

Magnetostimulation of Vision: Direct Noninvasive Stimulation of the Retina and the Visual Brain

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ABSTRACT

The history of magnetophosphenes and their closely related predecessor, electrophosphenes, is described from the mid-18th century to the present time. The current era of magnetic stimulation started in 1985 with the development of a practical capacitor-discharge electromagnetic stimulator by Barker and his colleagues at the University of Sheffield, and their application of it to the brain with Merton and Morton at the National Hospital, London. The safety of magnetostimulation of the brain is discussed as well as the advantages of magnetostimulation over electrostimulation. Principles of magnetostimulation of nerves and magnetic measurement are considered. Effects on motor and sensory systems of the brain are described including magnetic perceptual suppression in the visual cortex and other pioneering work of Amassian, Cracco and Maccabee at SUNY Health, Brooklyn. Magnetophosphenes from retinal and cortical magnetostimulation are distinguished. Now that visual cortical stimulation is possible with the strong magnetic pulses generated by capacitor-discharge instruments, the functional viability of the visual cortex may be tested directly and noninvasively.

Key Words: magnetic stimulation, magnetophosphene, electric stimulation, electrophosphene, retina, visual cortex

Phosphenes are sensations of light produced by stimuli other than light. The visual percept of a blow on the head is characterized as "seeing stars," which are phosphenes generated by the mechanical stimulation of the brain or the retina. Similarly, phosphenes can be elicited by magnetic or electrical stimulation of these tissues.

The word phosphene comes from the Greek *phos*, light, and *phainein*, to show. In the physiologic literature, phosphene generally refers to a luminous sensation produced by stimuli other than light. Some extend this definition to internally triggered luminous or form sensations such as the "fortification spectra" of optical migraine headaches and

of visual illusions induced by hallucinogenic drugs such as LSD.¹ It is reasonable to conclude that seeing a phosphene is not a hallucination because the stimulus is known.

Phosphenes are rarely elicited by clinicians because the stimulus is hard to control and limit. Magnetostimulation and magnetophosphenes may overcome these disadvantages and provide new insights into visual function and new clinical tests.

ELECTROPHOSPHENES

Electrophosphenes, as opposed to magnetic, were first reported 2½ centuries ago. In a shocking attempt to cure blindness, Charles LeRoy, a distinguished French chemist and physician in 1755 discharged a Leyden jar (actually a large vessel forming a high-voltage capacitor of about 1 nanofarad, invented approximately 10 years earlier and used in early experiments with static electricity) through the head of a blind man.² Therein lies a story.

In the mid-18th century in Dorchester, England, the newspapers of the time told of a 7-year-old boy who was cured of blindness, having suffered an attack of "goutte sereine." He was cured by electric shock. The tale was also mentioned in a report by a member of the Royal Society, London, in a treatise on electricity.

LeRoy's patient, young Granger, 21 years of age, had been blind for 3 months as a result of an acute disease with high fever and rash. After making the rounds of the best specialists in Paris, his parents took him to LeRoy and implored him to shock their son and restore his sight, as was reported done in England. Although LeRoy was very skeptical, he finally gave in. He knew that Benjamin Franklin had reported that animals had *lost* their sight by electric shock but young Granger's parents were so confident and insistent that LeRoy could not refuse them. On December 6, 1753 LeRoy started treatment. Initially iron or brass wire was wound two or three times around the head like the rim of a hat and another led to the right leg. Possibly the first bioelectrode was fashioned, making contact at the supraorbital ridges and the occiput (Fig. 1). A well-charged Leyden jar or bottle was connected and 12 shocks were administered, provoking terrible cries. Young Granger saw a flame descending rapidly

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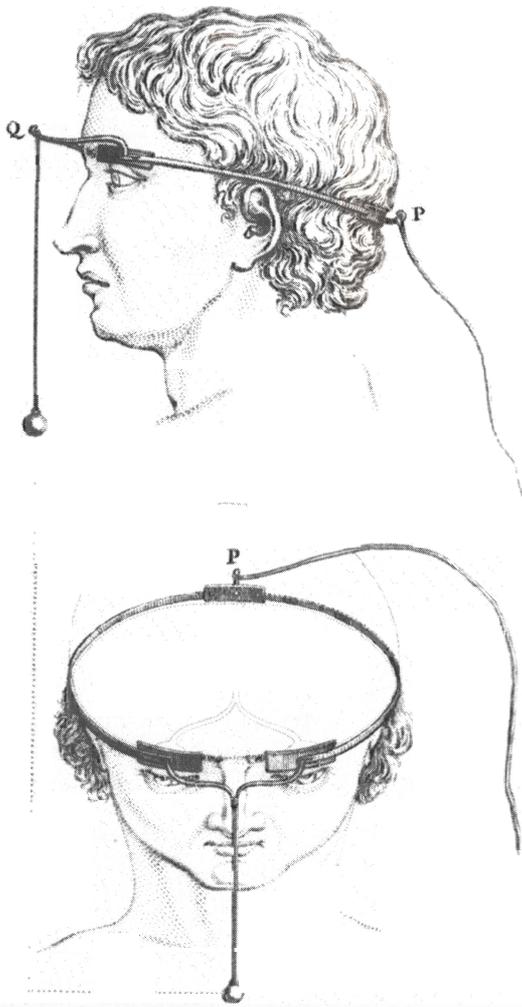


Figure 1. The electrodes (possibly the first bioelectrodes designed specifically for human stimulation) of Charles LeRoy in 1755.² They were connected to a Leyden jar, the first capacitor, which had been invented recently in Holland. It can be seen graphically that the then-known central visual pathway from the eyes to the chiasma where the two optic nerves join is correct. The rest of the path, a single bundle to the occipital region, is not correct. The actual path including optic tracts, lateral geniculate nuclei, and optic radiations was discovered a century later with the development of histological methods. It is interesting that at that time it seems to have been assumed that vision was seated in the back of the brain. From reference 2 from the Bancroft Library, Berkeley, CA.

before his eyes. This must be the first reported electrophosphene. LeRoy proposed using electric shock as a test of optic nerve function. Despite dozens of shocks on subsequent days, needless to say young Granger remained blind.

As for the malady, *goutte seréine* was translated by Helmholtz as "cataract" but an old French dictionary defines it as "amaurosis, paralysis of the optic nerve."³ In any case, ignorance of biology in the 18th century made diagnosis an art rather than a science 100 years before the advent of the ophthalmoscope. From the context of LeRoy's paper the amaurosis did not seem to be from cataracts but more likely from optic neuritis or meningococcal meningitis. However, Franklin's electric shock blinded his animals by cataract, an effect demonstrated in the ophthalmological literature 1½ centuries later.

