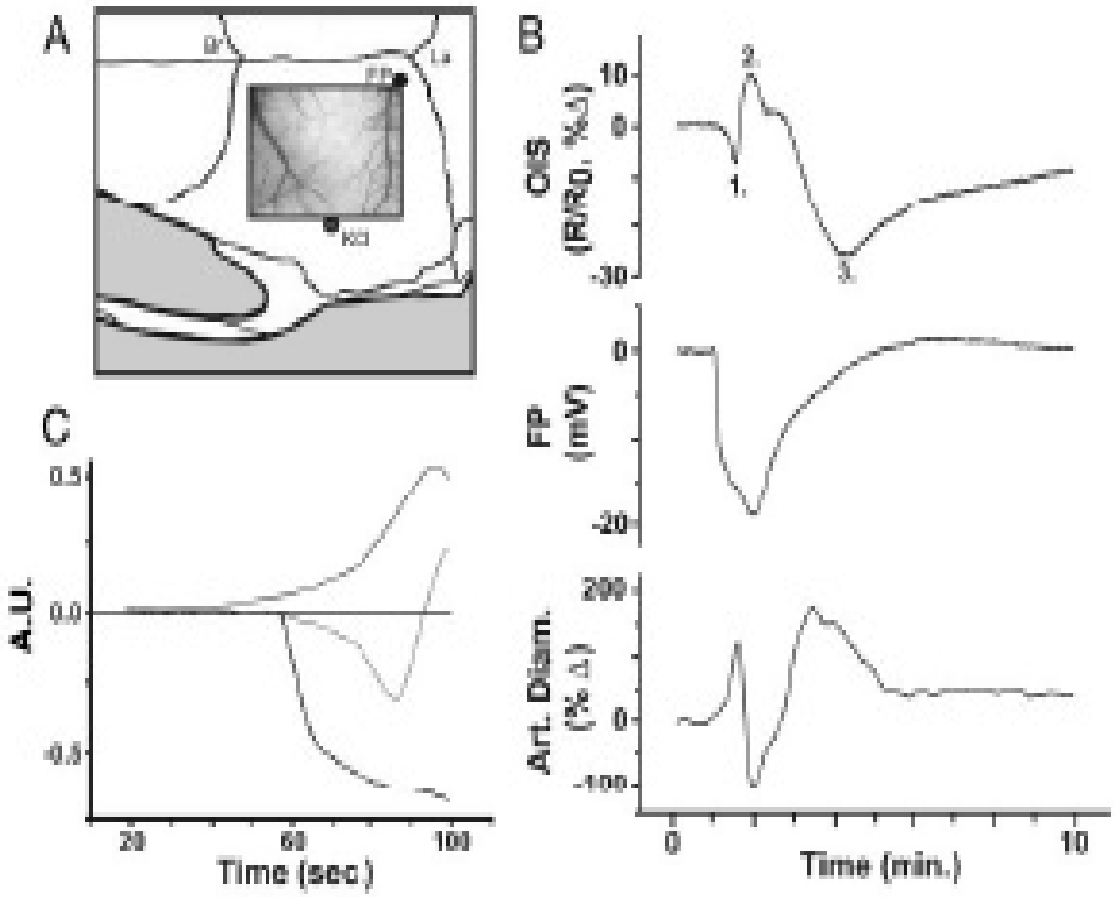

FIG. 1. Mouse optical intrinsic signal (OIS), electrophysiological, and vascular changes during cortical spreading depression (CSD). *A*: experimental setup showing area of thinned skull in mouse. Thinned area is surrounded by intact skull, into which 2 burr holes are drilled. FP, location of field potential electrode. KCl, location of KCl-filled CSD induction pipette. Br, bregma; La, lambda. *B*: plots of OIS, electrophysiological, and vascular responses with CSD. Data are averages of 10 experiments in mice: 1,000 OIS regions of interest (ROIs), 10 field potential plots, and 40 vascular regions of interest. *Top*: biphasic change in reflectance (phases are numbered) whose onset coincides with onset of DC shift. *Middle*: negative DC shift in field potential. *Bottom*: changes in arteriolar diameter with CSD. Arterioles dilate ahead of the CSD wavefront, then undergo profound constriction, before a larger dilation and return to baseline. Note that the post-CSD baseline is more dilated than the original baseline. OIS, optical intrinsic signal; FP, fieldpotential; Art. Diam, arteriolar diameter. *C*: vascular (dark gray), OIS parenchymal (light gray), and electrophysiological (black) changes at higher resolution. Note that vascular dilatation precedes both electrophysiological and parenchymal changes; *y*-axis: normalized changes from baseline. Data have been scaled and smoothed (5-point adjacent averaging) for clarity.

