Hello Eleanor - I hope something here is of interest. The ♀ + ♂ differences in cortical thickness are striking. ♂ R>L; ♀ R=L. mariam

EDITORIAL

Sex and the Cerebral Cortex

"Why can't a woman be more like a man?" Rex Harrison sang in the musical, *My Fair Lady*. But can she, or why should she? To gain a better understanding of the differential role of gender in brain development we need to study the brain directly. But for various reasons it has so far not been feasible to conduct longtime longitudinal studies of the development of the human brain. Even the noninvasive technique of magnetic resonance imaging does not offer the degree of resolution necessary to map such features as cerebral cortical thickness with the accuracy achieved by actually measuring histological sections from, say, rodent brains. That is why our most thorough studies of sex differences in cortical development have been done on the rat—actually over 700 rats in my series. Hopefully these may serve as guidelines for the later study of human brains as technology advances.

In one recent study of this question, cortical thickness was first measured in nine samples from the frontal, somatosensory, and occipital cortex of male rats at successive intervals over the period of 6 to 900 days of age (for details see Diamond 1988). All regions grew equally rapidly after birth until somewhere between 26 and 41 days of age, when they began a gentle but steady decline for the remainder of their lives. The overall postnatal cortical increase amounted to about 45% before the peak was reached and the decline began. In contrast, the development of the female cortex followed a different course, with some regional variation. The frontal cortex was quite well developed at birth, growing only by 2% in the week from 7 to 14 days of age, reaching a peak by 18 days of age. Area 39, however, the area least developed at birth, grew by 40% during that 7 to 14 day period, and did not reach its peak until 33 days of age. The female somatosensory cortex was also more developed at birth than that of the male. In other words, various regions of the female cortex grew at rates different from those of the male cortex.

In a human cortical study Chugani et al. (1987), using 2-deoxy-glucose positron emission tomography, found that the uptake of glucose increased during the first 5–6 years after birth. By 8–10 years the rate of uptake began to gradually decrease, indicating a pattern similar to the development seen in the rat. Unfortunately in this human study there was no separate analysis of the data by sex.

From an evolutionary point of view it may be that the female cortex is more highly developed at birth to ensure a better start for the reproduction of the species. The fact that she has fewer opportunities to reproduce (for humans about 420 ovulations per reproductive period compared to 200,000,000 sperm per single ejaculation) suggests the importance of early adaptive success for the female.

Other sex differences in brain development can be noted. Since the middle of the nineteenth century scientists have been aware of the relevance of brain asymmetry to speech, body awareness, and other functions, but sex differences in asymmetry of the cerebral cortex were not noted until late in the twentieth century. We now know that in the newborn male rat the right cerebral cortex is typically thicker than the left, and this

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pattern persists into advanced maturity. However, at a very old age, 900 days, the differences are no longer significant. Area 17, the primary visual cortex, shows the most marked and consistent right preponderance at every age. In fact, in one study this area was shown to be 5% greater in the right human cortex than in the left, again indicating the heuristic value of rat studies for these brain measures.

The asymmetrical cortical patterns in the female rat are different from those seen in the male. In general, the left cortex is thicker than the right, but the differences are not significant. Quite interestingly, in the aging female the right occipital cortex becomes significantly thicker than the left. In other words, the male loses his right dominance with aging, while the female gains right dominance in one particular region, the occipital, suggesting that some gender features may be reversed with aging.

It is not only the cortex that demonstrates these gender differences, but the hippocampal-dentate complex as well. The male shows a very pronounced right dominance during the first three weeks of life, but this disappears by 400 days of age. The female hippocampal-dentate complex shows a nonsignificant left dominance for most of her life, except at the initial period of sexual maturity when left dominance becomes significant.

Several pieces of evidence indicate that the sex steroid hormones play a role in determining these patterns of cortical asymmetry. In the male, developing cortex estrogen receptors exist in greater concentration in the left hemisphere; in the female the pattern is reversed. Furthermore, exogenous estrogen can decrease cortical thickness. This finding correlates positively with the greater number of receptors in the thinner side of the cortex.

If the ovaries are removed at birth, a typically masculine right dominant cortical pattern develops in the female after three months. From birth to three months of age in the male lacking testes the anterior frontal and somatosensory cortical areas show the female left-greater-than-right pattern, but the occipital cortex retains its right dominance. In another example of the effect of sex hormones on cortical dominance patterns, Fleming et al. (1986) showed that if the pregnant female is stressed during her last trimester, her male pups no longer exhibit the dominant right cortical pattern. Behaviorally these male pups later simulate female behavior during the sexual act by displaying lordosis and being submissive to the other males. These findings suggest that there may be a biological basis for one form of homosexuality, and serve to remind us of the importance of cortical asymmetry in its relationship to behavior.

Over the years we have learned that cortical thickness can be accounted for by a number of factors, including the number of neurons and glial cells, the area of perikaryon and its nucleus, the number and length of dendritic branches, the number of dendritic spines, and the length of the postsynaptic thickening. In other words, every measured part of the neuron shows changes correlated with cortical thickening.

In our gender studies neuronal and glial counts were taken in area 39 of the rat cortex. In the male there were more neurons and glia in a sample of right cortex compared with its counterpart on the left; in the female it was the left sample that contained more cells than the right. These results suggest that cortical asymmetries are due in part to the number of cells present in each hemisphere.

Having gathered these data on sex differences in the forebrain of rats living in standard colony conditions, we were interested in learning how male and female rat cortices were affected by exposure to enriched or impoverished living environments. In the enriched condition a dozen rats lived together in a large cage with many objects (toys) to explore. In contrast, in the impoverished condition, rats lived individually in small cages without "toys" to explore. In two separate experiments male and female rats were placed in either

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of these two environments for the same period of time. In the male the occipital cortex changed more than the other cortical areas. The frontal cortex showed less change, and the somatosensory cortex showed no significant change at all. In the female these three cortical regions changed about equally, with the occipital cortex changing significantly less than in the male, but with the somatosensory cortex changing more. This seems to indicate that under similar environmental conditions males have a more responsive visual cortex than females, while females have a more responsive general sensory cortex. One professor quipped in response to these findings, "It just shows that men are more visual, and women more feeling."

One needs to keep in mind that these differences represent averages, some significant and some not, and the variations are many: in human beings the variations would no doubt be much greater. Taken as a whole these data alert us to the possibility of real gender differences in higher cognitive functions of the brain. More details on these findings can be found elsewhere (Diamond 1988). Any married couple working together in the tedious task of uncovering the biological bases of our behavior can draw some encouragement from the fact that they may have four well-balanced brains doing the job instead of two: a male right-left and a female left-right.

Marian Cleeves Diamond

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