At about the same time Benjamin Franklin, possibly the inventor of bifocals, who defined positive and negative electric current in his one fluid theory of electricity as it is used today, discharged two large Leyden jars through six men (in series), each holding one hand on the head of the man to one

side.⁴ The result was stunning. Upon closing the circuit all fell down.⁵ They did not see the light nor hear the crackling noise of the shocking spark so it seems likely they did not observe a phosphene either. The pathway of the electric current was not directed through the retina or visual cortex as it was with LeRoy's electrodes.

In the year 1800 Count Alessandro Volta wrote a letter to Sir Joseph Banks (a botanist and president of the Royal Society, who voyaged with Captain James Cook on the *Endeavor*) in London.⁶ Volta, from the University of Padua, coupled silver and zinc separated by a layer of brine-soaked cloth, producing an electric current. He applied one of these metals to the eye or wetted lid and the other either to the other eye or to the mouth. This, he said, gave the most beautiful "éclair" (flash or phosphene). Using a number of these cells in a voltaic pile or battery did not improve the phosphene.

Many details of 19th century physiologists who worked with electrical phosphenes, including Purkinje, are related by Helmholtz.⁷

Earlier in this century, neurosurgeons elicited phosphenes by applying electrodes to the surface of

the visual cortex in conscious patients undergoing a craniotomy, usually for epilepsy.^{8,9} Attempts have been made to design and build a visual prosthesis consisting of an array of electrodes implanted on the visual cortex which would transmit electrical pulses to provide a form of vision for people who are blind due to problems anterior to the visual cortex; that is, in the eyes or the visual pathways (for example, Brindley and Lewin,¹⁰ and Marg et al.¹¹). Magnetic stimulation of the cortex is more difficult than electrical in this context, as will be explained later.

HISTORY OF MAGNETOPHOSPHENES

The first reported magnetophosphene was late in the 19th century by d'Arsonval, the inventor of the moving coil electric meter (Fig. 2).¹² Until the present era, all magnetophosphenes were from stimulation of the retina, not the cortex.

Magnetism as a science grew from observations in ancient Greece that magnetic stones (Fe_3O_4) called magnetite would attract bits of iron. The word magnetism comes from *Magnetes*, the people of ancient Magnesia in Thessaly where lodestones were found. A lodestone (or loadstone) literally means leading stone or compass. Ferromagnetic substances such as iron are permanently magnetizable.¹³

In 1896, d'Arsonval, as a byproduct of his work on the measurement of alternating current, reported the induction of phosphenes by magnetic fields.¹² He saw phosphenes when he placed his head in a coil which carried 30 amps and 110 V, at 42 Hz. [For practical purposes, the field strength of a magnetic coil of a given geometry is represented by the number of ampere-turns (which is directly proportional to the magnetic flux density) but the number of turns was not mentioned in the brief communication.]¹³ The coil also gave him vertigo

to the point of (sic) "fainting" (falling). With a smaller coil, only 5 cm in diameter, d'Arsonval also saw phosphenes and experienced some muscular contractions as well.

In Vienna in 1902, Beer surveyed the research of the physiologic effects of magnetic stimulation.¹⁴ He told of the interest and the activity in the field in the 1880s, despite negative results. He related that at the turn of the century E.K. Müller, a Swiss electrical engineer, saw a "flimmer" (flicker) upon applying an electromagnet to the eye. Beer was able to spend a few weeks working with Müller's magnet and confirmed his results. The specifications of the magnet were not given but the alternating current was 15 to 20 amps.

In 1910, S. P. Thompson,¹⁵ who at the beginning of this century headed the British Institution of Electrical Engineers and the Physical Society, apparently independently rediscovered this phenomenon and coined the term for these luminous sensations *magnetophosphenes* (Fig. 3). His coil had 32 turns of thick copper-stranded wire wound with a 9-in inside diameter and about 8 in in length. The current could be increased up to 180 amps and the peak maximum intensity of the magnetic field at the center of the coil was about 1400 CGS units. These centimeter-gram-second units were later named after Gauss. (In current measure, the flux density was 0.14 teslas.) When Thompson's head was in the magnetic field, the flickering phosphene was visible even in daylight. Several of his subjects noticed a strange taste after exposing their heads for 2 or 3 min to this field.

In 1911, Dunlap at Johns Hopkins University reported **generating** magnetophosphenes¹⁶ after having read Thompson's paper. Dunlap used a similar method although his coil was slightly larger in diameter and used a 60 Hz ac source. With 200 amps, the coil gave a field of 5400 ampere-turns as compared with the 5760 in Thompson's experiment.

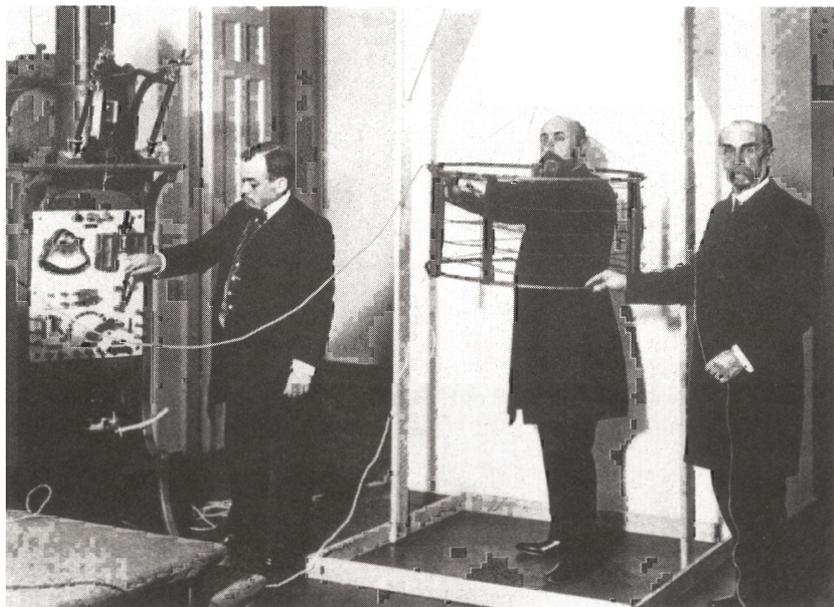


Figure 2. Arsène d'Arsonval, on the right, with two assistants demonstrating the effects of the flow of alternating current in 1911, some 16 years after he reported the first magnetophosphenes.¹² He was a member of l'Académie de Sciences and a physician as well. From the Archives of the Académie de Sciences, Paris, France.



Figure 3. Silvanus Phillips Thompson (1851–1916) with his apparatus by which he induced magnetophosphenes in himself. He was a Principal and Professor of Applied Physics and Engineering at a technical college in London and coined the term magnetophosphene. From the Archives, Imperial College, London, England.

