Neuropsychologia, Vol. 28, No. 6, pp. 529–546, 1990.
Printed in Great Britain.

0028-3932/90 $3.00 + 0.00

INDIVIDUAL VARIABILITY IN CORTICAL ORGANIZATION: ITS RELATIONSHIP TO BRAIN LATERALITY AND IMPLICATIONS TO FUNCTION

ALBERT M. GALABURDA,* GLENN D. ROSEN and GORDON F. SHERMAN

Dyslexia Research Laboratory and the Charles A. Dana Research Institute, Beth Israel Hospital; Department of Neurology, Beth Israel Hospital, 330 Brookline Avenue, Boston MA 02115, U.S.A. and Harvard Medical School, Boston, MA 02115, U.S.A.

Abstract—The human brain and the brains of most mammals studied for this purpose demonstrate hemispheric asymmetry of gross anatomical landmarks and/or architectonic cortical subdivisions. The magnitude as well as the direction of these cortical asymmetries vary among individuals, and in some species there exist significant population directional biases. The magnitude, if not the direction, of cortical asymmetry is found to predict for relative numbers of neurons comprising a given pair of hemispheric architectonic homologues such that the more asymmetric the region is, the smaller the number of neurons. Similarly, the more asymmetric a region is, the smaller the density of interhemispheric connections and (probably) the greater the density of intrahemispheric connections. Developmentally, the decrease in the number of neurons characterizing the more asymmetrical regions appears to reflect mainly increased unilateral ontogenetic cell loss, and diminished callosal connectivity might signify increased developmental axonal pruning. These relationships between cell numbers, callosal connections, and presumed intrahemispheric relationships can be entertained to explain variability in anatomo-clinical correlations for language function and aphasia between left- and right-handers and men and women.

INTRODUCTION

IT IS widely accepted that the two hemispheres of the human brain are functionally specialized for different cognitive, attentional and emotional tasks, at least as assessed by the effects of lateralized lesions or of hemispheric stimulation. However, this functional specialization shows substantial individual variability. For instance, the size and exact location of a left hemisphere lesion that will produce a given form of aphasia varies in different individuals, e.g. in some, a small inferior prefrontal lesion will lead to a permanent Broca's aphasia, whereas in others a much larger lesion is needed for the same syndrome to emerge [58], and many cases of crossed aphasia (arising from right hemisphere lesions) are known (see [34, 35, 39, 43, 83]). "Negative cases" are commonly found [6], particularly now that it is possible to discover "silent" language-area lesions in patients undergoing neuroimaging investigations, who never exhibited the expected behavioral deficits.

There is very little explanatory evidence for these variability effects in the literature, other than the intimation that the findings can be explained by random individual variability of

*To whom all correspondence should be addressed.

language area size, localization and degree of lateralization. However, some consistent clinical patterns after brain damage at variance with expected deficits are seen with regard to handedness (and to a lesser extent, and more controversially, with regard to gender). For example, left-handers (and non-right-handers in general) are more likely to become aphasic from lesions in the right hemisphere [31, 37, 60], and both right and left hemisphere lesions often lead to atypical aphasic syndromes in terms of language findings and duration of the deficit. Similarly atypical responses are seen in studies of functional hemispheric capacities [37, 38].

Non-right-handers are more likely to have anatomically symmetric brain areas related to language, or otherwise anomalous patterns of cerebral asymmetry. For example, the pattern of asymmetry of the Sylvian fissures that is most often found among right-handers (see below) is less common in non-right-handers, who instead exhibit symmetric Sylvian fissures and reverse asymmetry more commonly [40]. Interestingly, when the Sylvian pattern is symmetric, it corresponds bilaterally to the appearance of the left, not the right, Sylvian fissure (this pattern of two left–none right is seen in another structure; see below). A bias of left-handers for exhibiting more symmetric brain areas is seen in CT scans, whereby the typical left occipital petalia is found less often [50]. Finally, unexpected patterns of distribution of cerebral asymmetry are seen in individuals with developmental dyslexia [21], a group with an overrepresentation of non-right-handedness [26].

Although explanations involving anatomical variability have figured prominently in neuropsychology, and despite great advances in neuroscience methods capable of demonstrating even subtle anatomical individual differences, relatively little interest has been shown in the specification of rules and principles that determine patterns of anatomical variability in mammalian brains and their eventual relationship to function. Only recently heritability factors accounting for individual differences in sulcal patterns in human and animal brains have been studied, and it appears likely that inheritance plays an important role. However, issues of developmental plasticity having to do with environmental influences on brain morphology may also play a major role. For instance, the exact topography and size of distinct architectonic areas in the cortex reflect, at least in part, inputs from the periphery that can be environmentally modified [68]. Although the environmental manipulations have thus far been severe, e.g. involving enucleation of an eye or physical injury to a lateral geniculate nucleus in very young animals, it is possible that more subtle modifications of the visual input lead to limited cortical changes as well. Together with shifts in cytoarchitectonic topography and size, there may be accompanying changes in cortical connectivity.

Thalamic cortical afferents appear to exhibit a complementary relationship with callosal projections to cortical targets, at least in some species and in some cortical systems that have been studied [66]. This raises the possibility that variability in thalamic connectivity dictated by genetic and/or environmental factors is associated with variability in callosal connectivity. Callosal connections are most certainly at the core of interhemispheric relationships and the phenomenon of cerebral dominance, and variability in this system of connections is likely to be reflected in variability in hemispheric specialization and response to injury. In the present paper we will review variability in brain morphology at the level of gross anatomy, cytoarchitecture, and callosal connectivity with respect to cerebral lateralization, hoping to show that such variability relates in a consistent and predictable way to brain asymmetry and could explain some heretofore puzzling aspects of structural variability and functional lateralization.

HUMAN CEREBRAL ASYMMETRY

Planum temporale and Sylvian fissure

GESCHWIND and LEVITSKY [30] reported dominant patterns of gross anatomical asymmetry in the human cerebral hemispheres. They examined the outside border of the planum temporale (a language-related area on the posterior superior temporal plane) and found that 65 of the 100 brains they examined had a larger left planum, 11 had the reverse asymmetry, and 24 had no bias. They also found that the lateral border of the planum was, on the average, 33% longer on the left side. These results have since been confirmed in a number of different studies. In 100 adult brains, WADA *et al.* [77] reported that 82% were leftward-biased, 10% were rightward biased, and 8% showed no asymmetry; WITELSON and PALLIE [82] found that 69% of the brains they examined had a larger left planum, with 31% having the reverse asymmetry. Still other investigators looked at anatomical asymmetries of the planum temporale in autopsy material [73, 74], made direct measurements in living subjects through computerized axial brain tomograms [50, 67] and other radiological techniques [40, 48]. Asymmetries in the lengths of the Sylvian fissures were assessed directly on brains [73] and in endocranial cast markings and fossil skulls [33, 46, 47]. These studies taken together have demonstrated that the left planum is larger and the left Sylvian fissure longer in the majority of brains. Furthermore, these asymmetries are present early in life, as documented by studies of fetal and infant brains [7, 77, 82].

Cytoarchitectonic asymmetries have also been demonstrated in the superior temporal plane. We [24] measured the planum temporale and cytoarchitectonic area Tpt (an auditory association cortex located partly within the planum temporale) in four brains from the Yakovlev collection of normative brains and found striking asymmetries in area Tpt. Moreover, ranked cytoarchitectonic asymmetry correlated perfectly with the ranked planum asymmetry, which supported the hypothesis that gross asymmetries in the planum reflected asymmetries at the level of architecture. In summary, asymmetry in the temporal lobe has been demonstrated in linear, areal and volumetric measures.