(Brennan KC et al. J Neurophysiol 2007; 97: 4143-51)

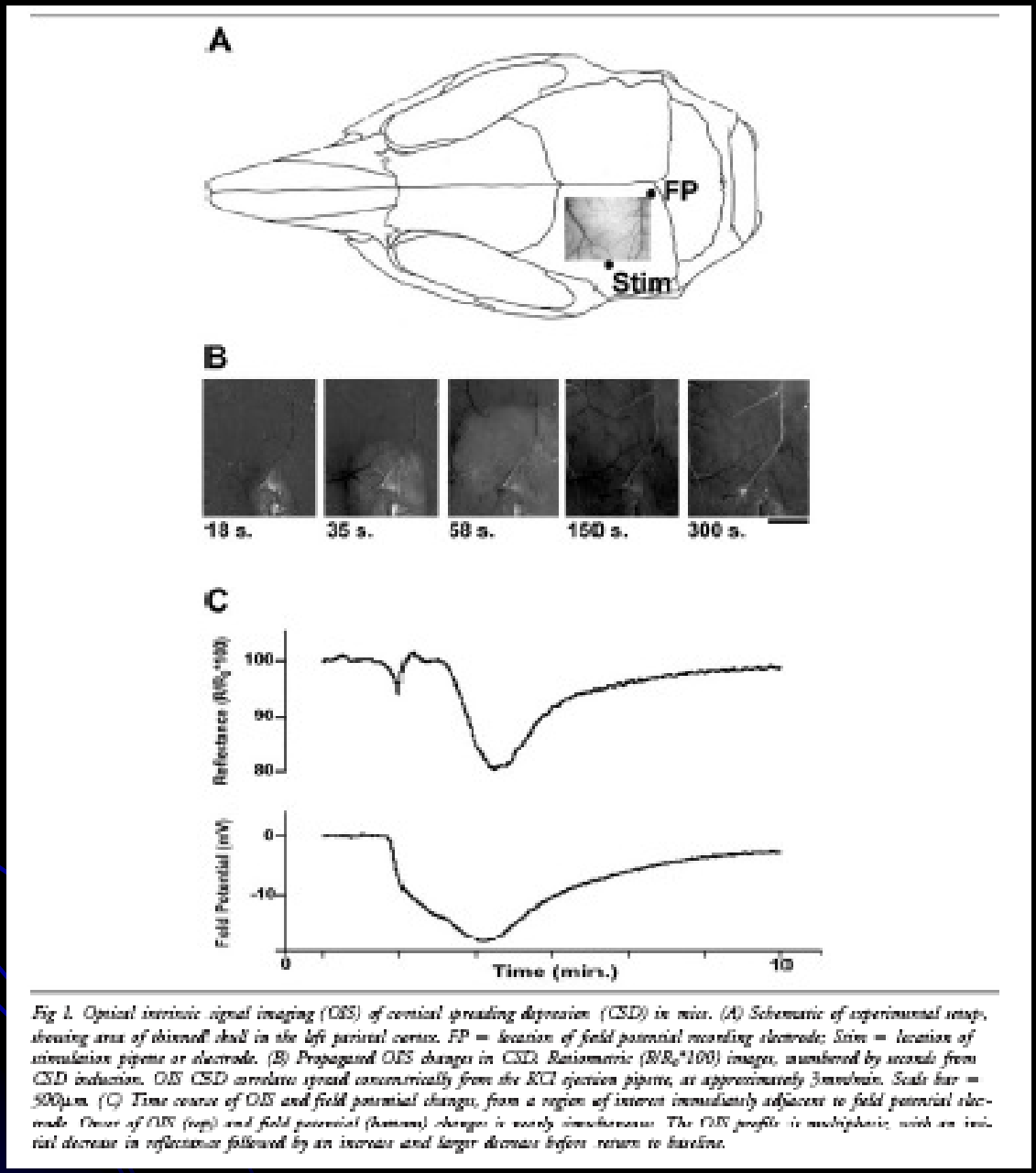

*Fig 1. Optical intrinsic signal imaging (OIS) of cortical spreading depression (CSD) in mice. (A) Schematic of experimental setup, showing area of thinned skull in the left parietal cortex. FP = location of field potential recording electrode; Stim = location of stimulation pipette or electrode. (B) Propagated OIS changes in CSD. Ratiometric (R/R0*100) images, numbered by seconds from CSD induction. OIS CSD correlate spread concentrically from the KCl ejection pipette, at approximately 3mm/min. Scale bar = 500μm. (C) Time course of OIS and field potential change, from a region of interest immediately adjacent to field potential electrode. Onset of OIS (top) and field potential (bottom) change is nearly simultaneous. The OIS profile is multiphasic, with an initial decrease in reflectance followed by an increase and larger decrease before return to baseline.*

(Brennan KC et al. Ann Neurol 2007; 61: 603-06)

Imaging of cortical spreading depression or migraine aura

did male mice, perhaps helping to explain the higher prevalence of migraine among women than men.

(Brennan KC et al. Ann Neurol 2007; 61: 603-06)

- Ayata and colleagues have shown that common migraine prophylactic medications do suppress CSD in rats. Rats pretreated with topiramate, valproate, propranolol, amitriptyline, or methysergide had less frequent CSD and higher CSD electrical stimulation thresholds. CSD frequency was reduced by 40-80% in rats pretreated over weeks and months, with longer treatment duration producing a greater

Imaging of cortical spreading depression or migraine aura

degree of CSD suppression.

(Ayata C et al. Ann Neurol 2006; 59: 652-61)

- However, it is not clear that CSD is a prerequisite for migraine headaches nor that suppression of CSD is the mechanism by which prophylactic medications reduce headache frequency.

