

Interactive Protocol

Mapping of the human visual cortex using image-guided transcranial magnetic stimulation

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Abstract

We describe a protocol using transcranial magnetic stimulation (TMS) to systematically map the visual sensations induced by focal and non-invasive stimulation of the human occipital cortex. TMS is applied with a figure of eight coil to 28 positions arranged in a 2×2-cm grid over the occipital area. A digitizing tablet connected to a PC computer running customized software, and audio and video recording are used for detailed and accurate data collection and analysis of evoked phosphenes. A frameless image-guided neuronavigational device is used to describe the position of the actual sites of the stimulation coils relative to the cortical surface. Our results show that TMS is able to elicit phosphenes in almost all sighted subjects and in a proportion of blind subjects. Evoked phosphenes are topographically organized. Despite minor inter-individual variations, the mapping results are reproducible and show good congruence among different subjects. This procedure has potential to improve our understanding of physiologic organization and plastic changes in the human visual system and to establish the degree of remaining functional visual cortex in blind subjects. Such a non-invasive method is critical for selection of suitable subjects for a cortical visual prosthesis.

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Theme: Sensory systems

Topic: Visual cortex: striate

Keywords: Transcranial magnetic stimulation; Mapping; Occipital cortex; Phosphenes; Blind

1. Type of research

- (i) Magnetic stimulation studies of cognitive functions [7,12,31,41].
- (ii) Cortical excitability [5,6,10,19,32].
- (iii) Mapping of the human visual cortex [11,18,20,24,26,36,40].
- (iv) Implementing visual maps in behavioral studies [1,2,4–6,11,15,23,27].

2. Time required

- (i) MRI of the whole brain: 15 min.
- (ii) Processing of the MRI images: 10 min.
- (iii) Preparation of subject and determination of scalp stimulation sites: 10 min.
- (iv) Visual cortex mapping: 30 min.

2.1. Total protocol

The required amount of time is usually 60–70 min.

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3. Materials

- (i) Elastic caps.
- (ii) Personal computer (486/33 MHz or faster) running Microsoft Windows 95 (Microsoft) or any higher version.
- (iii) Digitizing tablet.
- (iv) Magnetic stimulator (Cadwell MES-10 or High Speed Magnetic Stimulator, Cadwell Labs, Kennewick, WA, USA; Dantec Magpro or Maglite Stimulator, Medtronic, Minneapolis, MN, USA; or Magstim 200 or Rapid Magnetic Stimulator, Magstim, Withland, UK) providing a maximum stimulus strength of ~2 T, connected with a figure-of-eight coil of ~70 mm (Magstim, UK) or 75 mm (Cadwell Labs, Kennewick, WA, USA) in outer diameter.
- (v) Magnetic resonance scanner (Siemens, GE Phillips, etc.).
- (vi) A frameless image-guided neuronavigational device (Brainsight-Frameless 1.4β, Rogue Research, Montreal, Canada or any other frameless stereotaxy system).

4. Detailed procedure

(i) Anatomical MR images are obtained using a Siemens Vision Symphony/Quantum 1.5 T scanner. Subjects are resting in a supine position within the bore of the magnet. A bite-bar might be used to minimize head movements. The structural scan consists of a 3-dimensional magnetization prepared rapid gradient echo (3-D MPRAGE) T1-weighted MRI scan (TR, 11.08 ms; TE, 4.3 ms; flip angle 8°). The images are acquired in the sagittal plane (1-mm slice thickness). The location of point CZ in the EEG International 10–20 system is marked with a vitamin E capsule at the time of the MRI scan. This point is later used as a landmark with the interactive frameless stereotactic system (Brainsight, Rogue Industries, Canada) to guide precise location of the TMS coil to stimulate a specific ROI. Once the MRI is registered, the MRI file needs to be translated to (*.hdr, and *.img) format to be compatible with the Brainsight system. This procedure can be done using MRIcro software package, which allows analysis of native files from MRI scanners and transforms them to universal format files. Once images are translated to *.hdr and *.img format, the anatomical files can be reconstructed off-line into 3-D using the Brainsight program, stored on CD, and brought to the laboratory where the TMS stimulation will take place.

(ii) We complete a physical and neurological examination to assess any motor or somatosensory deficits and rule out cognitive impairments. Exclusion criteria include a history of neurological, psychiatric or medical disease, as well as a family history of seizures, pregnancy, metal implants in the head (except dental fillings), increased intracranial pressure, defibrillators, heart disease, pacer-

makers and perfusion pumps. All the accepted recommendations for the use and safety of TMS [21,33,42] are followed.

(iii) Subjects adapt to darkness for 10 min in order to enhance the excitability of their visual cortex [6]. The subjects sit on an armchair wearing a blindfold, which prevents any light perception.

