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BIOLOGICAL SUBSTRATES OF ANATOMIC ASYMMETRY

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

Dyslexia Research Laboratory and Charles A. Dana Research Institute, Beth Israel Hospital; Department of Neurology, Beth Israel Hospital and Harvard Medical School, Boston, MA 02215, U.S.A.

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1. INTRODUCTION

Lateralization of function has been an active area of investigation since the time of Broca's initial report (Broca, 1861) of a left hemisphere infarct leading to a disturbance of speech. It is generally accepted that the left hemisphere is specialized for the processing of some aspects of language while the right hemisphere dominates over many spatial, emotional and musical functions (see Springer and Deutsch, 1981). It is also believed that lateralization of function is present from birth (e.g. Molfese *et al.*, 1975; Entus, 1977; Michel, 1981).

Lateralization of function is also seen in non-human species: Passerine birds produce song predominantly with their left hemisphere (Nottebohm, 1971; Nottebohm, 1972; Nottebohm and Nottebohm, 1976) and Japanese macaques have a right ear advantage for the processing of species-specific vocalizations, indicating left hemisphere preference (Petersen *et al.*, 1978). As with the human, there are also functions in some animals that appear to be preferentially processed in the right hemisphere: In the rat, for example, spatial information is differentially processed by the hemispheres, with the right hemisphere purported to be dominant (Denenberg *et al.*, 1978; Sherman *et al.*, 1980; Denenberg, 1981). Interestingly, and perhaps akin to the neonatal tonic neck response of humans (Michel, 1981), neonatal tail posture asymmetries in rats predict their adult pattern of spatial preference, thereby indicating that lateralization is present at birth in these animals (Ross *et al.*, 1981; Denenberg *et al.*, 1982; Rosen *et al.*, 1984). Numerous other examples of behavioral lateralization in animals have been documented (see Denenberg, 1981 for review).

The search for anatomical asymmetries is fueled by the hope of understanding biological substrates for functional lateralization. In humans, therefore, investigations have centered around the classical language areas. In the first study of the modern era, Geschwind and Levitsky (1968) measured the lateral border of the planum temporale, a region containing auditory association areas (see Fig. 1), and found that 65% of the brains they examined had a larger left planum whereas only 11% had the reverse asymmetry (24% showed no bias). Asymmetry in this region has been replicated by additional measurements on autopsy material (Teszner *et al.*, 1972; Witelson and Pallie, 1973; Wada *et al.*, 1975; Rubens *et al.*, 1976) and on computerized axial tomography and MRI (Pieniadz and Naeser, 1984; Steinmetz *et al.*, 1989). Furthermore, asymmetries have been documented in young brains, with 56–79% of the fetuses or infants measured having a larger left planum (Witelson and Pallie, 1973; Wada *et al.*, 1975; Chi *et al.*, 1977). Cytoarchitectonic areas Tpt (an auditory association cortex located partially within the planum temporale) and PG (von Economo and Koskinas, 1925) are larger on the left, and their asymmetry directly relates to planum asymmetry (Galaburda *et al.*, 1978; Eidelberg and Galaburda, 1984).

Anatomical asymmetries also occur in non-human animals. The left Sylvian fissure of chimpanzees is longer on the left in 80% of the animals, with 12% having no asymmetry and 8% exhibiting the reversed asymmetry (Yeni-Komshian and Benson, 1976), a pattern similar to that seen in humans (Gundara and Zivanovic, 1968; LeMay and Geschwind, 1975; Rubens *et al.*, 1976; Yeni-Komshian and Benson, 1976). LeMay (1976) found no asymmetry in the lesser apes and monkeys but did find a longer Sylvian fissure length on the left in great apes. In baboon brains, the right frontal pole was longer in 6 of 7 brains, with the seventh brain having poles of equal length (Cain and Wada, 1979). These are similar to