The phosphene flicker was best perceived when the eyes were closed or the room darkened but the magnetic coil screened out much of the ambient light. Some subjects saw nothing. In order to obtain a stronger stimulus, Dunlap took his apparatus to an electric power testing plant and was initially able to increase his stimulus to 440 amps. The responses were improved by switching to 480 amps of 25 Hz current, almost 13,000 ampere-turns, during which the flicker was easily apparent. Dunlap pointed out that his main difficulty was in controlling the necessary high currents and voltage; in effect, the power to the people who were his subjects.

At about the same time, Magnusson and Stevens investigated the effects of magnetic stimulation of the head with direct and alternating current in four subjects.^{17,18} Using direct current, they saw nothing except upon closing or opening the circuit which actions, of course, produced a change in the magnetic field. They reported that the intensity of visual sensation seemed to depend on the intensity and rate of change of the magnetic field. With the alternating current they varied the frequency from 8 to 66 Hz, also varying the current so that they

applied from about 3,000 to 14,000 ampere-turns. The most effective frequency was between 20 and 30 Hz. Below 15 Hz the light pulsates as a succession of flashes but at 20 to 35 Hz the light was seen as patterns superimposed on a quivering, flickering effect. The effect was graded within the temporal field. Above 40 Hz the light became more uniform and the flicker much more rapid. The magnetic field caused in some but not all subjects a twitching of the orbicularis oculi muscle which they characterized as winking. The phosphenes were not affected by afterimages from a bright light.

Magnusson and Stevens saw phosphenes with a coil of 205 turns which provided 5740 ampere-turns at 60 Hz. The ampere-turn value was approximately the same as that used by Thompson. In addition, a second coil of 263 turns was made to slip over the outside of the first coil and increase magnetic flux; together the 2 coils had 468 turns. Later, provisions were made for additional coils (Fig. 4).

Magnusson and Stevens pointed out that the polarity of the magnet, whether north was up or down, made no difference. In switching the current, the phosphene was more intense on closing the circuit than on turning it off. Also, fatigue reduced the response.

In 1947, Barlow et al., using a magneto (a per-



Figure 4. The magnetic coils of Magnusson and Stevens reported in 1911 and 1914.^{17,18} Additional sections of coils could be energized to increase the magnetic field.

manent-magnet electric generator) and varying the frequency from 10 to 90 Hz, were able to obtain 0.09 T (tesla = 10^4 Gauss) with 20 amps.¹⁹ A laminated core was put in the center of the coil of 400 turns which had inside and outside diameters of 10.5 and 20.3 cm, respectively. The end of the core was pointed close to the temple so that it tended to concentrate the magnetic field in the eye. A threshold phosphene could be seen when the tip of the core was several centimeters from the eye. Phosphenes were generally colorless and in the peripheral visual field.

No phosphenes were elicited by placing the coil at the occipital region, over the visual cortex, even at maximum field strength. With a core tapered to a few millimeters and pointed to different parts of the eye, the positions of the phosphenes could be localized in the visual field, corresponding to the position of the part of the retina stimulated. This evidence indicated that the stimulation was effected at the retina rather than the optic nerve or the brain. Further support for retinal reception came from pressure ischemia of the eye which blocked the phosphenes. The time for recovery after a stimulus varied with the duration of the stimulation. The authors confirmed that phosphenes lasted longer with movement of the eye or lids. They also confirmed that the phosphene was difficult to detect in intense illumination but could be seen with the eyes opened or shut, and lasted only a few seconds. The phosphenes filled a large part of the visual field, approaching the central field from the peripheral. If the two poles are placed at the temporal orbits, one on each side of the head, the phosphenes are in the middle of the visual field. If the poles are brought down to the lower head (stimulating the lower retina), the phosphene appears in the upper visual field.

The literature on magnetophosphenes was reviewed up to 1955 by Valentinuzzi,²⁰ who then theorized on their origin by assuming certain retinal circuitry. He summarized that the frequency for maximum intensity of magnetophosphenes was between 20 and 30 Hz. At less than 20 Hz, the individual pulses can be counted. At higher frequencies there is a confused mixture of wavy luminance effects which are more intense in the temporal retina. One should avoid very intense fields, he related, that is, greater than that produced by 14,000 ampere-turns because of possible undesired reactions (about which he did not elaborate). Beer¹⁴ considered diamagnetic properties of organic tissues to be involved in the origin of the phosphenes but Valentinuzzi thought that Beer was wrong because stimulation must be based on magnetic induction of an electric current. It is generally accepted today that the stimulation is from a magnetically induced electric current, not the magnetic field *per se*.

Siedel²¹ stimulated threshold phosphenes with a magnetic coil as a function of stimulus frequency in 60 subjects in a range of 10 to 50 Hz. The

magnetic field ranged from about 450 G (Gauss) at approximately 15 Hz to almost 1000 G at close to 50 Hz.

Bickford and Fremming²² tried using strong magnetic pulses for stimulation. Their system produced 2 to 3 T [teslas] with a 300- μ s duration powered by a bank of capacitors. Although they could cause muscle contraction by motor nerve stimulation when the eye was stimulated, none of their six subjects reported a phosphene. This failure may have been at least in part because of the rigid incorporation of the magnetic coil in a table which prevented selectively and flexibly positioning the coil to find optimum orientations, which can be critical.²³

Lövsund et al.²⁴ did a quantitative analysis of magnetophosphene thresholds. Their U-shaped electromagnet was oriented so that the poles were directly over the eyes at the temples and the magnet was adjustable so that it would fit differing head widths. They used a stimulus frequency of 10 to 50 Hz which was obtained from a generator, power-amplified and fed to the magnetic coil. The eye was placed at the center of curvature of a 1-m hemisphere painted white. Three monochromatic-colored background lights were obtained with special spectacles which incorporated interference filters at wavelengths matched to the human cone pigment maxima. Thresholds were about 10 mT (100 G) and at frequencies of 20 to 30 Hz. The sensitivity curve from magnetophosphenes during dark-adaptation reached an asymptote at about 16 min.

Two totally blind subjects were tested to try to get a better concept of the precise site of stimulation in the eye. One of the blind subjects had retinitis pigmentosa, a retinal disease which affects the photoreceptors, mainly rods, and pigment epithelium. The rest of the retina may have been relatively normal. This totally blind subject saw phosphenes but no threshold curve could be determined because of persistent afterimages. From this evidence they concluded that the phosphenes are not elicited in the photoreceptors. (However, some blind subjects report they often "see" lights or ghost images which may be taken for phosphenes.) The other subject had had both eyes removed because of glaucoma and saw no phosphenes, which would tend to eliminate the optic nerve as a receptive site (assuming incomplete optic atrophy) and therefore would point to the retina. As related earlier, Barlow et al.,¹⁹ showing local visual field specificity, concluded that it was likely that the phosphenes originated in the retina.