A wax pencil or undeletable pen is used for marking positions on the elastic lycra swimming cap. A total of 28 occipital scalp positions, arranged in a 2×2-cm grid centered at theinion are drawn. Each sampled position has a single number, which allows its identification without ambiguity. In previous experiments we used smaller spacing widths (1 and 1.5 cm) to study the optimal distance within scalp positions, considering the spatial resolution of the coil. Although this procedure provides greater spatial sensitivity, the total number of stimuli needed in order to produce a full map made experiments too long (more than 2 h) increasing tiredness in the subjects. Therefore, given the territory that needs to be covered, and the spatial resolution of the coil, 2-cm spacing seems appropriate to produce a reliable map in a reasonable period of time.

(iv) The subject's MRI is brought up on a computer monitor, and the Brainsight program is used to guide the precise location of the TMS coil relative to the head and brain surfaces. The position of the TMS coil and the subject's head are co-registered from small pieces of refractory material (trackers) placed on them. Trackers are monitored, or 'seen' by an infrared optical position sensor. This information is sent to a computer which, after a calibration procedure, displays the position and orientation of the coil relative to the subject's MRI (Fig. 1). This procedure allows analysis of the visual induced perceptions related to the cortical site stimulated, which is not reliable with external landmarks given the individual variability of this region of the head.

(v) The strategy for mapping the occipital area susceptible to induce visual perceptions evoked by TMS is to use a standard stimulus magnitude, either related to the stimulator (any % of maximal output) or to the individual threshold for phosphenes (any % of phosphene threshold), and move the figure-of-eight focal coil over the 28 previously marked occipital positions.

The order of coil positions is randomized for each subject, and each position is stimulated a total of four times. Subjects have to concentrate on holding their gaze straight aimed at the tip of their imagined stretched out arm. Immediately after each TMS stimulus, subjects are asked if they perceived anything and specifically if they had visual perceptions. If the response is affirmative subjects are asked to describe their sensations with respect to the shape, color, brightness (from 1 to 10) and possible motion of the evoked perceptions. In addition they are requested to make drawings of the perceptions, with particular emphasis on their localization within the visual

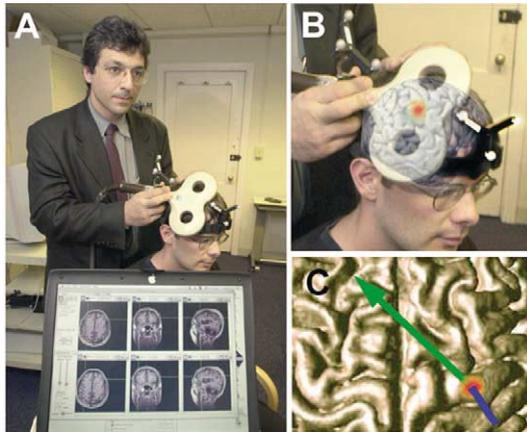


Fig. 1. Brainsight-Frameless interface to aid in the positioning of the transcranial magnetic stimulator coil over a subject's brain. This technique enables use of anatomical information as an interactive navigational guide for stimulator coil position and allows recording of the position and orientation of the coil at the instant of stimulation for later correlation with the response data. (A) An example of the live display. (B) Location of the cortical surface intersected by the peak TMS induced electric field (shown as the red extension below the TMS coil) and the small pieces of refractory materials (trackers) placed on the stimulating coil. These trackers are monitored, or 'seen' by an infrared optical position sensor in order to establish the orientation of the TMS coil for each scalp placement. (C) Detail of the 3D reconstructed cortical surface and the peak TMS induced electric field. The green arrow shows the degree of twist angle for scalp placement of the TMS coil.

field. To facilitate the recording of data, subjects are provided with a digitizing tablet connected to a PC computer. After each TMS pulse they make drawings of phosphenes on the digitizing tablet, referenced to a small pin placed in the center of the tablet for tactile reference and orientation of the visual field. A customized program allows easy collection and analysis of collected data (Fig. 2). All the experiments are recorded on video and verbal responses are matched with the respective drawing for eventual detailed analysis. Baseline trials (to control for side-effects due to the coil click or somatosensory scalp stimulation) are randomly intermingled with test conditions by using a sham coil.

(vi) In some subjects, especially those with visual impairments, single pulses are not able to elicit visual perceptions. In these cases the whole mapping of the occipital cortex is repeated using trains of four consecutive TMS pulses at 15 Hz delivered to a single scalp site, instead of single pulses.

(vii) In some experiments, stimulus-response curves for number and intensity of visual perceptions are obtained at 40–80% of the maximum stimulator output (10% steps, three stimulations over each point). Such a procedure provides more quantitative information about the cortical excitability and the input–output relation between TMS intensity and the perception of phosphenes. This can be useful in the serial study of a given subject in time (for example in response to visual deprivation) or in the

comparison of subject populations (for example blind versus sighted subjects or patients with migraine versus controls).

