

# Phosphenes Induced by Magnetic Stimulation Over the Occipital Brain: Description and Probable Site of Stimulation

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## ABSTRACT

Phosphenes were elicited by brief, intense magnetic pulses directed to the occipital area of the brain with two different magnetic stimulators and various coils. The observed phosphenes were described or sketched by the subject. Phosphenes were usually wedge-shaped flashes of light in the midperiphery, although occasionally structured phosphenes were reported (stripes or grids). The depth of effective stimulation was measured by determining the phosphene threshold for two different size coils. Additional depth measurements were made at the cortical motor strip for threshold finger twitches. The visual stimulation site was clearly deeper (~4 cm) than the site for motor stimulation (~2 cm), and lay near the midline. Both foveal and peripheral phosphenes had identical stimulation depths, implying a subcortical stimulation site, possibly in the optic radiation fibers adjacent to the posterior tip of the lateral ventricles. Fibers closest to the ventricle, representing the horizontal meridian of the visual field, would be preferentially stimulated, in agreement with experimental results.

**Key Words:** phosphene, magnetic stimulation, occipital, optic radiation, ventricle

Since 1896, experimenters have elicited sensations of light called magnetophosphenes by magnetic induction, reviewed by Marg.<sup>1</sup> Until recently, these phosphenes were produced through stimulation of the retina by electro-magnetic fields.<sup>1</sup> Later it was found that a sufficiently strong and fast magnetic pulse can elicit phosphenes directly from the brain in the region of the occipital cortex, as demonstrated by Marg and Newman.<sup>2</sup> These phosphenes are evanescent and often difficult for the subject to describe in detail. However, it is possible to produce them in most people with currently available magnetic stimulators which are used in neurological practice.

The phosphenes were produced by a Digitimer D-190 stimulator which provided strong, single magnetic pulses. On some of the later subjects, we used a Cadwell Rapid Rate Stimulator which generates pulse trains resulting in phosphenes very similar to those elicited by a single pulse, but that are more easily perceived and described because they are brighter and last longer. Although the coils of the two stimulators were of different sizes, and the pulse duration and wave form were also different, there seemed to be no apparent difference in the responses elicited by the two stimulators. There was also no apparent difference in basic phosphenes for the two types of coils, round and figure-8.

It soon became clear that although most of the subjects had rather similar phosphenes, there were some individual differences. In particular, phosphenes were elicited in only certain regions of the visual field for each individual. Phosphenes were relatively invariant in position or form to shifts in the location or orientation of the coil. It also became evident that there were some areas of the visual field where phosphenes were more common among all subjects. Thus the ability to stimulate, at will, specific parts of the visual system for experimental or clinical purposes is limited, because phosphene threshold and location seem to be related to individual topology.

The goals of this paper are to describe the phosphenes we and our subjects have observed and to attempt to localize the site of stimulation by measuring the depth of stimulation<sup>3</sup> and by relating the pattern and location of the phosphenes in the visual field to the visual neuro-anatomical pathways. Special attention will be given to the phenomenon of localized low threshold areas (colloquially referred to as "hot spots") which seem to be present in the visual area and have been observed by others in the peripheral nervous system when using magnetic stimulation.<sup>4-10</sup> A preliminary report on our work has been given elsewhere.<sup>11</sup>

## METHODS

Magnetic stimulation was produced with a Digitimer D-190 stimulator. This instrument generates

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a single, monophasic induced voltage pulse approximately triangular in shape (maximum induced voltage being at the start of the pulse). Four different coils were used: 2 round coils with 12 and 7 cm nominal diameters, and 2 "butterfly" or "figure-8" coils with 12 and 9 cm nominal diameters for each loop. Pulse duration was defined as the time from the peak induced voltage, at  $t = 0$ , to when the induced voltage declined to zero. This is identical to the rise time to the peak magnetic field or peak induced charge density in the tissue. Pulse duration depended on the inductances of the different coils, being 459 and 433  $\mu\text{s}$  for the large and small round coils, and 258 and 239  $\mu\text{s}$  for the larger and smaller butterfly coils. Later in the investigation, we included a Cadwell Rapid Rate Stimulator with a biphasic, sinusoidal waveform 1 period long (220  $\mu\text{s}$ ) and the initial quarter period "pulse" being 55  $\mu\text{s}$ . Generally, this stimulator was used at 25 Hz with 3 to 5 pulses, beyond which no increase or change in the phosphene response was observed. The resulting phosphenes were brighter and of longer duration than from a single pulse stimulator and, therefore, were more vivid and easily described. The Cadwell coils were a round coil of 8 cm nominal diameter and a square figure-8 with a nominal side length of 4 cm. However, we were unable to elicit any phosphenes with the Cadwell figure-8 coil, no doubt due to its small size and poor penetration power.

The depth of stimulation was determined with the Digitimer stimulator by using two different size coils (either the pair of butterflies or the pair of round coils) and plotting the threshold-induced electric fields for each coil vs. depth below the scalp surface (i.e., the perpendicular distance from the coil plane directly beneath the coil windings). The two field profiles cross at some distance below the scalp. Because the two fields are equivalent at this point, this is the presumed depth of stimulation.<sup>3</sup> Coils were always tangential to the scalp surface with the stimulating coil edge approximately 2 to 3 cm above theinion over the occipital lobe. Determination of the induced electric field in air for each coil was the same as described by Epstein et al.,<sup>3</sup> as is the basic technique of stimulus depth determination.<sup>9</sup> A long, narrow (2 by 40 cm) rectangular search coil (1 turn) was used with the narrow edge

parallel to the coil current and the long edges perpendicular to the plane of the coil loop. Induced voltages in the two long wire segments are equal in magnitude but opposite in sign, and cancel. The induced electric field, therefore, is given by the induced voltage across the short wire segment divided by the length of the segment (2 cm). In round coils, the maximum induced electric field lies under the coil windings, not along the central axis of the coil, where it is zero. Therefore, in the plotted electric field profiles, points represent the maximum electric field measured at a given perpendicular distance from the coil plane beneath the coil windings. The situation with figure-8 coils is slightly different. These coils are basically two overlapping round coils, with the overlapping coil windings at the center carrying current in the same direction. This effectively doubles the induced voltage under the common central winding compared to the voltage induced under the outer edges of the individual loops. Thus, in a figure-8 coil, the maximum induced electric field at a given distance lies directly beneath the central winding.

