Functional MRI-BOLD of Visually Triggered Headache in Patients With Migraine

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Background: Spreading depression of Leao has been hypothesized as the basis for the visual aura of the migraine attack, supported by cerebral blood flow measurements of spreading hypoperfusion. The early depolarizing or activation phase of experimental spreading depression, however, is associated with a transient but pronounced cerebral blood flow increase that precedes spreading hypoperfusion.

Objective: To study this early phase of the migraine attack, we investigated visually triggered attacks of headache and visual symptoms using a red-green checkerboard stimulus in patients with migraine.

Interventions: We studied occipital cortex activation during visual stimulation by measuring occipital cortex perfusion with functional magnetic resonance imaging–blood oxygenation level-dependent contrast in 10 patients with migraine with aura and 2 patients with migraine without aura and 6 healthy subjects.

Results: In 6 patients with migraine with aura and 2 patients with migraine without aura, their typical headache with (n = 2) or without visual change was visually triggered at 7.3 minutes (mean time) after visual stimulation began. In 5 of these patients, the onset of headache or visual change, or both, was preceded by suppression of initial activation (mean onset time, 4.3 minutes; P < .001). The suppression slowly propagated into contiguous occipital cortex at a rate ranging from 3 to 6 mm/min. This neuronal suppression was accompanied by baseline contrast intensity increases that indicated vasodilatation and tissue hyperoxygenation.

Conclusions: We conclude that visually triggered headache and visual change in patients with migraine is accompanied by spreading suppression of initial neuronal activation and increased occipital cortex oxygenation. We postulate that this spreading suppression may be associated with initial activation of a migraine attack, independent of whether there are associated aura symptoms. We further postulate that there may be an association between vasodilation accompanying the initial stage of suppression and the induction of headache.

THE VISUAL aura of the migraine attack has been explained by the spreading depression (SD) of Leao, a neuroelectric event beginning in the occipital cortex and propagating into contiguous brain regions. This hypothesis was initially based on the stimulative followed by suppressive and slowly spreading clinical features of the aura, and later supported by cerebral blood flow (CBF) measurements of spreading hypoperfusion. The early depolarizing or activation phase of experimental SD, however, is associated with a transient but pronounced CBF increase that precedes spreading hypoperfusion, presumably in response to the increased substrate demand of neurons attempting to repolarize. This has not been documented in patients except possibly in an early study when migraine attacks were triggered during intracarotid xenon-133 CBF measurements. To achieve information at this critical stage, we attempted to visually trigger migraine attacks in susceptible individuals. By using recently developed functional magnetic resonance imaging based on the blood oxygenation level-dependent (fMRI-BOLD) technique, we were able to measure, with millimeter resolution, second-to-second activation of occipital cortex to visual stimulation in these patients, and to observe suppression of neuronal activation before and during attacks. Our results also suggest that neuronal suppression is accompanied by hyperoxygenation of the occipital cortex during the early minute of the attack.

RESULTS

Clinical details are summarized in the Table. No control subjects developed headache at any time during the visual activation experiment. Six of the 12 patients with MwA (patients 1-6 in the Table 1) developed headache. Two (patients 1 and 2) of the 6 who developed headache experienced visual change that coincided with the onset of headache or occurred shortly after. They described the visual changes as atypical of their aura.

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PATIENTS, MATERIALS, AND METHODS

PATIENTS

Twelve patients with migraine (10 with migraine with aura [MwoA] and visual symptoms, 2 with migraine without aura [MwoA]; 11 women, 1 man; mean age, 38.8 years) and 6 healthy subjects participated in the study (5 women, 1 man; mean age, 31 years). The diagnosis was made according to the criteria of the International Headache Society.9 The protocol was approved by the Human Rights Committee, Henry Ford Hospital, Detroit, Mich. Written consent was obtained from all subjects prior to the study. Patients had suffered no more than 4 attacks a month and had not suffered a migraine attack 1 week prior to study. Eight patients had not taken medications for acute migraine attacks within 1 week of the study. Five patients were taking preventive migraine drugs at the time of study, which were propranolol, amitriptyline, verapamil, fluoxetine, and gabapentin.