5. Results

The protocol was applied on a group of 19 sighted (15 were right handed and four left handed and all had normal or corrected to normal vision) and 13 legally blind volunteers (Table 1). All gave their written informed consent prior to entering the study, which had been approved by the institutional review board. All subjects tolerated the procedure without complications. Specifically no seizure activity was induced by TMS.

Almost all (18 out of 19) sighted subjects perceived phosphenes using single TMS pulses and the intensity of 80% of maximal stimulator output, although not in all sampled scalp projections (average 14.2 ± 12.8), hence the relevance of a systematic sampling. The most frequently induced phosphenes were spots of light in shades of gray, which were extremely brief and never occurred after the stimulation. The induction of the subjective sensation of 'darkness' or 'scotoma' was comparatively less frequent.

It was more difficult to elicit visual perceptions on blind subjects. Only two of the 13 blind subjects (15%) reported phosphenes by using single TMS pulses. However, phosphenes could be induced in 54% of blind subjects by using short trains of four consecutive 15-Hz TMS pulses (particularly those severely visually impaired but with some residual vision and late blind subjects). The proportion of scalp positions able to induce phosphenes was also significantly reduced in blind subjects (on average 9.5 ± 4.5 sites using rTMS). Table 2 shows a summary of the characteristics of phosphenes induced by TMS in sighted and blind subjects.

Our procedure allows to easy calculation of the area of each phosphene from the coordinates of the drawings. We estimate that the perceived visual field from the most central (0°) to the most peripheral region has an average of 80° and thus for phosphene area quantification we divided the visual space into $160 \times 160^\circ$. The size of the perceived phosphenes ranged from a 'pinpoint' to almost the whole visual field (mean 30.0° , S.D. = 19.2) and was different for each subject ($P < 0.01$). Thus some subjects consistently reported small spots of light whereas other usually perceived large areas. Phosphene size was not correlated with phosphene intensity nor with other characteristics (number of phosphenes evoked in each stimulus, color of the phosphenes, etc.) of the perceived phosphenes.

Image-guided TMS allows localization of the real site of stimulation in occipital cortex saving the variation induced by anatomical variability. Phosphenes induced at any cortical surface loci could be related to characteristic positions in the visual field, depending mainly on the cortical location being stimulated (Fig. 3 shows a sample