  (Wolthausen J et al. Cephalalgia 2009; 29: 244-49)

- Tonabersat (a benzoylamino benzopyran with anti-convulsant properties) has been shown to inhibit CSD in animals, but did not clearly show benefit in prevention of migraine

Imaging of cortical spreading depression or migraine aura

headache in a randomized clinical trial.

(Read SJ et al. Brain Res 2001; 891: 69-77, Smith MI et al. Cephalalgia 2000; 20:546-53, Goadsby PJ et al. Cephalalgia 2009)

- Further work is needed to investigate the relation between CSD, production of migraine pain, and the effects of CSD suppression on migraine headaches.

	Findings
Functional MRI[11]	Increase in BOLD signal in extrastriate cortex, which progressed contiguously over the occipital cortex at 3·5 mm/min
Perfusion-weighted MRI[6]	Decreased cerebral blood flow and blood volume and increased mean transit time in occipital lobe
PET[7,10]	Bilateral hypoperfusion in occipital, temporal, and parietal lobes

BOLD=blood oxygen level dependent.

Table 2: Functional brain events during migraine aura identified by modern imaging techniques

(Schwedt TJ et al. Lancet Neurol 2009; 8: 560-68)

Conclusions

- No longer can migraine be considered a vascular or neurovascular disorder, **but instead should be thought of as a disease mediated by the CNS.**
- The identification of CSD in migraine with, and possibly without, aura suggests that CSD could be a common physiological process that occurs at the onset of both migraine subtypes.
- Equally plausible is that altered activity of brainstem nuclei that project diffusely to the cortex results in changes in glial activity, cortical neuronal activity, and cerebral blood flow in all patients with migraine, but that CSD is triggered only in

Conclusions

genetically predisposed migraineurs with aura.

Thanks for your attention