Other gross anatomical asymmetries

WADA *et al.* [77] found that the area of the convexity of the frontal operculum was greater on the right. However, they observed greater folding on the left, and stated that the asymmetry could well be in the opposite direction if buried cortex was included. Evidence from arteriograms [48], which give an indirect measure of the size of the frontal operculum, indicates a larger left frontal operculum. One of us [20] measured the volume of architectonic area 44 within the pars opercularis of the frontal operculum in 10 brains and found an asymmetry in favor of the left in most cases.

The parietal lobe, too, is asymmetric. We [15] parceled the inferior parietal lobule and found that area PEG, which is architectonically linked to the non-language-related areas of the superior parietal lobule, was larger on the right, while language-related PG on the angular gyrus was larger on the left. In addition, there was a significant positive correlation between asymmetry of the planum temporale and of PG—both language-related—but no relationship between asymmetry of PEG and that of a language-related area.

BRAIN ASYMMETRIES IN OTHER ANIMALS

Functional cerebral lateralization has been demonstrated in non-human species. Generally, lateralization is less biased to the right or left at the population level than it is in

the human, but individual animals are significantly and often substantially lateralized [11]. Anatomical asymmetries are seen as well. YENI-KOMSHIAN and BENSON [84] measured Sylvian fissure lengths in chimpanzees and found a significantly longer left fissure. LEMAY and GESCHWIND [49] found no asymmetry in the lesser apes and monkeys, but reported a longer Sylvian fissure on the left in some great apes. GROVES and HUMPHREY [32] found the skull of the mountain gorilla to be asymmetric. CAIN and WADA [5] reported the right frontal pole of baboon brains to be longer, which is similar to the findings in humans of right frontal protrusion [36, 50].

Morphologic cerebral asymmetries were also found in Old World monkeys. FALK [18] analyzed the endocasts of 88 skulls representing 8 genera. These endocasts revealed details of external brain morphology, including sulcal patterns. The author found that, contrary to reports in humans and great apes, the right temporal sulcus and Sylvian fissure were longer. She hypothesized that the expanded frontal and parietal cortices on the left side obscured the corresponding Sylvian and temporal sulci.

There are reports of asymmetry in the habenular nuclei of some fishes, amphibians and reptiles (see [4]). For example, some species of frogs have two nuclei on the left and one on the right. In addition, there is a report [16] of a connectional and cytoarchitectonic asymmetry in one species of lizard, the slide-blotched lizard, whereby the habenula of this animal has two distinct architectonic nuclei on the left and one on the right, and the centripetal fibers of the parietal eye ganglion cells project only to one of the left nuclei.

CEREBRAL ASYMMETRIES IN THE RAT

The rat is becoming a useful animal for the study of brain asymmetry, both anatomical and behavioral. DIAMOND *et al.* [13] examined the forebrains of male Long-Evans rats at several ages ranging from 6 to 300 days, and found that the right neocortex was thicker than the left at all ages. Female rats had a slightly thicker left neocortex, although not significantly so [14]. Females ovariectomized at birth developed a significantly thicker right neocortex, thus mimicking the male pattern and moreover disclosing an environmental effect involving sex hormones in asymmetry variation. We found that male rats have larger right neocortical volumes, whereas females have a nonsignificant bias to the left. Architectonic cortical parcellation indicated that the primary visual and sensorimotor cortices tended to be larger on the right side, whereas the motor region was symmetric (unpublished observations). KOLB *et al.* [44] found that the right hemisphere weighed more in adult and 15-day-old Long-Evans rats, and that that hemisphere was longer, wider and taller, and the cortex thicker.

STUDIES OF CONNECTIONS IN THE RAT BRAIN RELEVANT TO BRAIN ASYMMETRY

The adult pattern of callosal connections

Visual cortex. The visual cortex is often asymmetric in the rat (see above), and visual areas are callosally connected. The main location of callosal cells of origin in area 17 (primary visual cortex) of the rat is along its border with area 18a [42, 57, 62, 63, 65]—an area that corresponds to the electrophysiologically-determined vertical meridian [75]. Neurons in all

cortical laminae are involved, although those in layers II, III and V are more heavily represented. Homotopic callosal terminations are also found at this border [8, 9, 41, 85]. Cells at the border of 17 and 18a send also heterotopic projections to the contralateral hemisphere [56], and some heterotopic callosal cells are found in the more medial portions of area 17 [63]. The rest of area 18a is devoid of callosal cells of origin, except for a few in the infragranular layers [63]. Area 18a receives patchy areas of callosal terminations, which presumably surround "islands" of striate–extrastriate projections [62]. Heterotopic callosal connections [56] have also been reported from area 18a to area 18b (medial to area 17).

Somatosensory–somatomotor cortices. Most callosal cells of origin of SM-I are found to surround the densely granular cores that characterize this area. There are no callosal terminations within these cores, which instead receive dense thalamocortical input. Callosal neurons originate in layers III and V and terminate reciprocally in a series of nearly vertical bands that appear columnar in coronal sections. A heterotopic projection to SM-II has also been reported, which has a similar appearance to that of the homotopic projection of SM-I [1, 80, 85].

The development of callosal connections in the rat

Normal development. During early development, cells giving rise to callosal projections are diffusely distributed in the cerebral cortex [41, 57, 65, 80]. Over the first 2 weeks of life, these cells progressively restrict themselves to discrete laminar and columnar locations [42, 52, 65]. Injections of anterograde tracers into the posterior cortex of the neonatal rat reveal that callosal terminations are initially distributed diffusely beneath the cortical plate, and penetrate the cortical plate widely (but inhomogeneously) by 6 days of age [57]. Soon after their entry into the cortex, the callosal afferents begin to restrict themselves to the border of area 17 and 18a, and achieve their mature pattern by 12 days of age [57]. There is some controversy as to the timing of these events, since some authors [65] contend that even as early as day 3, when the callosal afferents start penetration of the cortical plate, they do so only in the more restricted locations. In either event, it is thought that this progressive restriction of callosal cells of origin and terminations is likely to result from axonal pruning that occurs, at least in part, before their entry into the cortical plate [57, 65].

The pattern of development seen in the visual cortices is also noted in the parietal somatosensory–somatomotor cortices. Specifically, callosal cells of origin are distributed widely throughout these cortices early in development and progressively restrict themselves in the first 2 weeks of life to the adult pattern of laminar and areal specificity. Likewise, callosal terminations are diffusely represented beneath the cortical plate at birth and begin to enter the cortical plate around the third day of life. Initially, these fibers grow somewhat diffusely in SM-I, but they arrive at their more restricted adult-like distribution by the end of the first week of life [80].

Effects of experimental manipulation on the development of the corpus callosum. Variability in adult patterns of callosal connections undoubtedly relate, at least in part, to variability in developmental pruning of callosal axons. Neonatal enucleation has profound effects on the organization of the callosal connections of the visual cortices of the rat. After either monocular or binocular enucleation, loci within area 17 having callosal neurons and terminations expand [10, 52, 72], a finding also seen in hamsters and mice [64, 69, 70]. Anomalous connections following neonatal monocular enucleation are more prominent in the hemisphere ipsilateral to the remaining eye. On the other hand, binocular enucleation results in bihemispheric reduction of callosal labeling in the 17/18a border and more labeled

cells in the rest of area 17 [61]. Neonatal enucleation, however, does not disturb the developmental time course of callosal connectivity, and enucleation after day 6 has no permanent effects on the pattern of callosal connections in the visual cortex [61]. Less is known about the outcome of more subtle alterations of early visual cortical input on callosal connectional architecture, but it is likely that the plasticity demonstrated by severe early injury is available, albeit to a more limited extent, to physiological fluctuations taking place during normal development.

