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24. Transdermal water transport was measured as in the insulin experiments at an ultrasound intensity of 125 mW/cm^2, except that the donor compartment was filled with a 1 μCi of radiolabeled water (^{3}H) per milliliter of solution. The concentration of water in the receiver compartment was measured by means of a scintillation counter. The permeability was calculated by the methods described in (*18*).
25. The transport properties of hairless rat and hairless mouse skin have been shown to resemble those of human skin. The passive permeability of the hairless rat skin to many compounds is within a factor of 2 to 5 of the human skin permeability. [Y. Morimoto, T. Hatanaka, K. Sugibayashi, H. Omiya, *J. Pharm. Pharmacol.* **44**, 634 (1992); R. Wester and H. I. Maibach, in (*7*), pp. 333–347.]
26. The histological studies of the hairless rat skin exposed to ultrasound were performed at Deborah Heart and Lung Institute, NJ. The skin samples exposed to ultrasound, as well as those not exposed to ultrasound (controls), were stained with hematoxylin and eosin. The samples were later observed under a light microscope (40-fold magnification) to be assessed for possible structural damage. Five control skin samples and 20 skin samples exposed to ultrasound (five samples measured at each ultrasound intensity in the range of 12.5 to 225 mW/cm^2) were analyzed.
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30. All animal procedures were in accordance with approved institutional protocols. The hairless rats were anesthetized with a mixture of ketamine (60 mg/kg) and xylazine (10 mg/kg). After about an hour, a flanged glass cylinder (Crown Glass; diameter, 20 mm; height, 2 cm) was glued onto the back of each rat with a minimal amount of superglue (Permabond, Englewood, NJ) or vacuum grease (Dow Chemicals) on the outer edge of the flange. The center of the cylinder was located about 3 cm from the rear end of the rat. This particular site was chosen so that application of ultrasound directly on a sharp bone close to the body surface was avoided, which otherwise could cause a damage to the blood capillaries near the edge of the bone. This could be especially relevant in the case of young rats (<6 weeks old) because these rats have bones close to the skin surface. The cylinder was filled with an insulin solution (100 U/ml). Ultrasound (20 kHz, 100-ms pulse applied every second) at different intensities was applied by immersion of the transducer (VCX 400, Sonics and Materials) in the insulin solution about 1 cm away from the skin. Duplicate samples of the blood glucose concentration in the tail-vein blood were measured every 30 min with a glucose monitoring device (AccucheckAdvantage, Boeheringer Mannheim).
31. We thank M. Prausnitz for helpful suggestions, S. Liauw and A. Patel for technical assistance, and J. Kost and M. Johnson for helpful discussions. We also thank L. Brown for assistance with diabetic hairless rats, B. Schloo for performing histological studies, and R. Gingerich for assistance with insulin measurements. Supported by NIH grant GM44884 and a gift from the Zachary Miller Fund to R.L., and a fellowship from Schering-Plough Foundation. D.B. acknowledges the support of a NSF Presidential Young Investigator Award.

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Parietal Contributions to Visual Feature Binding: Evidence from a Patient with Bilateral Lesions

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Neurophysiologists have documented the existence of multiple cortical areas responsive to different visual features. This modular organization has sparked theoretical interest in how the "binding problem" is solved. Recent data from a neurological patient (R.M.) with bilateral parietal-occipital lesions demonstrates that the binding problem is not just a hypothetical construct; it can be a practical problem, as rare as the selective inability to perceive motion or color. R.M. miscombines colors and shapes even under free viewing conditions and is unable to judge either relative or absolute visual locations. The evidence suggests that a single explanation—an inadequate spatial representation—can account for R.M.'s spatial judgment and feature-binding deficits.

A perplexing question in vision research is how the brain solves the "binding problem." Primate brains contain more than 20 visual areas, many of which are highly specialized for processing specific visual features (*1*). Data from human and nonhuman subjects demonstrate that object features such as color or shape are represented in hierarchical interconnected areas in a ventral visual pathway that extends from the occipital to the temporal cortex, whereas spatial features are represented in a dorsal pathway from the occipital to the parietal cortex (*2*). The wide cortical distribution of visual features, the large receptive fields of inferotemporal neurons, and the separation of spatial and object pathways lead to the question of how unified perception (or "binding") of visual objects results (*3*). Several neurophysiological studies have proposed temporally correlated neuronal activity as a mechanism for intra- and interareal coordination (*4*). Although research in cats and monkeys has been directed at exploring the neural substrate of binding, there are no documented cases of animals with binding deficits.