VISUAL STIMULATION

In the fMRI-BOLD experiment, we used an MRI compatible visual system (Resonance Technology Co, Van Nuys, Calif) to project a red-green checkerboard on a screen that subjects saw through mirror goggles within the magnet. The visual system was controlled by a 486-PC computer. The checkerboard had an 11.3° radius and 2° check size that alternated colors (red and green) at 9 Hz, and was on or off every 14 seconds. The control condition during the off period was a fixation point. To monitor the attention of a subject during visual stimulation, crosses were displayed randomly over time in the center of the annular checkerboard and the subject was instructed to count the number of crosses.

visual symptoms described were floating white spots by 1 patient and bright scintillating lights by the other. Three (patients 1-3) of the patients with MwoA judged their headache to be severe and typical of their migraine attacks. Patient 4 had typical headache that was judged to be mild. Patient 5 had headache triggered in each of 2 separate studies; in the first his headache was severe and in the second mild. (The data obtained from this patient’s first study could not be analyzed because of motion artifact.) One (patient 6) of the patients with MwoA complained of a sensation of pulsation in both temples and mild continuous head pain at these locations toward the end of study. In 4 of these patients the headache was hemispheric in localization (2 right, 2 left) and in 1 the headache began hemispheric and became bilateral. Another was bilateral. Those patients with MwoA who did not have visual change in the study had previously experienced MwoA.

The only 2 patients with MwoA (patients 7 and 8) included in the study developed headache, one severe and one mild; with the exception of the mild degree of pain, they described their headache as typical of their migraine attacks. Both headaches were hemispheric at first and later became bilateral. Neither patient reported visual change. In all patients (patients 1-8) the clinical symptoms persisted after the experiments were terminated and, with the exception of the mild attacks, required the customary use of abortive medications. Two patients with MwoA (patients 1 and 5) were studied twice, more than 1 month apart; on both occasions 1 developed headache and the other developed headache and visual change. Of the 5 patients receiving migraine prophylaxis, 4 (patients 2, 3, 7, and 8) developed headache and 1 (patient 10) did not. Three of the patients who developed severe headache had associated features of nausea and photophobia.

MAGNETIC RESONANCE IMAGING

All MRI experiments were performed on a 3.0-T scanner with a resonator head coil. First, a fast scan was used to simultaneously collect single axial and sagittal slices. These 2 images were used to locate the calcarine fissure and as a guide for adjustment of subject position. A rapid radiofrequency spoiled gradient echo pulse sequence, multislice interleaved excitation cycles,10 was used to produce $T_2^{*-}$-weighted images ($128 \times 64$ matrix over a 24-cm field of view). During the visual stimulation, 3 axial sections of 10-mm thickness were obtained through the calcarine fissure (repetition and echo time, 52/30 milliseconds; flip angle, 25°, and 1 excitation in 3.5 seconds). Each experimental scan consisted of 7 alternating periods of 14-second visual stimulation and 14-second control condition. Fifty-six repeated images for each anatomic section were collected in 1 scan that took 3.11 minutes. The scan was repeated 4 times. To prevent amplifier heating, we allowed 2 minutes to elapse between every 3.11 minutes scan but the visual stimulation continued. Finally, multislice axial $T_1$-weighted brain images were acquired for each subject. The entire MRI study time was approximately 1 hour. To reduce head motion, each subject’s head was immobilized in a head brace tightened by a plastic rim.

During visual stimulation, if headache or aura were triggered, patients pressed a buzzer to inform a staff member, the timing of which was immediately recorded. Details of the patient’s symptoms were obtained at the end of the experiment and also checked when the patient was free of symptoms in some cases. The type of headache was categorized by an independent neurologist who was unaware of the results of data analysis. Headaches were rated on a scale of none, mild, moderate, or severe according to the 0 to 3 rating scale used for drug trials.11

Continued on next page
DATA ANALYSIS

Images obtained from the 4 series of scans (a total of 224 images for each anatomical section) were aligned sequentially for data analysis. Data analysis consisted of image registration, statistical analysis of activated pixels, calculation of suppression of visual activation, estimation of the rate of propagation of suppression, and calculation of baseline $T_1$-weighted image intensity changes.

