

Transcranial magnetic stimulation of visual area V5 in migraine

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Abstract—Objective: To examine visual cortical excitability in persons with migraine using transcranial magnetic stimulation (TMS) over an extrastriate area of the brain, area V5. **Background:** Previous studies found that persons with migraine have a lower phosphene threshold than healthy control subjects with TMS delivered over the primary visual cortical area V1. The result suggests that the occipital cortex in migraineurs between migraine attacks is hyperexcitable. However, it is not known whether interictal cortical hyperexcitability is also present in areas of the association visual cortex. **Method:** To investigate this, single-pulse TMS was delivered over visual area V5, the motion cortex, to 16 persons with migraine and visual aura, nine migraineurs without visual aura, and 16 healthy control subjects. TMS was delivered at intensities ranging from 30 to 100% of maximum stimulator output or until the participant reported seeing phosphenes (visual illusions characterized by flashes of light). Thresholds to phosphenes were obtained for each participant using a staircase procedure. **Result:** Significantly lower phosphene thresholds for TMS delivered over V5 were found in migraineurs as compared with control subjects. Qualitatively, the migraineurs' experience of phosphenes were more vivid, florid, and sustained compared with that of control subjects. **Conclusion:** Results of this study indicate that hyperexcitability of the visual cortex in migraine goes beyond visual area V1 and demonstrates for the first time a significant difference in threshold for excitability of visual area V5 in persons with migraine.

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Migraine aura may include visual or sensory symptoms, or hemiparesis or dysphasia. Visual illusions are the most common phenomena, occurring in 82¹ to 90%² of persons who experience aura. Such visual aura can also occur without ensuing headache.³ Results of neurophysiologic studies⁴ suggest that in persons with migraine and visual aura, secondary visual areas, such as area V5 in addition to area V1 and regions of the association cortex in the parietal lobes, may also be affected.⁵ Data from PET⁶ and fMRI studies support this hypothesis. In an fMRI study⁷ of migraineurs, it has been shown that blood flow during visually triggered migraine headaches extends to involve the parieto-occipital cortex in persons with migraine both with and without visual aura.

Transcranial magnetic stimulation (TMS) induces visual phosphenes with stimulation of area V1 at a lower threshold in persons with migraine compared with healthy control subjects.^{8,9} To explore the possibility that cortical areas beyond the striate cortex may be involved, an established procedure of evaluating phosphene threshold with TMS was used.¹⁰⁻¹² Subjective impressions of the phosphenes were also recorded.

Subjects and methods. *Subjects.* We used the International Headache Society criteria for migraine. Forty-one participants were studied—16 healthy controls (age range 16 to 58 years, mean 40 ± 14) with no personal history of migraine headache, 16 persons with migraine with visual

aura (MA; age range 22 to 64 years, mean 42 ± 14), and nine persons with migraine without visual aura (MoA; age range 13 to 57 years, mean 35 ± 15). All participants were tested at least 2 weeks after their last migraine attack. Persons with migraine on long-term prophylactic medications were not recruited for the study because participants were asked to be off all prophylactic migraine medication and drugs capable of modifying cortical excitability for 24 hours before the study. This is a prospective study, therefore detailed history and demographic data were taken first-hand by one investigator and a questionnaire was completed at that time. Although many participants had experienced migraine for many years, they had been diagnosed with migraine only recently. Finally, the examiner was not blinded to the participants' headache status, although he did not know the exact diagnosis for each subject. However, the experimenter knew whether or not the participant had visual aura because one of the points of the study was to know whether the visual illusion they experienced with TMS resembled their visual aura. Signed informed consent was obtained for all participants.

Protocol. Participants were seated in a semidarkened room, blindfolded, and instructed to keep their eyes closed. They wore a silk swimmer's cap with a reference point positioned over theinion. A 3 × 3 cm grid of 9 points was centered 3 cm dorsal and 5 cm lateral to theinion approximately over area V5, both for the left and the right hemispheres. TMS was delivered using a MagStim Model 200 stimulator (MagStim Company Ltd., Whitland, Wales, UK) connected to a figure-of-eight coil (mean lobe diameter: 70

