ture studies with animal models of epilepsy and seizure may provide additional insights into the mechanisms, factors, and detailed temporal events that are important in nuclear reorganization, when specific chromosomal probes for these species become available. Although the X chromosome appears to be selectively altered in the present study, additional chromosomes should be sampled.

The current studies provide a novel structural approach for the delineation of nuclear changes in disease processes. Some of the observations here suggest different mechanisms than previously considered in human epilepsy. In the kindling model of focal epilepsy, repeated subclinical stimulation is thought to result in functional alterations in an epileptic focus which then assumes an independent capability to initiate seizures (*22*). Many studies have focused on long-term neuronal membrane potentiation effects and on synaptic modulation to explain kindling. We propose that specific nuclear patterns involving specific chromosome rearrangements may be more or less permanently established from a variety of causes (for example, trauma, developmental abnormalities, scarring, toxins and membrane/seizure activity itself), and that such nuclear changes underlie or give rise to intractable foci of neuronal activity. In this context, relevant genes on the X chromosome, possibly those arrayed near the centromere, deserve further attention.

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12. Briefly, samples were placed in picric acid–paraformaldehyde fixative in the operating room, and multiple blocks were cut under fixative 30 minutes to 1 hour later. Vibratome slices of ~35 μm were freeze-thawed (*5*) to increase penetration of DNA probes. Plasmids were labeled with bio 11 dUTP by nick translation to an average length of ~300 bp. Tissue slices and labeled DNA were denatured together and hybridized overnight at relatively high stringencies (60% formamide–2× SSC, 39°C) as described in (*6*), and T. C. Cremer *et al.*, *Exp. Cell Res.* **176**, 199 (1988). Hybrid molecules were detected either with strepavidin and biotinylated alkaline phosphatase, or alternatively with rabbit antibody to biotin (anti-biotin) followed by goat anti-rabbit peroxidase. Representative slices of the latter were flat embedded in Epon for thin sectioning; silver intensifications of peroxidase signals (*9*) prior to embedding increased the minor cytoplasmic signals disproportionately (Fig. 1), probably due to more rapid penetration of the cytoplasm in these ~3-minute reactions; BrdU was used to label late replicating DNA for banding of lymphocyte metaphase chromosomes in studies of probe specificity; BrdU bands were detected with fluoroscein isothiocyanate in an antibody sandwich technique, and hybridized sites were simultaneously detected with alkaline phosphatase (*6*). A Hamamatsu video camera attached to a digitizing board (512 by 512 by 8 bits pixel resolution, 256 gray levels) on a Vax Graphics Workstation II was used to examine and store 0.3-μm step optical sections for pseudocoloring, volume determinations, and solid model reconstructions. Programs have been described in detail (*6, 16, 17*) and source codes [J. Borden, M.D. thesis, Yale Medical School (1988)] are available with consent of the authors.
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Complementary Hemispheric Specialization in Monkeys

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Twenty-five split-brain monkeys were taught to discriminate two types of visual stimuli that engage lateralized cerebral processing in human subjects. Differential lateralization for the two kinds of discriminations was found; the left hemisphere was better at distinguishing between tilted lines and the right hemisphere was better at discriminating faces. These results indicate that lateralization of cognitive processing appeared in primates independently of language or handedness. In addition, cerebral lateralization in monkeys may provide an appropriate model for studying the biological basis of hemispheric specialization.

IT IS IMPORTANT TO KNOW WHETHER nonhuman primates have complementary specialization of the cerebral hemispheres corresponding to the well-known differences described for human beings (*1–5*), in whom some types of information are typically processed better by the left side of the brain and other types better by the right (*2*). For example, such information would help to determine whether the lateralization of handedness or language in humans led to more global hemispheric specialization for cognitive processing, as is frequently stated (*3, 4*), or whether hemispheric differences in cognition are independent of handedness

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and language.

Although examples of simple behavioral and neural asymmetries in animals have been known for a long time (*6*), evidence for laterality of more cognitive processes did not appear until 1970 (*7*). Despite the numerous biochemical, structural, and behavioral asymmetries reported since then (*6, 8*), only a few can be readily likened to human laterality (*9*), and none of the asymmetries have been associated with complementary superiorities of the two hemispheres in the same animal. In order to look more definitively for cognitive lateralization in animals, we tested each hemisphere of split-brain monkeys with types of stimuli that evoke lateralized processing in human subjects. These tests revealed a striking dissociation of processing, with difficult spatial cues more effectively handled by the left hemisphere and facial characteristics by the right.