Up to this time, all the magnetophosphenes had been from ac magnetic fields or from pulses caused by making and breaking contact with dc supplied to a magnetic coil.

CURRENT ERA OF MAGNETOSTIMULATION

In a prelude to magnetic stimulation, Merton and Morton^{25,26} in 1980 demonstrated that electrical

transcranial stimulation of the cortex was clinically possible and practical (if uncomfortable at best). Pain can be minimized by careful electrode placement, short pulses, and the reduction of current density with extended electrode surface. They used a 2-KV pulse with a decay time constant of 10 μ s through electrodes on the scalp. Applying electrodes to the back of the head, they proved that the phosphenes were from the brain by pressure ischemia of the eyes which prevented any phosphene transmission from the retina. This control ruled out the retina, which has a lower threshold than the cortex to electrical stimulation, and eliminated the possibility of generation of phosphenes from the retina by stray currents. Considerable discomfort arose from strong contraction of the neck muscles, causing the head to jerk.

A magnetic stimulating coil producing a strong, fast pulse from a capacitor discharge was developed by Barker and his colleagues and applied to peripheral nerve stimulation. They took their instrument to Merton and Morton, who applied it to the motor cortex and effectively stimulated limb muscles through the brain.²⁷⁻²⁹ There was no electrode preparation, discomfort, or pain as in electrical stimulation. Magnetostimulation of the brain was established.

The original magnetic stimulator by Barker et al. became the prototype for the commercial model manufactured by Magstim.^a A somewhat different design by Merton and Morton published in 1986³⁰ appears to have formed the basis, with some modification, for the commercial magnetic stimulator made by Digitimer.^b Both instruments use a large capacitor-discharge through a coil controlled by a thyristor switch. The Digitimer model with electrolytic capacitors yields a monophasic pulse. Similar magnetic stimulators are also made now by Cadwell^c and Dantec.^d

SAFETY OF CENTRAL MAGNETOSTIMULATION

Barker and colleagues have published a series of papers on magnetostimulation³¹⁻³³ and have considered the safety aspects.^{34,35} They calculated the induced electrical, magnetic, and thermal energy of the stimulus and found them all comparable with or much less than those associated with direct electrical stimulation of the brain during electroconvulsive therapy and induced currents from magnetic resonance imaging (MRI). They point out that

an epileptic focus cannot be triggered by repetitive stimulation (kindling) regardless of the number of stimuli as long as the stimulus frequency is less than 3 Hz. Available magnetic stimulators today have a stimulus repetition rate at maximum output of less than 1 Hz, limited by the time needed to recharge the capacitors. (An experimental machine made by Cadwell does repeat stimuli up to more than 10 Hz but this upper range has not been tested systemically on human subjects.) The peak total current induced at maximum output of Barker's stimulator (Magstim) is approximately 0.25 amps, comparable to that of Merton and Morton's electrical stimulation. The maximal charge is approximately 6.6 μ C/cc from the magnetic stimulator, which is similar to that obtained with electrical stimulation. It is approximately 0.05 to 0.005% of the charge used in electroconvulsive therapy, 100 mC to 1 C. The average power set free in the brain is less than 53 μ W. This represents less than 0.001% of the heat generated in the brain from normal basal metabolism. Barker and his colleagues reported no apparent side-effects for either electrical or magnetic brain stimulation; they have subjected themselves to thousands of stimuli over a half-dozen years without any untoward reaction.³⁵

Barker et al. calculated that for a peak magnetic field value of 1.4 T at the surface of the brain, their magnetic stimulator induces a maximum brain current at its surface of 9.1 mA \cdot cm⁻² and a maximum brain charge density of about 0.8 μ C \cdot cm⁻² per phase. Although magnetic stimulators have not been able to cause fibrillation of the heart in animals, or even an extra systole, they should not be used in the vicinity of a cardiac pacemaker or other electronic devices; the induced currents could damage the electronic circuits.³⁴ There are now more than 500 magnetic stimulators being used by neuroscientists and neurologists in various parts of the world and, other than a slight headache in some individuals now and then, no other untoward events have been noticed or reported with the possible exceptions noted below. Obviously design changes increasing the field strength or repetition rate by an order of magnitude or more may not remain completely benign.

Generally, magnetic stimulation of the brain does not seem to disrupt its subsequent function. This may be because of the extremely brief duration of the pulse. Cohen and Hallet compared electroencephalograms before and after electric and magnetic stimulation and found no changes afterwards.³⁶ The conclusions of Gordon et al.³⁷ as to the safety of electrical stimulation can be applied to magnetic stimulation. Barker estimated that patients being examined routinely with his machine would receive less than 100 cortical stimuli and probably less than 10 at high output. This corresponds to less than 1/10,000 of the total charge density/phase and less than 1/100 of the total charge used by Gordon (A. T. Barker, personal communication).

^a Magstim Ltd., Whiteland Industrial Estate, Whiteland Dyfed, Wales.
^b Digitimer Ltd., Welwyn Garden City, Herts., England. Represented in the U.S.A. by Medical Systems Corp., Greenvale, NY.
^c Cadwell Laboratories, Inc., Kennewick, WA.
^d Dantec Elektronik Medicinsk A/S, Skovlund, Denmark. Represented in the U.S.A. by Dantec Electronics, Inc., Santa Clara, CA.

Recently Hömberg and Netz³⁸ reported that contrary to all their previous experience as well as that of others, they may have induced seizures in a 57-year-old patient with a large ischemic scar caused by a middle cerebral artery infarction. This patient was 1 of 150 patients with hemispheric strokes whom they had tested of a total of more than 700 patients. They speculate that the susceptible patient may have been more vulnerable because he had a larger ischemic scar than in most of the others. This seizure occurred despite the failure to induce seizures in patients with known idiopathic temporal lobe epilepsy. The authors concluded that magnetic stimulation should be avoided on those patients with large ischemic scars.

Kandler³⁹ pointed out in a reply to Hömberg and Netz that she had done more than 800 transcranial magnetic stimulation studies on controls and on patients with neurological conditions, including 76 on stroke patients, without ever observing a seizure.

Hufnagel et al.⁴⁰ reduced the antiepileptic medication of a 26-year-old woman during presurgical evaluation. She then suffered four complex partial seizures. She also had an identical seizure after 56 magnetic pulses to the head. There was no evidence that the magnetic stimuli induced it.

Tassinari et al.⁴¹ studied 58 patients with partial or general epilepsy without observing any seizures caused by magnetic stimulation. One of these patients did have seizures before, during, and after the stimulation period but they did not appear related to the stimulation. Long-term follow-up showed that the epilepsy was not worsened by the transcranial magnetic stimulation.

