

# The Role of Area 17 in Visual Imagery: Convergent Evidence from PET and rTMS

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Visual imagery is used in a wide range of mental activities, ranging from memory to reasoning, and also plays a role in perception proper. The contribution of early visual cortex, specifically Area 17, to visual mental imagery was examined by the use of two convergent techniques. In one, subjects closed their eyes during positron emission tomography (PET) while they visualized and compared properties (for example, relative length) of sets of stripes. The results showed that when people perform this task, Area 17 is activated. In the other, repetitive transcranial magnetic stimulation (rTMS) was applied to medial occipital cortex before presentation of the same task. Performance was impaired after rTMS compared with a sham control condition; similar results were obtained when the subjects performed the task by actually looking at the stimuli. In sum, the PET results showed that when patterns of stripes are visualized, Area 17 is activated, and the rTMS results showed that such activation underlies information processing.

Many people report that they visualize when they recall information about the shape, color, or texture of an object that was encoded only incidentally, when they reason about space, understand descriptions of scenes, and so on. Although these reports are not in dispute, what they signal about mental processes has been a thorny problem for centuries (1). One issue focuses on whether the experience of visualization is a hallmark of an internal representation that depicts shapes. Such a “depictive” representation is extended in space and represents each part of an object so that the distances among the parts in the representation correspond to the distances among the corresponding parts of the object. The activation of topographically organized areas of visual cortex during visual mental imagery has been taken as evidence that such representations are present (2). However, it is possible that such activation is a nonfunctional byproduct of activation in other areas and itself plays no actual role in representing information during imagery. Here we demonstrate that the activation in topographically organized cortex engendered by an imagery

task underlies processing used to carry out that task.

Numerous neuroimaging experiments have investigated the neural underpinning of imagery by the use of various techniques, including positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). The results of these studies are mixed, but about half of the studies have found activation during visual imagery in medial occipital cortex (corresponding to either Area 17 or 18, both of which are topographically organized in the human brain), whereas the remaining studies did not find such activation (3). The experiments differ in many ways, ranging from the nature of the task to the specific neuroimaging techniques used, and thus there are many possible reasons for the disparities. One way that the studies differ is in the requirement that subjects actually must form a depictive image (4).

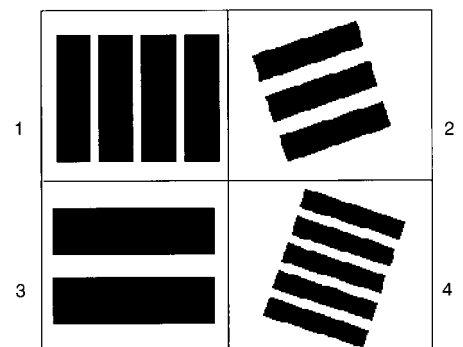
**Fig. 1.** Illustration of stimuli used in the task. All sets of stripes together were about 5 inches high and 5 inches wide (subtending  $\sim 13^\circ$  of visual angle from the subject's point of view). As illustrated, the stripes varied in length, width, orientation, and the amount of space between the bars. The numbers 1, 2, 3, and 4 were used to label the four quadrants, each of which contained a set of stripes. After memorizing the display, the subjects closed their eyes, visualized the entire display, heard the names of two quadrants, and then heard the name of a comparison term (for example, “length”); the subjects then decided whether the stripes in the first-named quadrant had more of the named property than those in the second. Subjects were told to make their judgments by visualizing the stripes.

In this investigation we used a task that clearly requires one to visualize patterns that depict information. Moreover, we investigated the same task with PET and repetitive transcranial magnetic stimulation (rTMS), showing not only that Area 17 is activated when people perform the task, but also that performance of this task is impaired when neural activity in this region of cortex is disrupted by rTMS.