Motion registration was carried out by 2-dimensional cross-correlation to correct for possible in-plane translation and rotation of the head between serial images. Each image in the series was registered with the first image by applying a range of test transformations consisting of planar translations and rotations. The first image was subtracted on a pixel-by-pixel basis from the transformed image. The transformation that yielded the minimum difference in magnitude between the paired images was selected as the optimal correction for the subject movement. A rotation of 0.125° and a translation of 0.12 mm were used to test for minimum rotation and translation, respectively. If major movement of the head occurred, motion artifacts could not be corrected (usually $>$1.5 mm translation) and the data were discarded. Such patients were later called back for another study.

Statistical analysis of activated pixels was based on combinations of temporal cross-correlation of the time course of the MRI signals with a complex reference function and cluster size thresholding to justify multiple comparisons in an image. The threshold of temporal cross-correlation was set at a level of 1-tailed type 1 error of 0.0025 per pixel. A second threshold of a cluster size at 3 pixels or more was further applied, resulting in an estimated false-positive probability of $P < 0.001$ per pixel.

Moving time window analysis was applied to extract dynamic changes in the brain during visual stimulation (Figure 1, left). The time course of signal intensity of each pixel, originally representing 28 periods of the stimulation and control condition, was filtered by applying cross-correlation analysis to “windows” of 4 periods. These windows were moved along the time course in steps of 2 periods of stimulation and control condition to yield a filtered time course of cross-correlation coefficients. The initial activation of a pixel was identified at the time when it passed both thresholds of temporal cross-correlation ($P < 0.002$ and cluster size $>3$), resulting in $P < 0.001$ (Figure 1, right). Then, evaluation of $P$ values along the time course continued until $P > 0.10$ was found. Changes of $P$ values from $P < 0.001$ to $P > 0.10$ indicated a transition from activation to suppression at the pixel location. The time at the middle of the analysis window that yielded $P > 0.10$ was assigned as the time at which there was transition to suppression. A time map of this transition was generated. Colors were used to encode the transition time in the time maps, in which a hot color (red) indicated the earliest transition and a cold color (blue) denoted the latest transition. The color changes in the transition maps along the brain cortex were used to detect propagation of suppression after initial activation. The rate of propagation of suppression of activation was estimated from the transition maps by dividing the distance between suppressed pixels by the time difference of the transition between the pixels.

On a continuous basis over time, we also processed the changes in signal intensity of the $T_1$-weighted images independent of the activation effects, hereafter referred to as baseline intensity changes. Statistical analysis of the baseline intensity changes over time was carried out by Student $t$ test. The first 56 images were used as control. The remainder of the images formed 3 groups, image numbers from 57 to 112, from 113 to 168, and from 169 to 224, thus permitting the evaluation of signal changes over time. The signal changes were thresholded at the level of $P < 0.001$ by using 2-tailed Student $t$ tests. Because these studies were exploratory we did not perform trend analysis on the data.

Patients with migraine who did not develop headache had visual activation patterns that did not differ from controls throughout the study. Suppression was observed in previously activated pixels in 6 of 8 patients who developed headache and visual change or both ($n = 2$) (Figure 3). One patient who developed mild headache (patient 5) showed no suppression. Another patient (patient 7) developed headache almost immediately (1.3 minutes) on visual stimulation; activation was not observed until late into the study and therefore transition to suppression could not be measured. In these 6 patients who exhibited suppression (patients 1-4, 6, and 8) the mean ± SD time between the start of visual activation to suppression was $4.6 ± 4.2$ minutes (Table 1). In 5 of these 6 patients, suppression was detected before headache. In 1 patient with MwA (patient 2), suppression was observed 3.0 minutes after headache began, but 1.3 minutes before sudden intensification of headache and 8.5 minutes before visual change was noticed. Of those patients with suppression of activation (Table 1), only patient 3 had suppression on the opposite side of headache. Unilateral headache was associated with bilateral suppression in patient 2. Bilateral headache was associated with bilateral suppression in patients 6 and 8, and unilateral suppression in patient 1. Patient 4 had left-sided suppression and left hemicrania.