Thresholds were determined in both the motor and visual areas. In the motor strip, the threshold criterion was a minimum finger twitch. In the visual system it was a forced-choice discrimination between the presence or absence of a phosphene in the central or peripheral field. Special care was taken that induced current from each coil was in the same direction to avoid possible directional effects.<sup>12, 13</sup> Coil placement proved to be critical, especially in the motor area, where a small shift in position of a few millimeters from the optimum site or a change in the orientation of the current would appreciably raise thresholds. Measurements were repeated until a consistent, lowest threshold was obtained for each coil.

The analog voltmeter on the Digitimer stimulator is divided into 100 units. Uncertainty in reading the dial was less than  $\pm 1/2$  unit, whereas experimental uncertainty in determination of the threshold endpoint for each coil was on the order of  $\pm 1/2$  to 1 unit. Thus, the overall uncertainty in threshold was of the order of 1 unit. The percentage error depended upon the absolute threshold. For example, if the threshold was 50 units, the error was about  $\pm 2\%$ . The combined maximum error for both coils was typically  $\pm 3$  to 5%, depending on thresholds. When the threshold electric field profiles for each coil were plotted, these threshold uncertainties translated into very different errors in the stimulus depths for the round coil pair and the butterfly coil pair. Because the figure-8 coils were more similar in size than the round coils, the intersection angle of their profiles is more acute (Figs. 2 and 3). Therefore, the same relative uncertainty in threshold causes a much larger shift in the profile intersection point in the figure-8 coils. A  $\pm 3$  to 5% relative uncertainty in threshold between figure-8 coils translated into about a  $\pm 6$  to 10 mm uncertainty in depth, whereas it was only about  $\pm 1.5$  to

<sup>9</sup> Unlike Epstein et al., we applied a small correction factor to the threshold electric field of the coil with the smaller inductance and pulse duration (the smaller round and butterfly coils). The threshold is elevated for two reasons: (1) because of the strength/duration relation governing nerve thresholds and (2) because the stimulator is less efficient at transferring energy to the coil. For the round coil pair, the smaller coil threshold had to be multiplied by 0.97, and for the butterfly coil pair, the threshold had to be multiplied by 0.94 to correct for the artifactual threshold elevation. The effect of this correction was to reduce stimulation depths by about 2 mm (round coils) and 12 mm (butterfly coils) from those derived from uncorrected electric field profiles. The correction technique will be described in another paper (in preparation).

2.5 mm for the round coils. These uncertainties in depth are indicated by the horizontal error bars in Figs. 2 and 3 about the intersection points (arrows). Despite the potential for large error with the figure-8 coils, depths obtained with these coils were typically within 1 to 2 mm of those found with the round coils, with one exception, in the visual area, where they differed by about 1 cm (Figs. 2 and 3).

Subjects in the visual and motor depth-determining experiments were all males in good health, ranging in age from 23 to 73 years. The subjects in the visual portion all had binocular acuities correctable to 6/6 (20/20) or better. However, subject JR (Fig. 2) was amblyopic in one eye with a best correctable acuity of only 6/30 (20/100).

Subjects in the subjective phosphene description experiment were males and females, in good health, and 22 to 73 years of age. Except as noted for the one subject above, all were normally sighted, with correctable acuities of 6/6 (20/20) or better.

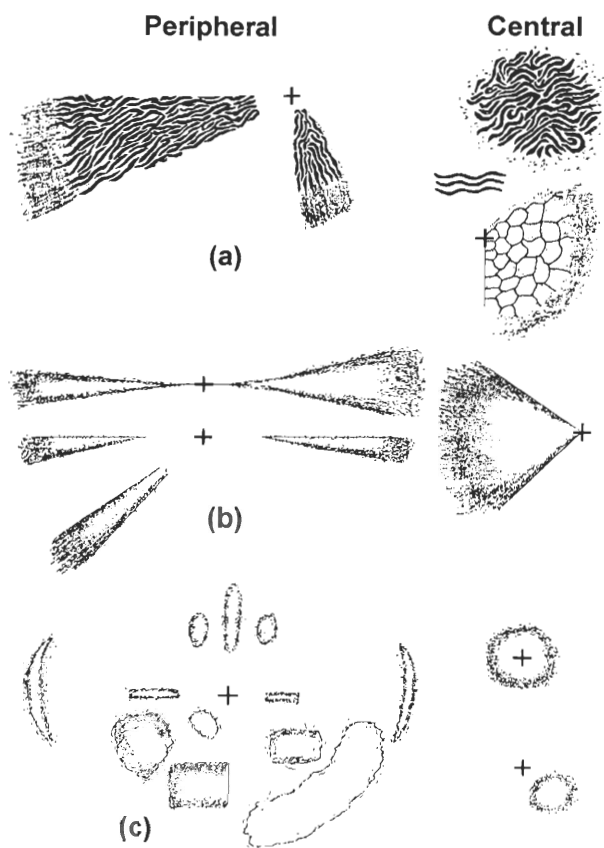
Phosphenes were best perceived in a darkened room and with the eyes closed. Because of the brief and usually subtle nature of the phosphenes, subjects often had to be stimulated dozens of times before they could formulate a description of their perceptions. Results were recorded as verbal reports from the subjects as they were being stimulated and also as drawings made by the subjects at frequent intervals during the session. Subjects were asked to note the positions of the phosphenes in the visual field relative to fixation, their approximate distance from fixation, their shape and extent, their brightness or vividness, color (if any), and any other features they considered to be noteworthy (e.g., fuzzy or sharp edges). Initially phosphene size and distance from fixation were estimated. Later subjects were seated 1 m from a black tangent screen where they could circumscribe the region of the phosphene on the screen with a pointer.

## RESULTS

### Phosphene Descriptions

Despite some negative reports of magnetophosphenes by others<sup>14</sup> (also Pascual-Leone, personal communication), we found it was possible to elicit phosphenes in most of our subjects (11/16). The phosphenes tended to be characteristic in any one individual, but many common features were described by the 11 subjects, as shown in Fig. 1. These artistic impressions are composites based on subject reports or drawings. The left column shows phosphenes seen in the periphery (more than 5° from the fixation point) and the right column shows phosphenes in the central field (<5°). The distinction between central and peripheral phosphenes is not totally arbitrary, because phosphenes were usually reported in one region or the other, but not both in 7/11 subjects. Also 3/4 subjects who reported textured phosphenes saw them only in the central field (see below).