RECENT ASYMMETRY STUDIES IN OUR LABORATORY

Planum temporale size and asymmetry

Phrenologic thinking would hold that areas may become asymmetric as a result of the greater growth of one of the sides for the purpose of accommodating a demanding cognitive function on that side. For example, the left-sided language areas are ordinarily larger so that the left hemisphere can carry the burden of language activity in the brain. This extra growth might occur by genetic and/or epigenetic induction or instruction. On the other hand, asymmetry may result from the asymmetric pruning down of an area during development—as by selection, rather than induction, of a more restricted, and asymmetric, network of neurons and connections from a more numerous and symmetric one. For example, left hemisphere language areas are not really larger; right hemisphere language areas are actually "atrophied". But, as previously suggested (see [27, 28, 29]), asymmetry may not come about by either induction of selection, but rather symmetry and asymmetry may result simply from differences in allocation or storage of an anatomical substrate that does not vary in size (at least not with respect to asymmetry), whereby in asymmetrical cases the allocation is unequal and in symmetrical cases equal between the hemispheres.

Based on the above mentioned possibilities, *a priori* analysis of asymmetric and symmetric brain substrates yields three conceivable relationships, which are illustrated in Fig. 1. Asymmetric brains can result from (1) an increase in the size of one of the sides, (2) a decrease of one of the sides, or (3) a combination of an increase in one side and decrease in the other. In the first situation, the total amount of substrate would be greater in the asymmetric than in the symmetric case, whereas the opposite would be true in the second situation; in the third situation the total amount of brain substrate would be constant with respect to symmetry and asymmetry.

Measurements of the right and left planum areas (rather than of the lengths of the external border) were made in the same 100 brains studied by GESCHWIND and LEVITSKY [30]. As with their findings, a leftward asymmetry was seen in 63%, 21% were right-biased, and 16% were symmetric. The total planum area (right + left) correlated negatively with asymmetry coefficient (δ), indicating that as asymmetry increased, the total planum area decreased ($r = -0.530$, $t = 6.19$, d.f. $= 98$, $P < 0.001$). Moreover, the area of the smaller of the two plana significantly predicted for degree of asymmetry ($r = -0.831$, $t = 14.79$, d.f. $= 98$, $P < 0.001$), while there was no correlation between degree of asymmetry and the size of the larger planum ($r = -0.065$, $t = 0.64$, d.f. $= 98$, ns). These results support the hypothesis that the asymmetric case represents a reduced version of the symmetric case, and that reduction occurs primarily in one of the sides rather than in both sides [23]. It would appear, moreover, that left hemisphere language substrates do not vary among individuals with respect to lateralization, but rather it is the size of the right side which varies.

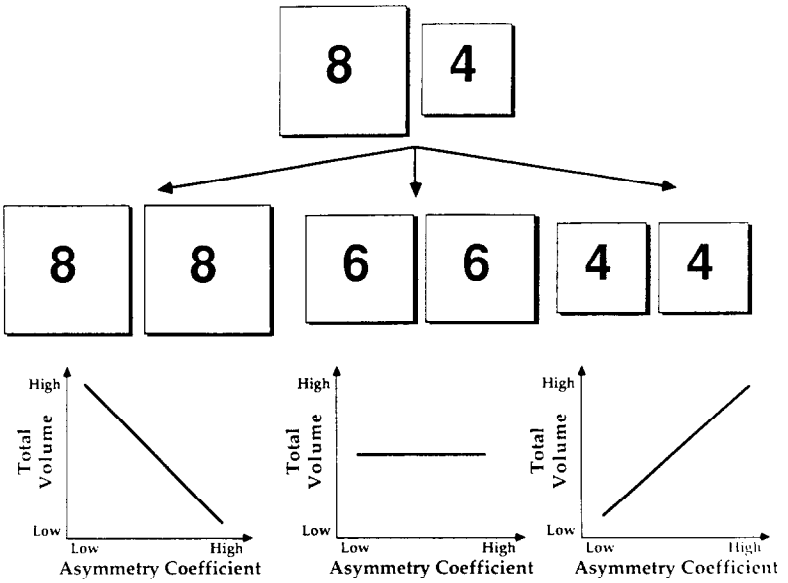

Fig. 1. Schematic illustration of the three hypothetical cases that relate an asymmetric brain substrate (top layer) to a symmetric one (middle layer). The symmetric substrate can be made up of two large sides (left middle layer), two small sides (right middle layer), or two medium-sized sides (center middle layer). Each of these possibilities predicts a different relationship between total amount of substrate (R + L) and degree of asymmetry (asymmetry coefficient (δ) = (R − L) ÷ [(0.5) (R + L)]). Thus, when the symmetric brain region is made up of two large sides, one would expect a negative correlation between these two variables (left bottom layer); a positive correlation would be predicted if symmetric brain regions were composed of two smaller sides (right bottom layer); in the case of the medium-sized symmetric brain regions, there would be no change in total volume with changes in asymmetry coefficient (center bottom layer). Also, see text.

HISTOLOGY OF ARCHITECTONIC ASYMMETRY

There are three ways by which a cortical area can be reduced in size: by diminishing the number of neurons, by diminishing the space (increasing the packing density) between neurons (such as by diminishing neuronal or extraneuronal components), and by a combination of both factors. There are, therefore, three hypothetical cases that could account for the difference between asymmetric and symmetric brain substrates: (1) unilateral decrease in cell numers in the asymmetric case, (2) unilateral increase in cell-packing density (decreased space between cells) in the asymmetric case, or (3) a combination of increased density and decreased numbers of cells (Fig. 2).

In order to distinguish among these possibilities, we examined asymmetry coefficients and neuronal packing densities in the visual cortex of the rat (area 17). This region was chosen because its borders were easy to delineate with precision, and because previous research had shown it to be asymmetric, both in individual animals and in population samples ([12]; personal observations). As in the human planum temporale, there was a negative correlation between the total volume of 17 and asymmetry coefficient ($r = -0.489$, $t = 2.31$, d.f. = 17, $P < 0.05$). Furthermore, again suggesting that volumetric changes occur predominatly in one side as asymmetry coefficient varies, the smaller of the two sides was inversely related to degree of asymmetry ($r = -0.609$, $t = 3.17$, d.f. = 17, $P < 0.05$) but not the larger side ($r = -0.347$, $t = 1.53$, d.f. = 17, ns). Thus, as with humans, rats with asymmetric brain regions have smaller overall substrates than those that are symmetric.

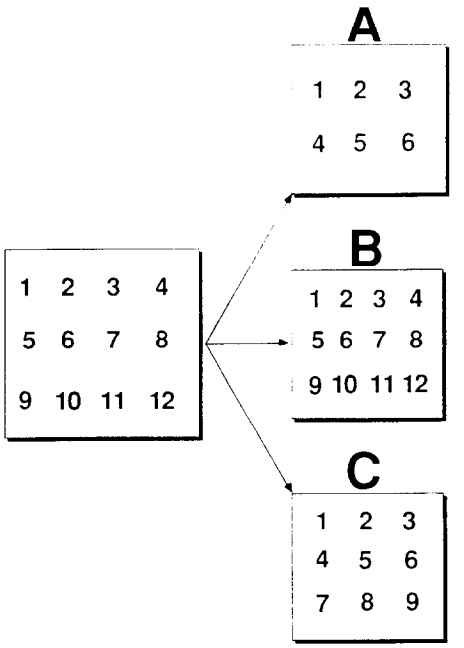

Fig. 2. Schematic diagram demonstrating the three hypothetical cases of histologic differences between the two sides of an asymmetric brain region. Changes could occur in (A) cell numbers, with no changes in cell-packing density, (B) cell-packing density, with no changes in cell numbers, or (C) changes in both cell-packing density and cell numbers. Likewise, symmetric and asymmetric substrates (see Fig. 1), could differ by cell-packing density, cell numbers, or a combination of both.

Our neuronal counts in area 17 disclosed no consistent relationship between asymmetry of cell-packing density and asymmetry of architectonic volume, thus indicating that asymmetric substrates differ in the number of neurons [22]. Also, another study [68] showed that reduction in cortical cytoarchitectonic perimeter resulted from lowering of cell numbers, not increased cell-packing density; in another situation, asymmetry of neuronal numbers has been documented in the lateral geniculate nucleus [79]. Finally, preliminary data from our laboratory on developmental neuronal death showed that with changes in neuronal numbers predictable changes in area asymmetry can be seen (unpublished observations).

