phylactic or even therapeutic effectiveness among this class of anti-TSE agents is especially promising.

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8. Transgenic mice (Tg7) were derived with a hamster PrP-sen gene under the control of the native PrP promoter as described previously for the transgenic mouse line Tg10 (*18*) and were crossed onto a mouse $Prp^{o/o}$ background (*19*). Thus, Tg7 mice do not express endogenous mouse PrP-sen but express high levels of hamster PrP-sen in a wide variety of tissues including brain. Because Tg7 mice have substantially shorter disease incubation times than Syrian hamsters when infected with hamster 263K scrapie either IP (about 82 days compared with 120 days) or intracranially (about 45 days compared with 75 days), they were used to test the therapeutic potential of the porphyrins and phthalocyanines.
9. The compounds tested were used as received from Porphyrin Products (Logan, UT) and dissolved in sterile water at the indicated concentrations: PcTS at 5 mg/ml and TMPP-Fe^{3+} at 10 mg/ml. DPG_2-Fe^{3+} was dissolved at a concentration of 30 mg/ml in 100% DMSO and stored as a stock solution at room temperature.
10. Animals were infected IP with 0.05 ml of a 1:10 dilution of a stock 10% brain homogenate of hamster 263K scrapie. The stock had an intracranial median lethal dose of 1×10^{10}/ml. Animals were injected IP with 0.05 ml of the drug solution three times a week for 4 weeks starting at 0 or 28 dpi. Treatments started at 56 dpi were continued three times a week until the animal was near terminal and killed. For each treatment, the doses given were as follows: PcTS, 5 mg/kg; DPG_2-Fe^{3+}, 30 mg/kg; and TMPP-Fe^{3+}, 10 mg/kg. Uninfected animals treated with the compound alone showed no ill effects (*11*). Because DPG_2-Fe^{3+} was dissolved in 100% DMSO, a group of infected animals was treated with 100% DMSO IP with the same treatment regimen to control for any effect of DMSO on disease progression. All results were analyzed with the unpaired student's t test. Animals were monitored for clinical signs and killed when in the terminal phases of disease. To confirm the diagnosis of scrapie, we removed the brain and spleen and analyzed them by Western blot with the hamster PrP-specific antibody 3F4 for the presence of PrP-res as described previously (*18*).
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12. Experiments in progress at the time of publication indicate that when PcTS treatment of Tg7 mice is initiated at 14 or 28 days before infection, disease is delayed by at least several weeks, suggesting that PcTS can be used prophylactically (*11*).
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Mirror-Image Confusion in Single Neurons of the Macaque Inferotemporal Cortex

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Humans and animals confuse lateral mirror images, such as the letters "b" and "d," more often than vertical mirror images, such as the letters "b" and "p." Experiments were performed to find a neural correlate of this phenomenon. Visually responsive pattern-selective neurons in the inferotemporal cortex of macaque monkeys responded more similarly to members of a lateral mirror-image pair than to members of a vertical mirror-image pair. The phenomenon developed within 20 milliseconds of the onset of the visual response and persisted to its end. It occurred during presentation of stimuli both at the fovea and in the periphery.

Behavioral tests in many species (including octopus, pigeon, monkey, and human, both child and adult) have demonstrated that confusion between lateral mirror images is more common than confusion between vertical mirror images (*1–5*). Speculation about why this is so has centered on two general ideas (*6*). The first idea is based on the fact that lateral reversals usually result from a change of viewpoint and thus convey little information about the object viewed (a tiger is equally threatening when seen in right or left profile), whereas vertical reversals usually do not result from a change of viewpoint and thus do convey information about the object (a tiger is less of a threat upside down than right side up). If lateral reversals convey little information, then brain resources dedicated to representing them may have become relatively limited, through an adaptive phylogenetic or ontogenetic process. The second idea is that confusion between lateral mirror images is an accidental consequence of the bilateral symmetry of the nervous system. To the degree that the hemispheres are mirror images of each other and interhemispheric pathways link corresponding points, neurons in the left hemisphere activated by a "b" must be linked to neurons in the right hemisphere activated by a "d," with the consequence that either stimulus will activate both populations, giving rise to confusion. Whichever account is correct, the question remains as to where in the brain the neural correlate of mirror-image confusion resides. One candidate is the inferotemporal cortex (IT), an area critical for visual object recognition in both monkeys and humans (*7*). Visually responsive neurons in IT are selective for particular shapes and for the orientations at which those shapes are presented (*8*). We hypothesized that individual IT neurons would manifest lateral mirror-image confusion by responding more similarly to members of lateral mirror-image pairs than to members of vertical mirror-image pairs.