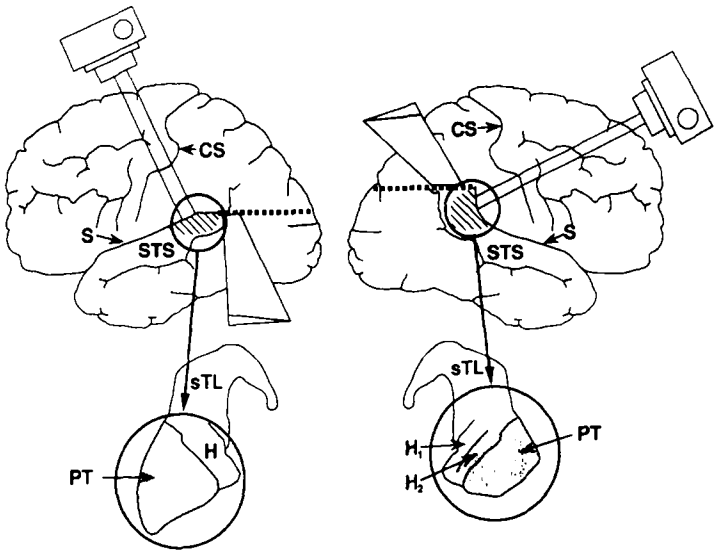

FIG. 1. Diagram of the left and right cerebral hemispheres to show places of dissection (interrupted lines and blades) and photographic angles (from cameras) to visualize the full extent of the planum temporale (PT; hatching) as well as the superior surface of the temporale lobe (sTL). Note the left side often has one transverse gyrus of Heschl (H) while the right side often has two (H_1 H_2). H_2 is included in the measurement of the planum. In the bottom part of the figure, the anterior portion of the temporal lobe is located at the top. Other abbreviations: CS—central sulcus, S—sylvian fissure, STS—superior temporal sulcus.

the findings in humans, in whom the right frontal pole protrudes farther (Hadziselimovic and Cus, 1966).

Other than in primates, anatomic asymmetries have been found in species ranging from reptiles (Engbretson *et al.*, 1981) to amphibians (Kemali, 1983; Kemali *et al.*, 1990) to birds (DeVoogd *et al.*, 1991) to rodents. In male rats, for example, the right neocortex is thicker than the left (Diamond *et al.*, 1975), wider and taller (Kolb *et al.*, 1982); female rats show slightly thicker left neocortices (Diamond *et al.*, 1981). Females ovariectomized at birth had significantly thicker right neocortices than left—the same asymmetric pattern seen in male rats. Others have found that prenatal stress reversed the patterns of asymmetry in male rats, making them more like the females (Fleming *et al.*, 1986). The right hemisphere had a larger wet weight than the left in both adult and 15-day old Long-Evans rats.

1.1. SUMMARY

While anatomic cerebral asymmetry appears in all animals that have been examined, its link to functional lateralization is not clear. Most workers, for example, find that approximately two-thirds of all human brains have a leftward anatomic asymmetry in language-related regions. These authors believe that the problem lies with the measurement of functional lateralization, whereby most available methods underestimate the frequency of bilateral representation. Another contributor to this imperfect relationship between structure and function may be that in some brains bigger is not necessarily better (cf. the findings in the brain of individuals with developmental dyslexia: Galaburda and Kemper, 1979; Galaburda *et al.*, 1985).

Stimulated by our research findings in the brains of dyslexics, in which absence of asymmetry rather than reversal of asymmetry directionality is the rule, we have found it more profitable to compare brains that have asymmetric architectonic areas to those in which those areas are symmetric. For this we have used the rat brain, which exhibits the full range of asymmetry in the visual and somatosensory cortices, as well as other areas. The hypothesis we began to test was that areas that are asymmetric function differently than symmetric areas because of fundamental differences in the cellular, connectional and probably also subcellular and molecular make-up.

2. MECHANISMS OF BRAIN ANATOMIC ASYMMETRY

2.1. GROSS VOLUMETRIC ASYMMETRY

The comparison of morphometric characteristics of symmetric and asymmetric brain regions is schematized in Fig. 2. With respect to symmetric brain regions, asymmetry can result developmentally from either an increase in size of one side, a decrease in the other larger side, or a combination of the two processes. In the first case, the measure of total brain area of symmetric brain regions would be larger than their asymmetric counterparts whereas the opposite would be true in the second case. Brain areas would be similar if the third scenario were true.