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mm; maximum stimulator output: 2 T). The coil was positioned tangentially to the surface of the skull. The grid system was the same as used in previous successful studies.¹³ Participants were not informed about what to expect but were asked to report all sensory experiences during stimulation, including muscle twitching and visual, olfactory, and taste sensations. Stimulation was delivered over the central area of the V5 grid with an intensity of 30% of stimulator output (0.6 T) and was increased in steps no greater than 10% until the participant reported visual illusions or until 100% (2 T) stimulator output was reached. Using a staircase method in which the procedure was repeated for three reversals, the threshold was determined as the average reversal intensity. If no visual illusions were reported, the coil was moved 1 cm rostrally or caudally along the grid until a phosphene threshold was found or all nine positions were tested at 100% stimulator output. After the session, all participants were asked to draw the visual illusions they observed and, in case they saw motion, they were instructed to draw arrows indicating the direction of the motion. The same procedure was used for both the right and the left V5 area.

To control for any cognitive or expectation effects, sham trials were randomly interspersed between actual stimulations. During sham trials the coil was held at the same site as previously stimulated with the same intensity; however, the coil was rotated 90° such that no magnetic pulse was delivered to the cortex, but the click noise perceived by the participant remained unvaried. There was a minimum of 5 seconds between individual pulses, and the participants received no more than 24 pulses for each cortical site; intertrial interval was several seconds to allow verbal reporting. Finally, we kept the sessions short to avoid any adaptation effect.¹²

Results. Separate analyses of variance for each stimulation site were run with migraine as a between-subject factor (MA, MoA, and controls) and phosphene thresholds as a within-subject factor. Results show that the phosphene thresholds differed in the three groups for both left V5 ($F = 8.5, p = 0.0009$) and right V5 ($F = 7.5, p = 0.001$) TMS. A Fisher's exact probability test was applied to compare the three groups (MA, MoA, and controls) for each stimulation site: left V5 and right V5. The phosphene thresholds obtained for left and right V5 stimulation were lower for both MA and MoA as compared with controls ($p = 0.002$ and $p = 0.01$ for left V5; $p = 0.001$ and $p = 0.003$ for right V5). Figure 1 shows the average phosphene thresholds for each stimulation site and each group of participants. To perform the analysis on the thresholds, a value of 110% was assigned when no phosphene was perceived even at the highest stimulation intensity (100%) of the stimulator output, to distinguish from those participants who saw phosphenes at 100%.

The percentage of participants who did not experience phosphenes at maximum stimulator output for stimulation over left V5 was 94% healthy controls, 35% MA, and 33% MoA, whereas for right V5 it was 81% healthy controls, 41% MA, and 22% MoA.

A comparison of grid positions which produced phosphenes indicated that among those participants (both migraineurs and controls) who saw moving phosphenes with stimulation over left V5, 9 of 13 subjects perceived the visual illusion with stimulation positioned 3 cm above and

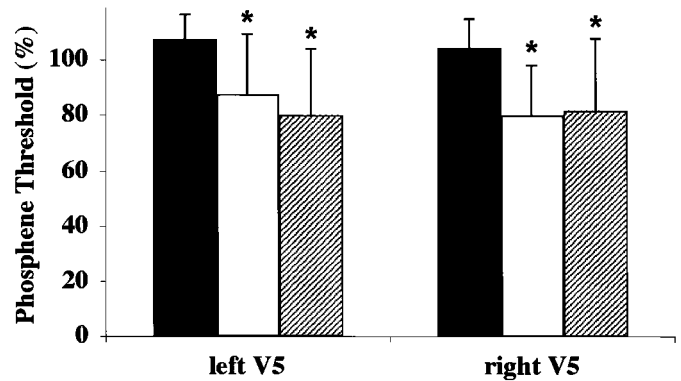


Figure 1. Phosphene average thresholds (percent of maximum stimulator output) as a function of group of subjects. Black bars = control subjects; white bars = subjects with migraine without aura (MoA); striped bars = subjects with migraine and aura (MA). Mean and SD were 108 ± 9 , 88 ± 22 , and 80 ± 24 for left V5 and 104 ± 11 , 80 ± 18 , and 82 ± 26 for right V5 for control subjects, MoA, and MA. *Significantly different from control subjects.