We prepared two monkeys for microelectrode recording of single-neuron activity in IT (*9*) (Fig. 1). During each recording session, the monkey fixated on the center of a monitor while a series of stimuli was presented at the fovea. Initially, we presented images from a library of 28 white chiral shapes, each ~3° in height and width, in order to find a shape that elicited a strong response from the neuron. Having found such a shape, we then carried out testing with eight variants: the shape itself at orientations in the viewing plane of 0°, 90°, 180°, and 270° and its mirror image at the same four orientations. A

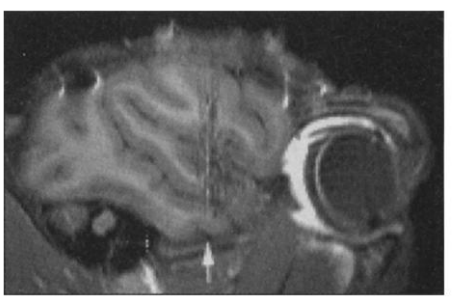

Fig. 1. Parasagittal magnetic resonance image of the right hemisphere of monkey 1. Arrow indicates the center of the recording zone. Also visible are guide-tube tracks in overlying tissue and a dark artifact from a titanium skull screw above the parieto-occipital cortex.

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representative set of eight variants of one shape is shown next to the histograms in Fig. 2, A through H. The stimuli were presented on successive trials in pseudorandom sequence until ~16 trials had been completed for each stimulus (*10*).

We collected data from 200 right-hemisphere IT neurons (111 neurons in monkey 1 and 89 neurons in monkey 2). We observed instances in which neuronal responses to two members of a lateral mirror-image pair were more similar than responses to members of a vertical mirror-image pair. In the example shown in Fig. 2, histograms representing responses to lateral mirror images are beside each other, whereas histograms representing responses to vertical mirror images are juxtaposed vertically (panels A versus C, B versus D, E versus G, and F versus H).

We used a *t* test to determine whether the mean firing rate associated with two members of a mirror-image pair was significantly different ($P < 0.05$) during the period from 50 to 500 ms after onset of the stimulus. For each neuron, this test was applied to four lateral and four vertical mirror-image pairs. We summarize the results for all image pairs tested (800 lateral and 800 vertical pairs) and for all neurons tested (200 neurons). The results in each case were not significantly different between monkeys and were therefore combined. Across image pairs, instances of significant selectivity between vertical mirror images were more numerous than instances of significant selectivity between lateral mirror images by a factor of 1.4 (Table 1, foveal section, left). This effect was highly significant (χ^2 test, $P = 0.0004$). Across neurons, those selective between more vertical than lateral mirror images (vertical > lateral) outnumbered those exhibiting the opposite pattern by a factor of 1.8 (Fig. 3B, fovea, and Table 1, foveal section, right). This effect was also highly significant (χ^2 test, $P = 0.002$). Thus, there was a consistent tendency for IT neurons to confuse lateral mirror images more often than vertical mirror images (*11*).