There are, of course, certain routine precautions that should be taken to avoid potential injury. Ferromagnetic objects will obviously be attracted to the coil when it is energized and nonmagnetic electrical conducting objects will be repelled if very near the magnetic coil. (The repulsion of nonmagnetic metal articles is caused by the induction of eddy currents in the metal conductor by the original magnetic field, which in itself sets up a contrary magnetic field to push against the original source.) Moving coil electric meters may be demagnetized. It may be prudent to remove metal earrings before stimulating around the head. The most distressing magnetic effect to some people may be having the coded magnetic strip of their credit card or computer diskette erased. The magnetic stimulating coil should not be used in the vicinity of someone who has a cardiac pacemaker or other implanted electronic devices. As of early 1991, magnetic stimulation is approved by the Food and Drug Administration for peripheral stimulation, but not for the central nervous system. There is no such restriction for use outside the U.S.A.

MAGNETIC vs. ELECTRICAL STIMULATION

Electrical stimulation is of limited clinical acceptability because it can be painful,^{42,43} especially

when care is not exercised to minimize it. Of course, there is no problem with pain when electrical stimulation is used during surgery with general anesthesia to determine the patency of neural pathways. Magnetic stimulation, although not always pleasant, is not painful. In both methods the excitable nerve is activated by an electric current depolarizing a cell membrane. Because both magnetic and electric stimulation induce a depolarizing current in the neuron, there must be some difference in the path of the current in electric vs. magnetic stimulation that accounts for the pain. If the skin is stimulated with an electric current, the flow falls off as a function of the impedance of the intervening tissue to the target. In order to get to the targeted neural tissue the current must be increased on the skin much more than is needed at the neural tissue target itself. Therefore higher voltage has to be applied. This activates pain receptors in the intervening tissues. A magnetic field penetrates the tissue without alteration except for the magnetic effect of eddy currents. The flux density of the near field falls off roughly linearly with the distance but the current generated in the skin will be less than that from electrical stimulation. For example, to produce stimulation of the hand areas requires a threshold value of typically 60 V/cm between electrodes for electrical stimulation, whereas for a similar effect from magnetic stimulation the potential gradient along the scalp surface will be only 1 V/cm. (Personal communication, Reginald Newman.) The comparison of electric and magnetic stimulation is also discussed by Barker et al.³⁵

Geddes⁴² suggests that because the mechanism of magnetic stimulation is electrical, the procedure should be called "electrodeless stimulation." The short pulse of a capacitor discharge is of the order of 100 μ s, which can meet the chronaxie of the neural target.^{44,45}

SITE OF MAGNETOSTIMULATION

The brain itself is too complex to be used to work out some of the basic principles of magnetic stimulation of neural tissue. In addition to working with peripheral nerves,^{46,47} Maccabee et al. used the facial nerve in humans to reveal some of the principles of electric stimulation of neurons in a volume conductor through magnetic induction.⁴⁸ It had been shown that a magnetic stimulating coil could excite the facial nerve intracranially, possibly where it enters the facial canal. By comparing the effects of electrical and magnetic stimulation, an estimate could be made of the site where the magnetic stimulation occurred. The point of electrical stimulation was obviously very close to the active electrode at the posterior tragus by the pinna of the ear. The point of magnetic stimulation was found by comparing electrical and magnetic latencies. The neural conduction velocity with electrical stimulation from the tragus to the cheek was 50 to 60 m/s and it is assumed that the velocity was the same for the rest

of the facial nerve, central to the posterior tragus. An increased latency of 1 to 1.3 ms of facial muscle activation through the facial nerve using a magnetic coil over the parieto occipital scalp compared to electrical stimulation at the posterior tragus pointed to a site of activation about 6 cm central to the point of electrical stimulation at the posterior tragus. That is close to the exit of the facial nerve from the brainstem.

MAGNETIC FIELD SHAPE AND NEUROSTIMULATION

It is difficult to shape a magnetic field, especially a strong one. It can neither be focused nor sharpened by refraction, reflection, or diffraction, nor limited by absorption, as can visible or electromagnetic radiation. The only way that magnetic fields can be somewhat concentrated or sharpened is by the physical design of the magnetic coil and its poles. An iron core in a magnetic coil can help concentrate the magnetic flux field. However, in magnetic pulse stimulation, the pulse time is very short, comparable to a high frequency. With a flux density of several teslas, ferrite or similar cores become saturated and therefore cannot be used to confine the field.

The magnitude of the magnetic flux out from the center of the plane of the coil in both directions is about one-third of the maximum at a distance equal to the coil radius. The flux does not originate at a point radiating out in all directions and therefore does not follow an inverse square law. Our measurements indicate that in the limited range used of 1 to 3 cm from the plane of the coil, the fall-off is approximately linear.

GEOMETRY OF MAGNETIC STIMULATION

Induced Currents in a Volume Conductor

The effectiveness of a magnetic coil in stimulating a nerve in the body, a volume conductor, depends on the orientation of the coil relative to the target nerve. The effect of orientation of a round magnetic coil relative to a wire is shown in Fig. 5. The current distribution in a volume conductor is similar except that it spreads out laterally, not being confined by a limited wire conductor path. Maccabee et al.⁴⁶ and Maccabee et al.⁴⁹ studied the three-dimensional voltage distributions induced in a homogeneous volume conductor with ordinary round magnetic coils as well as with a figure-8 coil (sometimes termed, according to minor differences in shape, a double D, double square, or butterfly magnetic coil). The most effective position for a round magnetic coil for stimulating a nerve is tangential to it (like a wheel ready to roll along the nerve axis). To reduce the area of stimulation the figure-8 coil magnetic field clearly is more discrete and therefore generally more desirable.

Electrical stimulation of a neuron or of a nerve

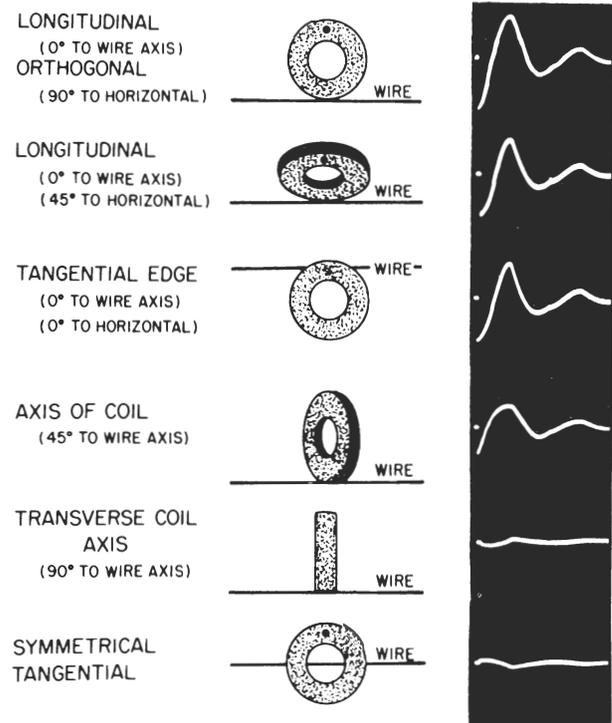


Figure 5. Voltage induced in a wire by various orientations of a round magnetic coil. In a volume conductor such as the brain the current would spread out broadly but the effects of orientation relative to a nerve would be similar. Maximum power, positive up. From reference 49 with permission of Dr. Cracco.