We used the imagery task designed by Kosslyn, Sukel, and Bly (5). Eight subjects (6) memorized a display that contained four quadrants, each of which contained a set of stripes (Fig. 1). The subjects were scanned as they closed their eyes and visualized the display (7), and then heard two numbers, which they had previously learned were labels for specific quadrants, followed by the name of a dimension (such as “length”). They were to decide whether the set of stripes in the first-named quadrant was greater along that dimension than the set of stripes in the second-named quadrant. The resulting brain activation was compared with a control condition in which the same type of auditory stimuli were delivered but no imagery was used (8).

The PET data were analyzed with publicly available statistical parametric mapping software (9). The key result was that we found activation in Area 17 (Fig. 2). Other areas were also activated, including Areas 18/19 (Fig. 2), but they are not relevant for the present issue (10).

Neuroimaging can only establish the association between task performance and a pattern of cortical activation. In contrast, by transiently disrupting the function of a targeted cortical region, rTMS allows one to test the causal link between activity in that region and task performance (11). This technique essentially creates a temporary, reversible “lesion”; this lesion need only be severe enough to produce observable decrements in performance. In 1989, Amassian *et al.* (12) demonstrated that single pulses of transcranial magnetic stimulation (TMS) delivered to the occipital cortex 60 to 140 ms after a



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visual stimulus disrupt performance on a letter-identification task. Since then, the suppressive effects of single-pulse TMS on visual cortex have been replicated in various experiments (13). Such single-pulse studies require both temporal and spatial knowledge: where to stimulate and when. In contrast, rTMS can modulate the level of excitability of a given cortical area beyond the duration

of the rTMS train itself, thereby providing an opportunity to test the contribution of that cortical area to a given task without stringent temporal constraints (14). For example, after being delivered at a rate of 1 Hz, rTMS decreases cortical excitability for minutes afterward (15), thereby providing a transient, partial "functional lesion" of a specific cortical region and allowing one to test its causal

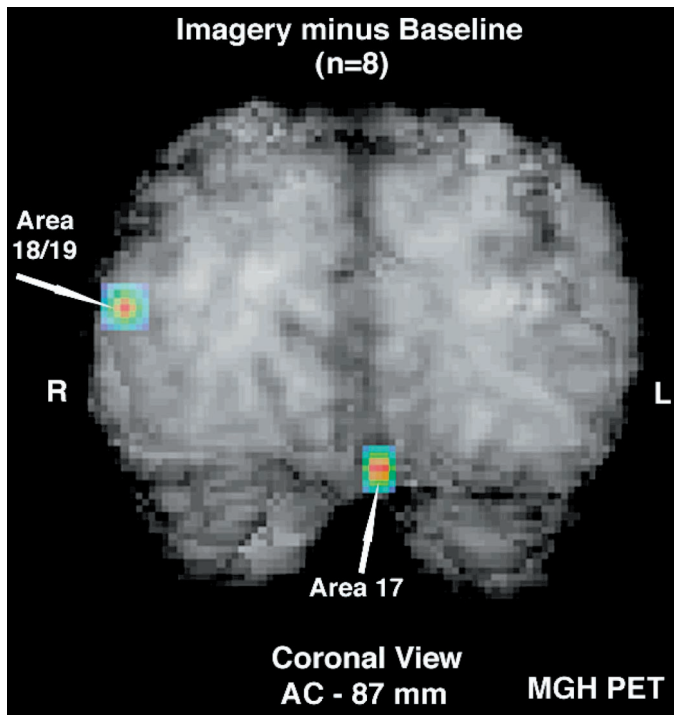
link to performance in a task.

Using 1-Hz real or sham rTMS (16), we stimulated five subjects (17) over the occipital pole, targeting Area 17 (18). Real or sham rTMS was applied before performance of an imagery or a perceptual version of the task used in the PET study (19–21). In the perceptual version of the task subjects compared the sets of stripes on a visible display. If we did not succeed in disrupting perception in the same task, we would have little evidence that we had interfered with the function of the visual cortex per se. As shown in Fig. 3, TMS delivered to medial occipital cortex did in fact disrupt both perception and imagery.