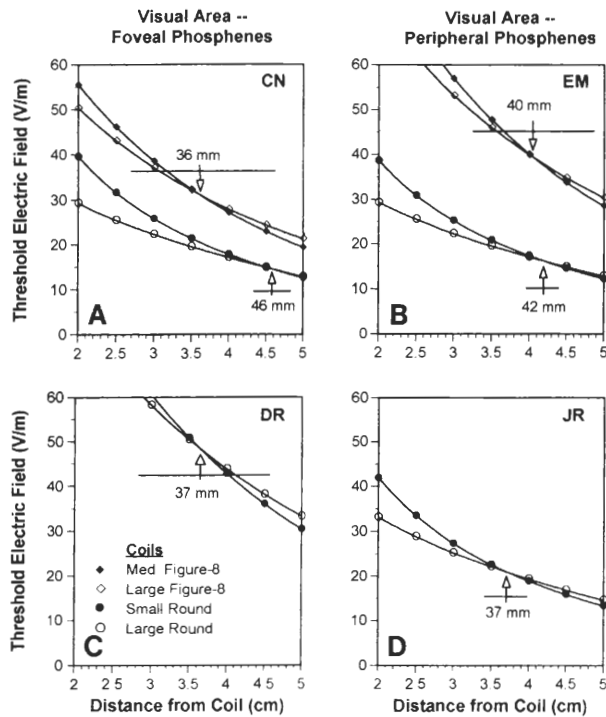
The phosphenes are usually seen as flashes of



**Figure 1.** Artistic impressions of phosphenes reported by subjects. Left column: peripheral phosphenes (>5°); right column: central phosphenes (<5°). (a) Structured phosphenes: stripes, grids, or wavy lines; (b) sector-shaped light flashes, usually near the horizontal meridian, showing well defined edges; and (c) light flashes with indefinite edges ("blobs"): arcs, ovals, rectangles.

light (8/11 subjects; Fig. 1, b and c) but sometimes exhibit structure or texture (4/11; Fig. 1a). The light flashes are usually a pale white or gray. Sometimes a very unsaturated color is seen (3/11). Peripheral phosphenes are more easily stimulated (9/11) than central field ones (6/11). Of these, the horizontal meridian is much easier to stimulate (8/9) than the vertical meridian (4/9). Phosphenes along the horizontal meridian either straddle it or are confined to the lower field where they have a sharp upper boundary along the meridian (Fig 1b). Sometimes, but infrequently (2/11), a sharp edge is seen between the left and right hemifields. Sector-shaped phosphenes (pointing to fixation) are common both peripherally (6/9) and more centrally (3/6); Fig. 1, a and b. Their radial edges are generally well defined but the most peripheral boundary is fuzzy. Phosphenes with indefinite edges (fuzzy phosphenes or "blobs", Fig. 1c) are arc, oval, rectangular, and sector (triangular)-shaped (5/11).

Less frequently, phosphenes appear structured or textured (4/11) and are usually seen only in the central field (Fig. 1a). One subject saw them extending into the periphery up to 40° with the repetitive Cadwell stimulator. They are usually seen



**Figure 2.** Depth of phosphene stimulation in the occipital area. The presumed stimulation site lies at a depth where the threshold-induced electric fields from different size coils are equal (arrows). The depth is about 4 cm below the scalp over the visual cortex at the occipital pole for phosphenes at the fovea and in the peripheral visual field. Horizontal lines show depth measurement error resulting from uncertainty in thresholds. Note also that the results in this figure and Fig. 3 are similar for round and figure-8 coils.<sup>a</sup>

as roughly parallel wavy lines, sometimes resembling zebra stripes, and radiating outward from the center. Near threshold (particularly with single pulses) they may appear grid-like or resemble honeycombs, possibly due to the bends and whorls in the striped pattern. They may be called structured or *form* phosphenes as opposed to the usual homogeneous light or *flash* phosphenes.

In a few cases, the perception was not of a light flash or static form but of a disturbance in the visual field. This may appear as a circular central scotoma, or as a brief punctate or linear distortion of the field that seems to "tear," "rip," "pop," or "collapse." These perceptions might be called "negative" phosphenes and may appear to be "darker than black." Possibly they reflect activation of inhibitory processes.

### Retinotopic Mapping and Stimulus Location

When a round magnetic coil is applied over the brain, the induced currents are maximum under the coil winding around the circumference of the coil and decrease as they approach the coil center, where they disappear. One edge of a coil can be used to map roughly the area of stimulation. This provides a crude retinotopic map with the expected left/

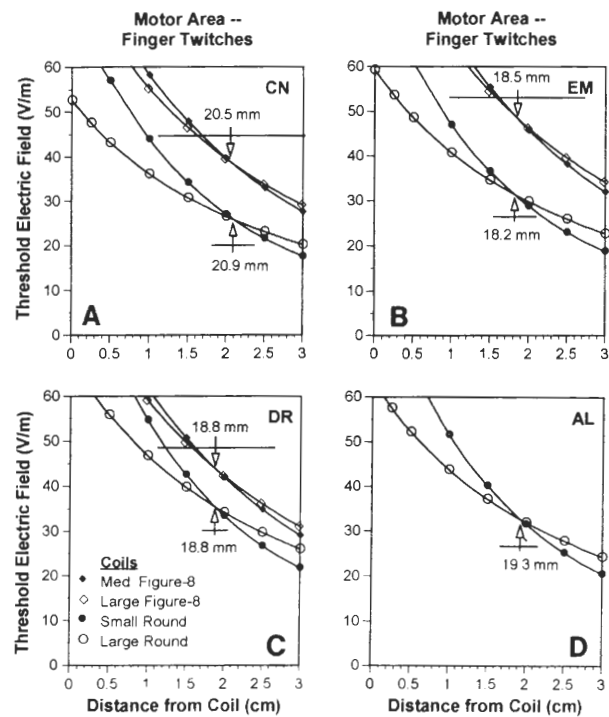
right, up/down inversion of the visual field. Phosphenes can be elicited simultaneously in the right and left hemifield (in some subjects) with a vertical coil edge on the midline or a horizontal edge crossing the midline. Moving the vertical edge of the coil to the right or left of the midline confines phosphenes to the contralateral field. Moving a few centimeters further horizontally usually fails to elicit a phosphene. (Paradoxical ipsilateral phosphenes may occur when stimulating substantially above threshold due to nonlocalized current spread or if one of the coil edges is carelessly placed over the "non-stimulated" hemisphere.) Moving the coil up and forward along the midline usually moves phosphenes down and further to the periphery (but in some subjects they hardly move). However, phosphenes disappear if the coil edge is moved forward more than about 10 cm from the inion, or beyond the anterior boundary of the occipital lobe.