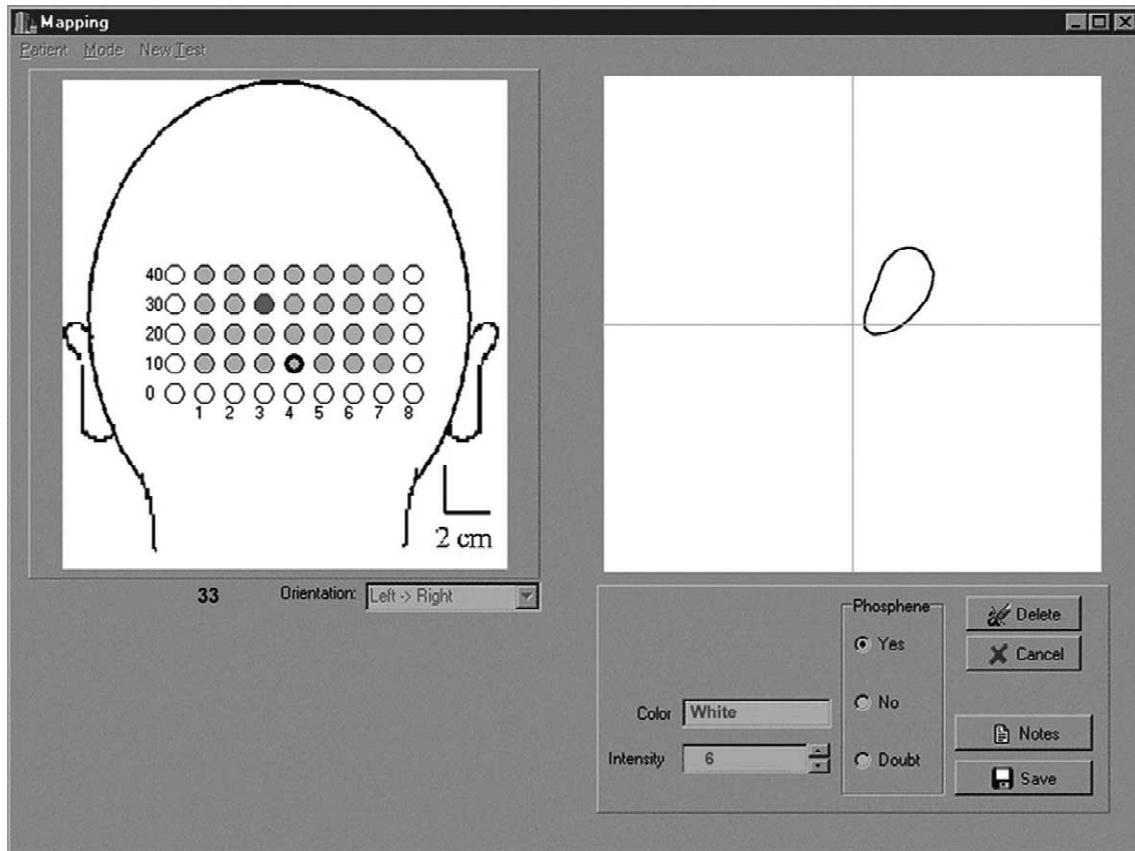


Fig. 2. Interface of the customized program developed to facilitate the recording of phosphene data. The software is written in Microsoft C++ Builder and provides a quick, easy and interactive way to record and access all the data.

for sighted subject #14). We also found a preferential location of different types of phosphenes as a function of the occipital position stimulated. Thus scotomas and complex shaped phosphenes (triangles, squares, etc.) were preferentially elicited at both sides of the midsagittal line, while kinetic phosphenes as well as multiple phosphenes were more easily induced when the coil was at peripheral locations (Fig. 4). Despite differences in frequency of phosphenes by location, there were no statistically signifi-

Table 1
Features of blind subjects

Cause of blindness	Age	Residual vision
Retinopathy of prematurity	14	–
Retinopathy of prematurity	15	–
Optic nerve atrophy	49	+
Childhood trauma	70	–
Cone cell dystrophy	68	+
Retinosis pigmentosa and cataract	70	+
Retinosis pigmentosa and cataract	30	+
Retinosis pigmentosa	50	+
Uveitis and cataract	59	–
Optic nerve atrophy	36	–
Optic nerve atrophy	68	+
Optic nerve atrophy	37	–
Citomegalovirus (CMV) retinitis	36	–

cant differences in phosphene intensity among the different scalp positions tested.

To further validate our procedure and to evaluate the intra-individual reproducibility of our results, four sighted volunteers participated in two sessions on different days, each consisting of identical TMS protocols. The results showed that stimulation of the same scalp positions in the same subjects, usually resulted in the same sensation each time, even when the experiments were performed several months later. Similarly, we found only minor changes in the shape and color of the phosphenes when the coil was moved to other scalp sites and back again to the same

Table 2
Percentage of different types of phosphenes elicited by TMS stimulation of occipital cortex in sighted and blind subjects

Description	Sighted subjects		Blind subjects	
	TMS	rTMS	TMS	rTMS
Static and non-colored phosphenes, %	71.2		60.8	33.3
Scotomas (visual suppression %)	10.4		0	1.4
Complex phosphenes, %	18.4		39.1	65.3

Complex phosphenes were (in proportion) more frequently elicited in blind subjects and included complex shaped phosphenes (triangles, squares, etc.) as well as chromatic and kinetic phosphenes. TMS, single TMS pulses; rTMS, trains of four consecutive 15-Hz TMS pulses.