To analyze the time course of this effect, we analyzed data from 147 neurons (74 in monkey 1 and 73 in monkey 2) whose firing rate varied significantly across the eight test stimuli (analysis of variance, $P < 0.05$). For each neuron, for each 20-ms epoch during the trial, we computed the absolute difference between the mean firing rates elicited by the two members of each mirror-image pair. Then, we computed a vertical discrimination index (the mean of the absolute differences for the four vertical mirror-image pairs) and a lateral discrimination index (the mean of the absolute differences for the four lateral mirror-image pairs). Finally, we computed the average, across all neurons, of the vertical and lateral indices at each time point (Fig. 3A). In each monkey, (i) the earliest increase in population activity elicited by the stimulus occurred in the interval between 80 and 100 ms following the onset of the stimulus, (ii) both discrimination indices rose above baseline at this same time, and (iii) the vertical index began to exceed the lateral index in the interval from 100 to 120 ms following stimulus onset. Because the vertical-lateral difference developed later than the earliest visual response, we conclude that recurrent activity in intrinsic or interareal circuits may have contributed to this difference. From the fact that it developed only ~20 ms later, we conclude that the difference did not depend critically on the monkey's behavioral responses to the stimuli.

We next asked whether lateral mirror-image confusion is specific to images at the fovea or

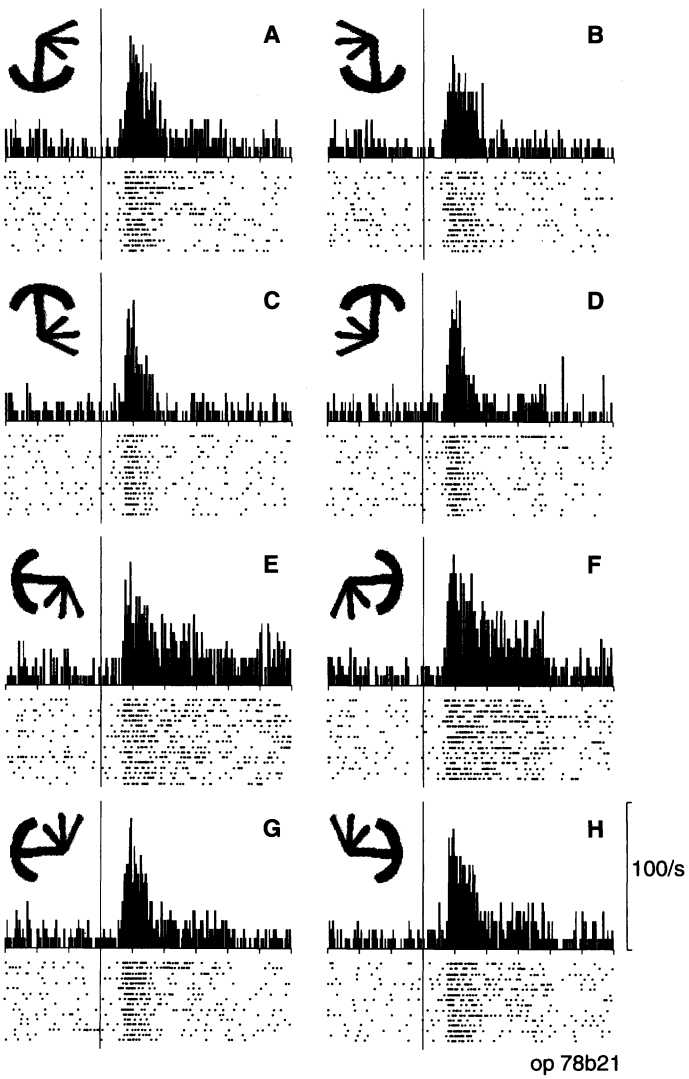

Fig. 2. (**A** through **H**) Responses of a single neuron in IT to eight variants of the same image presented at the fovea. A stimulus appeared 600 ms after the attainment of central fixation and remained on for 600 ms. Data were aligned on the stimulus onset (vertical line traversing histogram and rasters). Vertical calibration bar, 100 spikes/s; tick marks on the horizontal axis, 200 ms; histogram bin width, 10 ms.