It is not surprising that changes in cell numbers, not cell-packing density, account for the bulk of volumetric asymmetry. For example, some architectonic asymmetries in the human brain may reach a sixfold difference between the sides. Side differences in cell-packing density large enough to produce this degree of asymmetry would distort the cytoarchitectonic appearance of the areas to such a degree that their identification as hemispheric architectonic homologues would not be possible.

ASYMMETRY AND INTERHEMISPHERIC CONNECTIVITY

It is possible that differences in regional asymmetries, such as seen in left-handers [40] and in left- and right-handed developmental dyslexics [25], is reflected in the cortical

connectivity. One set of studies (reviewed in [27–29]) on the pyramidal decussations in the human medulla shows asymmetries in the pattern of decussation and in the numbers of decussating fibers in this structure, and the authors suggest that the pattern may vary according to handedness. Furthermore, a study has shown the left-handers have greater midsagittal callosal cross-sectional areas [81], although nothing is known about numbers and sizes of axons in the right- and left-handed cases.

The corpus callosum has been implicated in the phenomenon of cerebral dominance (see [78]), a reasonable role for a structure that determines to a major extent interhemispheric relationships. As noted, the rat's visual cortices send and receive interhemispheric projections traveling in the corpus callosum, a finding that together with their asymmetry status suggested them as a suitable model for studying the relationship between callosal connectivity and magnitude of cortical asymmetry. Therefore, we sectioned the corpora callosa of 15 90-day-old Wistar rats and processed the brains in serial histologic sections using a modification of the FINK–HEIMER method [19] for demonstrating degenerating axon terminals. An adjacent series was mounted onto slides and stained with cresyl violet for cytoarchitecture. Eight rats had nearly complete destruction of the corpus callosum, together with minimal extracallosal involvement. Dark-field images from the Fink–Heimer series were digitized and saved to disk, and architectonic area SM-I was parceled on the Nissl stained sections. The two series were video-overlayed, and the borders in the Nissl series were traced onto the Fink–Heimer series. The percent degeneration of callosal terminations and the non-directional asymmetry coefficient $[\delta = (R - L) \div \{(0.5)(R + L)\}]$ were determined for SM-I [86] in each animal.

There was an inverse relationship between $\delta_{SM\text{-}I}$ and the average density of terminations in this area ($r = -0.899$, $t = 4.76$, d.f. $= 6$, $P < 0.05$). This indicated that the more symmetric areas had a greater percentage of callosal terminations than the more asymmetric ones. This greater percentage of callosal terminations might reflect greater number of callosal fibers in the brains that are more symmetric. Furthermore, because the development of callosal connectivity involves some pruning and redirection of axons [57, 65], greater numbers of callosal fibers in the symmetrical brains would implicate diminished pruning and redirection in these brains. The fact that left-handers, who tend to be more symmetric in neuroanatomic studies, have been found to exhibit greater midsagittal cross-sectional areas of their corpora callosa is supportive of the notion of greater numbers of callosal fibers in symmetric brains.

In brains with asymmetric areas, which are characterized by fewer neurons than symmetrical areas (see above), a diminution in the number of callosal fibers would be expected even if only some of the neurons lost are callosally related. Furthermore, the loss of callosal fibers would be expected to be proportional to the loss of callosally related cell somata, and consequently the percent degeneration of callosal projections would not be expected to change. However, the decrease in the percent degeneration of callosal projections in these cases suggests that callosal fibers are lost out of proportion to neuronal bodies. We would suggest that some of the neurons that are not lost in the brains with asymmetric areas withdraw their callosal projections and re-route them within the ipsilateral hemisphere during development. This set of events would lead to a situation whereby brains with symmetric areas are organized in a relatively interhemispheric fashion, while those with asymmetric areas are relatively more intrahemispherically connected. The notion that the more symmetrical brain areas are more interhemispherically organized while those that are more asymmetrical are more intrahemispherically connected may lead to the following functional hypotheses.

HANDEDNESS AND SEX DIFFERENCES IN HEMISPHERIC SPECIALIZATION: A STRUCTURAL–FUNCTIONAL HYPOTHESIS

There have been numerous discussions in the literature regarding handedness- and sex-related differences in functional hemispheric specialization (for instance, see [53]). Based on findings of cytoarchitecture and callosal projections *vis à vis* anatomical asymmetry and symmetry, significantly different patterns of anatomical asymmetry might be compatible with similar and even paradoxically different patterns of functional lateralization between left- and right-handers and between the sexes. For example, it has been suggested that left-handers are more symmetrical [40], and that on the average the female brain is anatomically more asymmetrical (usually to the left) and that of the male less asymmetrical in either direction [27, 28, 29] (see Fig. 3). These observations combined would tend to group maleness and left-handedness on one extreme and femaleness and right-handedness on the other, with left-handed men and right-handed women being most distant *vis à vis* asymmetry. Many of the functional data would support the view that left-handers are less lateralized for language [37, 38], but also most of the available gender data show that women are less lateralized for language than men, which is not predicted by the anatomical claim that female brains are more asymmetric [27–29]. A model based on the findings of anatomy of asymmetry described above is proposed that attempts to deal with this paradox.

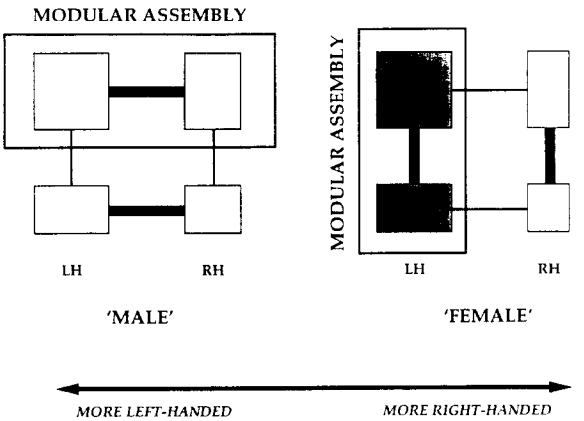

Fig. 3. Hypothetical cases of the male–female/left-handed–right-handed neural styles of organization for language function. In the male/left-handed, the neuronal (modular) assemblies are conceived as less asymmetrical, more contralaterally interconnected, and less ipsilaterally interconnected. In the female/right-handed, the assemblies are conceived as more asymmetrical, less contralaterally interconnected, and more ipsilaterally interconnected. Moreover, the intact male case is conceived as less efficient (light shading) and the female's more efficient (dark shading). Also see text.

The assumptions of the model are that the intact male human is on the average less good in language than the female [53] and that his brain is anatomically more symmetric, interhemispherically more connected (and "dependent") and intrahemispherically less connected (and "dependent"). The typical left-handed man would be even more strictly symmetric and interhemispherically connected. Contrariwise, the intact female human is on the average better at language and her brain is anatomically more asymmetric, intrahemispherically more connected (and "dependent"), and interhemispherically less

connected (and "dependent"). The typical right-handed woman would be most asymmetrical and intrahemispherically connected.