By overlaying the time transition color maps onto anatomical images, in 6 patients it was possible to track the movement of the suppression as it progressed from the initiating pixel cluster into contiguous cortical pixels, often spreading along the same gyral contour (Figure 3), evidence that this was not a random pattern of suppression. Furthermore, toward the end of the experiment, it was possible to follow recovery of activation or at least loss of suppression occurring in a timed and ordered fashion along the track of the original suppression wave. These findings distinguished the patients with migraine who experienced headache and visual change from those who did not, and healthy subjects in whom the time transition maps showed only random suppression in time and anatomical distribution. Suppression was often bilateral, beginning in the primary visual cortex spreading laterally or visual association cortex spreading medially. Because we imaged only occipital cortex it was not possible to follow suppression patterns into temporal or parietal cortex. The rate of propagation of suppression ranged from 2.9 to 6.0 mm/min (mean ± SD, $4.1 ± 1.3$) (Table 1). The observed suppression ranged in duration from minutes to the end of the study.

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**Clinical and Experimental Details of Patients With Visually Activated Migraine**

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Triggered Location</th>
<th>Subjective Pain Scale</th>
<th>Minutes From H Onset</th>
<th>Minutes From SA Onset</th>
<th>Rate, mm/min</th>
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<td>H/SA/BI</td>
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</table>

*H indicates headache; VC, visual changes; SA, suppression of visual activation; BI, baseline intensity increase; F, female; M, male; MwoA, migraine without aura; MwA, migraine with aura; Y, yes; N, No; R, right; L, left; B, bilateral; NC, no change; and ellipses, not applicable.
†The time of onset of pulsatile sensation on both temples.

**Figure 1.** Left, Time courses of signal intensity from a healthy subject and a patient with migraine with aura. The signal intensity changes from the healthy subject responded to on and off visual stimuli over the experimental period. The intensity changes from the patient, however, lost their stimulus response after approximately 2 minutes associated with an increase in baseline intensity. The 3 horizontal bars represent the first 3 time windows in which a cross-correlation analysis was applied. Right, Cross-correlation coefficients (CCC) over time obtained from the data in Figure 1, left. Triangles indicate CCC from the healthy subject; open squares, CCC from the patient. If a false-positive CCC of a pixel is less than 0.0025 (corresponding to CCC > 0.49), and at least 2 adjacent pixels meet the same criteria, this pixel is as signed as significantly activated (P < .001) during the time window. If the false-positive CCC of this pixel increases to greater than 0.1, this pixel is designed as inhibited subsequent to activation.