Twenty-five monkeys (*Macaca mulatta*) underwent midsagittal division of the corpus callosum, hippocampal and anterior commissures, and the optic chiasm (*10*). Using a conventional split-brain training box (*11*), we tested the discriminative abilities of the surgically separated hemispheres by temporarily restricting vision to the eye now connected only to the hemisphere on the ipsilateral side and requiring a response with the contralateral hand, which is also connected to the same hemisphere. Depending on the problem taught, a vertical panel attached to the box contained one or two hinged screens that could be pushed by the monkey when stimuli were back-projected onto them. For each presentation of a stimulus, a correct response was rewarded with a banana-flavored pellet. All responses were followed by a 10-s interval before the next trial could begin. The hemisphere trained first was systematically varied within and between subjects in a design balanced for sex, handedness, and side of surgical approach (*12*). The relative difference in learning ability between the two hemispheres was assessed for each subject on each discrimination by calculating a dominance index, $DI = 100(R - L)/(R + L)$, where R represents the numbers of errors made by the right hemisphere while learning a problem (criterion was 90% correct responses in 40 consecutive trials) and L represents the analogous errors made by the left hemisphere. Thus, 100 indicates complete dominance by the left hemisphere, 0 indicates no dominance, and −100 indicates complete dominance by the right hemisphere. In tests for which the initial level of correct performance was of interest, hemispheric superiorities were estimated from the difference in percentage of correct responses in the first group of 20 trials made by the left and by the right sides (L − R). We looked for significant hemispheric differences in learning or performing discriminations based on three classes of visual stimuli—geometric patterns, oriented lines, and faces of monkeys—anticipating from human experiments little dominance for the first and significant lateralization for the other two classes.

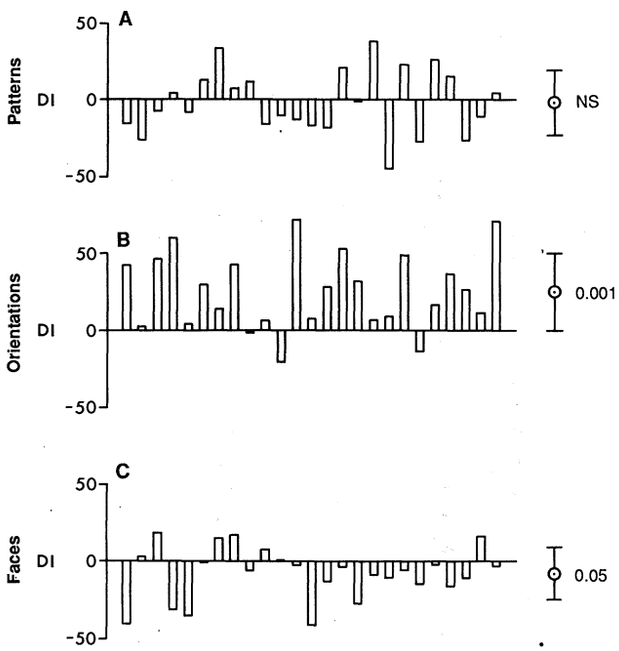

Fig. 1. Laterality for learning to discriminate three classes of visual stimuli. The first 12 bars represent male monkeys ordered from the most left-handed monkey on the left to the most right-handed on the right; the other 13 bars represent female monkeys similarly ordered. (**A**) The average DI for learning to discriminate geometrical patterns is plotted for each monkey. The overall DI (±SD) is not significant. (**B**) The overall DI for discriminating oriented lines indicates a significant left hemispheric advantage. (**C**) The overall DI for discriminating faces shows a significant right hemispheric advantage.