To test these hypotheses, we examined the same photographs of the 100 brains that were used by Geschwind and Levitsky (1968) and measured the total planum area in the left and right sides (Galaburda *et al.*, 1987). Similar to their findings, we found a leftward asymmetry in 63%, while 21% were

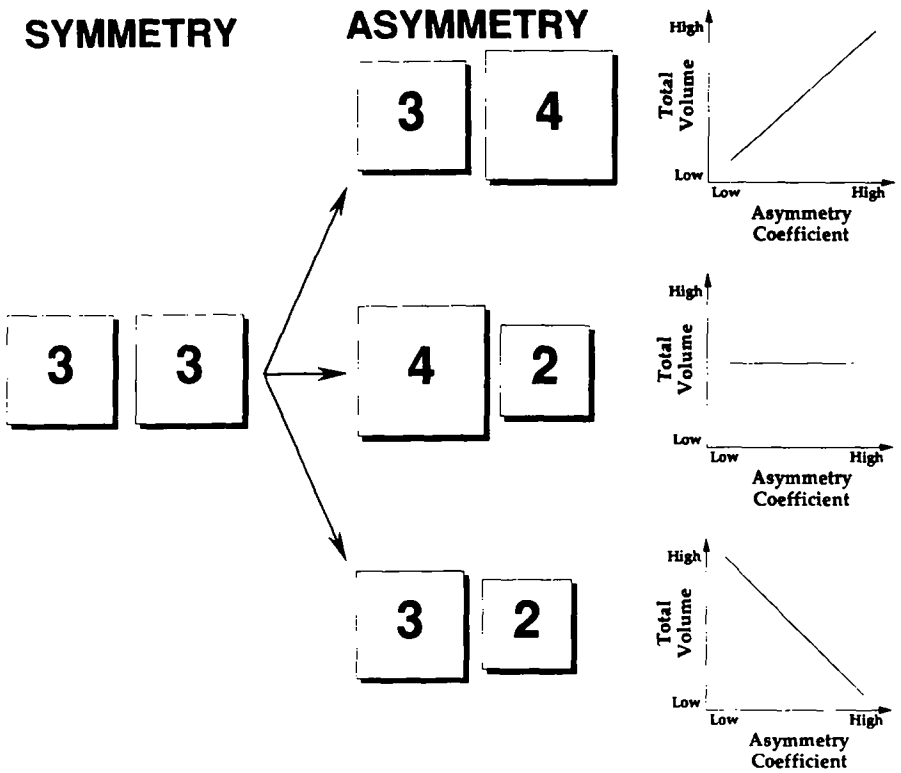

FIG. 2. Schematic illustrating the three hypothetical possibilities when comparing a symmetric to asymmetric brain regions. With respect to the symmetric brain, asymmetric brain regions can result from an increase in one side (top), a decrease in one side (bottom), or an increase in one side and a decrease in the other (middle). Each of these possibilities carries with them predictable outcomes based on the comparison of the total (right + left) area (or volume) of a region to the asymmetry coefficient $[(R - L)/(0.5)(R + L)]$. Thus, when the asymmetric brain region results from a decrease of one side, a negative correlation between these two variables occurs. On the other hand, a positive correlation would be predicted if asymmetric brain regions resulted from an increase in one side. In the case of the asymmetric brain region consisting of an increase in one side and a decrease in the other, there would be no change in total volume with changes in asymmetry coefficient.

rightward asymmetric and 16% had no bias. When we plotted the total planum area (right + left) against a measure of directionless asymmetry, we found a significant negative correlation, indicating that as asymmetry increased, the total planum area decreased (Fig. 3a). Moreover, the area of the smaller of the two plana significantly predicted the degree of asymmetry, whereas there was no correlation between the degree of asymmetry and the size of the larger planum (Figs 3b, 3c). These results, then, support the hypothesis that asymmetry is the result of the production of a small side rather than the production of a large side.

2.2. HISTOLOGIC CELLULAR BASIS OF ASYMMETRY

The previous study demonstrated that a symmetric brain region is made up of two large areas when compared to its asymmetric counterpart. The next question we wished to address was the histologic basis of this difference. There are only two parameters of cellular arrangement that determine architectonic volume: cell-packing density and cell numbers. Thus, the volumetric difference between asymmetric and symmetric brains may be explained by: (1) a difference in cell numbers without any change in cell-packing density, (2) changes in cell-packing density without differences in cell numbers, or (3) a combination of changes in cell-packing density and the number of cells.

We measured the volume of cortical area 17 (the primary visual cortex) of the rat and found a negative correlation between the total volume of area 17 and degree of asymmetry, thus replicating the relationship seen in the human planum temporale. Similarly, the smaller of the two sides was also inversely related to degree of asymmetry whereas there was no relationship between the larger side and total volume asymmetry (Fig. 4). Thus, rats with asymmetric brain regions have, like the human, smaller regions than those with symmetric ones. This having been established, we estimated cell-packing densities in area 17 of each hemisphere and found that there were no asymmetries in this measure irrespective of the degree of areal asymmetry. We concluded, therefore, that architectonic areal asymmetry must be due to changes in total numbers of neurons (Galaburda *et al.*, 1986).