5 cm lateral from theinion. For stimulation over right V5, 9 of 14 subjects saw phosphenes when the coil was positioned 3 cm above and 5 cm lateral from theinion. These data indicate a consistency across participants; that is, the localization of the sites of stimulation which were most likely to provoke phosphenes overlapped significantly across subjects. A correlation of stimulation location to the MRI of the participants was not performed. However, other studies that have used TMS at or near our coordinates have produced phosphenes^{14,15} or disrupted motion perception.^{16,17}

Only one migraineur had a migraine visual aura during the procedure, while stimulated over left V5 at 80% of the stimulator output. The TMS-induced visual aura was characterized by moving scintillating dots on the periphery of the visual field; they were moving downward and were localized in the right visual field. This resembled her usual visual aura. There was no associated headache. Three participants with migraine clearly perceived the provoked visual illusion as phosphenes colored blue, purple, and green. From the participants' verbal reports and from the analysis of their drawings, phosphenes displayed a consistent retinotopic organization, although not for all subjects. Stimulation over the left hemisphere produced phosphenes in the right half of the visual field whereas stimulation over the right hemisphere produced phosphenes in the left half of the visual field. Moving phosphenes were mostly reported in the upper part of the visual field both for left and right V5 stimulation. Sixteen participants also reported a directional component (more often phosphenes were reported to be moving centrifugally) when stimulated over V5. Migraineurs compared with control subjects always identified the motion sensation as clearer. During sham trials no phosphenes were reported.

There was no correlation between phosphene thresholds and any features of migraine headache. Average duration of migraine headaches was 12.3 years, ranging from 0.5 to 32 years since onset of migraine. The average frequency of headaches for our participants was 38 per year, ranging from 2 to 300 per year. The average duration of migraine attack was 22.7 hours, ranging from 0.2 to 72 hours.

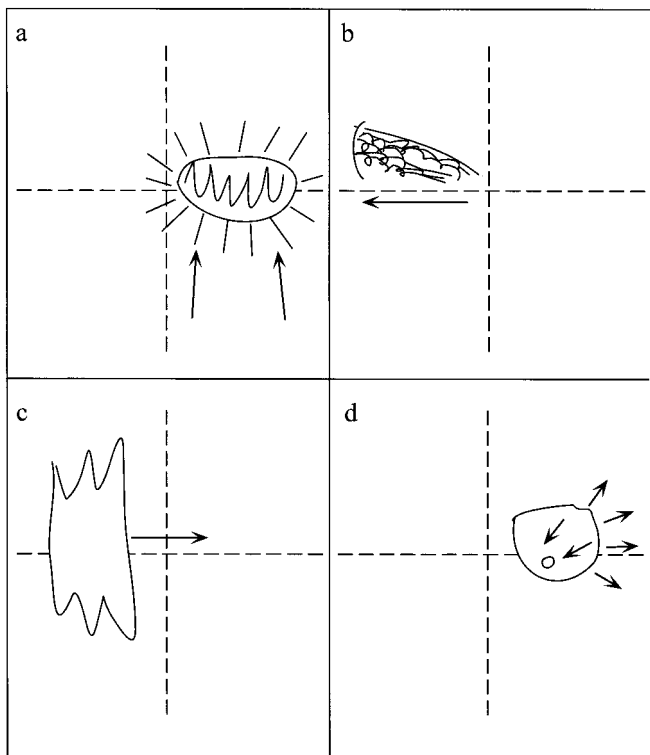


Figure 2. Four subjects' impressions of phosphenes elicited by stimulation of area V5. The dotted lines bisect left, right top and left, right bottom visual quadrants. The arrows indicate motion. (a) The subject with migraine and aura (MA) described this as a "bright spot with streaks in the middle, moving upward." Stimulation site: right hemisphere 3 cm above and 5 cm lateral toinion; stimulation intensity: 90%. (b) The subject with migraine without aura (MoA) described this as "horizontal streaks moving to the left." Stimulation site: left hemisphere 3 cm above and 5 cm lateral toinion; stimulation intensity: 70%. (c) The MA subject described this as a "silver, white shape moving to the right." Stimulation site: left hemisphere 3 cm above and 5 cm lateral toinion; stimulation intensity: 40%. (d) The MoA subject described this as "a bright light expanding and shrinking." Stimulation site: right hemisphere 4 cm above and 6 cm lateral toinion; stimulation intensity: 70%.