bundle consisting of multiple neurons depends on the angle between the flow of current and direction of the nerve. The relation was suggested in the middle of the last century by duBois Reymond. Subsequently, a number of investigators sought to demonstrate it quantitatively. Rushton⁵⁰ showed that stimulation is a function of the cosine of the angle between the direction of flow of current and the nerve axis. Thus when the flow is along the neuroaxis, the angle is 0 and the cosine is 1 and the stimulus is 100%. When the current flow is perpendicular to the nerve bundle, the angle is 90°, the cosine of the angle equals 0. The same principle would hold, of course, for magnetic stimulation because magnetic stimulation is generally considered to be effected by the induction of an electric current in the tissue as a volume conductor. A ring-shaped magnetic coil placed flat or tangentially against an arm produces rings of current, the effect depending upon the position of the coil relative to the targeted neural structures. In Fig. 6 the magnetic stimulating coil is shown in three positions with the direction of current in the coil and the induced current in the adjacent brain.⁴⁷ The current flow in the tissue is the opposite to that of the coil.

When such a coil is placed transversely (horizontally) on the vertex (top) of the head, like a crown, and is bisected by the midsagittal plane of the brain, motor stimulation from a monophasic magnetic pulse is greater on one side of the brain than on the

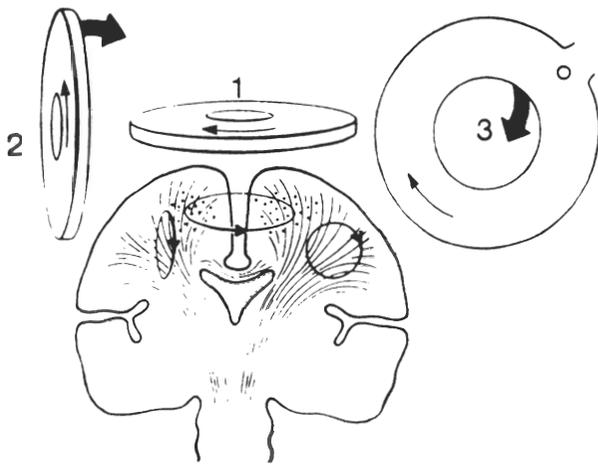


Figure 6. Representation of the electric currents in round magnetic coils and their transfer by magnetic induction to the brain. (1) The coil is placed at the top of the head (vertex), current flowing in a clockwise direction. The induced current below is shown by a ring with an arrow in a counter-clockwise direction. (2) The coil is placed sagittally with a variable tilt medially as indicated by the thick arrow. (3) The coil is in a coronal or transverse plane with a variable tilt anteriorly as indicated by the thick arrow. Note that in each case the direction of current flow induced is parallel and opposite to that in the coil. Taken from reference 47 with permission of Dr. Cracco.

other. Current flowing from anterior to posterior in that part of the brain is more effective than the reverse. The reason for this polarity is unknown. A coil surface is usually marked with a + and a - on one side to show the direction of the current, which can be reversed by flipping the coil over 180°.

As stated earlier, the electric current induced by a magnetic pulse is most effective for stimulating a nerve when the neuroaxis is in the same direction as the current flow and is not effective if the nerve is perpendicular to the direction of the current. Also, a larger diameter neuron has a lower threshold and can be stimulated more easily than a smaller one. If the two nerves are equidistant from the stimulating current source, the larger nerve will have the lower threshold.

A stimulating coil produces magnetic flux lines emanating in arcs around the coil. The current flow induced in the tissues will be parallel and opposite to the direction of flow in the magnetic coil. There will be a magnetic field projecting out from the plane of the coil in both directions, becoming smaller and weaker, attenuating to less than one-third of maximum at a distance beyond one coil radius. The greatest flux density is nearest the coil.

Basic Magnetic Units

B is called the magnetic flux density. Other names are also used, which can be confusing, such as magnetic induction, magnetic field, or magnetic strength.^{13,51} It is represented by the density of the "lines of induction," which are visualized by the patterns formed by iron filings in a magnetic field.

These lines represent magnetic flux, ϕ , which is the magnetic induction, B, times the surface area.

Given an electric charge, q_0 , at rest at point P near a permanent magnet, no force acts on q_0 . But if q_0 is moved through point P with a velocity v , a sideways force acts on it at right angles to v . This defines the magnetic flux density at point P in terms of force, F , v , and q_0 .

$$B = \frac{F}{q_0 v} \quad (1)$$

when the velocity and field B are at right angles.

If the angle between B and v is θ

$$F = q_0 v B \sin \theta \quad (2)$$

Thus, if the charge moves parallel to the field, there is no force.

A charge q of one coulomb flowing past a point on a wire in 1 s by definition equals 1 amp of electric current. The unit of B that follows from equation 2 is the Newton/(coulomb) · (meter/s), which is called a tesla or T. The unit of magnetic flux, ϕ , is the Weber or Wb. A tesla equals 1 Wb/m², which is the magnetic flux density, B.

$$B[\text{in T}] = \frac{F[\text{in Newtons}]}{q[\text{in coulombs}]V(\text{meters/s})} \quad (3)$$

but coulombs/s = amperes

$$B = \frac{F}{\text{ampere meters}} \quad (4)$$

The earth's magnetic field is about 1 G, which equals 10⁻⁴ T.

The magnetic flux, ϕ , in Wb can be measured experimentally using a small "search" coil. The changing flux through the coil induces a voltage in it. The relation between units is:

$$\text{volts} = V = \text{Wb/s} \quad B = \text{Wb/m}^2 \quad (5)$$

where m² is the area in square meters of the one turn measuring search coil.

Hence

$$V = \frac{Bm^2}{s} \quad (6)$$

If the search coil has N turns,

$$V = N \frac{Bm^2}{s} \quad (7)$$

$$\therefore B = \frac{Vs}{Nm^2} \quad (8)$$

By further manipulation of units it can be shown that B (in teslas) has units of amps/meter or B (in Gauss) has units of amp/cm. For example, the magnetic field at a distance r from an infinite, straight wire carrying a current I is

$$B[\text{tesla}] = \frac{\mu_0}{2\pi} \cdot \frac{I[\text{amp}]}{r[\text{m}]} \quad (9)$$

where μ_0 is a constant = $4\pi \times 10^{-7}$ T-m/amp.