That changes in cell numbers rather than cell packing density relate to asymmetry is not surprising because changes in cell-packing density large enough to account for the substantial areal asymmetries

would clearly distort the cytoarchitectonic appearance and make recognition of homologous areas impossible. Others have shown (Rakic and Williams, 1986) that changes between cytoarchitectonic intrahemispheric borders are subject to the same mechanism—specifically, changes in cell numbers and not cell packing density.

2.3. The Ontogeny of Anatomic Asymmetry

Because asymmetries in some areas of the human brain are visible shortly after the middle of gestation, it is likely that the production of cerebrocortical asymmetry depends on early developmental factors that determine neuronal numbers in the cerebral cortex. The work of Rakic (1988) suggests mechanisms by which neuronal numbers can be ontogenetically regulated. According to the 'radial unit' hypothesis, the number of neurons within a cortical area is determined by: (a) the number of early progenitor cell divisions, which affects the number of proliferative 'radial units' and hence the tangential extension of a cortical area; (b) the number of later divisions of neuroblasts within a proliferative unit (i.e. those occurring after the birth of the first neuron) which may affect the thickness of the cortex; (c) the contacts between newly arrived migrating neurons and thalamocortical and corticocortical afferents, which regulate the placement of architectonic boundaries; and (d) ontogenetic neuronal death, which can

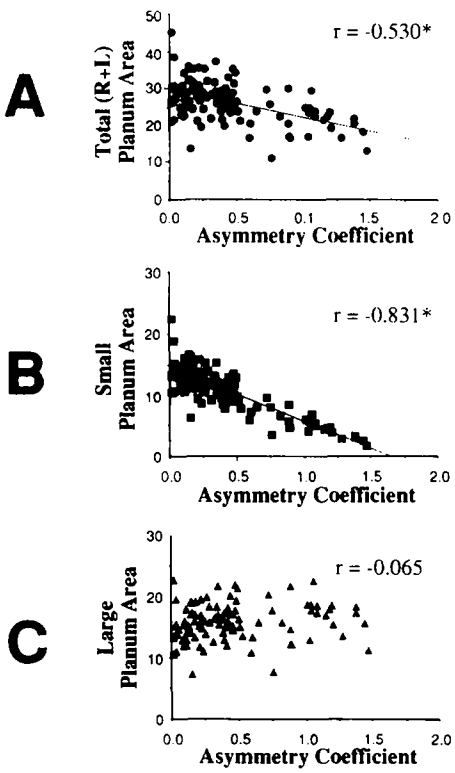

FIG. 3. Scatterplot showing relationship of asymmetry coefficient and (A) total area of the planum temporale, (B) the area of the smaller of the two sides, and (C) the area of the larger of the two sides in 100 human brains previously examined by Geschwind and Levitsky (1968). r = Pearson product-moment correlation coefficient ($^*p < 0.001$).

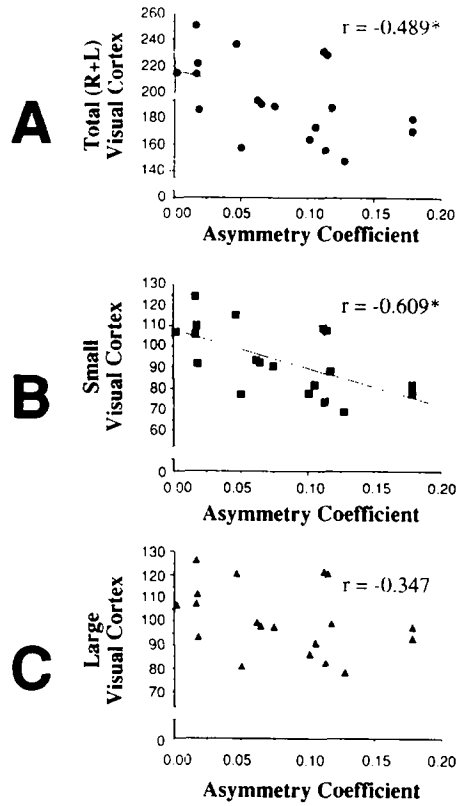

FIG. 4. Scatterplot showing relationship of asymmetry coefficient and (A) total area of the primary visual cortex, (B) the area of the smaller of the sides, and (C) the area of the larger of the sides in 19 rat brains. r = Pearson product-moment correlation coefficient ($^*p < 0.05$).

occur either early (affecting the proliferative units) or late (affecting the numbers of neurons within a radial unit). Using the radial unit hypothesis as a guideline, volume asymmetry of cytoarchitectonic areas could be the result of side differences in (1) the generation and elimination of proliferative units, (2) the generation and loss of neurons within ontogenetic cortical columns, and/or (3) the loss of portions of the area to neighboring regions by shifts in boundary placement.