Among participants with migraine and visual aura there was no correlation between phosphene threshold and aura frequency (average: 18 per year; range: 1 to 80 per year) or aura duration (average: 19.4 minutes; range: 3 to 60 minutes).

Discussion. Single-pulse TMS over visual area V5 can induce visual phosphenes at lower stimulation intensities in migraineurs with or without visual aura between migraine attacks compared with healthy control subjects. These data support the concept of interictal neuronal hyperexcitability in migraine, and the lower phosphene thresholds for V5 show for the first time that an extrastriate cortical area is hyperexcitable, like area V1, in the brain of migraineurs.¹⁸

In addition, our results are similar to those of

others.¹⁹ TMS-induced phosphene threshold over visual area V1 was lower for patients with and without aura compared with headache-free control subjects. Therefore, our findings lend support to the notion that a cortical phenomenon underpins migraine with and without aura. We recognize, as did others,²⁰ that there are limitations to using TMS to study the visual cortex. Visual phosphenes are subjective sensory illusions, difficult to describe and occasionally confused with quick visual sensations generated by muscle or eye twitching. However, the participants were blinded to the purpose of the study, and to overcome all possible biases each participant was asked to report any kind of sensation, including taste or smell. When phosphenes were elicited most participants reported seeing them in the appropriate visual half-field with respect to the stimulation site. Sham stimulations were also performed as an additional control condition, and all participants failed to see any visual illusions during the trials. The quantitative difference between the groups was matched by a qualitative difference in the phosphene experience. Participants with migraine always reported visual sensations promptly, with no hesitations and with very accurate descriptions evident in their drawings. Figure 2 illustrates four subjects' impressions of phosphenes; the arrows accurately indicate the direction of movement. These illustrations show very clearly the pattern of the photopsias seen and are in contrast to control subjects who found the illusion extremely difficult to draw because of its brief appearance and lack of clarity.

Other investigators have elicited visual phosphenes with TMS using repetitive or paired pulses,^{11,15} but we consider single-pulse TMS to be reliable for detecting neuronal hyperexcitability. Single-pulse TMS also has been used successfully to study the role of visual cortical area V5 in visual attention during motion perception¹³ in addition to eliciting moving visual phosphenes.¹¹

We also have studied motion perception in migraineurs psychophysically (Battelli L, Wray SH, Vaina L, unpublished observation) and found impaired speed discrimination and motion coherence tasks²¹ in participants with migraine compared with healthy control subjects but no difference in performance of a direction discrimination test. Migraineurs were impaired when the task was to detect a target area of dots all coherently moving in one direction and embedded in a background noise of randomly moving dots, indicating that the participants were unable to filter out noise and to perform the task normally. This detrimental performance by participants with migraine might be caused by abnormalities in visual areas involved in motion perception, such as V5,²² and the inability to filter out background noise may be a consequence of neuronal hyperexcitability or lack of intracortical inhibition.

TMS over V5 did not provoke a migraine headache in any of our participants, and only one participant with migraine with aura developed a visual aura

characterized by scintillating moving dots in the peripheral field similar to a migraine aura preceding her headaches. Changes in blood flow in the posterior cerebral artery, induced simultaneously with the onset of the aura, may explain this observation, a possibility supported by circulation studies.²³ However, the role of hemodynamic changes and triggering aura is still not fully understood. This patient had a record of almost daily or weekly aura; the coincidental may be explained by her prophylactic medications being stopped.

Several factors may explain the resting state of hyperexcitable cortical neurons between migraine attacks—brain damage, mitochondrial dysfunction, damage caused by metabolic imbalance, ischemic changes, or a genetic factor may play an important role.

The presence of a genetic factor has been corroborated by an association between migraine with or without aura and the chromosome 19p familial hemiplegic migraine (FHM) locus based on sibling pair and parametric linkage analysis of 28 families with migraine.^{24,25} However, the exact role of the mutated calcium channel gene in the pathway leading to hemiplegic migraine or migraine with and without aura is yet to be established. Changes in the electrophysiologic properties of the mutated forms of the CACNL1A4 calcium channel expressed in heterologous systems help establish the functional significance of the mutations and suggest that chromosome 19p-linked FHM, an episodic disorder, represents a CNS channelopathy. The possibility of a genetic predisposition to neuronal hyperexcitability in migraine opens an exciting era in the investigation of cellular pathophysiology in migraine with and without aura.

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