Treisman and Gelade (*5*) proposed that attention to spatial locations in normal human brains was necessary to properly bind the features of objects. Feature binding should therefore be disrupted by attentional overload or inaccurate spatial information. The effects of divided or reduced attention have been tested in neurologically normal people and in patient populations (*6*, *7*). When presented with brief displays of colored letters and asked to report the identity of a simultaneously presented digit, subjects experienced illusory conjunctions (ICs), as predicted. For example, if presented with a red X and a blue O, subjects sometimes confidently reported seeing a red O or a blue X. Patients with unilateral neural damage have exhibited an attentional bias away from objects in the contralesional field and have been shown to make more ICs in the contralesional than in the ipsilesional field when stimuli were briefly presented (*7*).

The binding problem seldom poses a serious challenge in nonlaboratory environments. Intact primate brains are so adept at solving the binding problem that severe limitations on processing must be imposed to observe ICs: ICs are seen in normal people only when attentional demands are high and displays are brief (200 ms) or peripheral (*6*, *8*). We have been testing, with informed consent, a 58-year-old patient (R.M.) for whom the binding problem is a significant practical challenge. R.M. has nearly symmetrical bilateral parieto-occipital lesions (Fig. 1, A to C) (*9*), with no temporal or frontal lobe involvement. R.M. did not exhibit an attentional bias for the left or right visual field but did have great difficulty in reporting where objects were located even when he directed his gaze at them. We could therefore investigate the effects of degraded spatial information on feature binding. We assessed R.M.'s ability to properly conjoin features by presenting displays containing two colored letters. His task was to report the name and color of the first letter he saw (*10*). R.M. had an IC rate of 13% even when display times were as long as 10 s and even when his attention was undivided (Fig. 2). In earlier testing sessions, his error rate was 25%, but no

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systematic evaluation of his spatial abilities was done at that time.

In the later sessions, R.M. was also tested with displays containing two elementary geometrical shapes of various sizes and asked to report which shape was taller (*11*). R.M. made significantly more errors when stimuli were presented simultaneously than when they were presented sequentially, even though the total display time was twice as long in the simultaneous condition as in the sequential condition. Figure 3 reveals that the ICs were not due to simple failures of size discrimination; if they were, the greatest number of errors would have occurred at the smallest difference in size.

It is interesting that R.M. made significantly more IC errors during simultaneous displays, because this pattern is exactly the opposite of results found in neurologically normal people (*12*). R.M. was less impaired when conjoining features with sequential displays, which suggests that he can use temporal coincidence better than shared spatial location to specify which features belong together. This result specifically implicates his spatial deficits in the binding errors, rather than indicating a generalized problem in integrating features to form perceptual objects.

The parietal lobes have been implicated in spatial attention, visually guided movements, and representations of spatial information (*3*, *13*). We tested R.M.'s spatial abilities by asking him to judge the location of an item on a computer screen. In two blocked conditions, a letter X was presented by itself in one of five locations along the horizontal meridian or in one of five locations along the vertical meridian. R.M. indicated whether the X was to the left, right, or center of the screen in one block, or whether it was up, down, or center in the other block. In the other two blocked conditions, the X appeared along with the letter O. R.M. was instructed to ignore the O and just report the screen location of the X (*14*). R.M. was impaired in judging the screen position of a single item. He averaged only 70% correct across all conditions. Although this represents above-chance accuracy for the three-alternative forced choice (AFC) task, it is very low for such a simple task and such a large spatial difference. His performance was the same regardless of whether the X was presented by itself or in the presence of a distracting letter O ($\chi^2 = 0.025$, $P = 0.874$ for horizontal positional judgments; $\chi^2 = 1.88$, $P = 0.1707$ for vertical judgments). Performance was the same for vertical and horizontal displays ($\chi^2 = 1.5$, $P = 0.225$ for X presented by itself; $\chi^2 = 0$, $P = 1.0$ for presentation of both X and O).

We also tested R.M.'s ability to judge the location of the X relative to the O. The same display locations and times were used, but R.M. was required to attend to both the X and the O and to report whether the X was to the left or right of the O in the horizontal block, or above or below the O in the vertical block. Additionally, we presented the X and O sequentially and asked R.M. to judge whether the two letters appeared in the same location or in different locations (*15*). When asked to report the relative position of the X, he performed no better than chance (approximately 50% correct) in this two-AFC test (Fig. 4). Hor-