We attempted to determine the contribution of late neuroblast division to the production of asymmetry of neuronal numbers in asymmetric architectonic areas by labeling with [^{3}H]thymidine neurons undergoing their last mitosis. After neuronal migration and postmigrational ontogenetic neuronal death, the number of heavily labeled neurons present in a cortical area would reflect those neurons that were born at the time of injection minus those that died or were otherwise lost to neighboring architectonic areas by fluctuations in boundary placement. We reasoned that changes in the ratio of labeled to unlabeled neurons (labeling ratio) between architectonic regions would reflect differences in production of neurons during the late phase of corticogenesis, while postmigrational neuronal loss of neurons would have no effect on this measure, since both labeled and unlabeled cells would be equally affected. Furthermore, early proliferative cell division, which takes place before the injection of thymidine would likewise have

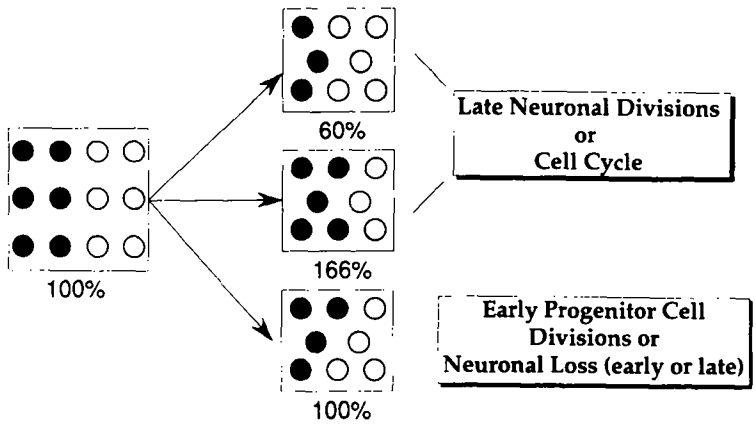

FIG. 5. Schematic illustrating explanations for potential differences in the labeling ratio between two hemispheres. Any change in this measure between hemispheres (or between brain regions) would indicate differences in cell cycle or in late (after generation of the first neuron) neuronal division. No difference in the labeling ratio would point to either early neuroblast divisions or neuronal loss.

no effect on this ratio. Therefore, assuming appropriate sampling over the course of neurogenesis, any differences in the labeling ratio between two cortical areas, including homologous hemispheric areas, must reflect differences in late neuroblast division (see Fig. 5).

If the lengths of the cell cycles differ in two cortical areas after pulse injections of thymidine, then a substantial difference in neuronal production could occur without changing the labeling ratio. A shorter cycle can lead to more cells being produced by a radial unit over time, which, if it does not grow in radial length, must result in increased cell-packing density. We assessed potential cell cycle differences by estimating and comparing cell-packing densities and the numbers of labeled neurons between two sides of symmetric and asymmetric cases.

We injected pregnant rats with [^{3}H]thymidine on either embryonic day (E) E15, E17 and E19 and their pups were sacrificed on postnatal day (P) P10, P30, or P60. The neocortical architectonic boundaries of primary visual area 17 and visual association area 18a were determined (Krieg, 1946b; Krieg, 1946a), their volumes computed in both the right and left hemispheres, and the numbers of labeled and unlabeled neurons were counted within these cytoarchitectonic areas.

There were never hemispheric differences in labeling ratios between left and right sides, regardless of degree of asymmetry. Thus, we did not find that later neuroblast divisions play a significant role in the production of asymmetry. There were, however, differences in the labeling ratios of architectonic areas 17 and 18a, thus demonstrating that architectonic specification can be explained, at least in part, by areal differences in late neuronal production (Fig. 6A). This premigrational role for architectonic specification is in contrast to the claim that this process is entirely post migrational and due to thalamic input only (O'Leary, 1989), and instead supports the role of both input and premigrational factors (Rakic, 1988).