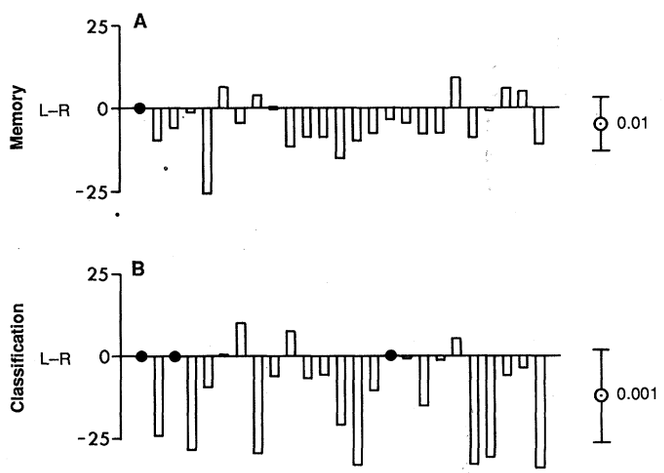

Fig. 2. Laterality for performing facial discriminations learned previously. The position of subjects is the same as in Fig. 1; untested monkeys are indicated by a dot. (**A**) The difference between the two hemispheres (L − R) in percentage of correct responses on the first 20 trials for memory of the eight facial discriminations shows a significant advantage for the right hemisphere. The solid bar at the ninth position represents a zero value of DI. (**B**) The difference between the two hemispheres (L − R) in percentage of correct classifications of new examples for four of the facial discriminations also demonstrates a significant right hemispheric advantage.

Several pairs of black and white patterns were presented as two-choice discriminations to test for laterality in differentiating geometric figures (*13*). Although individual subjects varied considerably (Fig. 1A), the proportion of monkeys with left superiority to those with right superiority was not different from chance [11:14, $\chi^2 = 0.36$, not significant (NS)], and the average DI was close to zero [DI = −2.00, $t(24) = -0.48$, NS]. Therefore, there is no evidence that monkeys learn to discriminate these control patterns more readily with either of the two hemispheres, in keeping with previous results for split-brain monkeys (*9*).

Four pairs of straight lines differing in slope by 15° (30°/15°, 75°/60°, 105°/120°, and 150°/165°) were used to test for laterality in discriminating orientation; for each pair the more vertical line was designated as positive. Only one stimulus of a pair was presented during each trial in order to increase the difficulty of the discrimination by requiring a comparison to a remembered line (*14*). The results (Fig. 1B) showed that most monkeys learned these discriminations more readily with the left hemisphere than with the right (22:3, $\chi^2 = 14.44$,

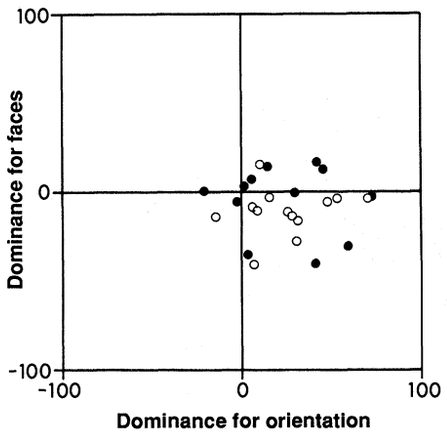

Fig. 3. Comparison of lateralization (DI) for learning facial and spatial discriminations. Open circles, female monkeys, and filled circles, male monkeys. Complementary hemispheric specialization within monkeys is indicated by the significant grouping of symbols in the lower right quadrant.

$P < 0.005$) and that the average DI was significantly different from zero [DI = 24.91, $t(24) = 4.99$, $P < 0.001$]. We conclude, therefore, that the left hemisphere is superior to the right for discriminating these tilted lines.

Laterality for processing facial characteristics was tested with eight discriminations, four based on distinguishing between colored photographs of two different monkeys that displayed the same expression, and four based on distinguishing between two facial expressions made by a single monkey. The monkeys and expressions varied across problems. Each discrimination was composed of five different colored photographs of the positive face intermixed with five different photographs of the negative face in an 80-trial repeating sequence. One stimulus at a time was presented on a screen 30° across in a Go/No-Go paradigm (*15*). The results (Fig. 1C) showed a right hemispheric advantage over the left in most monkeys when they were learning to discriminate facial characteristics (7:18, $\chi^2 = 4.84$, $P < 0.05$) and that the average DI was significantly different from zero [DI = −7.80, $t(24) = -2.30$, $P < 0.05$].