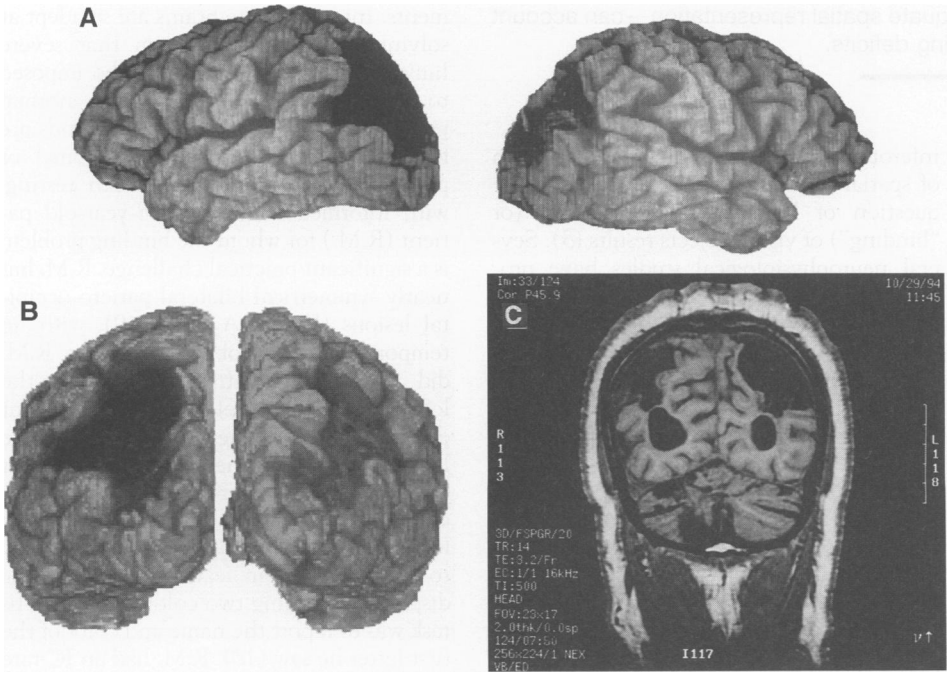

Fig. 1. Three-dimensional reconstruction of R.M.'s brain. (**A**) Dark areas in lateral views show damage to the parietal cortex, whereas temporal lobes appear normal. (**B**) Occipital view demonstrates that the primary visual cortex is spared. (**C**) One coronal MRI is shown; the 3D images were reconstructed from 3-mm slices of MRI images (*8*).

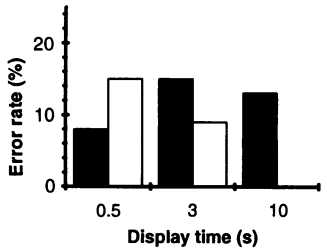

Fig 2. Form × color IC errors. Solid bars represent data from the December 1993 testing session; open bars are data collected in July 1994. There were no significant differences between the error rates at the various display times tested in December ($\chi^2 = 2.1$, $P = 0.351$) nor between the two display times used in July ($\chi^2 = 1.8$, $P = 0.185$). Nor was there a significant difference between testing dates ($\chi^2 = 1.7$, $P = 0.197$ for 0.5-s displays; $\chi^2 = 2.0$, $P = 0.155$ for 3-s displays), which indicates that R.M.'s binding deficit remained relatively stable over this 7-month period.

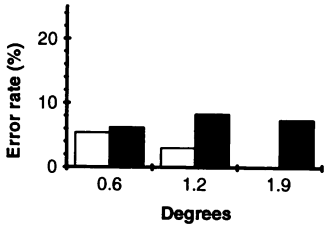

Fig. 3. Size × shape IC errors; simultaneous versus sequential displays. Errors are plotted as a function of the experimental condition (solid bars indicate simultaneous presentation; open bars indicate sequential presentation) and of the size difference in degrees of visual angle between the "short" and the "tall" item in the display. R.M. made significantly more errors during simultaneous than during sequential presentation ($\chi^2 = 5.0$, $P = 0.026$).

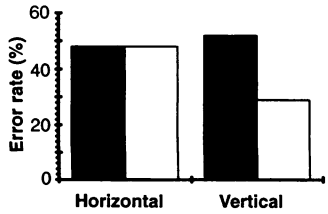

Fig. 4. R.M.'s performance when asked to report the location of the X relative to the O. Letters were presented horizontally (bars at left) or vertically (bars at right). In two conditions, R.M. indicated the relative position of the X, using place labels such as "left" or "above" (solid bars). In the other two experimental conditions, R.M. indicated whether the X was in the "same" location as a sequentially presented O (open bars).

izontal and vertical relative positional judgments were equally impaired ($\chi^2 = 0.16$, $P = 0.689$). He simply could not say whether one item was to the left or right of another item. When asked to judge whether two sequentially presented letters were located in the same or different locations, R.M.'s acccuracy was also at a rate that would be produced by chance for letters presented on the horizontal axis, although it was somewhat above chance (77% correct) for vertical locations. R.M.'s errors reflected a tendency to state that objects appeared in the same position when, in fact, they appeared in different positions. Thus, for combined vertical and horizontal data, R.M.'s error rate was 60% when the letters were in different locations and 20% when they were in the same location.