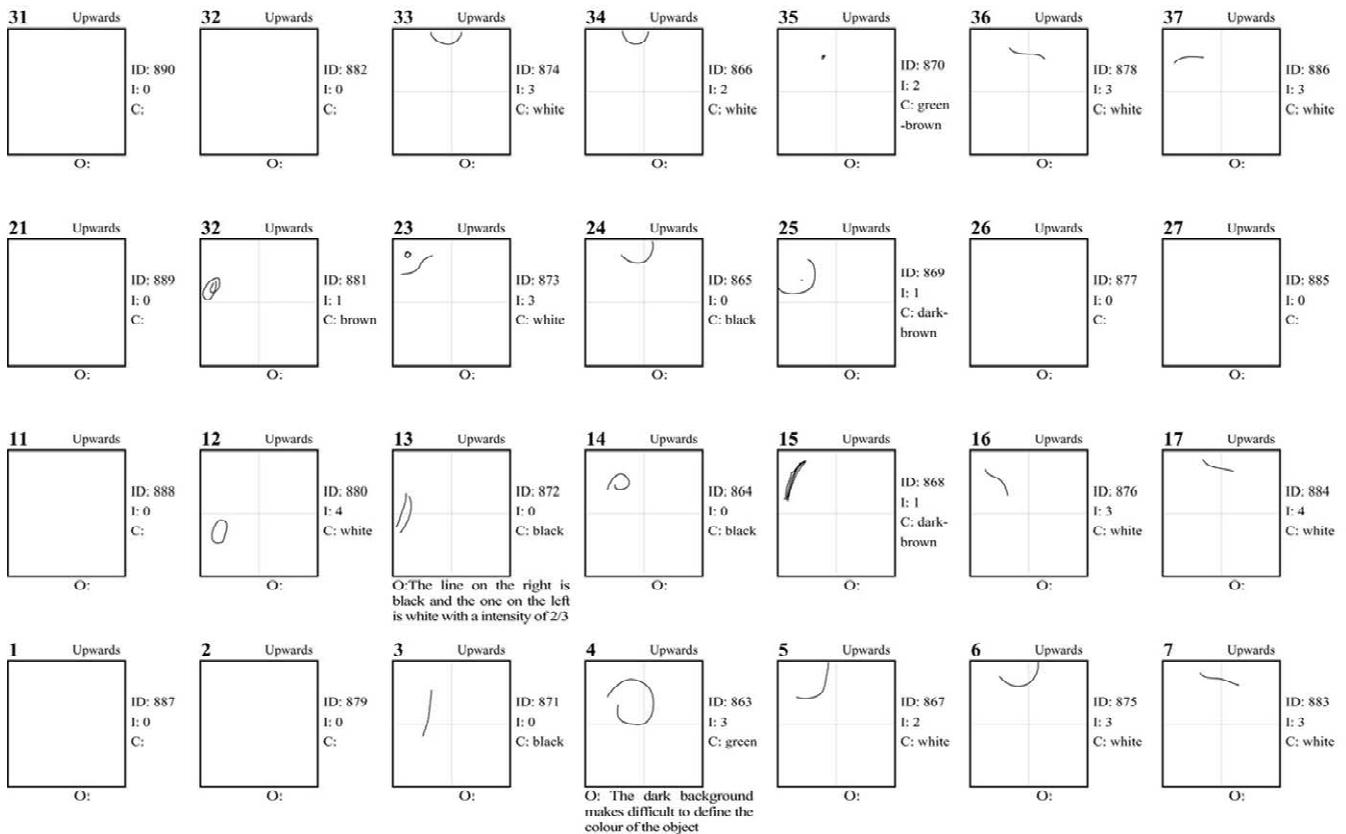


Fig. 3. Sample printout of the location and characteristics of the phosphenes within the visual field for subject #14. The whole visual field is plotted at the corresponding TMS coil location on the scalp. Although our customized program includes its own graphics, it also has the option of exporting the data in ASCII format for use by any other statistical or graphical package.

position. In order to achieve this reliability, the precise tracking of the location and orientation of the TMS coil relative to the cortical area are very important, since even small errors in its placement and/or orientation might lead to big differences in the neurons excited by the TMS pulses.

6. Discussion

TMS is a non-invasive technique for topographic mapping of the human cerebral cortex and represents a valuable tool for the localization of brain functions [20]. When TMS is applied to the occipital cortex, localized visual sensations are frequently evoked [2,40], but there is limited agreement about the characteristics of these perceptions. Thus, whereas some authors found that TMS can evoke localized phosphenes [23,26,28,37], other studies reported that the effects are mostly suppressive [1,4,17,22,25,27]. To date, a method to reliably induce phosphenes is not available and no sampling standards have been yet described for topographic mapping of the human visual cortex by TMS. It seems probable that both kinds of perceptions (phosphenes and scotomata) are evoked by similar mechanisms [23] and differences re-

spond to the different conditions in which such perceptions are evoked. When TMS is applied during a visual task performance, the induction of a deficit in the visual field (scotoma) appears most common. However, when subjects are habituated to darkness and are at rest, they usually report 'phosphenes' in the way we have described, and only occasionally do they report 'scotoma-like' sensations as 'darker than dark'. Whether both of these phenomena respond to the same TMS effects or not remains unclear. Nevertheless, it seems certain that it is essential to conduct such TMS experiments in constant conditions of luminance and behavioral demands to the subjects.

Phosphenes are subjective perceptions, and their descriptions are highly variable. This makes it necessary to build a protocol to analyze together the location of the stimulation, the region of the visual field activated and the evoked perception. We have attempted to introduce such a systematic protocol. We have to take into account that the relative position of skull landmarks and brain in the posterior regions of the head is quite variable and that there is considerable asymmetry between the right and left occipital poles. For instance, in one study of 16 subjects, the distance between the inion and the posterior tip of the calcarine fissure measured by MRI, differed by as much as 4 cm [39]. Furthermore as the focus of neurostimulation is