Further tests supported a right hemispheric advantage for facial processing even more strongly. Facial memory was tested in each hemisphere 6 months later for the eight facial discriminations. Most monkeys (Fig. 2A) immediately performed better with the right hemisphere (5:18, $\chi^2 = 7.35$, $P < 0.01$), and the difference in percentage of correct performance between the left and right hemispheres during the first 20 trials was significant [L − R = −5.03, $t(23) = -3.15$, $P < 0.01$]. Twenty-two of the subjects were tested again on four of the discriminations, each modified by the addition of 20 new photographs of the positive and negative faces. The ability to correctly classify the new photographs was determined by noting whether the monkeys pushed or withheld a response when presented with the new examples. Most monkeys (Fig. 2B) classified the novel photographs more accurately with the right hemisphere (4:18, $\chi^2 = 8.91$, $P < 0.005$), and the hemispheric difference in percentage of correct categorization of the new photographs was significant [L − R = −12.42, $t(21) = -4.07$, $P < 0.001$]. The average performance by the two hemispheres when classifying the new photographs was above chance from the start [percentage correct = 69.57, $t(21) = 14.64$, $P < 0.001$], showing that the characteristics originally learned were the identities and expressions of the faces, not irrelevant details present in each photograph. From all of these results we conclude that facial identity and expression are more readily discriminated by the right hemisphere than by the left.

If we plot the DIs for discriminating faces against the DIs for discriminating orientations (Fig. 3), we find that the distribution of DIs in the four quadrants is far from chance (16:6:1:2, $\chi^2 = 22.52$, $P < 0.005$) and that the correlation coefficient is not significant ($r = 0.01$). The finding that 16 of the 25 monkeys had both a left hemispheric advantage for orientations and a right hemispheric advantage for faces shows that complementary hemispheric superiorities characterized most of the subjects. The negligible correlation and the frequencies of occurrence in the four quadrants are exactly what would be expected if laterality for processing the two discriminations was determined independently (*2*). If the DI for faces is subtracted from the DI for orientations for each monkey, the average difference is significant [ΔDI = 32.92, $t(24) = 5.40$, $P < 0.001$]. Pairing the data in this way removes unrecognized lateral biases that might have occurred because of inadvertent asymmetries in surgery, training, or behavioral predispositions of particular monkeys. We conclude, therefore, that rhesus monkeys have complementary hemispheric superiorities for learning these facial and spatial discriminations.

How similar is this laterality in monkeys to hemispheric specialization in human beings? The absence of laterality for discriminating patterns and its presence when discriminating tilted lines and facial characteristics parallels the findings with human subjects (*3, 5*). For discrimination of orientation, however, most human studies indicate better performance by the right hemisphere. Because other experiments with monkeys have also demonstrated left hemispheric advantages for discriminating stimuli that differ in spatial detail, for example, direction of movement of a field of dots or the position of a dot within an outline square (*9, 16*), our results are not atypical and may reflect meaningful differences between species in behavioral strategy or structural laterality. For facial discriminations, it is likely that similar mechanisms are operative in both species because tests of facial recognition in human beings also reveal right hemispheric superiorities (*5*). In support of this, inverting facial stimuli eliminates the right hemispheric advantage in monkeys (*17*), just as it does with human subjects (*18*). Finally, the contrasting nature of hemispheric superiorities that we found in monkeys strikingly resembles the type of complementary specialization present in human beings (*2*).

Finding complementary hemispheric differences in monkeys indicates that hemispheric specialization for cognitive processing can evolve independently of human-like handedness or language. The suggestion is reinforced that lateralization of cognitive processing in human beings may have preceded the development of language (*19*) rather than the converse sequence, which is commonly favored (*3, 4*). On the practical side, the existence of hemispheric specialization in monkeys should permit more direct study of the neural mechanisms by which the two hemispheres differentially process information.

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12. There were 12 male and 13 female monkeys. The degree of handedness measured before surgery formed a flat distribution from completely left-handed to almost completely right-handed; seven male and four female monkeys reached for food more often with their left hand, whereas the others were nominally right-handed. Seven monkeys had the left hemisphere retracted during surgery, five the right, and 13 had retraction of each side in successive operations. Analysis of variance indicated no reliable differences in lateralization associated with any of these variables. The order in which the different sets of stimuli were taught to the monkeys varied considerably, depending on the availability of subjects and training boxes.
13. The average number of discriminations learned was 14 (range 4 to 18). Most problems were taught as simultaneous two-choice discriminations in which the monkey was rewarded for pushing the correct one of two stimuli, one of which was projected on the upper of two screens and the other on the lower. The location of the correct stimulus on the two screens was randomized across trials. The rest of the problems were learned as successively presented two-choice discriminations, a procedure described in (*14*). The two methods gave similar results and are combined. Seventeen monkeys were also tested with six Go/No-Go (*15*) discriminations; again, no laterality was found.
14. One stimulus was presented on the upper of two screens. For stimuli designated correct, the upper screen should be pushed; for incorrect stimuli, the lower screen should be pushed.
15. In order to receive a food reward the monkey had to push the photograph of the positive face within 5 s, or withhold pushing the photograph of the negative face for 5 s. Both normal and left/right mirror image orientations of the photographs were used to control for lateral asymmetries inherent in naturalistic stimuli. Because laterality for discriminating monkeys and expressions did not differ significantly, the results are combined for this report.
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Contributions of Quisqualate and NMDA Receptors to the Induction and Expression of LTP