Although R.M.'s loss of spatial information is dramatic, it was expected: Parietal damage has long been associated with spatial disorders in human and nonhuman primates. On the other hand, impaired object recognition is usually associated with damage to the ventral pathway. R.M.'s temporal lobes are completely intact; even the supramarginal gyri have been spared. Yet although R.M. can recognize letters and shapes, he has great difficulty in correctly binding the colors and sizes of two or more shapes. A complete representation of an object should specify not just its shape, but also its color, direction of motion, size, and texture. Our data suggest that the explicit spatial information associated with the dorsal pathway is also necessary to correctly bind features (*16*).

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9. R.M. suffered his first embolic infarct in June 1991 and a second in March 1992. In the fall of 1992, R.M. was clinically evaluated as presenting with spatial disorientation, optic ataxia, psychic paralysis of gaze, hyperattention to a single object, and difficulty reporting more than one object in natural scenes (Balint's syndrome). Dysarthria was also noted, but no additional clinical deficits were observed. R.M.'s visual fields, as tested by automated static perimetry in the fall of 1992, revealed an inferior arc of hemianopia about 10° from the fovea. Goldmann perimetry in June 1994 showed intact fields, with some inferior nasal depression in the left eye. Stereopsis, as tested with random dot stereograms, was normal, but R.M.'s accuracy was the same as would be produced by chance when he estimated the depth of objects, and he could not accurately judge whether an object was moved toward or away from him. Color vision was normal. Uncorrected visual acuity tested with one letter at a time was normal [20/30 oculus sinister (OS) (left eye), oculus dexter (OD) (right eye) when tested in 1992; 20/15 OS, OD when tested in 1994]. Contrast sensitivity, assessed by Vis-tech sine wave gratings, was normal. R.M. has had no further neurological difficulties in the past 2.5 years. Three-dimensional (3D) models of R.M.'s brain were reconstructed from 3-mm magnetic resonance imaging (MRI) slices with the use of BRAINVOX [H. Damasio and R. Frank, *Arch. Neurol.* **49**, 137 (1992)]. The lesions are concentrated primarily in Brodmann's areas 7 and 39 and possibly include some of areas 5 and 19. Additionally, there is a small (volume <0.3 cm^3) lacuna in Brodmann's area 6 (supplementary motor area) of the right hemisphere, and asymmetrical cerebellar lesions are present (volume = 0.3 cm^3 in the left hemisphere and 6.0 cm^3 in the right hemisphere.)
10. In each trial, two differently colored letters (1° in height and centered 2° apart) were presented simultaneously. The stimulus set consisted of red, blue, and yellow T's, X's, and O's. R.M. was tested on many variations of this basic form × color conjunction task on several dates between June 1993 and August 1994. Here, we have chosen to report data from the two testing dates (December 1993 and July 1994) closest to the testing dates for the spatial tasks reported below, although there appeared to have been some recovery relative to IC rates in earlier sessions. In December 1993, R.M. completed two experimental blocks of each of three conditions (display times of 500, 3000, and 10,000 ms). Each block contained 72 trials. In July 1994, R.M. was tested with one block each of 500- and 3000-ms displays. For a display containing a red X and a blue O, there were several types of possible errors: an IC error (report of a red O or a blue X) or an "intrusion error" (report of "yellow" or "T"). Intrusion errors provide an estimate of the proportion of feature misperceptions or guesses (*6*). The intrusion rate in fact averaged less than 3%. The IC rates reported are corrected for guessing [see (*6*) for details].
11. The stimulus set consisted of black plus signs, squares, and diamonds of five different sizes (1.3°, 1.9°, 2.5°, 3.2°, and 3.8° of visual angle). Two test stimuli were presented simultaneously (slightly off of screen center, 2.7° to the left or right) for 3332 ms or sequentially (in the center of the screen) for 833 ms each. This design pitted ICs for objects occurring in the same position at different times against ICs for objects occurring in different positions at the same time. R.M. completed a total of 200 trials in interleaved blocks of 50 trials.
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14. Stimuli were white letters, 0.75° in height and width, displayed on a black background for 1000 ms. R.M. was given as long as he needed to answer. Eye position was not monitored, and R.M.'s head was not restrained. Screen positions along the horizontal meridian were as follows: center, 3.5° and 7.0° to the left or right of center. For vertical meridian blocks, positions were as follows: center, 2.5° and 5.0° above or below center. R.M. completed 100 trials of each of the four experimental conditions, in interleaved blocks of 50 trials, in a single session in March 1994. R.M. knew the meaning of left and right, because he could accurately move his eyes in each direction on command.
15. R.M.'s ability to make relative spatial judgments was tested in the same session as his ability to judge screen position. The displays were exactly the same; the only difference was whether R.M. was required to report the screen position of the X or its position relative to the O. R.M. was able to complete one 50-trial block for each of these two conditions, but only with great difficulty and much coaxing by the experimenter. Same-different judgments were tested in July 1994. R.M. completed 100 trials each for horizontal and vertical judgments.
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