There was no difference in cell cycles between the hemispheres in areas 18a or 17, as assessed by labeled cell-packing density and radial extent. On the other hand, we found no significant differences in labeled cell packing densities between area 17 and area 18a. Thus, cell cycle length appears not to differ between homologous areas, asymmetric or not, but differs

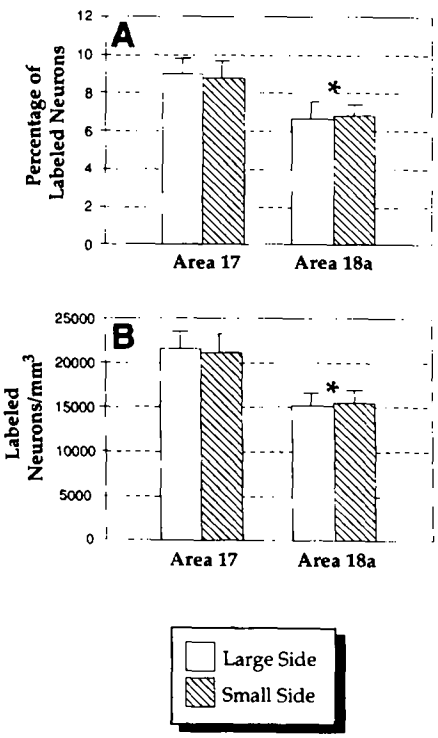

FIG. 6. (A) The labeling ratio within the large (white) and small (striped) sides of architectonic areas 17 and 18a of the rat neocortex. This measure is sensitive to events that occur late in corticogenesis (see Fig. 5). While there are no hemispheric differences, there is a significant difference between area 17 and area 18a. (B) The number of labeled neurons per mm^3 (a measure of cell-packing density that reflects changes in cell cycles during corticogenesis) within the same architectonic areas seen above. As with A, there are no hemispheric differences, although areas 17 and 18a differ significantly. *Differs from area 17, $P < 0.05$. $N = 39$.

between non-homologous cytoarchitectonic areas (see Fig. 6B).

In summary, our data support the notion that events occurring early in corticogenesis—specifically during the period of progenitor cell proliferation and/or death (before the birth of the first neuron)—are important for the formation of asymmetric cortical areas such that division and death of progenitor cells change the number of radial units on the two sides. We found no evidence that late neuronal production contributes to asymmetry. Given the lack of cell-packing density differences between the sides, it is unlikely that postmigrational neuronal death plays a significant role. However, our experiments do not definitively exclude a modest contribution of asymmetric neuronal death within radial units to the enhancement of already present asymmetry of cell number (Rosen *et al.*, 1991).

2.4. Interhemispheric Connectivity

It has long been speculated that the mechanism for cerebral dominance might lie in the callosal connectivity—that the dominant hemisphere exerts control over its homologue through the corpus callosum (Weiskrantz, 1977). By this reasoning, one might expect that the larger, dominant brain region, which has more cells than its homologue, sends more (and different?) projections across the corpus callosum. Alternatively, it could be the case that symmetric and asymmetric brains differ in the number and pattern of connections.

We sought to investigate the latter question by severing the corpus callosum of the rat and looking at the pattern of axonal terminal degeneration (Rosen *et al.*, 1989) with reference to asymmetry in the callosally related areas. Specifically, we parceled the somatosensory–somatomotor (SM-I; areas 3, 1 and 2) cortices and determined the percent of callosal terminal degeneration (callosal ratio). As previously reported for other brain regions (see above) we found a negative correlation again between the degree of asymmetry and total (right + left) volume of SM-I (Fig. 7A) indicating that as the degree of asymmetry of the architectonic region increased, the total volume of the region decreased. In addition, there was a significant inverse relationship between asymmetry coefficient and callosal ratio (Fig. 7B). This indicated that in symmetric regions a greater percentage of SMI received callosal terminations than in asymmetric regions.

Because callosal projections in the rat segregate into patches of termination, these results—that symmetric brains have a greater callosal ratio than asymmetric brains—suggest a number of possible interpretations as illustrated in Fig. 8. It could be that there are more patches of termination in symmetric brain regions as compared to asymmetric. Alternatively, if there were similar numbers of patches of degeneration in symmetric and asymmetric regions, the width of these patches would be greater in the symmetric cases. A third possibility is that there are more patches of callosal termination in asymmetric brains but that these patches in symmetric regions occupy a greater proportion of the region.