This formula clearly illustrates that the magnetic field produced by a current is directly proportional to the current. The falloff in field is particularly simple, being inversely proportional to the distance from the wire.

In the case of a circular loop of radius b (in m), the field at the center of the loop is

$$B[\text{tesla}] = \frac{\mu_0}{2} \cdot \frac{I \text{ amp}}{b \text{ m}} \quad (10)$$

If the wire is wound into a coil with N turns or loops, each turn of the wire behaves like a separate loop. Every loop adds to the field, so

$$B = \frac{\mu_0}{2} \cdot \frac{NI}{b} \quad (11)$$

The magnetic field or flux density of the coil is directly proportional to ampere-turns (NI). If the coil is made larger (b increased) the magnetic flux is spread over a greater area and the flux density (B) decreases. Moving along the central axis directly above or below by a distance z (m), the flux density is

$$B_z = \frac{\mu_0}{2} \cdot \frac{NI}{b} \left(1 + \frac{z}{b^2}\right)^{-3/2} \quad (12)$$

This reduces to the previous formula when $z = 0$. The falloff in field is clearly more complicated than in the case of a straight wire but it can be interpreted as follows. All else being equal (ampere-turns constant), a larger coil has a slower falloff in flux density as one moves away from the coil even though the smaller coil has a greater flux density near the coil. If one moves far enough away, the flux density of a larger coil may exceed that of a small one. Thus the magnetic field of a large coil can penetrate more deeply into the brain but its field is more diffuse.

The peak value of the magnetic flux density is usually given to show the strength of a stimulator. But the effective stimulation is dependent on the pulse width in that for a given field strength shorter rise times (down to the region of $60 \mu\text{s}$) are more effective.^{44,45} The average current required by the coil to produce the field strength from a capacitor source depends on the capacity (C in farads) and the initial charge in volts.

$$I_{\text{mean}} \approx \frac{CV}{\text{pulse width in s}} \quad (13)$$

DISCRETE CENTRAL MAGNETIC STIMULATION

Amassian et al.⁵² compared focal electric with magnetic stimulation of the human cerebral cortex. Using a Cadwell MES-10 Stimulator with a peak of 2.2 T, they employed a series of different magnetic coils. With a round coil (92-mm outside di-

ameter, 46-mm inside diameter, and an edge thickness of 12 mm) they were able to elicit short latency, compound motor action potentials due to focal activation of the motor cortex by threshold stimulation. Although relatively discrete movement, such as that predominantly of a single digit, was elicited, such focal stimulation could be accomplished much more readily by another coil, a double square (or figure-8) magnetic coil.

The Cadwell stimulator using paper capacitors, unlike the Digitimer stimulator, yields an oscillatory wave which is damped in a few cycles. After a rapid rise the wave falls, becoming negative at $70 \mu\text{s}$ and positive at $200 \mu\text{s}$, undulating out to about $800 \mu\text{s}$. Damping depends on the capacitance where the charge is stored, the impedance of the magnetic coil, and resistance in the circuit. This waveform seems to give a stronger stimulation because of the short pulse durations (although the effect of the waveform is not clear) but it is more likely to be unpleasant and does not seem to elicit phosphenes as well.

Maccabee et al. were able to obtain from Cadwell an experimental magnetic coil, shaped like two contiguous squares, measuring 7 cm per side, with one side of each adjoining.^{47,49}

Such coils are also known by the names of similar shapes, as a figure-8, or a double D, or a butterfly coil. When the coil is wound as a figure-8 is written, where the two sides adjoin there is a doubling of the magnetic flux of any of the single sides of the coils. The double strength magnetic field lobe from the double side is available for relatively discrete local stimulation. Placing this coil over the precentral motor area of the brain can stimulate a limb or even a few digits in isolation. Coil shape and size are also discussed by Rösler et al.⁵³

A small coil stimulates a small area but is limited in penetration distance. Cohen and Cuffin⁵⁴ pointed out there is a limit to how small one can make a magnetic coil. The limit is reached when the coil explodes from the magnetic forces! They have made figure-8 coils as small as 1-in diameter per section and are working toward 1 cm. At a distance of $2\frac{1}{2}$ cm the stimulus area is roughly a spheroid of $\frac{3}{4}$ -cm diameter. Ultimately it may be possible to produce a localized field of up to 17 T, although the necessary penetration to reach and stimulate the brain would be lacking.

EVIDENCE OF COROLLARY DISCHARGE

Amassian et al.⁵⁵ applied a pressure cuff to the upper arm producing an ischemic block of the motor and sensory neurons innervating the hand. After 0.5 h of ischemia, all distal movements, both voluntary and from magnetic coil stimulation at the motor cortex, were abolished. However, magnetic stimulation still gave a clear sense of movement, isolated even to one digit. This sensation was made greater by increasing the magnetic stimulus, and was projected elsewhere when the magnetic coil was

repositioned. The limb was isolated from its motor and sensory communication with the brain by the ischemic pressure from the cuff. It was concluded that the magnetic pulse elicited what is normally a corollary discharge. This is the neural basis of a sense of movement that normally originates from the neural source of the motor stimulation in the brain, independent of the peripheral neuromuscular mechanisms.

SENSORY vs. MOTOR STIMULATION THRESHOLDS

Magnetic stimulation of the motor cortex appears to elicit a motor response much more readily than stimulation of the sensory cortex does a sensory response.⁵⁶ This was demonstrated by using a smaller, experimental figure-8 coil over the post-central sensory cortex, each section of the coil having a dimension 5 by 4.8 cm and joined at one side. It was possible to obtain paraesthesias in only one of eight subjects tested compared with all subjects responding to motor cortex stimulation.

TRANSCALLOSAL STIMULATION

Merton and Morton, stimulating the cortex electrically with a 10- μ s pulse, evoked a contralateral, short-latency hand movement.^{25,26} They also obtained retinal and cortical electrophosphenes. Amassian and Cracco⁵⁷ and Cracco et al.⁵⁸ investigated simian and human transcallosal responses evoked by both magnetic coil and electrical stimulation. The 9.2-cm diameter (outside diameter) magnetic coil was placed in the lateral sagittal plane over the right hemisphere. The edge contacted the scalp midway between F₄ and C₄. (These letters and numbers refer to the international 10-20 system of electroencephalography electrode placement.) Progressively tilting the coil toward the horizontal, a position was found which gave a response, and then the coil was rotated carefully to provide minimal stimulation artifacts. That and surrounding sites were explored until an optimum electrical response was recorded by 7-mm diameter disk electrodes on the opposite scalp between S₃ and C₃. MRI has shown that location of the calcarine fissure relative to the inion may vary by 4 cm.⁵⁹ The indifferent or the reference electrode was placed laterally at least 6 cm away and a grounded stainless steel strip was placed between the active or focal recording electrode and the magnetic coil to reduce stimulus artifacts. The response was summated up to 10 times. In order to minimize further the major problem of shock artifact caused by the passage of large currents between the stimulating electrodes, a variable resistor, usually 10 Kohm, was adjusted at the reference electrode. The recording bandwidth was 0.8 Hz to 1 or 2 KHz.