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The contributions of two subclasses of excitatory amino acid transmitter receptors to the induction and expression of long-term potentiation (LTP) were analyzed in hippocampal slices. The quisqualate/kainate receptor antagonist DNQX (6,7-dinitroquinoxaline-2,3-dione) blocked 85% of the evoked field potential, leaving a small response that was sensitive to D-AP5 (D-2-amino-5-phosphonopentanoate), an *N*-methyl-D-aspartate (NMDA) receptor blocker. This residual D-AP5–sensitive response was of comparable size in control and previously potentiated inputs. High-frequency stimulation in the presence of DNQX did not result in the development of robust LTP. Washout of the drug, however, revealed the potentiation effect. Thus NMDA-mediated responses can induce, but are not greatly affected by, LTP; non-NMDA receptors, conversely, mediate responses that are not needed to elicit LTP but that are required for its expression.

SYNAPTIC RESPONSES IN THE HIPPOCAMPUS and other sites in the forebrain involve two types of excitatory amino acid receptors (*1*). Recent work suggests that LTP, a form of synaptic plasticity that may be involved in memory (*2*), changes those aspects of the response mediated by only one of these two receptor classes. Specifically, an antagonist of the NMDA receptor reduced the size of potentiated and control potentials in hippocampal slices by about the same absolute amount, in experiments with either single stimulation pulses in low Mg^{2+} media (*3*) or repetitive stimulation in normal medium (*4*) to elicit NMDA receptor–dependent responses. These results led to the curious conclusion that, although the currents initiated by the NMDA receptor are necessary for the induction of LTP, they are not themselves greatly influenced by the potentiation effect.

The introduction of drugs that selectively block non-NMDA excitatory amino acid transmitter receptors [for example, the quisqualate site (*5*)] allows for more direct tests of the idea that different classes of postsynaptic receptors contribute differentially to the induction and expression of LTP. Three experiments of this type are described here. First, we compared the effect of DNQX, a quisqualate/kainate receptor antagonist, on control and previously potentiated responses in hippocampal slices maintained in low-Mg^{2+} medium [reduction of extracellular Mg^{2+} attenuates the voltage-dependent blockade of the NMDA receptor ionophore (*6*)]. If NMDA-mediated currents are not affected by induction of LTP, then blocking the non-NMDA sites should eliminate the difference between control and potentiated responses. Second, we tested the prediction that high-frequency stimulation of the NMDA-mediated responses that remain after blockade of quisqualate receptors will not result in the development of a potentiation effect. Note, however, that this experiment could not distinguish between the absence of induction of LTP and the absence of its expression. Accordingly, we carried out a third study in which high-frequency stimulation was applied in the presence of DNQX to one of two pathways and then the drug was washed out of the slices. If potentiation can be triggered by repetitive stimulation of NMDA responses alone but is not expressed, then washing out the drug should reveal a difference between the two pathways.

Hippocampal slices (400 to 450 μm thick) were prepared from male Sprague-Dawley rats and maintained in an interface chamber under perfusion with a medium containing 124 m*M* NaCl, 3 m*M* KCl, 3 m*M* $CaCl_2$, 1 m*M* $MgCl_2$, 26 m*M* $NaHCO_3$, 1.25 m*M* KH_2PO_4, 10 m*M* glucose, and 2 m*M* L-ascorbate. The slices were incubated for 60 min in this medium before being switched to a medium containing only 20 to 100 μ*M* Mg^{2+}, a condition that substantially increases NMDA receptor–mediated potentials. After 1 hour of incubation, the flow was stopped, and the experiments were carried out in static conditions. Synaptic field potentials were recorded extracellularly in the stratum radiatum of CA1 and evoked by two independent groups of Schaffer-commissural afferents with two stimulating electrodes placed on either side of the recording pipette. The stimulation intensities were adjusted so that the electrodes evoked responses of similar sizes (between 2 and 3 mV) and, after 20 min of stable recordings, LTP was induced on one input by using short trains of high-frequency stimulation (ten bursts at 5 Hz com-

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