In order to distinguish among these possibilities, we counted the number of patches of callosal termination and found a negative relationship between them and the asymmetry coefficient indicating that there are more patches of callosal termination in the symmetric, as opposed to asymmetric, brain regions (Fig. 8, inset).

Our results are compatible with the notion that more symmetric brains have relatively greater numbers of callosal fibers and that there are more patches of termination in symmetric brains. If the detailed architecture of connections, as well as their number, affects functional capacity, symmetric and asymmetric brains may differ in their preferred cognitive strategies as well as in their extent of hemispheric lateralization. For example, Witelson (1985) has demonstrated a difference in the midsagittal area of the corpus callosum between left and right handers whereby left handers, whose brains are more likely to be symmetric (LeMay and Culebras, 1972), had larger midsagittal corpus callosum areas (the result of more and/or thicker fibers) than did their right-handed counterparts. It is possible that the greater cross-sectional area of the corpus callosum in left handers reflects cerebral symmetry.

Variability in the pattern and number of callosal terminations may be considered with regard to the ontogeny of the callosal connections. During early development, callosal cells of origin are diffusely represented throughout the cerebral cortex (Wise and Jones, 1976; Ivy *et al.*, 1979; Ivy and Killackey, 1981; Innocenti and Clarke, 1983). As the brain matures, callosal cells of origin appear only in discrete laminar and columnar locations (Jacobson and Trojanowski, 1974; Zaborszky and Wolff, 1982). Likewise, the axonal terminations of these cells are distributed diffusely beneath the cortical plate until they penetrate it in discrete bundles and terminate on their

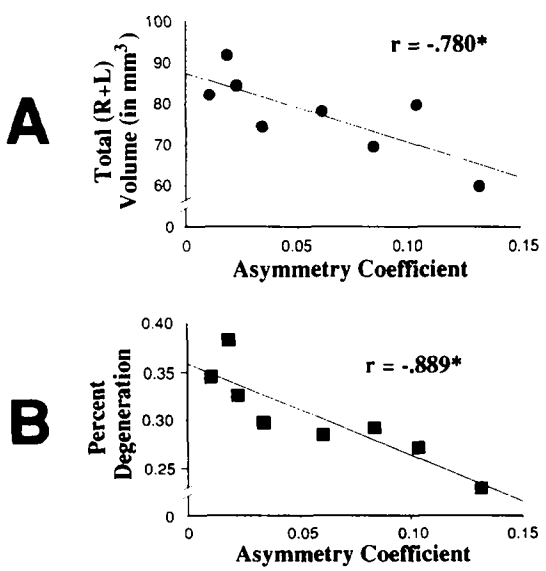

FIG. 7. (A) Scatterplot of total (right plus left) architectonic volume of SM-I (in mm^3) versus the asymmetry coefficient of that region. (B) Scatterplot of percent of callosal terminal degeneration (callosal ratio) versus asymmetry coefficient of SM-I. $^*P < 0.05$.

appropriate targets (Zaborszky and Wolff, 1982; Olavarria and van Sluyters, 1985). The progressive restriction of callosal cells of origin and terminations is thought to result from axonal pruning rather than from the death of neurons (Ivy *et al.*, 1979; Ivy and Killackey, 1981; O'Leary *et al.*, 1981). The present findings of decreased callosal connections in asymmetric SM-I, are consistent with an increased pruning of callosal axons and maintenance of ipsilateral cortical projections during development of this region, as has been previously demonstrated (Ivy and Killackey, 1982).

Because asymmetric areas have fewer neurons than symmetric areas, and since some of these neurons may be callosally connected, it is reasonable to suggest that asymmetric areas could have fewer callosal connections (Witelson and Nowakowski, 1991). But, according to this reasoning, it is not expected