The model, as stated, makes the following functional predictions: dichotic and tachistoscopic studies attempting transiently to isolate the hemispheres would demonstrate linguistic asymmetry in both men and women, mostly in favor of left hemisphere superiority in both cases. In typical left-handed men the functional asymmetry would be least striking, whereas in right-handed women it would be most striking. The functional capacity of the right side would appear greater in women than in men, because the women's right-sided component is (1) part of a more efficient system, (2) less connected to the left and therefore less dependent on callosal information, and (3) because stimuli arriving in the right hemisphere can be checked against additional right hemisphere information *via* its relatively superior intrahemispheric connectivity (see Fig. 3, right), particularly in strongly right-handed, asymmetric women. Conversely, the functional capacity of a man's right side would appear to be inferior to that of the woman, because it is part of a system with diminished capacity, because it has greater connectivity with (and dependence on) its left hemisphere component that is not tapped by the time-restricted test, and because it can profit less from other right hemisphere structures by virtue of its diminished intrahemispheric connectivity. Symmetric left-handed men might show a lesser degree of interhemispheric functional asymmetry, but the degree of competence of at least the left hemisphere might be diminished by comparison to other men and women in general. Therefore, greater anatomical asymmetry of the type proposed in this model leads to paradoxically greater non-dominant functional capacity, as assessed by dichotic and tachistoscopic studies. It is possible, therefore, that (particularly extremely right-handed) women are not less lateralized, but simply fare better in language with their non-dominant hemispheres within the constraints of unilateral hemisphere testing, while (again extremely left-handed) men are not more lateralized but instead require bihemispheric participation to perform linguistic tasks that are even of an inferior level.

The model also makes predictions as to the effects of injury to neuronal assemblies involved in language function. Thus, right hemisphere damage would tend spare language in men and women, as well as right-handers, because in each the dominant portion of the system, which is of comparable size (albeit not in "quality"), remains unhurt (Fig. 4). However, it is expected that in men sparing of function may be less complete or consistent under close scrutiny, because the uninjured portion is less good and moreover has diminished access to uninvolved ipsilateral regions that might help in compensating for the injury. Left-handed men who exhibit the greatest symmetry might suffer most from right hemisphere damage, while right-handed women would suffer least.

Left hemisphere damage (Fig. 5) would lead to aphasia in both men and women, and right- and left-handers, because the dominant portion of the language area is injured. However, compared to men, small left hemisphere lesions in women would be apt to be less significant functionally, because a smaller proportion of the more efficient left hemisphere extended network would be affected. Thus, small left hemisphere lesions may be associated with frank aphasia less often in women than in men. On the other hand, there may be less distinction in the aphasic symptoms resulting from lesions in different left hemisphere sites in women because these sites are connectionally (and functionally) more interdependent than in men. The most symmetric left-handed men would be equally likely to become aphasic from left- as from right-sided lesions.

Recovery from aphasia must depend upon the anatomical characteristics of the lesion as

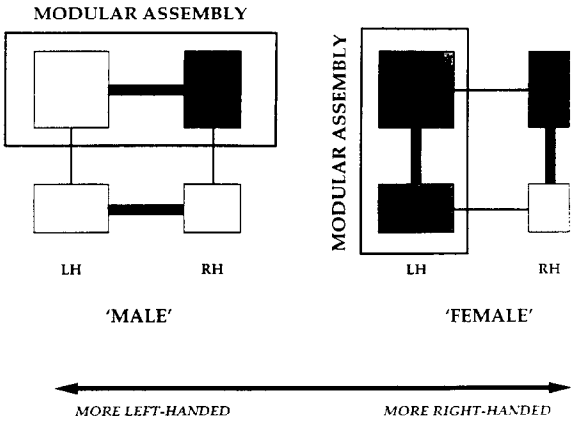

Fig. 4. The hypothetical male/left-handed and female/right-handed cases with right hemisphere damage (in black). In both cases a major portion of the language substrate is preserved, and no aphasia ensues. However, in the male/left-handed case subtle linguistic deficits might be found. Also see text.

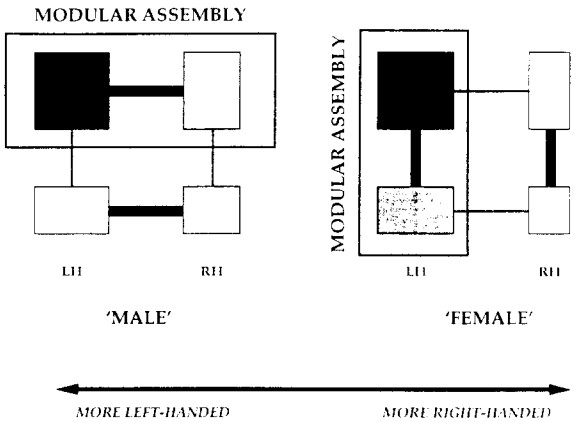

Fig. 5. The hypothetical male/left-handed and female/right-handed cases with left hemisphere damage (in black). In both cases the major portion of the language substrate is injured, and aphasia ensues. Small lesions may be less damaging functionally to the female case. Also see text.

well as on issues of plasticity and repair [54] and the personal strategies used to solve linguistic tasks (which depends in part on the learning history [45]), all of which may differ between the sexes. Assuming only issues of asymmetry and symmetry it is expected from the present model that recovery would occur predominantly from preserved contralateral structures in men, particularly left-handed, symmetric men, which are allegedly poor at linguistic tasks, and from preserved ipsilateral structures in women, particularly strongly right-handed women. Thus, bilateral hemisphere damage would be more serious and less likely to result in recovery in men (Fig. 6, top), while large left hemisphere damage would be more serious and less likely to result in recovery in women, particularly asymmetric, right-handed women (Fig. 6, bottom).

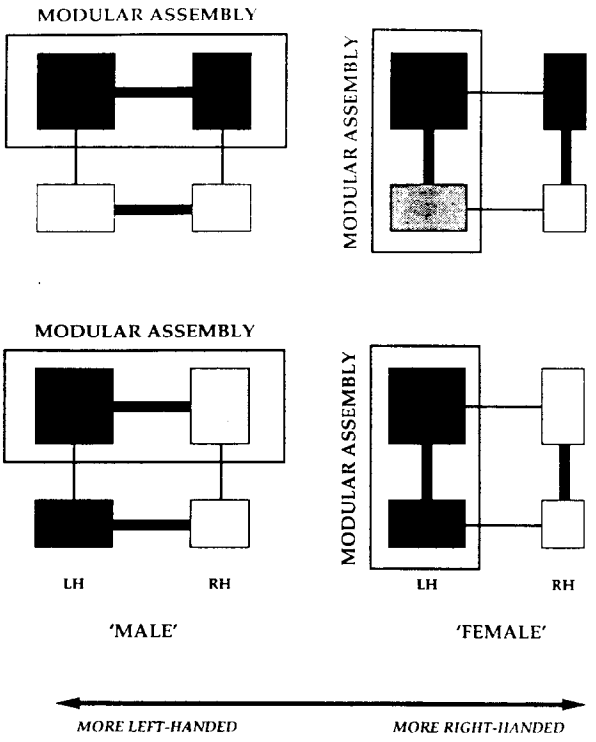

Fig. 6. The male/left-handed and female/right-handed cases with bilateral hemisphere damage (in black; top). In this situation recovery may be superior in women. The male/left-handed and female/right-handed cases with very large left hemisphere damage (in black; bottom). In this situation recovery may be superior in men, depending on how competent the preserved right female hemisphere is. Also see text.

An additional point in the discussion of this model is that the "male" and "female" systems differ in the number as well as in the geometry of neurons and connections, which may render them qualitatively as well as quantitatively different, leading to separate and distinct functional strategies in the two sexes. Therefore, location and size of lesion need not alone predict for functional deficits, since the remaining uninjured tissue is also of a different type in the "male" and "female" cases. Preliminary differences in processing style according to laterality, for instance, have been reported by BEVER *et al.* [3].

DEVELOPMENT OF ASYMMETRY

Most of the early work on the ontogenesis of lateralization looked at functional effects of early unilateral brain damage. From the work of BASSER [2], LENNEBERG [51] proposed the theory of equipotentiality—that language lateralization develops from an initial state in which both hemispheres are equally capable of language acquisition. Evidence gained since that time has established, however, that some lateralization of function is present at least at the time of birth [55]. Auditory evoked potentials in infants indicate greater left hemisphere activation during presentation of speech stimuli and greater right hemisphere activation during musical stimuli [59]. Infants have a left ear advantage for music and non-speech

sounds and a right ear advantage for speech [17], although there is some disagreement [76]. Perhaps in keeping with the notion of early functional lateralization, asymmetry of the planum temporale is visible already at 31 weeks of fetal age [7]. At that time generation of neurons destined to the neocortex and neuronal migration are virtually completed, and it is possible that asymmetry arises as a result of post-generational/post-migrational maturational effects. Conversely, the post-migrational period may be the earliest time at which asymmetries can be easily detected, but they could have been present earlier.