The left/right contralateral shift of phosphenes when the coil edge crosses the vertical midline of the brain is a good indication that phosphenes are being stimulated near the midline. The same crude topographic map from magnetostimulation of the occipital lobe has been described by Amassian et al.<sup>14</sup> for suppression of visual perception, and by Pascual-Leone et al. (personal communication) for evoking phosphenes in blind subjects.

### Depth Measurements

The depth of effective stimulation for the elicitation of phosphenes was calculated in four subjects according to the methods described above. Two of the subjects had structured phosphenes at the fovea (<3°) and two had light flash phosphenes lying in the midperiphery (5 to 20°). The results are shown in Fig. 2. Arrows point to the intersection points of the threshold electric fields and the calculated depths. Horizontal bars through the arrows show the uncertainty in the depth measurements arising from uncertainty in reading the stimulator voltage indicator and in determining threshold endpoints (about 3 to 5% overall error). All subjects have stimulation depths about 4 cm from the coil. Also, the stimulation depths for foveal phosphenes (subjects CN and DR) are comparable to those for peripheral phosphenes (subjects EM and JR). For all subjects, the average depth of stimulation was 4.0 cm with a range of 3.6 to 4.6 cm.

For comparison, depth measurements were made on the motor cortex of four subjects, three of whom were the same as in the visual measurements (Fig. 3). The criterion chosen was a minimal finger movement. The average depth for all subjects was 1.9 cm with a range of 1.8 to 2.1 cm. Although the skull is much thicker at the occiput (and perhaps the scalp as well) than that over the motor cortex, any difference in scalp and skull thickness cannot account for the 2 cm difference in the measured stimulation depth.



**Figure 3.** Depth of finger stimulation in the motor area. Here the depth is about 2 cm for a threshold finger movement. Note that thresholds at the depth of stimulation are substantially higher in the motor area than the visual area.<sup>a,b</sup>

### Thresholds at Depth of Stimulation

Besides differing in depth of stimulation, the motor and visual areas usually show significant threshold differences. In most cases, the visual area has a higher absolute threshold when measured at the surface of the scalp.<sup>b</sup> However, when thresholds are compared at the calculated depth of stimulation, they are substantially lower in the visual area (with one exception) by an average of 25%. For example, subject EM in Figs. 2b and 3b has an electric field threshold (at the intersection points of the round coils) of 17 V/m in the visual area and 31 V/m in the motor area. The motor area also has much more uniformity of thresholds, varying by less than 30% among subjects. In the visual area, however, depth thresholds vary by over 50%. Thus the triggering mechanism in the visual area is generally more potent (when adjusted for depth) but less uniform than the mechanism in the motor area. This suggests that there is some fundamental difference in the mode of stimulation between the two regions.

As an example of what the differing mechanisms might be, Amassian et al.<sup>15</sup> have suggested that in the motor area, the motor axons in the white matter are triggered at the point where they make a sharp

<sup>b</sup> Threshold comparisons must be made between the same pair of depth measuring coils in the two areas. Direct comparisons of Digitimer round and figure-8 coil thresholds are invalid because of large differences between these coils in inductance, pulse duration, and geometry.

turn before leaving the gyrus. In contrast, we suspect that phosphenes are triggered by the large conductivity change<sup>16</sup> between the posterior horn of the lateral ventricle and nearby visual axons, in particular the optic radiation fibers. The shape and depth of the posterior horn and the topography of nearby fibers is highly variable, whereas superficial motor cortex and white matter are relatively uniform across individuals.

## DISCUSSION

### Phosphene Shapes

The various phosphene shapes described by our subjects (sectors, arcs, rectangles, ovals, etc.) can be readily explained on the basis of bands of excitation within striate cortex or underlying geniculostriate fibers. Sector-shaped sections in the retinal visual field map (Fig. 6a) are deformed into roughly rectangular strips in the occipital lobe (Fig. 6e). Therefore, the shape of a region of excitation within the cortical map translated back into retinal coordinates takes on a different perceptual shape. For example, a rectangular band of excitation in the antero-posterior direction of the sagittal plane maps perceptually as a sector, the most common phosphene in our subjects. If the excitation band is trapezoidal, i.e., it narrows as the magnetic stimulus decreases anteriorly with distance from the coil, the corresponding perception will be rectangular. A narrow, rectangular band of excitation at right angles to this in the sagittal plane maps as a circular arc in perceptual coordinates. Other shapes, such as ovals, would be generated by excitation areas with slightly different shapes. The origin of stripes or grids within these shapes is less obvious. Several possibilities will be discussed below.

It is also interesting to compare phosphenes in our normal subjects with those reported by three blind subjects in a study by Pascual-Leone et al. (personal communication). (None of their seven normal subjects reported phosphenes.) These phosphenes differed markedly from our subjects' phosphenes in that they were usually brightly colored (whereas colored phosphenes for our subjects were unsaturated and very rare). There also seemed to be many more amorphous blobs and nondescript flashes of light. Occasional circles (or dots), rectangles, arcs, and sectors (lines to center?) were reported, but they were less common, particularly the sectors. Blind individuals seemed to have a greater variety of phosphenes and to report them in more areas of their visual field, including the upper hemifield, which was poorly represented in our subjects. The most striking difference was the frequent reports by blind subjects of complex visual hallucinations such as faces, trains, street scenes, or motion of objects.

Other aspects of these phosphenes seemed similar to ours. There were many more phosphenes in the periphery than in the center and also far more phosphenes near the horizontal than the vertical.

Differences between blind and normal subjects might be explained, in part, by lowered cortical thresholds in blind subjects (Pascual-Leone, personal communication), leading to excitation of visual areas for color, motion, and complex form.