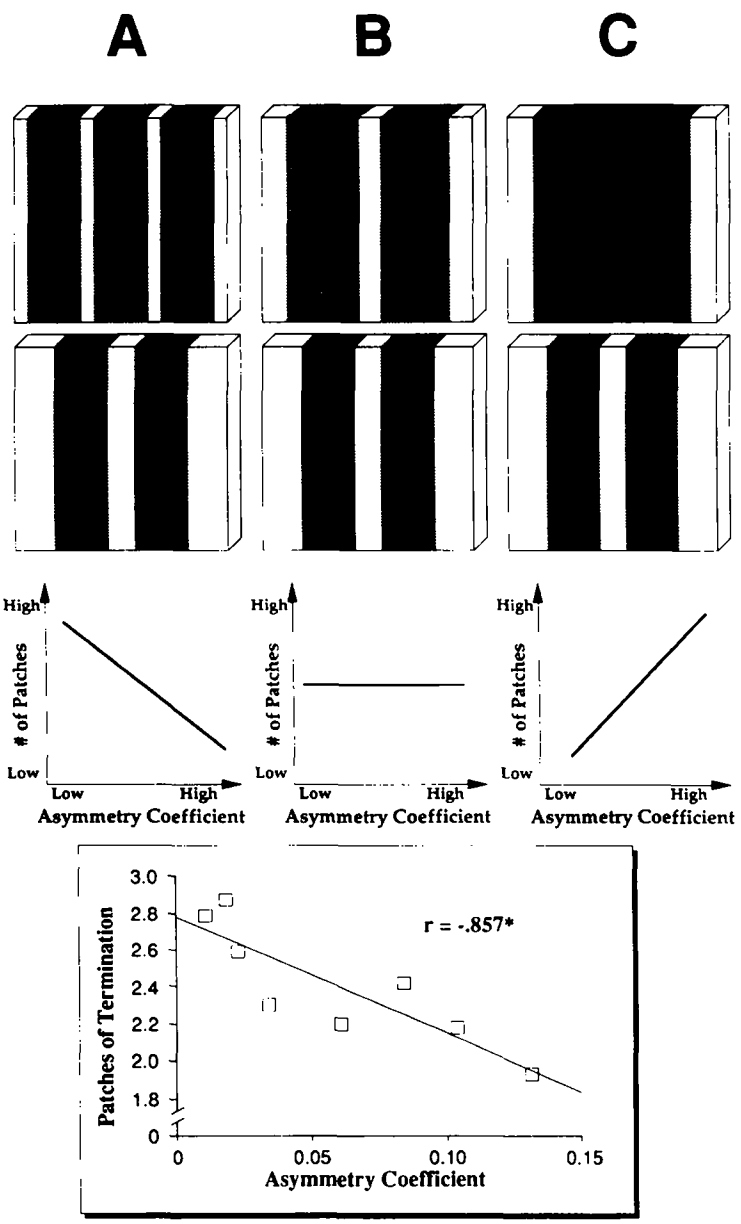

FIG. 8. Figure illustrating three possible outcomes based on the finding of an inverse relationship between volume asymmetry and callosal ratio. (**A**) Symmetric brains (top row) could have more patches of termination than asymmetric brains (second row); this would also produce a negative correlation between number of patches and asymmetry coefficient (third row). (**B**) Symmetric brains could have the same number of patches of termination as asymmetric brains, but they would be wider in the former; in this case there would be no correlation between numbers of patches and asymmetry coefficient (third row). (**C**) Finally, there could be fewer patches of termination in the symmetric brain, but they would occupy a greater proportion of the region. In this case, a negative correlation would be found between the asymmetry coefficient and number of patches of termination. Bottom row shows scatter-plot of actual data indicating that outcome **A** above is correct. $^*P < 0.05$.

that the callosal ratio would differ, since both neurons and axons would be proportionately reduced. Instead, callosal axons diminish out of proportion to cell numbers and this relative deficit of callosal connections must mean that with increasing asymmetry, some neurons withdraw their callosal axons during development while they maintain intrahemispheric connections. Alternatively, there could be a disproportionate loss of callosally related, as compared to noncallosal cells in the asymmetric case. However, we have failed to demonstrate any differences in proportions of cell types wholly or within specific lamina in symmetric and asymmetric brains (unpublished results from Galaburda *et al.*, 1986), and others have shown that neuronal death is not a major factor in the development of callosal projections in SM-I (O'Leary *et al.*, 1981; Ivy and Killackey, 1982).

3. SUMMARY

Asymmetric cortical areas differ in volume and in the number of neurons. There are also differences between asymmetric and symmetric areas. As asymmetry increases, the total area of the region decreases, suggesting that when a brain is symmetric, it is the result of two large sides rather than two small sides. Also, these volume differences are caused by changes in the number of cells, not changes in cell-packing density. The ontogenetic basis for this difference in cell numbers likely relates to events that occur quite early in corticogenesis before final mitosis of proliferative units, but definitive proof is lacking. Finally, the pattern and degree of callosal connections differ between symmetric and asymmetric brains, with differential axonal pruning being implicated as the likely mechanism.

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