The fact that the combined volumes of brain regions is greater in symmetric rather than asymmetric cases limits the possibilities by which asymmetric brain development arises. Thus, if the initial state of an area is asymmetric, then adult asymmetry is simply the result of preservation of the earlier pattern, while symmetry might reflect a later excessive growth of the normally smaller side, i.e. a difference in cell proliferation between the hemispheres. Conversely, an asymmetric adult brain area derived from a symmetric initial state would require a relative increase in neuronal loss on the side that ends up smaller. Alternatively, it could be that asymmetry begins as asymmetric germinal zones while symmetry begins as symmetric germinal zones, whereby the decision to generate and preserve equal or unequal numbers of neuroblasts in these zones was made earlier.

Therefore, the potential factors that can influence asymmetric development of the hemispheres are (1) the number of original germinal cells, (2) the number of cell divisions on either side, (3) and/or neuronal loss on either side, either by cell death or by shifts in the placement of architectonic borders such that whole segments of cortex are lost to the smaller side and instead assigned to a neighboring area prior to architectonic differentiation. Preliminary studies aimed at distinguishing among these factors have been carried out in our laboratory.

Time-mated Wistar rats were injected intraperitoneally with [^{3}H]thymidine on embryonic (E) days 13, 15, 17, 19, and 21. The pups from these mothers were killed on post-natal (P) day 5, 10, 30, or 60, and the brains were processed for autoradiography. There were few labeled neurons in the cerebral cortex of animals injected on E13 and E21, presumably because these injection dates fell outside the period of significant neuronogenesis, and those litters were excluded from the analysis. In addition, animals killed on P5 were excluded because of suboptimal histology and, more importantly, because of a general lack of architectonic differentiation (for quantitative purposes) at that age.

The numbers of labeled and unlabeled neurons were counted in animals injected on E15, E17, and E19 and killed on either P10, P30, or P60, and the ratios of labeled to unlabeled neurons were computed, which provides an estimate of the rates of neuronal production. No hemispheric differences in this measure were detected in either symmetric or asymmetric cortices [71]. Although subtle side differences in neuronogenesis could have been missed, we can consider more seriously the possibility that hemispheric differences in neuronal numbers in asymmetrical cortical areas reflect post-migrational asymmetry in neuronal loss by cell death or border shifting, or pre-migrational asymmetry in the original number of neuroblasts in the germinal zones.

The argument in favor of cell loss as the relevant mechanism is stronger than that for border shift. Thus, for instance, if area A becomes asymmetric because a border is moved "in", then area B, adjacent to A, would become asymmetric because a border is moved "out". In the latter case, an asymmetric area B would be overall larger than a symmetric area B, which would then violate the repeated finding (see above) that asymmetric areas are overall smaller symmetric areas.

The argument of asymmetric vs symmetric germinal zones only takes the problem back in ontogenetic time without changing the choices, whereby original germinal zones must undergo either border shifting or neuroblast death in order to become asymmetric and smaller at the same time. Again, asymmetric neuroblast death becomes the likelier mechanism over border shifting for the same reasons given for asymmetry generation during the post-migrational period.

We cannot exclude the possibility that asymmetry may already be present in the germinal zones. However, preliminary results show that asymmetry increases during post-migrational development in brain areas that are destined to be asymmetric, an increase that is accompanied by asymmetric post-migrational cell loss (unpublished observations). We can tentatively conclude that even if asymmetry is already present in the germinal zones, additional regressive factors, i.e. cell death, contribute to asymmetry formation in the post-migrational cortex.

FINAL COMMENTS

We have argued that the topography of architectonic areas on the cerebral cortex can vary in size and connectivity as a function of cerebral asymmetry. This anatomical variation is apt to be reflected in variability in functional architectures and in the effects of brain injury. The networks of neurons that emerge as a result of the greater or lesser development of cortical asymmetry differ in the numbers of cells and connections comprising them, and it is these sorts of differences, in addition to differences in learning and cultural experience, which can be more easily conceived to underlie variability in behavioral capacities and cognitive styles. Recently, for instance, BEVER *et al.* [3] reported distinctive linguistic styles in two groups of right-handers that differed by the presence in one group, but not the other, of left-handed relatives. Interestingly, subjects in the group with left-handed relatives derived meaning from discourse less from syntax and more from semantics than did those without such relatives. As we have learned that left-handedness is characterized by greater symmetry in the ordinarily asymmetrical language regions [40], the differences between the two groups might conceivably relate to the usage by the group with left-handed relatives of larger networks, containing more neurons and connections. In support of this hypothesis there is some computational data showing that synthetic networks with more processing units and connections learn well but require more trials for learning rules and arriving at generalizations (G. E. Hinton, oral communication to *Nature's* 11th International Conference, Cambridge, Massachusetts, U.S.A., 28–29 September 1988).

Injury to the cortex may result in different behavioral consequences based on the underlying cellular and connectional structure, which depends in part on brain asymmetry, and on the part of the network that is damaged. Similarly, development of these structures may lead to errors in which conceivably too many neurons and interhemispheric connections might be lost on one side leading to overly reduced asymmetrical networks and callosal deficits (which we suggest characterizes the underlying substrate of the callosal agenesis syndromes). Conversely, as we believe applies to developmental dyslexia [21, 25], inadequate numbers of cells and processes may be pruned, resulting in exuberant networks that fail in ways that exaggerate the characteristics of left-handed symmetrical brains.

With improving methods in neuroscience, an expanding database on the steps involved in the establishment of interconnected neuronal assemblies during mammalian brain development, and increasing sophistication of computational models that take into

consideration innate properties of real neuronal assemblies, it will be possible to test these hypotheses in animal models and to model them in computational devices.

Acknowledgements—The research cited in the present paper was supported, in part, by NIH grants HD 20806, HD 19819, by grants from the Carl W. Herzog Foundation and the Research Division of the Orton Dyslexia Society. The authors wish to to thank Francisco Aboitiz, Brian Butler, Joan Corsiglia, Kari Emsbo, Peter Humphreys, Walter Kaufmann, Claudia Mehler, Jennifer Stone and Antis Zalkalns for their collaboration and technical assistance.