### Ease of Eliciting Phosphenes

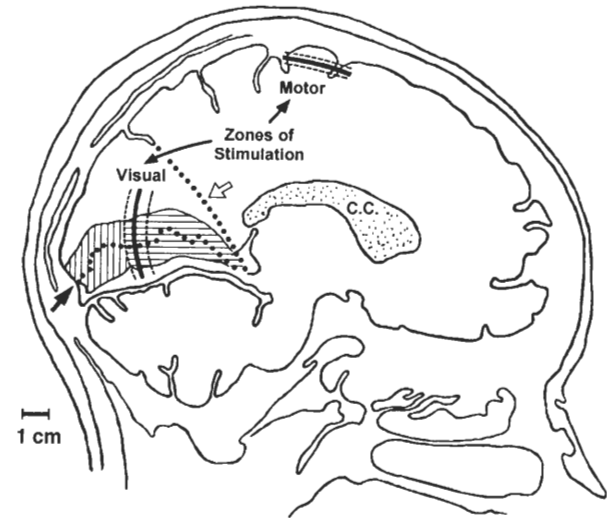
We were able to elicit phosphenes in about two-thirds of our subjects, but other groups have reported either failure or only rare success in eliciting phosphenes in normal subjects<sup>14</sup> (also Pascual-Leone, personal communication). We believe there are two main reasons for this. One is the relatively great depth at which phosphenes are elicited (3.6 to 4.6 cm). Smaller coils (such as the standard Cadwell 8-cm round and 4-cm butterfly and the Digitimer 7-cm round) penetrate poorly and may produce subthreshold fields at the phosphene stimulation site. Cortical magnetic stimulation of the legs is notoriously difficult for the same reason: representation of the legs in motor cortex also lies buried in the midline, 3 to 4 cm from the scalp surface. The second reason is the extremely ephemeral nature of the phosphenes when only single pulse stimulators are used. Many subjects had to be stimulated dozens of times before they were convinced the phosphenes were real or could describe them. (Closing the eyes and concentrating on the point of regard seemed to help.) It is difficult to estimate the subjective "duration" of these phosphenes, but they are extremely brief and probably initiated by a single action potential per axon for single pulse stimulators. Suppression of vision by magnetic stimulation of the occipital lobe provides one means of estimating duration. Amassian et al.<sup>14</sup> and Masur et al.<sup>17</sup> were able to totally suppress visual perception of letters over a narrow range of 20 ms, whereas partial suppression occurred over a range of 60 to 80 ms. These results indicate that single pulse magnetic stimulation (as in Masur et al.) causes visual perceptual changes that last 60 to 80 ms at most. Because phosphenes are induced at much lower stimulation levels and likely involve fewer fibers, the temporal summation duration for phosphenes probably would be less than this. It is interesting to note that Masur et al. also found that tachistoscopic target presentation longer than 4 ms resulted in incomplete suppression, i.e., the temporal summation effect of even these very brief presentations exceeded the 20-ms period for optimum suppression. Therefore, single-pulse magnetic stimulation of phosphenes is roughly equivalent perceptually to tachistoscopic visual stimulation of only a few milliseconds duration.

Phosphenes are much more vivid and easier to describe when several closely spaced (every 40 ms) pulses are used, as was possible with the Cadwell multi-pulse stimulator. One subject who perceived no phosphenes with the Digitimer stimulator perceived them easily when retested with the Cadwell stimulator. Similar results have been reported by Maccabee et al.<sup>13</sup> and Amassian et al.<sup>18</sup> for magne-

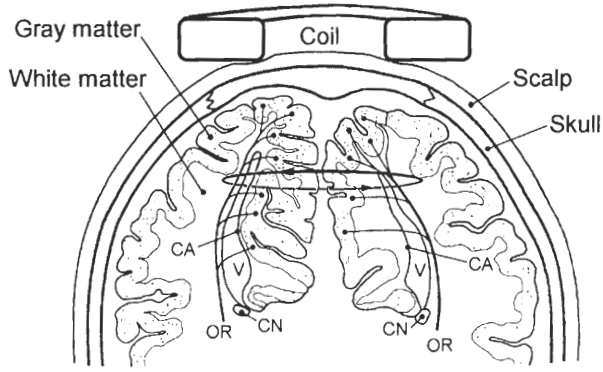
tosuppression of vision over the occipital lobe. Visual suppression was both enhanced and prolonged with several closely spaced (70 ms) pulses. In another study of somatosensory brain, Amassian et al.<sup>19</sup> reported that only one of eight subjects reported a paresthesia with a Cadwell single-pulse stimulator. More recent testing with a Cadwell multi-pulse has resulted in greater success (Amassian, personal communication).

### Stimulus Origin and Retinotopic Mapping

Using the various shape and size coils on four subjects, the depth of phosphene stimulation below the scalp surface at the posterior pole was calculated (Fig. 2).<sup>3</sup> For all subjects, the depth from the scalp surface averaged 4.0 cm and was essentially the same for both foveal (<3°) and peripheral phosphenes (5 to 20°). In contrast, the depth of stimulation producing a threshold finger movement at the motor cortex (Fig. 3) averaged 1.9 cm, in basic agreement with a previous study by others.<sup>3</sup> These results were unexpected for two reasons. First, the motor area was being stimulated relatively near the surface of the brain (Fig. 4), whereas the visual area was being stimulated approximately 2 to 3 cm deep from the brain surface at the posterior pole (the scalp, occipital skull, and meninges being about 1.5 cm thick; Figs. 4 and 5). Second, both foveal and peripheral phosphenes were being stimulated at the



**Figure 4.** Zones of excitation in motor and visual areas. The average depth of excitation is shown by a dark band. The range of measurement across subjects is shown as parallel dotted lines. The region for motor stimulation of the fingers appears to be in the white matter, just below the inner cortical surface, and about 2 cm below the scalp. In the striate cortex, the central visual field representation (<5°) is shown as parallel vertical lines and the peripheral representation as horizontal lines. The zone of stimulation for phosphenes is about 4 cm from the posterior surface of the scalp, near the midline and well removed from the foveal representation in striate cortex at the posterior pole (left arrow). CC, corpus callosum; dots at left arrow, calcarine sulcus; open arrow, parieto-occipital sulcus (adapted from Horton and Hoyt<sup>20</sup>).



**Figure 5.** Horizontal section through occipital cortex at level of the calcarine sulcus. The depth of the sulcus intrudes on the posterior horn of the lateral ventricle (V) forming the *calcar avis* (CA). Optic radiation fibers (OR) lie lateral to the ventricle, with various projections to striate cortex shown. Also shown is an induced current loop, about 4 cm from the stimulus coil, near the tips of the two ventricles.<sup>c</sup> OR fibers projecting to the sulcus and midline, representing the peripheral visual field, are roughly parallel to the current. Fibers projecting to the posterior pole (central field) are more oblique. CN, tail of caudate nucleus.