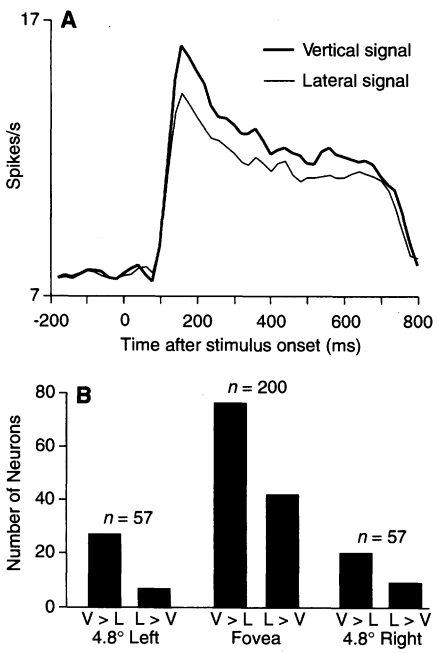

Fig. 3. (**A**) Vertical and lateral mirror-image discrimination indices, as a function of time during the trial, for stimuli presented at the fovea (mean across 147 neurons). Curves smoothed according to the formula $Y_{n'} = 0.25Y_{n-1} + 0.5Y_n + 0.25Y_{n+1}$ where Y_n is instantaneous firing rate. (**B**) Neurons that were most sensitive to vertical mirror inversion (V > L) outnumbered those that were most sensitive to lateral mirror inversion (L > V), regardless of the visual field location at which stimuli were presented (4.8° left, fovea, or 4.8° right).

Table 1. Significant differences in neuronal activity during the presentation of members of mirror-image pairs. Image-pair summary is based on eight comparisons (four lateral and four vertical) from each neuron. In the neuronal summary, each cell was categorized according to the results of eight image-pair comparisons of its data. If activity differed significantly between more lateral pairs than vertical pairs, it contributed to the lateral > vertical count and vice versa.

Subject	By image pair		By neuron	
	Lateral	Vertical	Lateral > vertical	Vertical > lateral
		Foveal		
Monkey 1	90/444	147/444	17/111	42/111
Monkey 2	117/356	139/356	25/89	34/89
Total	207/800	286/800	42/200	76/200
		Ipsilateral		
Monkey 1	29/132	56/132	6/33	18/33
Monkey 2	16/96	15/96	3/24	2/24
Total	45/228	71/228	9/57	20/57
		Contralateral		
Monkey 1	40/132	70/132	3/33	20/33
Monkey 2	29/96	35/96	4/24	7/24
Total	69/228	105/228	7/57	27/57

occurs with peripheral presentation as well. We analyzed data from 57 neurons monitored during presentation of images 4.8° to the right or left of fixation, with all other aspects of the testing procedure the same as before. All of these neurons were also studied under conditions of foveal presentation in a separate block of trials. Results from the two monkeys were not significantly different and were thus combined for statistical analysis. Instances of significant selectivity between members of a pair (assessed by a t test as described above) were fewer in the ipsilateral visual field (116 out of 456 pairs) than in the contralateral visual field (174 out of 456 pairs) or at the fovea (168 out of 456 pairs), and this difference was significant (χ^2 test, $P < 0.01$). However, there was no difference across the visual field with respect to lateral mirror-image confusion. Instances of significant selectivity between vertical mirror images outnumbered instances of significant selectivity between lateral mirror images in both the ipsilateral and contralateral visual field, reproducing the pattern obtained with foveal presentation (Fig. 3B and Table 1). At both locations, the difference in the percentages was significant (χ^2 test, $P < 0.05$), and at neither location did this measure deviate significantly from the measure obtained with foveal presentation (*12*). Thus, the tendency for IT neurons to confuse lateral mirror images is independent of visual field location within the tested range.

In all cases where a neuron significantly discriminated between members of a mirror-image pair in both hemifields, we asked whether the pattern of preference was the same or reversed across hemifields. In 36 out of 42 cases involving a vertical pair, the same member was preferred in both hemifields. In 10 out of 13 cases involving a lateral pair, different members were preferred. The frequency of "reversed" preference was significantly greater for lateral pairs as compared to vertical pairs (χ^2 test, $P = 0.00001$); however, the tendency for "reversed" instances to outnumber "identical" instances fell short of significance for lateral mirror-image pairs considered alone. Thus, although our results suggest that neurons prefer opposite members of a lateral mirror-image pair in opposite hemifields, they leave open the possibility that the preferences are simply uncorrelated across hemifields (*13, 14*).