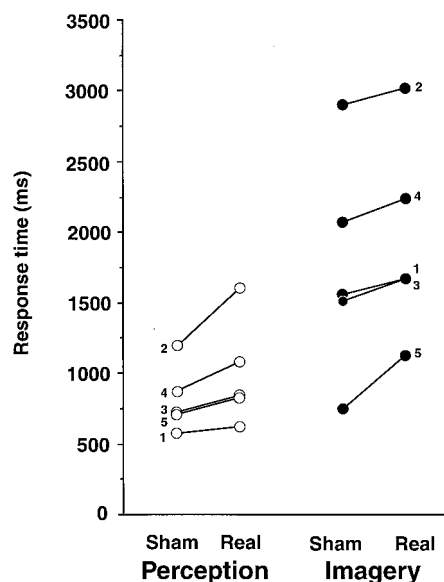
Real, compared with sham, rTMS targeted toward the subject's Area 17 led to impaired performance in both the perceptual and the imagery tasks. In the PET experiment we found multiple cortical areas activated, but previous research has shown that stimulating one visual area does not disrupt processing in other areas that are similar distances from the site at which TMS was directed (22).

In summary, we not only found that medial occipital cortex, specifically Area 17, was activated while people visualized and compared sets of stripes, but also that such activation was not "epiphenomenal" (that is, akin to the heat produced by a lightbulb when one is reading, which plays no functional role in allowing one to read). The TMS results show that the activation revealed by PET is indeed causally linked to performance of the task, that the early occipital visual cortical areas are indeed used in at least some forms of visual imagery as well as in visual perception.

**Fig. 2.** The results of PET scanning, showing activation in Area 17 [peak Z score of 3.38 at coordinates -2, -88, -12, according to the Talairach and Tournoux atlas (23)], during imagery compared with baseline. Activation in Areas 18/19 (peak Z score of 3.44 at coordinates 34, -86, 12) can also be seen in this slice plane. Strength of Z scores is illustrated according to color, with blue, green, yellow, and red representing increasingly high Z scores; in this slice plane, the highest Z score, located within Area 17, is 3.31.



**Fig. 3.** Results when rTMS was delivered before the imagery and perception conditions. "Real" rTMS occurred when the magnetic field was directed into Area 17, whereas "sham" rTMS occurred when the field was diverted away from this site. A two-way repeated analysis of variance (ANOVA) on the response times (trimmed to eliminate outliers) revealed a main effect of stimulation (real rTMS versus sham rTMS) [ $F(1,4) = 29.86, P < 0.01$ ] and a main effect of modality (imagery versus perception) [ $F(1,4) = 16.65, P < 0.02$ ]. There was no interaction between stimulation and modality [ $F(1,4) < 1$ ]. Contrasts revealed that the response times during real rTMS were greater than those during sham rTMS in both imagery [ $F(1,4) = 9.32, P < 0.04$ ] and perception [ $F(1,4) = 8.17, P < 0.05$ ] (1945 ms versus 1759 ms and 1002 ms versus 827 ms, respectively). As shown here, this response time increase was observed in all five subjects in both modalities. Digits next to each line indicate subject number. The corresponding ANOVA on the error rates revealed no significant effects (all  $F$ 's  $< 1$ , all  $P$ 's  $> 0.5$ ), which belies the possibility of a speed-accuracy trade-off (the means were as follows: sham perception, 13.3%; real perception, 13.3%, sham imagery, 9.2%; real imagery, 13.3%). The error rates during the TMS condition were lower than in the PET condition, which probably reflects the large number of practice trials used here versus the small number used in the PET study. For PET, we wanted the task to be as challenging as possible, thereby engendering maximal blood flow in relevant brain areas, but for rTMS we wanted to ensure that response times were not at ceiling, and thus included many more practice trials.