REFERENCES

1. AKERS, R. M. and KILLACKEY, H. P. Organization of corticocortical connections in the parietal cortex of the rat. *J. comp. Neurol.* **181,** 513–538, 1978.
2. BASSER, L. S. Hemiplegia of early onset and faculty of speech with special reference to the effects of hemispherectomy. *Brain* **85,** 427–460, 1962.
3. BEVER, T. G., CARRITHERS, C., COWART, W. and TOWNSEND, D. J. Language processing and familial handedness. In *From Reading to Neurons*, A. M. GALABURDA (Editor). MIT Press/Bradford Books, Cambridge, Massachusetts, 1989.
4. BRAITENBERG, V. and KEMALI, N. Exceptions to bilateral symmetry in the epithalamus of lower vertebrates. *J. comp. Neurol.* **138,** 137–146, 1971.
5. CAIN, D. P. and WADA, J. A. An anatomical asymmetry in the baboon brain. *Brain Behav. Evol.* **16,** 222–226, 1979.
6. CAPPA, S. F. and VIGNOLO, L. A. CT scan studies of aphasia. *Human Neurobiol.* **2,** 129–134, 1983.
7. CHI, J. G., DOOLING, E. C. and GILLES, F. H. Gyral development of the human brain. *Ann. Neurol.* **1,** 86–93, 1977.
8. CIPOLLONI, P. B. and PETERS, A. The bilaminar and banded distribution of the callosal terminals in the posterior neocortex of the rat. *Brain Res.* **176,** 33–47, 1979.
9. CUSICK, C. G. and LUND, R. D. The distribution of the callosal projection to the occipital visual cortex in rats and mice. *Brain Res.* **214,** 239–259, 1981.
10. CUSICK, C. G. and LUND, R. D. Modification of visual callosal projections in rats. *J. comp. Neurol.* **212,** 385–398, 1982.
11. DENENBERG, V. H. Hemispheric laterality in animals and the effects of early experience. *Behav. Brain Sci.* **4,** 1–49, 1981.
12. DIAMOND, M. C., DOWLING, G. A. and JOHNSON, R. E. Morphological cerebral cortical asymmetry in male and female rats. *Exp. Neurol.* **71,** 261–268, 1981.
13. DIAMOND, M. C., JOHNSON, R. E. and INGHAM, C. A. Morphological changes in the young, adult and aging rat cerebral cortex, hippocampus, and diencephalon. *Behav. Biol.* **14,** 163–174, 1975.
14. DIAMOND, M. C., YOUNG, D., SINGH, S. S. and JOHNSON, R. E. Age-related morphological differences in the rat cerebral cortex and hippocampus: male–female; right–left. *Exp. Neurol.* **81,** 1–13, 1981.
15. EIDELBERG, D. and GALABURDA, A. M. Inferior parietal lobule. Divergent architectonic asymmetries in the human brain. *Archs Neurol.* **41,** 843–852, 1984.
16. ENGBRETSON, G. A., REINER, A. and BRECHA, N. Habenular asymmetry and the central connections of the parietal eye of the lizard. *J. comp. Neurol.* **198,** 155–165, 1981.
17. ENTUS, A. K. Hemispheric asymmetry in processing of dichotically presented speech and nonspeech stimuli by infants. In *Language Development and Neurological Theory*, S. J. SEGALOWITZ, and F. A. GRUBER (Editors). Academic Press, New York, 1977.
18. FALK, D. Cerebral asymmetry in Old World monkeys. *Acta Anat.* **101,** 334–339, 1978.
19. FINK, R. P. and HEIMER, L. Two methods for selective silver impregnatation of degenerating axons and their synaptic endings in the central nervous system. *Brain Res.* **4,** 369–374, 1967.
20. GALABURDA, A. M. La région de Broca: observations anatomiques faites un siècle après la mort de son découvreur. *Rev. Neurol.* **136,** 609–616, 1980.
21. GALABURDA, A. M. The pathogenesis of childhood dyslexia. In *Language, Communication, and the Brain*, F. PLUM (Editor). Raven Press, New York, 1988.
22. GALABURDA, A. M., ABOITIZ, F., ROSEN, G. D. and SHERMAN, G. F. Histological asymmetry in the primary visual cortex of the rat: implications for mechanisms of cerebral asymmetry. *Cortex* **22,** 151–160, 1986.
23. GALABURDA, A. M., CORSIGLIA, J., ROSEN, G. D. and SHERMAN, G. F. Planum temporale asymmetry: reappraisal since Geschwind and Levitsky. *Neuropsychologia* **25,** 853–868, 1987.
24. GALABURDA, A. M., SANIDES, F. and GESCHWIND, N. Human brain: cytoarchitectonic left–right asymmetries in the temporal speech region. *Archs Neurol.* **35,** 812–817, 1978.
25. GALABURDA, A. M., SHERMAN, G. F., ROSEN, G. D., ABOITIZ, F. and GESCHWIND, N. Developmental dyslexia: four consecutive cases with cortical anomalies. *Ann. Neurol.* **18,** 222–233, 1985.

26. GESCHWIND, N. and BEHAN, P. O. Left-handedness: association with immune disease, migraine, and developmental disorder. *Proc. natn Acad. Sci.* U.S.A. **79,** 5097–5100, 1982.
27. GESCHWIND, N. and GALABURDA, A. M. Cerebral lateralization. Biological mechanisms, associations, and pathology: I. A hypothesis and a program for research. *Archs Neurol.* **42,** 428–521, 1985.
28. GESCHWIND, N. and GALABURDA, A. M. Cerebral lateralization. Biological mechanisms, associations, and pathology: II. A hypothesis and a program for research. *Archs Neurol.* **42,** 521–552, 1985.
29. GESCHWIND, N. and GALABURDA, A. M. Cerebral lateralization. Biological mechanisms, associations, and pathology: III. A hypothesis and a program for research. *Archs Neurol.* **42,** 634–654, 1985.
30. GESCHWIND, N. and LEVITSKY, W. Human brain: left–right asymmetries in temporal speech region. *Science* **161,** 186–187, 1968.
31. GLONING, I., GLONING, K., HAUB, G. and QUARTEMBER, R. Comparison of verbal behavior in right-handed and nonright-handed patients with anatomically verified lesions of one hemisphere. *Cortex* **5,** 43–52, 1969.
32. GROVES, C. P. and HUMPHREY, N. K. Asymmetry in gorilla skulls: evidence of lateralized brain asymmetry. *Nature, Lond.* **244,** 53–54, 1973.
33. GUNDARA, N. and ZIVANOVIC, S. Asymmetry in East African skulls. *Am. J. Phys. Anthropol.* **28,** 331–338, 1968.
34. HAALAND, K. Y. and MIRANDA, F. Psychometric and CT scan measurements in a case of crossed aphasia in a dextral. *Brain Lang.* **17,** 240–260, 1982.
35. HABIB, M., JOANETTE, Y., ALI-CHERIF, A. and PONCET, M. Crossed aphasia in dextrals: a case report with special reference to site of lesion. *Neuropsychologia* **21,** 413–418, 1983.
36. HADZISELIMOVIC, H. and CUS, H. The apperance of internal structures of the brain in relation to configuration of the human skull. *Acta Anat.* **63,** 289–299, 1966.
37. HÉCAEN, H. *Les Gauchers.* Presses Universitaires de France, Paris, 1984.
38. HERRON, J. *Neuropsychology of Left Handedness.* Academic Press, New York, 1980.
39. HINDSON, D. A., WESTMORELAND, D. E., CARROLL, W. A. and BODMER, B. A. Persistent Broca's aphasia after right cerebral infarction in a right-hander. *Neurology* **34,** 387–389, 1984.
40. HOCHBERG, F. H. and LEMAY, M. Arteriographic correlates of handedness. *Neurology* **25,** 218–222, 1975.
41. IVY, G. O., AKERS, R. M. and KILLACKEY, H. P. Differential distribution of callosal projections in the neonatal and adult rat. *Brain Res.* **173,** 532–537, 1979.
42. JACOBSON, S. and TROJANOWSKI, J. Q. The cells of origin of the corpus callosum in the rat, cat and rhesus monkey. *Brain Res.* **74,** 149–155, 1974.
43. KINSBOURNE, M. The minor cerebral hemisphere as a source of aphasic speech. *Archs Neurol.* **25,** 302–306, 1971.
44. KOLB, B., SUTHERLAND, R. J., NONNEMAN, A. J. and WHISHAW, I. Q. Asymmetry in the cerebral hemispheres of the rat, mouse, rabbit, and cat: the right hemisphere is larger. *Exp. Neurol.* **78,** 348–359, 1982.
45. LECOURS, A. R. Literacy and acquired aphasia. In *From Reading to Neurons,* A. M. GALABURDA (Editor). MIT Press/Bradford Books, Cambridge, Massachusetts, 1989.
46. LEMAY, M. Morphological cerebral asymmetries of modern man, fossil man, and nonhuman primate. *Ann. NY Acad. Sci.* **280,** 349–366, 1976.
47. LEMAY, M. Asymmetries of the skull and handedness: phrenology revisited. *J. Neurol. Sci.* **32,** 243–253, 1977.
48. LEMAY, M. and CULEBRAS, A. Human brain: morphologic differences in hemispheres demonstrable by carotid arteriography. *New Eng. J. Med.* **287,** 168–170, 1972.
49. LEMAY, M. and GESCHWIND, N. Hemispheric differences in the brains of great apes. *Brain Behav. Evol.* **11,** 48–52, 1975.
50. LEMAY, M. and KIDO, D. K. Asymmetries of the cerebral hemispheres on computed tomograms. *J. Comput. Assist. Tomog.* **2,** 471–476, 1978.
51. LENNEBERG, E. *Biological Foundations of Language.* Wiley Press, New York, 1967.
52. LUND, R. D., CHANG, R.-F. and LAND, P. W. The development of the callosal projections in normal and one-eyed rats. *Dev. Brain Res.* **14,** 139–142, 1984.
53. MCGLONE, J. Sex differences in human brain asymmetry: a critical survey. *Behav. Brain Sci.* **3,** 215–263, 1980.
54. MCKINLEY, P. A., JENKINS, W. M., SMITH, J. L. and MERZENICH, M. M. Age-dependent capacity for somatosensory cortex reorganization in chronic spinal cats. *Brain Res.* **428,** 136–139, 1987.
55. MEHLER, J. Language at the initial state. In *From Reading to Neurons,* A. M. GALABURDA (Editor). MIT Press/Bradford Books, Cambridge, Massachusetts, 1989.
56. MILLER, M. W. and VOGT, B. A. Heterotopic and homotopic callosal connections in rat visual cortex. *Brain Res.* **297,** 75–89, 1984.
57. MILLER, M. W. and VOGT, B. A. The postnatal growth of the callosal connections of primary and secondary visual cortex in the rats. *Dev. Brain Res.* **14,** 304–309, 1984.
58. MOHR, J. P., PRESSIN, M. S., FINKELSTEIN, S., FUNKENSTEIN, H. S., DUNCAN, G. W. and DAVIS, K. R. Broca aphasia: pathologic and clinical. *Neurology* **28,** 311–324, 1978.
59. MOLFESE, D. L., FREEMAN, R. B. and PALERMO, D. S. The ontogeny of brain lateralization for speech and nonspeech stimuli. *Brain Lang.* **2,** 356–368, 1975.
60. NAESER, M. A. and BOROD, J. C. Aphasia in left-handers: lesion site, lesion side, and hemispheric asymmetries on CT. *Neurology* **36,** 471–488, 1986.