**BASELINE DATA**

With the exception of a few isolated pixels close to the straight sinus and torcular regions, most likely associated with an artifact of blood flow, no statistically significant changes were measured in the T2*-weighted intensity baseline measures throughout the experimental paradigm in control subjects (Figure 2, right) or patients in whom we failed to trigger headache. Patients with triggered headache and visual change had statistically significant increases (P < .001, Student t test) in baseline intensity prior to the onset of headache or visual change (Figure 4). No intensity changes were observed in white matter regions. In most patients and brain regions, the increases in baseline intensity were associated with reduced amplitude of the BOLD effect, loss of statistical significance for visual activation, or subsequent achievement of a significance level of suppressed activation. These associations are best exemplified in Figure 1, left, which shows in the top recording the expected on or off contrast intensity activation responses of a healthy subject. The lower recording, from a patient who developed headache, shows loss of the contrast intensity response to visual stimulation after approximately 2 minutes and that this is time-locked with an increase in baseline contrast intensity. We believe this reflects vasodilatation and hypoxia associated with neuronal suppression. Figure 1, right, shows the statistical calculations in the same healthy subject and patient with headache, confirming sustained activation in the former and suppression of activation in the latter. Baseline intensity increases varied in magnitude from 2% to 20% of initial intensity; the magnitude and area of the intensity increases were of the lowest degree in the 3 patients with mild headache. The duration of intensity increases varied, in some patients lasting up to 5 minutes before returning to initial values, and in others remaining elevated at the end of the experiment, although declining toward initial intensity.
In patients 1 and 2, a decrease in baseline intensity was also observed. They were the only 2 to have experienced visual change in addition to headache. In patient 1 the intensity decrease occurred in the right occipital cortex, 4.7 minutes before the patient developed right-sided headache and coincident visual change, and preceded the baseline intensity increase (Figure 4). The intensity decrease was observed in regions of occipital cortex grey matter (Figure 4) that failed to activate on visual stimulation from the outset of the experiment. In patient 2, who had strictly right-sided headaches, the decreased intensity for the most part was limited to the anterior region of the right occipital cortex. No prior visual activation was observed in this region and there was some recovery to initial baseline intensity toward the end of the study. Bilateral intensity increases were associated with bilateral headache in patients 1 and 8, and unilateral headache in patients 2 and 3 (Table 1). In patients 1 and 2, the side of the initial baseline increase corresponded to the side of the earliest headache. Patient 7 had left-sided baseline increases only but bilateral headache.

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The fMRI-BOLD technique measures relative changes in oxygenation of the brain circulation and is now used extensively in brain activation and functional localization experiments in humans. Visual activation is perhaps the most straightforward of these paradigms and was among the first to be studied. In brief, when the activating stimulus evokes a neuronal response, local blood flow increases, possibly by a neurogenic reflex that, at least initially, bypasses metabolically mediated increases in flow. This vascular re-
sponse carries a redundancy of flow to the activated brain regions from which relatively less oxygen is extracted, with the consequence that hemoglobin becomes hyperoxygenated compared with before activation. The relative reduction in deoxyhemoglobin decreases the paramagnetic influence of free iron on T$_2$*-relaxation and produces increased signal intensity on a T$_2$*-weighted MRI. Under physiologic conditions, this signal intensity increase reflects increased oxygen perfusing the tissue and is an indirect qualitative measure of perfusion that localizes and identifies brain regions that are activated. For the purposes of our experiments the technique was ideal for monitoring the flow changes associated with neuronal activation and suppression at the same time as measuring, albeit indirectly, the oxygenation state in the immediate circulatory environment of the involved neurons. Furthermore, this was achieved nearly continuously in a second-to-second time frame with millimeter resolution, permitting us to monitor immediate events in triggered migraine attacks.

We chose visual activation with an alternating checkerboard because it is an established stimulus for fMRI studies. Migraine sufferers are especially susceptible to linear stimuli. The patients considered that their experience of headache for the most part typified their migraine attacks but the 2 who experienced visual change considered this to be atypical of their aura. Not surprisingly, migraine aura may be difficult to recognize under experimental conditions of visual stimulation via mirrored goggles or even in the confines and darkness of the magnet bore and head coil. For these reasons we have used the term visual change, not aura, in the patients who are visually triggered. For these same reasons, the precise timing of visual change relative to headache was difficult to validate.

We recorded spreading suppression of prior activation before the onset of visual change and headache in migraine sufferers. The only patient in whom suppression of activation occurred after the headache began experienced only mild headache before suppression, with subsequent intensification of headache and visual change after suppression began. The waves of suppressed activity we observed would have been undetectable by CBF methods of limited anatomical and time resolution such as were used previously. Suppression of visual activation began not only in the primary visual cortex but also in association cortex, often coinciding in onset at separate locations similar to experimentally induced SD. The suppression waves were of variable duration, lasting minutes to throughout the study period. The short duration suppressions might be explained by (1) real termination of suppression in certain regions, (2) movement of suppression into cortical regions not observed in the image slice such as deep sulci, or (3) movement of the suppression waves out of view of the image slice itself. We postulate that this spreading suppression may be associated with initial activation of a migraine attack, independent of whether there are associated aura symptoms.

