The Last 20 Years of fMRI Work on Aura and What it Taught Us About Migraine

F. Michael Cutrer, MD
Professor of Neurology
Headache Division Chair
Mayo Clinic

Disclosures

• None

Learning Objections

• To provide an organized Review of the findings from fMRI studies of migraine aura over the past two decades

Migraine aura as we have observed it

• Transient focal neurological symptoms typically lasting 5 to 60 minutes that occur just prior to during a migraine headache
• Typical Aura
  – Visual
  – Sensory
  – Language
  – Motor
• Recent additions
  – Brainstem
  – Retinal
• Neurological symptoms are bimodal, positive followed by negative symptoms
• Symptoms spread or migrate with time
• Sensory symptoms migrate across the face, into the mouth and down extremities
What was the state of knowledge about aura when fMRI techniques began to become available?

- **Vasogenic theory of migraine** was alive and well.
- Cortical spreading depression as cause of aura was supported by findings of Olesen and colleagues.
- Compton's scatter artifact was suggested as a means of explaining the Xenon Blood Flow data.

### Early fMRI studies

- **Spontaneous migraine visual aura** were captured.
- **Diffusion weighted imaging**: Reflects cells' loss of ability to maintain normal osmotic gradients...Negative.
- **Perfusion weighted imaging**: Gadolinium based technique generates images of rCBF, rCBV, Mean transit time.

These studies confirmed Olesen's findings in spontaneous migraine aura using a technique NOT susceptible to Compton's scatter.

PWI changes during aura were not seen in Spontaneous Attacks of Migraine without aura.

- Bilateral Spreading Decreases in Occipital blood flow were also reported in a single case of migraine captured during PET study although presence or absence of aura was unclear.

---

Sanchez de la Hoz et al., 1999.
BOLD Imaging During Migraine Aura

- Based on changes in Deoxyhemoglobin Concentration
- Technique often used mapping areas of brain activation

BOLD imaging was used to capture both spontaneous and induced visual auras.

In one individual we capture entire aura including the opening minutes.

BOLD allowed more accurate:
- Measurement of the rate of propagation changes underlying the visual field defect
- Mapping of the functional areas of visual cortex involved in the initiation of the aura and its propagation
- Detection of the dark phase, the brain changes seen during the scintillation phase of the aura

BOLD Signal Intensity During Migraine Aura

BOLD employs detection of a sign change of fMRI imaging that occur when oxygen is extraction from blood as it flows through certain parts of the brain.

Visual stimulus given to subject while in fMRI scanner. When the visual area of the brain is functionally normally, whenever the stimulus given, the signal level increases and decreases when the signal is removed giving an up and down sawtoothed pattern.

When we look at two points on the occipital cortex, the aura arrives at point a about 125 seconds before it passes point b.

These BOLD changes correlated with the appearance and spread of the patient visual aura, specifically, the scotoma and represent about 30 minutes.

Changes in the brain that occur during the migraine visual aura most closely resemble cortical spreading depression. **Shared characteristics include:**

- Spread at a slow rate of 3-5 mm per minute across contiguous cortex
- Positive hyper-excitatory phase followed by suppression
- Changes seen in both move across boundaries of vascular territory
Migraine patients exposed to a visual stimulation showed activation (hyperemia and volume increase) was seen in the red nucleus and substantia nigra when migraine symptoms visual scintillations and headaches were triggered.

BOLD fMRI studies suggest increased occipital cortical excitability in patients who experience aura. Migraine subject incongruent bar stimulation in migraine with aura patients elicited activation primary in occipital cortex but not in non-migraine controls. BOLD imaging showed migraineurs exhibited hyper-excitability of the visual cortex with a wider photosensitive area.

In cases with prolonged aura DWI is normal and early perfusion defects do not persist.
Hemiplegic migraine aura begins with cerebral hypoperfusion: imaging in the acute phase

Hansen, Ashina et al. Headache 2011

Left facial numbness & hemiparesis
Right hand numbness & aphasia

These findings are consistent with findings in typical aura

Sporadic Hemiplegic Migraine with Prolonged Aura symptoms can show changes in DWI and PWI that do not follow Vascular Territories

33 y/o F Day 5 of L hemianopia, L hemiparesis, confusion
8 y/o F with R hemiparesis, aphasia & ATP1A2 mutation

Susceptibility-Weighted Imaging shows prominence of venous structures in areas of impaired perfusion in Migraine with Aura

right hemi-paresthesia dysarthria
left homonymous hemianopsia hemi-paresthesia

DWI normal in both cases PWI showed defects SWI showed venous engorgement

Karaarslan et al. 2010
Dynamic contrast-enhanced imaging indicates increased brainstem perfusion, but no blood brain barrier disruption, during attacks of migraine with aura

19 MWA subjects studied during Headache phase (mean 7.6 hours)

Hyperemia was seen in brainstem structures but not increased permeability of the blood brain barrier

Shared fMRI characteristics have made a strong case for Cortical spreading depression as the phenomenon underlying aura:

- Both show initial hyperemia lasting about 3 to 4.5 minutes
- Hyperemia/hypoperfusion signal spreads across the cortex at a slow rate (2-5 mm/min)
- Evoked visual responses during both are suppressed and take about 15 minutes to recover
- Hyperemia in both is followed by mild hypoperfusion lasting 1-2 hours
- In both the BOLD signal complex halt at major sulci
- First affected area is the first to recover normal evoked responses

The knowledge that cortical spreading depression or its human analog underlies the migraine aura has allowed extension of the study of aura in genetic and animal models

CSD propagates into subcortical areas FHM type I knock-in mice

Reminiscent of spread of activation to subcortical nuclei reported in fMRI during visually evoked migraine and MWA

Migraine with aura: activation can result from CSD

After CSD, PANX1 forms a complex with the P2X7 cation channel which is critical to the release of Excitatory amino acids to sustain the propagation of CSD and neuroinflammatory trigeminovascular activation

After 2 Decades of Study of Aura in Humans with fMRI, what have we learned about migraine?

- Typical Aura as it occurs in humans is associated with decreases in blood flow that do not reach ischemic levels and resolve within hours to hyperemia
- The decrements in blood flow slowly spread over time and do not respect vascular boundaries
- Areas of decrease blood flow correlated with decreased BOLD activation to visual stimulation and do not show changes in DWI (loss of osmotic gradient control)
- In aggregate, the finding support CSD or it human analogue as the process underlying migraine aura
- Prolonged typical aura shows a similar pattern but some cases of prolonged sporadic hemiplegic migraine have shown transient DWI change
- Susceptibility weighted imaging shows distention of venous structures in areas of PWI decreased blood flow
What else we have learned?

- Both Human aura and induced CSD in knocked in migraine with FHM I genes can be associated with activation in subcortical structures.
- Migraine with aura patients studied during the headache phase with Dynamic contrast enhanced techniques show increased perfusion with in brainstem structures but no gross opening of the blood brain barrier.
- When CSD is used as the basis for animal and genetic based modeling possible mechanisms for activation of trigeminal afferents by events intrinsic to the cortex are identifiable.

fMRI techniques have taken us from clinical observation, through non-invasive blood flow and activation assessments to the molecular level where the essential cause and potential cures for migraine have always resided.