The magnetic coil was pulsed while the edge of the coil was contacting the scalp midway between F₄ and C₄. The transcallosal response gave a posi-

tive wave. Sometimes it was followed by a broad, low amplitude negative wave. The positive wave had an onset latency of 8.8 to 12.2 ms. It was defined sharply with a brief duration of 7 to 15 ms and up to a 20- μ V amplitude. A small displacement of the coil, of say 1 cm from the optimal site of stimulation, reduced the transcallosal response. This is evidence that the stimulation was that of a localized projection locally stimulated. The transcallosal response to magnetic and electrical stimulation was similar in latency, although the duration of the positive wave was briefer with magnetic stimulation. Cracco et al., in basic agreement with others, found a difference in latency of 7.8 to 8.0 ms with their stimulation, the minimal delay expected over the callosal conduction pathway.⁵⁸ They reckoned its length at about 126 mm. This yields a conduction velocity of 16 m/s; this rather slow velocity is what would be expected for the small diameter nerve fibers in the precentral corpus callosum. Cracco et al. pointed out that the magnetic coil is the desirable way to test the patency of the corpus callosal pathway. There is no electrode preparation nor pain.

PERCEPTUAL SUPPRESSION AT THE VISUAL CORTEX

Amassian et al. found and studied the suppression of visual perception by magnetic coil stimulation.⁶⁰ They used a round 9.2-cm diameter magnetic coil placed symmetrically at the back of the head but with the lower part of the coil 2 cm above the inion. To give the effect, 2 to 2.2 T were required, which was several-fold greater than that required for the stimulation of the lateral motor cortex. Phosphenes were not observed. Three letters of the alphabet chosen randomly were displayed tachistoscopically at a distance of 35 to 75 cm, subtending a visual angle of 0.4 to 0.8°. The correct response was obliterated when the magnetic pulse was generated between 80 and 100 ms after the visual stimulus presentation (Fig. 7). The percentage of letters correctly read was reduced when the pulse was triggered between 50 and 150 ms. They also demonstrated a lateral effect by shifting the coil to one side, which shifted the effect toward the opposite visual field. Further experiments by Maccabee et al.⁶¹ demonstrated backward masking and a delay of the effect with equiluminous colored targets.

RETINAL AND CORTICAL MAGNETOPHOSPHENE THRESHOLDS

Budinger et al.⁶² designed and constructed a device for magnetic stimulation capable of a peak dB/dt value of 8 T/s, which reached a peak B or magnetic field of 39 mT at a repetition rate of 15/s. A low output impedance power amplifier driven by a waveform generator provided the power to a water-cooled coil, approximately 37 by 30 cm, consisting of 52 turns of copper tubing. The threshold

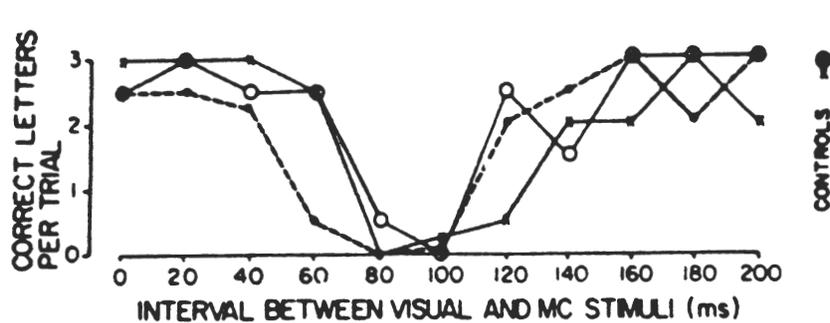


Figure 7. Number of correct letters in reading three briefly presented random letters in relation to the time of magnetic stimulation at the occiput. The letters subtended an angle of 0.4 to 0.8° at 35 to 75 cm or about 6/30 to 6/60 Snellen. All three subjects cannot read them between 80 and 100 ms. From reference 60 with permission of Dr. Cracco.

for dB/dt in older subjects was 1.9 T/s and in younger subjects, 1.3 T/s, both with a rise time of 2 ms. The magnetic field must change fast enough to induce a strong enough electric field for a phosphene. The authors propose an alternative stimulation mechanism to the generally accepted one of the induction of electric current. They speculate that retinal membrane depolarization results from mechanical forces associated with a torque on the retinal rods inasmuch as they have a known magnetic susceptibility and an anisotropy.

Retinal and cortical magnetophosphene thresholds were identified and compared by Marg and Newman in themselves.⁶³ Until the current era of capacitor discharge stimulators, magnetophosphenes have been elicited only from the eye and not from the cortex. The reason that attempts at cortical stimulation were not effective in the past became clear when they found that the eye has a five times lower threshold than the occipital cortex to magnetic stimulation.

Using a Digitimer D-190 Magnetic Stimulator, the small 7-cm diameter coil was at 20% power at the eye and 100% at the occiput for the thresholds. At maximum power the stimulator produces 5 kT/s and at 20%, 1 kT/s. The corresponding peak fields are 1.2 and 0.24 T, respectively. This finding demonstrates that the retina is much more sensitive to magnetic stimulation than the cortex, a conclusion reached earlier by Merton and Morton for electrical stimulation.²⁶

The retinal phosphenes appear in the extreme peripheral visual field. They may take the form of a crescent or an annulus. They usually appear diffuse, like distant lightning. The cortical phosphenes are generally in the midperipheral field and are more corporal. Stronger stimuli with a figure-8 coil can produce cortical phosphenes in the central field.

CONCLUSIONS

Magnetic pulse stimulation provides new data on the function of motor and sensory systems of the brain, noninvasively and painlessly. Retinal and cortical phosphenes are separately elicited. Current developments in the field promise to increase its utility. Use of magnetic stimulation in a functional visual prosthesis is ruled out because magnetic

fields cannot be "focused" to less than 1-mm diameter at the 1 cm or more distance between the scalp and the visual cortex. There seems little likelihood of producing such a finely focal magnetic field except perhaps through fundamental advances in the understanding of the physics of magnetism. However, in its current state of development, magnetic stimulation can be used to test the peripheral retina and visual cortex. Combined with appropriate visual stimuli, it may be possible to devise tests for specific functional aspects of the visual brain—examples are visual areas 4 and 5 (V4, V5), the inferotemporal cortex, superior colliculi, lateral geniculate nuclei, and other visual function centers.

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