**References and Notes**

1. S. M. Kosslyn, *Image and Mind* (Harvard Univ. Press, Cambridge, MA, 1980); *Image and Brain: The Resolution of the Imagery Debate* (MIT Press, Cambridge, MA, 1994); M. Tye, *The Imagery Debate* (MIT Press, Cambridge, MA, 1991).
2. These areas are spatially organized, both physically and functionally [see, for example, P. T. Fox *et al.*, *Nature* **323**, 806 (1986); R. B. H. Tootell, M. S. Silverman, E. Switkes, R. L. De Valois, *Science* **218**, 902 (1982)]. Thus, patterns of activation within them are themselves laid out in space and serve to depict information.
3. For reviews, see E. Mellet, L. Petit, B. Mazoyer, M. Denis, N. Tzourio, *NeuroImage* **8**, 129 (1998); W. L. Thompson and S. M. Kosslyn, in *Brain Mapping: The Systems*, A. W. Toga and J. C. Mazziotta, Eds. (Academic Press, San Diego, in press).
4. For example, in some tasks no behavior is assessed and subjects need not use imagery [for example, M. D'Esposito *et al.*, *Neuropsychologia* **35**, 725 (1997)], whereas in others the subjects are asked to perform spatial tasks, which may rely primarily on the parietal lobes [E. Mellet, N. Tzourio, M. Denis, B. Mazover, *J. Cognit. Neurosci.* **7**, 433 (1995)]. However, activation in Area 17 is probably not simply a consequence of needing high spatial resolution (see E. Mellet *et al.*, *NeuroImage*, in press).
5. S. M. Kosslyn, K. E. Sukel, B. M. Bly, *Mem. Cognit.*, in press. As illustrated in Fig. 1, sets of four stripes were created (with Aldus SuperPaint, Aldus Corporation, San Diego, CA). Forty-eight sound files also were created with Soundedit 1.6 (Macromedia, San Francisco, CA). Each sound file contained numbers that named two quadrants, followed by the name of a

