

# EUROBRAIN

## *Sex Differences in the Brain*

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IMPRINTING, BRAIN  
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The reason men seldom ask for directions and women usually do may lie in the structure of their brains, says Ruben Gur, Ph.D. and his colleagues at the University of Pennsylvania Medical Center. Their study, published in the May 15th 1999, issue of the *Journal of Neuroscience*, shows that male brains have a higher volume of cerebrospinal fluid and white matter (figure page 5). White matter is composed of long axons that reach from one region of the brain to another, facilitating the transfer of information across the brain, thus creating an individual's sense of spatial orientation. Women's brains, on the other hand, are denser in gray matter, consisting of neuronal cell tissue and connection-making dendrites, which enable women to make quick computations. What this has to do with finding one's way in a new city, says Gur, is that men, thanks to their more highly developed spatial skills (on the average)

are endowed with a kind of inherent global positioning system, which they rely on for navigation. Women, on the other hand, depend on their neuronal ability to link things together quickly to identify sequences of landmarks and figure out how they all connect. One method is not necessarily better than the other, he emphasizes, but the two ways of thinking are very different.

Gur and his wife-collaborator, Raquel Gur, M.D., Ph.D., used imaging technologies to scan the brains of forty healthy men and forty healthy women aged 18 to 45 and then compared the scans with the subjects' proficiency for language and spatial tasks. The researchers were interested in solving a conundrum: throughout the animal kingdom, a bigger brain correlates with higher intelligence. In humans, too, consistently a correlation has been made

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# *Genomic imprinting brain development*

## **THE X CHROMOSOME**

A considerable amount of data has accumulated on anatomical differences in the mammalian brain that are sex-linked, and for the most part are brought about by the influence of sex hormones produced by gonads. These differences stem from having a Y chromosome that contains the sex determining gene which results in the development of the testis. Developmentally, everything follows from this; differences in the male or female phenotype, including certain aspects of brain anatomy, are

determined by the presence or absence of androgens that are produced by the male testis.

An important corollary of the male possessing a Y chromosome and only a single X is the need for the female with two X chromosomes to compensate for this additional set of X genes. This is achieved by the silencing of one of the X chromosomes in all tissues of the body. In theory, therefore, women that lose an X chromosome (XO) should be no different from XX females with one X chromosome silenced. In reality, however, they are very different, as seen in Turner's syndrome, and this difference is amplified depending on whether the single X is of maternal or paternal origin. Turner's syndrome girls are of short stature, normal IQ, and delayed puberty due to ovarian insufficiency.

## **TURNER'S SYNDROME**

A recent study has shown that Turner's syndrome girls (XO) are different in their social disposition depending upon whether they inherit the X<sub>p</sub> (from father) or X<sub>m</sub> (from mother). In this study by David Skuse, girls inheriting the maternal X experienced clinically significant social difficulties (72%) and some had received a statement of special educational needs (40%) although there were no differences in IQ scores. Among the differences in their social cognition was an increased assertiveness (very demanding of people's time; difficult to reason with when upset; not responding to commands; unknowingly offending people), factors for which normal boys also score higher than normal girls. Girls who inherit the paternal X scored low on these social assertive parameters. Hence, there must be genes on the X chromosome that are only expressed from the paternally derived X chromosome and which account for these differences between X<sub>p</sub> and X<sub>m</sub> Turner's syndrome females.

Certain genes on the X chromosome must therefore escape the normal silencing mechanism and be expressed according to parent of origin. This expression of genes according to parent of origin also applies to other chromosomes and is called genomic imprinting.

Investigating which imprinted genes are expressed according to parent of origin and how they affect the brain has been achieved by the construction of embryonic chimeras containing either androgenetic/normal or parthenogenetic/normal cells. Parthenogenetic cells (Pg) and androgenetic cells (Ag) have the normal complement of chromosomes, but these will have come either exclusively from mother (Pg) or exclusively from father (Ag). Using such techniques, a clear and distinct patterning

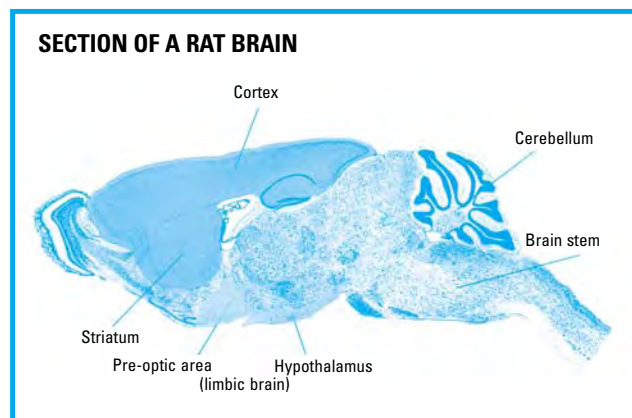
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# ng, t and behaviour

in the distribution of these androgenetic or parthenogenetic cells emerges during brain development. At birth, cells that have inherited their genome from the father contribute substantially to those parts of the brain that are important for primary motivated behaviour (e.g. the hypothalamus and parts of the limbic system) and are excluded from the developing neocortex and striatum. At the earliest stages of mouse brain development (days 9–10), androgenetic cells are present in all neural tissues and, as gestation progresses, they proliferate extensively in the deeper structures of the brain. At parturition, however, they are virtually absent from the central and anterior parts of the brain. By contrast, parthenogenetic cells (i.e. both alleles inherited from the mother) are excluded from these deeper brain areas, but accumulate selectively in those regions where androgenetic cells are excluded, especially the neocortex and striatum. Furthermore, growth of the brain of parthenogenetic chimeras is enhanced by this increased maternally expressed gene dosage, whereas the brains of androgenetic chimeras are smaller, both in absolute size and especially relative to body weight.