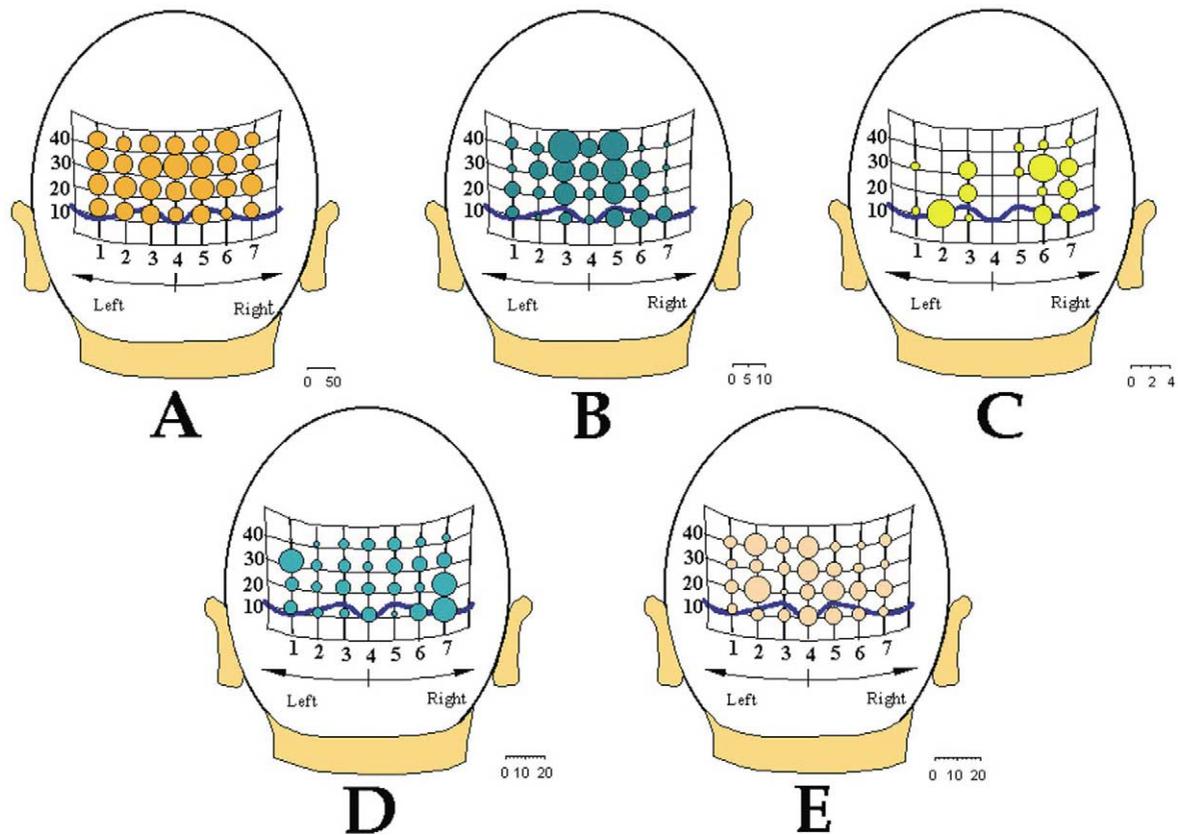


Fig. 4. Bubble map of responses to TMS at different sites over the occipital cortex in sighted subjects. (A) Elementary phosphenes; (B) scotomas; (C) kinetic phosphenes; (D) multiple phosphenes; (E) colored phosphenes. Bubble size indicates number of phosphenes (see attached scales).

remote from the coil, small errors in the placement of the coil or even in its orientation might lead to significant differences in the neurons excited and thereby contribute to the variability of the phosphene perceptions elicited by TMS. Thus precise tracking of the location and orientation of the TMS coil relative to the cortical area is needed in order to perform reproducible stimulation of the same occipital areas. In this sense, it has been recently shown in the motor area [19], that guided stimulation resulted in significantly improved spatial precision for exciting the corticospinal projection compared to blind stimulation.

Our approach allows the precise demonstration of the topographical organization of evoked phosphenes, and provides a method for their quantification. Our results show that it is possible to deliver TMS pulses at a number of scalp sites and correlate the characteristics of the phosphenes to the site stimulated. This extends the possibility of TMS in brain mapping, localizing functionally specific areas of non-motor cortex. With the proposed methodology, TMS can be used in the study of the visual cortex in analogous ways as it has been employed in the study of the motor cortex, enhancing the potential for non-invasive study of the visual processes.

TMS is able to reliably evoke phosphenes in almost all sighted subjects and in a proportion of blind subjects. The difficulties and limitations encountered in generating phos-

phenes in other studies [1,26,28] could be due, at least in part, to the different protocols, coils, and current intensities used, but also to the use of a non-systematic search. Thus at least several positions in each occipital hemisphere should be sampled. Although in the first experiments a distances between points of 1 and 1.5 cm were studied, we found that given the territory that needs to be covered, 2-cm spacing between scalp positions allows mapping in a reasonable period of time, especially when different coil orientations have to be tested. To facilitate the identification of each sampled position, each location has a single number assigned to it that allows its identification without ambiguity. This nomenclature is useful since experiments had to be performed by at least two researchers, one performing the stimulation and another recording the data.