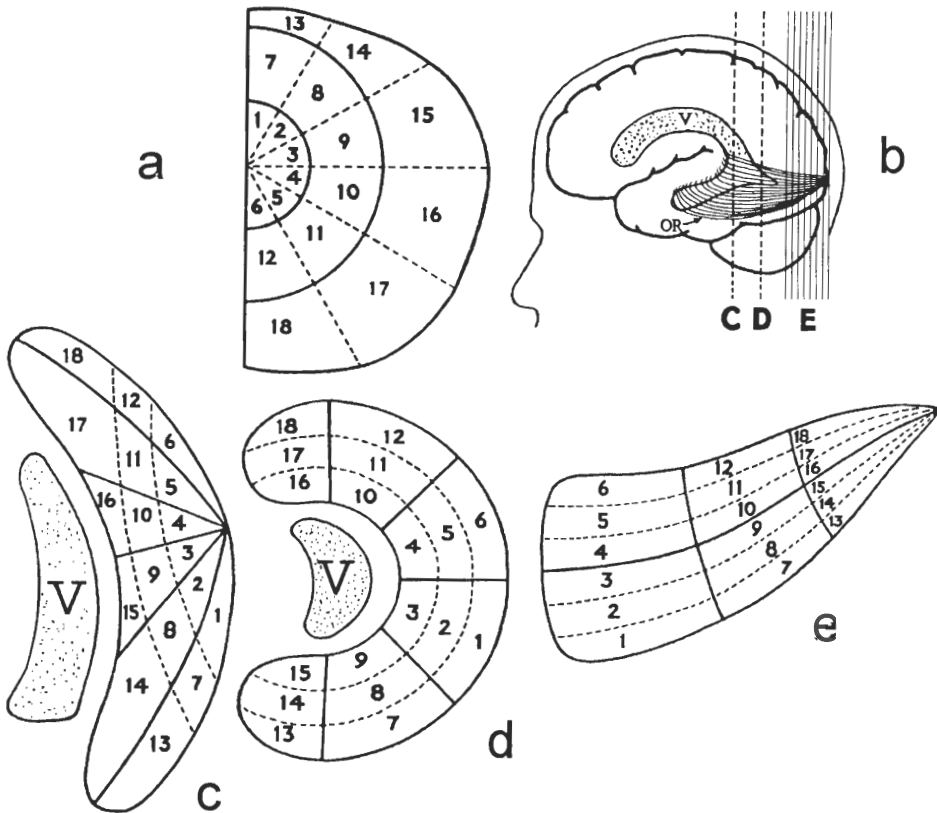
same depth (Fig. 2). However, the foveal representation in visual cortex lies near the posterior pole, far removed from the apparent region of stimulation, whereas the peripheral representation lies along the midline near the region of stimulation (Fig. 4). On the basis of recently revised maps of the visual cortex by Horton and Hoyt,<sup>20,21</sup> if stimulation took place in cortex at the site shown in Fig. 4, all phosphenes would lie about 10° from

fixation. Instead, they range from 0 to 50°. These results, by themselves, clearly indicate that stimulation cannot be at the level of the cortex, but must originate in the underlying white matter.

Another finding is that phosphene thresholds at the depth of stimulation are substantially lower than comparable thresholds for finger movements in the motor area. Again, this is surprising, because it suggests that two different physiological triggering mechanisms are at work in the two areas. Otherwise, it seems likely that the visual area would be stimulated more superficially, like the motor area, where induced currents and fields are much greater. This also would result in the cortical area representing the central visual field (which is more superficial) being more easily stimulated than the peripheral area, whereas exactly the opposite is true: peripheral phosphenes are more easily induced than central ones.

Thus there appears to be some subcortical low threshold site or “hot spot” for eliciting phosphenes, about 4 cm deep in the occipital lobe. Left/right field inversion of the phosphenes as the stimulating coil edge crosses the midline also indicates that the stimulus site must be near the midline. Is there some plausible physiological mechanism that can account for these results?

Other investigators have found “trigger points” elsewhere in the nervous system when using magnetic stimulators.<sup>4-10</sup> Movement of the stimulating coil several centimeters from the lowest threshold site fails to produce any shift in latency, indicating a very localized stimulus area. *In vitro* work<sup>15,22</sup> and



**Figure 6.** The relation of the visual field to optic radiation fibers (OR) in the region of the lateral ventricle (V). (Adapted from Harrington and Drake<sup>24</sup>.) a: The right homonymous visual half-field; b: sites of coronal sections—relationship of V and OR is shown; c: coronal section C through V and adjacent OR in parieto-temporal lobe; d: coronal section D through V and adjacent OR at the posterior horn; e: section E: medial, sagittal view of left striate cortex map.

theoretical arguments<sup>23</sup> indicate that large electric field gradients driving a charge across the nerve membrane will occur after large, sudden conductivity changes, or at sharp bends in, or terminations of, the nerve axon. Thus, stimulation is most likely to occur where there are sudden spatial changes in tissue homogeneity.

Maccabee et al.<sup>13</sup> have recently cited the latter two mechanisms as possible explanations for their visual suppression results in Area 17, or as the trigger mechanisms in motor cortex.<sup>15</sup> However, we find such mechanisms, by themselves, to be inadequate for explaining our results because they are nonlocalized, i.e., sharp nerve bends and terminations occur throughout the visual area. Therefore: (1) stimulation should occur preferentially closest to the coil (as in the motor area), favoring phosphenes in the central field; (2) at a given distance from fixation, no meridian or area of the visual field should be favored over another nor should phosphenes remain fixed in location in individuals; and (3) stimulation of the central and peripheral fields at threshold should be occurring at markedly different depths. However, none of these predictions is supported by our data.

We have also considered the effects of induced current orientation relative to the underlying optic radiation fibers. It is well-known that stimulus currents are least effective in triggering a nerve impulse when flowing across the neuroaxis (at 90°) and most effective when parallel to the neuroaxis. Currents induced by magnetic stimulators flow in closed loops parallel to the coil and the surface of the volume conductor (Fig. 5). If the lower edge of a round coil, e.g., is placed over the occiput, the lower portion of the current loop will flow perpendicular to the midline, or roughly parallel to peripheral radiation fibers projecting to their cortical representation along the midline (Fig. 5). On the other hand, central radiation fibers project backward to their cortical representation near the posterior pole of the occipital lobe, or oblique to the current loop.<sup>24-26</sup> Because peripheral fibers are more likely to be aligned with stimulus current than central ones, they should be more easily stimulated.