Our study demonstrates that neurons in IT respond more similarly to lateral than to vertical mirror images. Previous studies, although showing that IT neurons are selective for image orientation in the viewing plane (*15*) or in depth (*16*), have not systematically compared responses to lateral and vertical mirror-image pairs (*17*). Because the pattern of confusion exhibited by IT neurons parallels the pattern observed in studies of perception, it is reasonable to speculate that this neuronal phenomenon is a direct correlate of lateral mirror-image confusion as observed in perception (*18*).

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9. Recording sites localized to the ventral aspect of the temporal lobe by magnetic resonance imaging are as follows: H-C A18-22 (monkey 1); A18-19 (monkey 2); and tip of temporal lobe, H-C A26. Other aspects of methodology are discussed by C. R. Olson and S. N. Gettner [*J. Neurophysiol.* **81**, 2340 (1999)].
10. Eye position did not vary systematically across conditions.
11. Within each stimulus octet, there was no correlation between which tetrad (e.g., Fig. 2, A through D versus E through H) elicited stronger or more selective activity and which gave a more pronounced vertical > lateral effect.
12. Statistical tests treating each neuron as an observation (Table 1, right) yielded a parallel set of significant effects.
13. Both theories of mirror-image confusion received some support from these findings. Adaptive encoding predicts the common finding that a neuron should discriminate poorly between lateral mirror images in either hemifield. Anatomical symmetry predicts the rare finding that a neuron selective for "b" in the right visual field should be selective for a "d" in the left visual field because the right half of the receptive field depends on the left hemisphere and vice versa [C. G. Gross, D. B. Bender, M. Mishkin, *Brain Res.* **131**, 227 (1977)].
14. Even the existence of neurons selective for opposite members of a mirror-image pair in opposite hemifields is compatible with perceptual confusion [I. Biederman and E. E. Cooper, *Perception* **20**, 585 (1991)], because, without information about stimulus location, their activity would not indicate which member of a pair is present.
15. For any bilaterally symmetric image, rotation in the viewing plane is equivalent to a mirror transformation about some axis (e.g., an "M" rotated 90° counterclockwise is the lateral mirror image of an "M" rotated 90° clockwise). In such a case, orientation selectivity can be interpreted as selectivity between mirror images. K. Tanaka, H.-A. Saito, Y. Fukada, and M. Moriya [*J. Neurophysiol.* **66**, 170 (1991)] show orientation tuning curves for eight neurons that were (i) responsive to a bilaterally symmetric image and (ii) tested with the image at orientations such that the stimuli formed lateral and vertical mirror-image pairs (figures 7, E through H, and 12, B through F and H). In all but one case (figure 12B), the difference in firing rate was greater for vertical than for lateral mirror-image pairs. These results, although interpreted by the authors strictly in terms of orientation selectivity, are in accord with our findings on mirror-image selectivity.
16. For any bilaterally symmetric object, certain rotations in depth produce a mirror transformation of the image. In such a case, selectivity for orientation in depth can be interpreted as selectivity between mirror images. The right and left profiles of a head are a representative case. Some temporal lobe neurons respond best to the two profiles (lateral mirror images) as compared to other views of the head [D. I. Perrett *et al.*, *Exp. Brain Res.* **86**, 159 (1991)]. However, testing with upright and inverted profiles (vertical mirror images) was not carried out.
17. Mirror-image equivalence is not the same as viewpoint invariance because a neuron responding best to views of an object that are mirror images may yet respond differently to other views [N. K. Logothetis, J. Pauls, T. Poggio, *Curr. Biol.* **5**, 552 (1995)].
18. Because population signals elicited by members of a lateral mirror-image pair are more similar than those elicited by members of a vertical pair, they are more likely to be rendered indiscriminable by noise, as presumably occurs on occasions of perceptual confusion.

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