Finally our results are very similar to those obtained using direct stimulation of the exposed visual cortex in humans at the time of neurosurgical operations [3,8,9,14–16,34,35,38] and show that TMS may be used for the non-invasive study of excitability changes in the visual system [11]. Some blind subjects, particularly those severely visually impaired but not totally blind and late blind never fully adapt well to the loss of sight. In such circumstances, visual neuroprosthetic devices in which microelectrodes are implanted into the occipital cortex to generate visual percepts might be a therapeutic option

[13,29,30,38]. If this is to be the case, we suggest that the protocol described might be used to map the function of the remaining visual cortex in blind subjects devoted to vision and hence, aid in the determination of their suitability for the implantation of visual neuroprosthetic devices.

6.1. Trouble-shooting

The procedure described is safe, painless and sufficiently rapid to be tolerated by the majority of patients. Specifically no seizure activity was induced by TMS. In some preliminary experiments we stimulated occipital areas located 2 cm below the inion, but it was difficult to elicit phosphenes from these positions and often subjects reported unpleasant sensations (slight muscle twitches, eyeblinks, and neck twitches), probably due to stimulation of facial nerves and paraspinal cervical muscles. To overcome these undesired effects, all subsequent experiments were conducted starting with the grid of scalp positions at the level of the inion.

Some of the earlier studies using TMS of human visual cortex were performed with round stimulation coils, which produce large and diffuse magnetic fields and coil placement was performed using only cranial landmarks, which does not take into account individual differences in cortical morphology. Thus, the location of the actual site of the

stimulating coil relative to the cortical surface could not be fully described. The image-guided TMS using any frameless neuronavigational system, which allows one to co-register scalp coordinates with MRI using an external tracking device is very useful in positioning the coil over the subject's brain. An alternative approach, when these neuronavigational systems are not available, is to use external landmarks on the elastic cap and MRI data to overlap the position of the TMS stimulator over the subject's brain. We have used an MRI of the subject's brain acquired with at least three external marks (vitamin E capsules) over known locations at the stimulating grid. Then the location of these marks, defined by X , Y , and Z coordinates are transformed to the subject's brain coordinates using customized software (HVBrain) which is freely available from the authors upon request. This procedure determines where the target regions are located in a given subject. In this manner the investigators can view the coil positions relative to the subject's MR image (Fig. 5).

As an alternative method to assess phosphene location in sighted people, we propose a clock-face system, with the subject's perceived visual space divided into 12 angular divisions. Each fraction of the circle is then divided into three segments to produce an inner, outer and middle portion, representing displacement between the fovea and the extreme visual periphery. This method requires a