This hypothesis would explain, in part, the relative preponderance of peripheral phosphenes over central ones despite the greater depth of peripheral radiation fibers and projecting cortex. However, it suffers from the same basic defect as the nerve bend and termination explanations in that it is nonlocalized. Optic radiation topology is far more complicated than described above due to the complex convolutions of the brain.<sup>24</sup> Some of the central field projections would also have optimal orientations closer to the surface and give rise to more superficial stimulation (Fig. 5). Phosphenes should be present throughout the visual field, shifting positions as the coil is moved, bringing different sets of fibers into alignment with the current. In practice, phosphenes were much more stable in individuals than this hypothesis would allow, being present

in only certain areas of the visual field. Attempts to elicit them elsewhere usually proved to be futile.

Instead, our results point to some *localized* anatomical structure acting as a trigger mechanism, located about 4 cm deep, and having a fixed relation to nearby visual fibers so that certain areas of the visual field are preferentially stimulated. The only major anatomical structure that intrudes on the otherwise homogeneous white/gray matter intermix in the occipital lobe is the posterior or optic horn of the lateral ventricle (Figs. 5 and 6). The tip of the horn has the following anatomical and physiological characteristics making it a likely trigger site.

1. It lies at about the same depth as the phosphene generation site<sup>c</sup> (with a range in four subjects of 3.6 to 4.6 cm).

2. The ventricle is filled with cerebrospinal fluid with an order of magnitude higher conductivity than surrounding myelinated nerve fibers.<sup>16</sup> The large impedance change at the ventricle/fiber boundary causes an abrupt, spatial distortion of the electric field near the boundary, creating a lowered threshold stimulation area.

3. Laterally, superiorly, and inferiorly the ventricle is surrounded by optic radiation fibers. Fig. 6, adapted from Harrington and Drake,<sup>25</sup> depicts the distribution of radiation fibers, near the optic horn, adjacent to the ventricle and their projection on the visual field. The fiber bundles representing the horizontal meridian lie closest to the ventricle and their projection fibers to the calcarine sulcus course over and under the ventricle. Radiation fibers representing the vertical meridian lie furthest from the ventricle.

4. Medially the ventricle is flanked by nerve fibers to and from the calcarine sulcus (Fig. 5). The depth of the sulcus forms a distinctive bulge in the ventricle, the *calcar avis*<sup>24,26</sup> (CA, Fig. 5) and also forms the horizontal peripheral meridian representation of the visual field in striate cortex. The vertical meridian representation, however, lies along the midline of the brain, well removed from the ventricle.

We believe the fact that horizontal meridian fibers (both to and from the striate cortex) lie closest to the ventricle explains why phosphenes near the horizontal are much more common than ones near the vertical.<sup>d</sup> Large conductivity changes can form

<sup>c</sup> Our own informal survey of the depth of the posterior horn tip from textbook illustrations and photos,<sup>24-26</sup> and MRI and CAT-scan images gave an average of about 43 mm and a range of 32 to 65 mm. Of 19 measurements, 16 were between 37 and 48 mm. The distance from the posterior pole to the scalp surface was assumed to be 15 mm.

<sup>d</sup> A possible complication with this hypothesis is the presence of a thin band of callosal fibers connecting the two visual hemispheres, the *tapetum*, lying between the radiation fibers and the ventricle laterally and superiorly, and representing the midline of the visual field.<sup>26,27</sup> However, reports of phosphenes adjacent to or straddling the midline were rare. In one unusual

potent, low-threshold trigger sites as has been demonstrated *in vitro* by Maccabee et al.<sup>22</sup> Straddling a nerve with two nonconducting lucite cylinders doubled the electric field as current “squeezed” through the narrow space, tripled the local electric field gradient, and dropped threshold by two-thirds. In similar (unpublished) experiments we found a 40% drop in threshold (to electrical stimulation) when only one side of a frog nerve was touched by a small lucite block. Threshold increased monotonically as the block was moved away from the nerve, returning to maximum about 1 cm from the nerve. From this, one would expect preferential stimulation of nerve fibers closest to a conductivity change. The ventricle differs from lucite in that it is a “rod” of *increased* conductivity. Current paths will bend and flow into it rather than around it, as they do a nonconductor. Otherwise, the stimulus mechanism is the same.

*In vivo* “hot spots” in the peripheral nervous system also probably arise from conductivity changes. For example, Schmid et al.<sup>4</sup> stimulated the facial nerve in surgical patients both electrically and magnetically. By comparing latency measurements, they were able to conclude that magnetic stimulation occurred at the end of the labyrinthal segment of the nerve where it ceases to be surrounded by cerebrospinal fluid with its high electrical conductivity and enters the high resistance tissue of the petrous bone. Maccabee et al.<sup>3</sup> arrived at the same conclusion in nonsurgical patients. Similar explanations may be applied to localized magnetic stimulation of: (1) the ulnar nerve at the elbow where it lies adjacent to bone;<sup>6</sup> (2) median nerve at the wrist, which also lies adjacent to bone and passes through tendon sheaths;<sup>7</sup> and (3) spinal nerve roots as they pass through the neuroforamina.<sup>8-10</sup>

Although we believe conductivity change is the primary phosphene trigger mechanism in the occipital lobe, other mechanisms such as nerve bends or terminations, or even the conductivity change that occurs at the gray/white matter interface,<sup>16</sup> may also play a role, particularly at the higher intensity levels apparently needed to get visual suppression.<sup>13, 14, 17</sup> Although we were unable to elicit phosphenes at 100% power with the small Cadwell figure-8 coil, Amassian et al.,<sup>14</sup> using this coil, were able to produce suppression of the foveal visual field at maximum intensity while stimulating over the occipital pole. This is suggestive of a more superficial site for visual suppression than for excitation of the central field. We also had one subject (EM, Fig. 2b) who reported a persistent central scotoma simultaneous with transient phosphenes in the midperiphery when using the Cadwell round coil. This subject never reported central phosphenes. One possible interpretation is that the central field representation in striate cortex lying close

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case, a central phosphene (a grid) was seen straddling the midline with a narrow, sharp vertical gap between left and right fields.

to the coil at the posterior pole was being inhibited by one mechanism while a peripheral phosphene was being excited at a deeper level by another. It is interesting to note in this regard that Masur et al.<sup>17</sup> have found evidence of separate “deep” and “shallow” visual suppression mechanisms with magnetic stimulation. One mechanism requires higher stimulus intensities, results in complete suppression of central vision, and has optimum suppression latencies 60 to 80 ms after visual stimulus onset. Using slightly lower stimulus intensities results in partial suppression, a shift in optimum suppression latencies to 80 to 110 ms, and a subjective sense that target letters are still seen but not recognized. The higher stimulus intensities and shorter latencies of the first mechanism are suggestive of deeper, afferent striate fibers being involved, whereas the lower stimulus intensities and increased latencies of the second mechanism suggest shallower, efferent fibers. Also, because all visual information must first pass through striate cortex, inhibition at the afferent fiber level could cause complete perceptual suppression. However, efferent fibers project to multiple cortical areas.<sup>27</sup> Therefore producing complete perceptual suppression at this level would be more difficult.