61. OLAVARRIA, J., MALACH, R. and VAN SLUYTERS, R. C. Development of visual callosal connections in neonatally enucleated rats. *J. comp. Neurol.* **260,** 321–348, 1987.
62. OLAVARRIA, J. and MONTERO, V. M. Relation of callosal and striate–extrastriate cortical connections in the rat. Morphological definition of extrastriate visual area. *Exp. Brain Res.* **54,** 240–252, 1984.
63. OLAVARRIA, J. and VAN SLUYTERS, R. C. Widespread callosal connections in infragranular visual cortex of the rat. *Brain Res.* **279,** 233–237, 1983.
64. OLAVARRIA, J. and VAN SLUYTERS, R. C. Callosal connections of the posterior neocortex in normal-eyed, congenitally anophthalamic and neonatally enucleated mice. *J. comp. Neurol.* **230,** 249–268, 1984.
65. OLAVARRIA, J. and VAN SLUYTERS, R. C. Organization and postnatal development of callosal connections in the visual cortex of the rat. *J. comp. Neurol.* **239,** 1–26, 1985.
66. OLAVARRIA, J., VAN SLUYTERS, R. C. and KILLACKEY, H. P. Evidence for the complementary organization of callosal and thalamic connections within rat somatosensory cortex. *Brain Res.* **291,** 364–368, 1984.
67. PIENIADZ, J. M. and NAESER, M. A. Computed tomographic scan cerebral asymmetries and morphological brain asymmetries: correlation in the same cases post mortem. *Archs Neurol.* **41,** 403–409, 1984.
68. RAKIC, P. and WILLIAMS, R. W. Thalamic regulation of cortical parcellation: an experimental perturbation of the striate cortex in rhesus monkeys. *Soc. Neurosci. Abstr.* **12,** 1499, 1986.
69. RHOADES, R. W. and DELLACROCE, D. D. Neonatal enucleation induces an asymmetric pattern of visual callosal connections in hamsters. *Brain Res.* **202,** 189–195, 1980.
70. RHOADES, R. W. and DELLACROCE, C. C. Visual callosal connections in the golden hamster. *Brain Res.* **190,** 248–254, 1980.
71. ROSEN, G. D., GALABURDA, A. M. and SHERMAN, G. F. The development of cerebral asymmetry in the rat: a thymidine study. *Soc. Neurosci. Abstr.* **14,** 1140, 1988.
72. ROTHBLAT, L. and HAYES, L. L. Age-related changes in the distribution of visual callosal neurons following monocular enucleation in the rat. *Brain Res.* **246,** 146–149, 1982.
73. RUBENS, A. B., MAHOWALD, M. W. and HUTTON, J. T. Asymmetry of lateral (Sylvian) fissures in man. *Neurology* **26,** 620–624, 1976.
74. TESZNER, D., TZAVARAS, A., GRUNER, J. and HÉCAEN, H. L'asymmétrie droite–gauche du planum temporale: a propos de l'étude anatomique de 100 cervaux. *Rev. Neurol. (Paris)* **126,** 444–449, 1972.
75. THOMAS, H. C. and ESPINOZA, S. G. Relationships between interhemispheric cortical connections and visual areas in hooded rats. *Brain Res.* **417,** 214–224, 1987.
76. VARGHA-KHADEM, F. and CORBALLIS, M. C. Cerebral asymmetry in infants. *Brain Lang.* **8,** 1–9, 1979.
77. WADA, J. A., CLARKE, R. and HAMM, A. Cerebral hemispheric asymmetry in humans. *Archs Neurol.* **32,** 239–246, 1975.
78. WEISKRANTZ, L. On the role of cerebral commissures in animals. In *Structure and Function of Cerebral Commissures*, I. S. RUSSELL, M. W. VAN HOF and G. BERLUCCHI (Editors). University Park Press, Baltimore, 1977.
79. WILLIAMS, R. W. and RAKIC, P. Elimination of neurons from the rhesus monkey's lateral geniculate nucleus during development. *J. comp. Neurol.* **272,** 424–436, 1988.
80. WISE, S. P. and JONES, E. G. The organization and postnatal development of the commissural projection of the rat somatic sensory cortex. *J. comp. Neurol.* **168,** 313–344, 1976.
81. WITELSON, S. F. The brain connection: the corpus callosum is larger in left handers. *Science* **229,** 665–668, 1985.
82. WITELSON, S. F. and PALLIE, W. Left hemisphere specialization for language in the newborn: neuroanatomical evidence of asymmetry. *Brain* **96,** 641–646, 1973.
83. YARNELL, P. R. Crossed dextral aphasia: a clinical radiological correlation. *Brain Lang.* **12,** 128–139, 1981.
84. YENI-KOMSHIAN, G. H. and BENSON, D. A. Anatomical study of cerebral asymmetry in the temporal lobe of humans, chimpanzees, and rhesus monkeys. *Science* **192,** 387–389, 1976.
85. ZABORSZKY, L. and WOLFF, J. R. Distributional patterns and individual variations of callosal connections in the albino rat. *Anat. Embryol.* **165,** 213–232, 1982.

Reference added in proof:
86. ROSEN, G. D., SHERMAN, G. F. and GALABURDA, A. M. Interhemispheric connections differ between symmetrical and asymmetrical brain regions. *Neuroscience* **33,** 525–533, 1990.