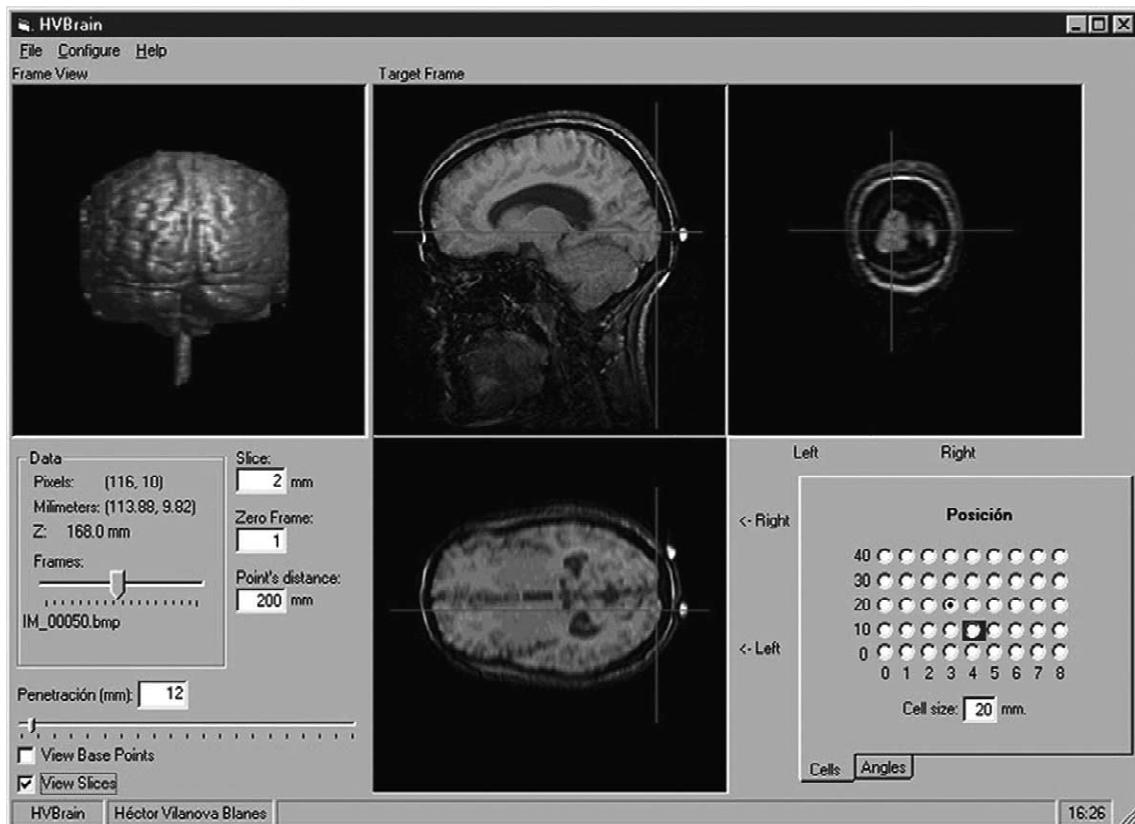


Fig. 5. HVBrain interface developed to identify the position of the TMS stimulator over the subject's MRI data set at several customized locations of the stimulating grid.

training session where the subject, looking at a computer screen, learns to identify the projection of a light spot over the clock-face frame. In the first trial the subject is provided with a full frame, with the 12 divisions labeled from 1 to 12, as on a regular clock. Then a light spot appears randomly in any of the 36 possible locations, and the subject must to identify the number (hour) and the position (inner, middle, outer). The procedure is repeated until the spot has appeared three times in each position. The second step consists of identifying the location of the spot over an unlabeled frame, giving the subject feedback about whether their response was or was not correct. Subjects repeat trials until they are able to identify 15 consecutive trials without mistake. The third step consists of showing the spot to the subjects without any frame of reference, asking the subject to guess the location of the spot over the frame that was shown in the previous task, giving the subject feedback with the full frame and the result (correct–incorrect) of their response. Training ends when subjects are able to identify correctly 15 consecutive trials. Once the training is finished, the subject is asked to identify the location of the induced phosphenes regarding the imaginary frame of the clock. This method increases the spatial resolution and the discrete characteristics of subject's responses, providing a faster method to assess reliability in the location of induced phosphenes. In addition, this method eliminates the need for written responses by the subjects that might be affected by visuo-motor transformation problems in certain experimental conditions. This procedure can be also used in blind subjects with the help of a circular dart board divided into the radial segments of a clock face, with three concentric annular zones. The subject would concentrate on holding his eye position as if he were looking straight ahead prior to and during the generation of each phosphene. Then he would place a dart in the board via tactile localization. Another simple procedure that has been recently used [18] is to use two semicircular screens. Subjects with normal or residual visual function indicated with a laser pointer the point on the screen where they had perceived the phosphenes. Subject without residual visual function pointed with their arm in the direction of the perceived phosphenes.

7. Quick procedures

(i) Anatomical MR images are obtained using a Siemens Vision Symphony/Quantum 1.5 T scanner and processed using Brainsight-Frameless 1.4 β .

(ii) Physical and neurological examination to assess motor, somatosensory deficits and the presence of cognitive impairments.

(iii) The subject sits comfortably on an armchair wearing a blindfold and an elastic cap. A total 28 occipital scalp

positions, arranged in a 2 \times 2-cm grid centered at theinion are drawn.

(iv) The subject's MRI is brought up on a computer monitor, and the Brainsight program is used to guide to precise location of the ROI to be stimulated with the TMS coil.

(v) The strategy for mapping the occipital area susceptible to induce visual perceptions evoked by TMS is to use a standard stimulus magnitude (usually 80% of maximal output) and move the figure-of-eight focal coil systematically over the 28 previously marked occipital positions. The order of coil positions is randomized for each subject and each position is stimulated a total of four times. A frameless neuronavigational system (Rogue Research, Canada) is used for the exact location of the actual site of the stimulating coil relative to the cortical surface. After each TMS stimulus, subjects are asked if they perceived anything and specifically if they have visual perceptions. If the response is affirmative subjects are asked to describe their sensations with respect to the shape, color, brightness (from 1 to 10) and possible motion of the evoked perceptions. In addition they are requested to make drawings of the perceptions, with particular emphasis on their localization within the visual field. All experiments are recorded on video.

(vi) In some subjects, especially those with visual impairments, single pulses are not able to elicit visual perceptions. In these cases the whole mapping of the occipital cortex is repeated using trains of four TMS pulses at 10–20 Hz.

(vii) In some experiments, stimulus-response curves for number and intensity of visual perceptions are obtained at 40–80% of the maximum stimulator output (10% steps, three stimulations over each point).

8. Essential references

Original papers: Refs. [2,6,11,18,23,24,36,41].

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