- property of the stripes, such as "1, 2, Length." The numbers specified which two quadrants were to be compared, and the property name indicated the comparison the subject was to make (length, width, orientation, or spacing between the stripes). For half the comparisons of each type, the stripes in the quadrant named first had more of the specified dimension, whereas for the other half the stripes in the quadrant named second were greater along this dimension. All of the cues were a single syllable (the word "tilt" cued orientation discriminations and "space" cued spacing discriminations). We created two sets of cues; one of them asked subjects to compare length or width and the other asked subjects to compare spacing or orientation. Half the subjects received one set of cues, and half received the other. The subjects were not aware of the possible comparisons while they studied and memorized the stimuli. For the baseline in the PET study, two additional words ("depth" and "height") were used so that the subjects would not have any idea of how they were to study the stimuli, once these were presented to them in the learning phase. The cues were presented with software on a Macintosh computer with an RGB monitor (Apple Computer, Cupertino, CA). The trial sequence within each block was random, except that the same number (which labeled a quadrant) and the same type of discrimination could not appear more than three times in succession.
6. Eight right-handed male students or professionals from the Boston area, aged 20 to 36 years (mean, 27 years), volunteered to participate in the PET study. All reported being in good health and free of any psychoactive medication. They were all unaware of the hypotheses of the experiment at the time of testing.
  7. Before the imagery condition, subjects memorized the stimulus display [using the procedure of (5)]. They also learned which quadrants were labeled by the numbers 1, 2, 3, and 4. During the imagery task, the subjects were asked to visualize the entire display, and then listen to the stimuli. If the stripes in the quadrant named first had a pattern that was greater on the named dimension than the stripes in the quadrant named second, they were to press the pedal under their left foot; if not, the pedal under their right foot. Subjects were told that they should visualize the entire display and "look" at the image in order to make the discrimination. They were to respond as quickly and accurately as possible. Subjects received two practice trials (with feedback regarding accuracy, which was not provided in the actual test trials) before the actual test trials. We wanted to ensure that the task was difficult, and hence likely to evoke detectable activation, and thus did not include many practice trials. Each block lasted about 85 s; subjects began the task 15 s before delivery of  $^{15}\text{O}_2$  began, and continued for 70 s, at which point the PET camera was turned off, and subjects were instructed to stop performing the task. All other aspects of the procedure were the same as in (5). The mean response time in the imagery condition was 2704 ms, and the mean error rate was 21.5%.
  8. The baseline condition was always presented first, before subjects had seen the stimuli or knew about the nature of the task. We were concerned that if subjects had participated in the imagery task, they might have visualized stimuli even during the baseline condition. In the baseline condition, the subjects closed their eyes and listened to the auditory stimuli that were prepared for that condition. They were told that they would be hearing sets of three words (the names of two numbers followed by another word), and that they were to respond as soon as they heard the third word. They were instructed to not pay attention to or try to assign meaning to any of the words they heard. They were asked to alternate the side of each response.
  9. SPM95 (Wellcome Department of Cognitive Neurology, London, UK), which is based on the theories presented in K. J. Friston *et al.*, *J. Cereb. Blood Flow Metab.* **11**, 690 (1991); *Hum. Brain Map* **2**, 189 (1995); K. J. Worsley, A. C. Evans, S. Marrett, P. Neelin, *J. Cereb. Blood Flow Metab.* **12**, 900 (1992). For further details on the PET analysis, see S. M. Kosslyn *et al.*, *Psychophysiology* **35**, 1 (1998).
  10. In addition to the findings shown in Fig. 2, other regions were found to be activated in the PET study during the imagery condition, relative to the baseline condition. In the left hemisphere, we found activation in superior parietal cortex, cerebellum, parahippocampal gyrus, superior frontal cortex, and dorsolateral prefrontal cortex; in the right hemisphere, we found activation in Areas 18/19, the occipito-parietal sulcus, cerebellum, inferior temporal cortex, thalamus, two points in Brodmann's Area 10 of the dorsolateral prefrontal cortex, and at the junction of the inferior frontal and dorsolateral prefrontal cortices. All areas were activated with a Z score greater than 3.09 ( $P < 0.001$ , uncorrected for multiple comparisons). Although Area 17 was activated along the midline, activation in other relatively early visual areas was lateralized to the right hemisphere. Marsolek and colleagues [for example, for a review see C. J. Marsolek and E. D. Burgund, in *Cerebral Asymmetries in Sensory and Perceptual Processing*, S. Christman, Ed. (Elsevier, Amsterdam, 1997)] have provided much evidence that visual memories for specific stimuli (as opposed to prototypes or categories) are stored and processed more effectively in the right hemisphere, whereas visual memories of categories and prototypes are stored and processed more effectively in the left hemisphere. The lateralization found here may reflect such specialization.
  11. L. G. Cohen *et al.*, *Nature* **389**, 180 (1997); E. M. Wassermann, J. Grafman, T. Paus, *Trends Cognit. Neurosci.* **1**, 199 (1997); A. Pascual-Leone *et al.*, *Neuropsychologia* **37**, 207 (1999).
  12. V. E. Amassian *et al.*, *Electroencephalogr. Clin. Neurophysiol.* **74**, 458 (1989).
  13. For recent reviews on TMS applications in studies on visual pathways, see V. E. Amassian *et al.*, *J. Clin. Neurophysiol.* **15**, 288 (1998); V. Walsh and A. Cowey, *Trends Cognit. Neurosci.* **2**, 103 (1998).
  14. A. Pascual-Leone, M. Hallett, J. Grafman, in *New Horizons in Cognitive Neuroscience*, M. Shugishita, Ed. (Elsevier, Amsterdam, 1994); A. Pascual-Leone *et al.*, in *Handbook of Neuropsychology*, J. Grafman and F. Boller, Eds. (Elsevier, Amsterdam, 1996), vol. 11.