The origin of the striped patterns and grids (Fig. 1a) seen by some individuals is still rather mysterious. These patterns are very stable, i.e., distinctive stripes and whorls are repeatable over days and remain fixed in place. In this respect, they seem to differ from fluctuating striped/grid patterns induced by stroboscopic stimulation,<sup>28</sup> or seen during migraines or drug-induced hallucinations, which may arise from excitatory and inhibitory feedback within a nerve network. Preferential stimulation of nerve fibers adjacent to the ventricle possibly could generate the patterns. This would require stratification of nerve fiber bundles from adjacent areas of the visual field. Those fibers that lie closest to the ventricle would be preferentially stimulated and “light up.” Those that lay further away would remain dark. However, this *ad hoc* explanation seems rather dubious.

The striped patterns bear a striking resemblance to the cortical orientation of ocular dominance columns, which have been visualized with various techniques.<sup>27</sup> However, it is not clear that there is any relation between perceptual stripes and physical striated cortical columns. Separation of radiation fibers from the two eyes (as in the temporal lobe<sup>25</sup>) near the posterior horn of the ventricle could lead to preferential stimulation of fibers from one eye. This would produce bands of excitation in the cortex as the ocular dominance stripes of one eye are activated. However, this will not necessarily generate a perceptual striped pattern. More likely, adjacent areas of the visual field from one eye would be excited, producing a diffuse light flash. The general orientation of the perceptual stripes is radial, away from fixation (Fig. 1a). If orientation columns were responsible for the perceptual stripes,

it would be difficult to explain the preferential stimulation of one group of orientation columns. Another mystery is why our subject population divided into two distinct groups: (1) those who perceived only flashes of light (the majority) and (2) those who perceived primarily or exclusively stripes or grids.

There are many other fiber tracts and nuclei throughout the brain that lie adjacent to the ventricles, e.g., the entire inferior surface of the corpus callosum (CC, Fig. 4), or the caudate nuclei (CN, Fig. 5). Unfortunately, most of these structures lie deeply buried in the head, 7 to 9 cm from the surface, inaccessible, perhaps, to even very large coils. However, structures adjacent to the inferior (temporal) horn of the lateral ventricles are much closer to the surface. For example, optic radiation fibers are adjacent to the superior and lateral surface of the inferior horn 3 to 4 cm deep (Fig. 6, b and c), the hippocampal formation lies on the medial surface, about 4 to 5 cm below the scalp, and the amygdaloid body is at the anterior tip of the horn. All these structures could be preferred sites for stimulation by magnetic coils because of their proximity to the ventricle.

We have made only tentative attempts to stimulate radiation fibers in the temporal area.<sup>6</sup> In one subject, stimulation over the temporal lobe produced flash phosphenes only in the mid to far periphery in the lower horizontal and oblique meridians, in basic agreement with standard projection maps (Fig. 6c). Projection fibers from the central retina and the vertical meridian lie furthest from the ventricle in this area and may be very difficult or impossible to stimulate.

Because radiation fibers can apparently be stimulated over a large area, caution must be exercised when experimenters attempt to stimulate extrastriate visual areas. Results may be confounded by the simultaneous stimulation of the optic radiation. For example, this may explain the wide disparity in motion suppression latencies recently reported by two groups to transcranial magnetic stimulation of parieto-occipital cortex.<sup>29, 30</sup>

Our finding of a deep stimulation site for both foveal and peripheral phosphenes is one more piece of evidence indicating that magnetic brain stimulation (and perhaps electrical as well) is occurring in the underlying white matter rather than in the gray matter. Epstein et al.<sup>3</sup> compared their magnetic stimulation depth measurements with MRI images in the motor area. Stimulation occurred near the gray/white matter boundary, although they placed the probable site in layer VI of the motor cortex. Data from our subjects (Fig. 3) plus

<sup>6</sup> It is difficult to study this region because the facial nerve is easily stimulated, causing strong unilateral contraction of facial muscles. Besides creating discomfort to the subject, muscle contractions around the eye may produce artifactual pressure phosphenes. Other sources of distraction and discomfort are coil noise near the ear and stimulation of the motor cortex.

reanalysis of their data, however, indicate that they slightly underestimated true depth (Rudiak and Marg, paper submitted for publication). Thus in the motor area, stimulation is probably occurring in the superficial white matter. Another strong piece of evidence was provided by Barker et al.,<sup>31</sup> who determined strength/duration time constants in the motor area and peripheral motor nerve. The time constants in the motor area were comparable to those of the obviously myelinated peripheral nerve, and an order of magnitude lower than would be expected in predominantly nonmyelinated gray matter. These results in the brain are the same as in the peripheral nervous system where it has long been known that larger, myelinated fibers have much lower excitation thresholds than smaller nonmyelinated ones.<sup>32</sup>

Clinically, it would be desirable to have some noninvasive means of selectively stimulating the visual cortical areas in humans. Our results, however, suggest that it is not always possible to elicit phosphenes even in normals. Even in those who did perceive phosphenes, our ability to control the location of the phosphenes in the visual field was either extremely limited or nonexistent. This does not necessarily preclude other clinical applications of magnetostimulation in vision. Perceptual latencies, e.g., can be measured in normals by inducing selective suppression of visual function with magnetic stimulators over different visual areas.<sup>14, 17, 29, 30</sup> Masur et al.<sup>17</sup> have applied this technique to patients with optic neuritis and demonstrated delays in perceptual latencies that correlate with delays in their pattern visual evoked potentials. In a few cases, perceptual latencies could be derived when the visual evoked potential was noninterpretable. Thus, magneto-suppression of vision may provide an additional clinical test for diagnosing and following the course of certain visual pathologies.

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