Baseline T$_2$*-weighted intensity increases were entirely limited to those patients who reported visual change or headache. The shifts in baseline intensity were unlikely to have been caused by an artifact of signal drift or head movement, either coincidental or caused by pain, because (1) headache was not severe at onset, (2) the shifts were spaced in time and anatomical distribution compatible with a spreading phenomenon, (3) the intensity shifts were consistently unidirectional, (4) there were no shifts recorded in white matter, (5) we were able to detect movement artifact on serial imaging (see the “Patients, Materials, and Methods” section) and rejected such data before analysis, and (6) the spoiled echo pulse sequence we used, multislice interleaved excitation cycles, was chosen to avoid
the signal drift that occurs with the more commonly used echo-planar imaging for fMRI studies. The mechanisms of the above changes, however, remain to be determined. Using $T_2^*$-weighted MRI and inducing SD by direct application of potassium to rat brain cortices, Gardner-Medwin et al. observed localized signal intensity increases that spread along cortical layers at a rate of 3 mm/min and interpreted this as oxygen increase in blood perfusing brain tissue during the early vasodilator stage of SD. Because the baseline intensity increases we recorded in patients coincided with suppression of visual activation (Figure 1), we believe this may reflect vasodilatation and tissue hyperoxia similar to that observed during the earliest phase of SD. (Without direct CBF measurements being made in addition, it would be impossible to identify when or if hyperoxia became secondary to any subsequent neuronal suppression and associated hyperperfusion phase of SD). But, even allowing for paramagnetic effects, intensity increases were more widespread anatomically than might be expected from the localized nature of the signal intensity increase of experimental SD, or of the spreading suppression of visual activation or neurologic symptoms in our patients. This dissociation between abnormal CBF, metabolism, and neurologic dysfunction in migraine attacks was substantiated by a recent case report and positron emission tomographic study in which bilateral occipital cortex hyperperfusion was observed approximately 45 minutes before any complaint of visual symptoms.21

Because of the sometime controversy of whether the neurologic deficit of the migraine aura is caused by ischemia, it is worthwhile to note that ischemia decreases $T_2^*$-weighted image intensity in both grey and white matter.23 Initial, but transient, decreased baseline $T_2^*$-weighted image intensity prior to the onset of suppression of activation in other occipital cortex regions distinguished the 2 patients who developed visual symptoms. This was confined to small regions of grey matter that also failed to show initial evidence of $T_2^*$-weighted image intensity increase on visual activation. Being confined to grey matter, and visual stimulation being unlikely to cause ischemia, we speculate that these $T_2^*$-weighted intensity decreases may reflect increased oxygen consumption of visually stressed neurons in regions where perfusion fails to meet demand, causing relatively decreased oxygenation of the tissue. Mindful that this was only observed in 2 patients whose visual symptoms were difficult to precisely localize, the importance of this association to the mechanisms of the aura remains to be determined.

Suppression and baseline intensity increases were observed to precede headache in our patients. In the 2 patients with visual change there was an association between laterality of early headache and the side of initial intensity increase. In each patient, either unilateral or bilateral headache corresponded to the laterality of either suppression or increased baseline $T_2^*$-weighted intensity. For example, the 1 patient with suppression in the hemisphere opposite to his or her hemianopia had bilateral increased intensity. In some patients, especially those with mild headache, the magnitude of the baseline intensity increase reflected the eventual severity of headache. Again, the importance of these associations is unknown. We postulate that there may be an association between the initial stage of SD and the eventual induction of headache; nitric oxide and calcitonin gene-related peptide release occurs during this vasodilator phase, perhaps trigeminally mediated.7 This could provide a focus for investigating the link between aura and trigeminovascular involvement in a migraine attack.

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