  15. R. Chen *et al.*, *Neurology* **48**, 1398 (1997); A. Pascual-Leone *et al.*, *J. Clin. Neurophysiol.* **15**, 333 (1998).
  16. Repetitive TMS was performed with a Magstim Super Rapid stimulator (Magstim, Whitland, UK) with a Magstim Double 70-mm figure-of-eight coil. The coil was firmly maintained in a constant position with a specially designed coil holder. A three-dimensional reconstructed MRI of each subject was used to determine the optimal coil placement to target the occipital pole, at the tip of the calcarine fissure. During real rTMS, the center of the coil was held tangentially to the scalp and symmetrically across the midline of the occipital pole, targeting the tip of the calcarine fissure. During sham rTMS, the coil was lowered by 3 cm and rotated so that the edge of the two wings of the coil rested at 90° on the scalp. In this sham rTMS condition, the induced magnetic field did not enter the brain, although the touch on the scalp, the sound of the coil being activated, and the induced muscle twitching are comparable to those in the real rTMS condition. Intracerebral measurements of the induced voltages by TMS with various coil orientations in primates document the appropriateness of the sham TMS condition used here [S. H. Lissman *et al.*, *Electroencephalogr. Clin. Neurophysiol.* **107**, 79P (1998)]. Repetitive TMS was delivered at 90% of the subject's motor threshold at 1-Hz stimulation frequency, in a single train of 10 min duration. Our hypothesis was that underlying cortical activity would be affected for at least 10 min after rTMS. To avoid carry-over effects between conditions, there was a pause of 30 min between tasks and thus between rTMS trains. Overall, each subject received 600 stimuli per train, and a total of 2400 stimuli (1200 real and 1200 sham stimuli). Stimulation was performed in accordance with current safety recommendations [E. M. Wassermann, *Electroencephalogr. Clin. Neurophysiol.* **108**, 1 (1998)] using a protocol approved by the local investigational review board and with an investigational device exemption from the Food and Drug Administration.
  17. Mindful of the possibility of carry-over effects (practice or fatigue), we tested a different set of volunteers in the PET and TMS conditions. Three men and two women, aged 19 to 41 years (mean 29 years), volunteered to participate as paid subjects in the rTMS experiment. All were right-handed according to the Edinburgh Handedness Scale. All were medication free, had normal neurological and physical exams, and had no personal or family history of neurological disorder, including seizures. Subjects provided written informed consent before entering the study.
  18. Although it remains unclear whether the effects of TMS to the occipital pole are due to direct intracortical effects or interference with connections from the affected area, functional disruption of Area 17 is well documented (12). Nevertheless, given the limitations in focality of TMS, interference with contiguous portions of Area 18 is likely [see, for example, G. F. Potts *et al.*, *J. Clin. Neurophysiol.* **15**, 344 (1998)]. However, the PET results did not show that this task activates contiguous parts of Area 18 but rather a part of Area 18 over 4 cm away, which is unlikely to have played a functional role in task performance (as noted below).
  19. The same task as in the PET experiment was administered [see (5)], and subjects again were asked to respond as quickly and accurately as possible (by pressing two different keys with the middle and index finger of their dominant hand). Response time was measured from the time of stimulus onset to the key response; error rates were also measured. Subjects learned the stimulus display as before. However, because response times and error rates were our only dependent measures, we included 24 practice trials before the study to ensure that there would not be a ceiling effect; if the task was too challenging, it would have been difficult to detect differences among the conditions.
  20. The same task was used in the imagery and perception conditions, but in the perception condition the entire stimulus display appeared for 500 ms immediately after the auditory cue was presented. Before each experimental task (imagery or perception), sham or real rTMS was applied. The subject received rTMS while sitting in front of the computer to be used for testing (Macintosh 17-inch RGB monitor, Apple Computer, Cupertino, CA). The task was initiated immediately after the end of the last magnetic stimulus. Therefore, each subject received a total of four sessions of rTMS. To control for potential learning effects, the subjects were randomly assigned to receive sham ( $n = 2$ ) or real rTMS ( $n = 3$ ) first. The imagery task was always conducted first to prevent the subjects from overlearning the stimuli (and thus not having to use imagery later), which may have occurred if the perceptual task was presented first.
  21. Repetitive TMS was tolerated well by all subjects, without undesirable side effects. No pre- or post-TMS differences in neurological status or visual acuity were noted in any of the subjects. None reported phosphenes during the stimulation.
  22. For example, G. Beckers and V. Homberg, [*Exp. Brain Res.* **87**, 421 (1991)] and G. Beckers and S. Zeki [*Brain*, **118**, 49 (1995)] showed that TMS over the presumed site of Area V5 impaired motion perception, but left color perception and shape perception unchanged; in contrast, TMS to V1 (Area 17) disrupted detection of visual stimuli without affecting motion perception. Areas V5 and V1 are interconnected, and therefore, if the effects of TMS on a given cortical area were secondary to transsynaptic effects, TMS to V1 should disrupt motion perception (by remote effects onto V5) and TMS to V5 should disrupt visual perception in general (by remote effects onto V1). This was not the case. Although transsynaptic effects of TMS on distant cortical and subcortical areas are possible [for example, R. J. Ilmoniemi *et al.*, *Neuroreport* **8**, 3537 (1997); T. Paus *et al.*, *J. Neurosci.* **17**, 3178 (1997)], these effects have not been found to produce significant changes in behavior within the time span studied here. TMS effects appear to originate from disruption of the same cortical areas that show activation on functional imaging studies, and originate primarily from disruption of the directly targeted cortical region. Among the

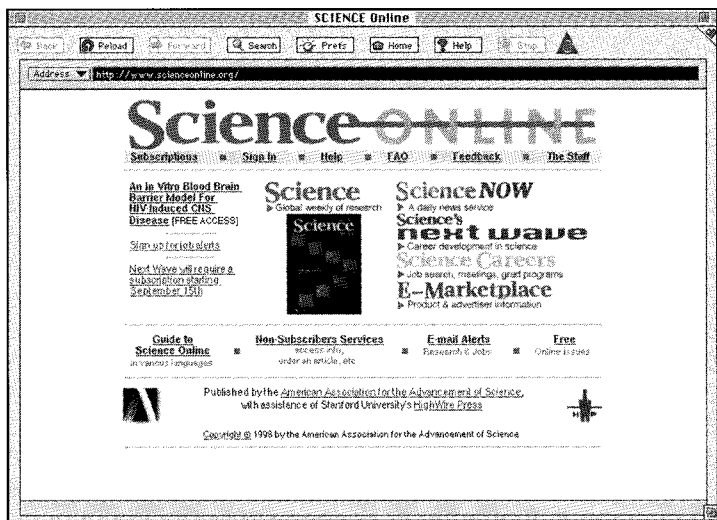
areas activated in our study [see (10)], the one closest to Area 17 (where TMS was delivered) was Areas 18/19, which was at a distance of 43.3 mm; the closest other areas that were activated were the cerebellum, 43.7 mm from Area 17, and the occipito-parietal sulcus, 45.3 mm from Area 17. Given the previous findings with TMS noted above, it is unlikely that TMS delivered to medial occipital cortex had its effects by disrupting one of the more remote areas that were activated during the task.

23. J. Talairach and P. Tournoux, *Co-planar Stereotaxic Atlas of the Human Brain*, M. Rayport, transl. (Thieme, New York, 1988).
24. This research was supported in part by grants from the Human Frontiers Science Program, National Eye Institute (RO1 EY12091), and the National Institute for Mental Health (RO1 MH57980). S.C. was a visiting scientist from the Department of Pediatrics, Division of Neurology, Faculty of Medicine, University of Chile. Subjects were tested according to American







Psychological Association rules and regulations. After the general purpose and possible risks of the experiment were explained, informed consent was obtained from each subject before the experimental procedure began. This research was approved by the respective Institutional Review Boards of the sponsoring institutions.

10 December 1998; accepted 4 March 1999

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