Not only is it surprising that parthenogenetic cells seem to proliferate at the expense of normal cells and produce a larger telencephalon in chimeras, but this enlarged brain appears anatomically and functionally normal. This is surprising because a large number of genes have been silenced in these cells (i.e. all the imprinted genes that are paternally expressed), and others that are maternally



expressed have been duplicated. This would seem to emphasize the importance of maternally expressed alleles in telencephalic development and the lack of importance of paternally imprinted genes in these regions. The distinct patterning in the distribution of parthenogenetic and androgenetic cells and their differential effects on brain growth suggest genomic imprinting may have been important in forebrain evolution. A comparison of those neural structures to which maternally or paternally imprinted genes differentially contribute reveals that a remodelling of the brain has occurred during mammalian evolution. On moving across species from insectivorous mammals to primates such as monkeys and humans, it can be seen that the neocortex and striatum have increased significantly in size relative to the rest of the brain and body, while the hypothalamus, and deeper brain areas such as the limbic system have decreased in size. Genomic imprinting may thus have

facilitated a rapid, nonlinear expansion of the brain (especially the neocortex and striatum) relative to body size during its development over an evolutionary time scale.

## GENOMIC IMPRINTING

It has been suggested that genomic imprinting has evolved in mammals to serve the differing interests of maternal and paternal genes within the offspring. From the available fossil records it would appear that many mammalian lineages have evolved increased cranial capacity, but differences in parental lifestyles may have subjected brain evolution to differential selection pressures that have favoured remodelling through genomic imprinting. Many primate societies are referred to as being “female bonded” whereas mobility from the group is common among males. Females provide social stability and group cohesion, are more affiliative and sustain the continuity of the group over

successive generations. Females are the primary care givers with social rank of daughters, but not sons, being related to the matriline. Males on the other hand, show greater mobility from the natal group with high levels of sexual promiscuity and aggression with more overt hierarchies. Therefore the brain's evolution may have benefited from differential selection pressures on its constituent parts created by the differences in lifestyle which are best suited to the reproductive success of each sex. Differential selection pressures may therefore have operated on the maternally and paternally imprinted genes, but such is the nature of genomic imprinting, the effects are transmitted to both sons and daughters, with the amplification of sex differences by the gonadal hormones.

#### PATERNALLY EXPRESSED GENES

Experiments with androgenetic chimeras are problematic for brain and behaviour studies since these chimeras rarely survive beyond day 1 after birth. However, recent work on two imprinted genes (*Mest* and *Peg1*) which are paternally expressed show a remarkable similarity in their expression with those regions of the brain to which androgenetic cells accumulate. These imprinted genes are expressed throughout the hypothalamus and areas of the limbic system. One function which is common to these recently discovered paternally expressed genes is their strong influence on maternal behaviour. Mice with a targeted mutation for each of these genes neglect their offspring, and fail to retrieve, nest build or nurture their offspring. So interestingly we

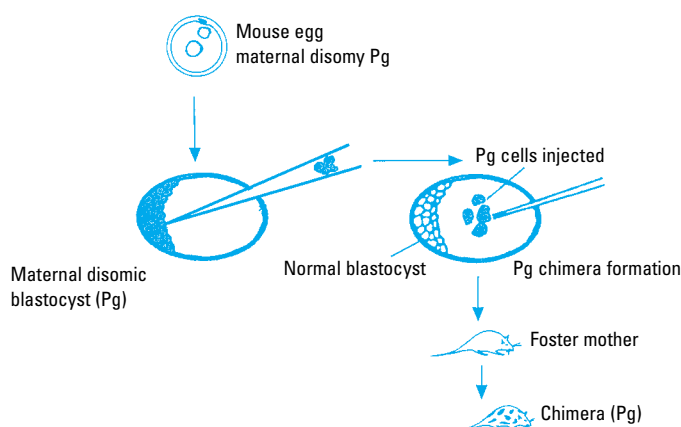
have genes which are only expressed through the patriline but this expression impacts on the female brain to regulate maternal behaviour.

As fascinating as these findings may be in opening-up new perspectives on brain evolution and behaviour, we have to be careful not to adopt a too simplistic interpretation. Imprinted genes tend to be regulatory genes which modulate the expression of other genes. In other words, they are embedded in the genome and do not function in isolation. Trying to consider single gene function in isolation from the genome would be like trying to understand the functioning of the brain from a single neuron. Nevertheless, it is interesting to note that a remodelling of the brain through genomic imprinting, influenced by

gender differences in parental lifestyle, has ameliorated the effectiveness of sex hormones on behaviour in favour of social influences.

By **E.B. Keverne**, University of Cambridge, England

#### HOW CHIMERAS ARE MADE



# Sex Differences in the Brain

(continued from page 1)

between larger craniums and greater smarts. However, while men generally have larger brains, says Gur, men and women consistently score equally well on intelligence tests. Yet, says Gur, research, including his own, has shown that men score higher on tests related to spatial skills while women are more proficient at verbal tests. Gur believes this is because of the proportional difference between gray and white matter.

“For spatial tasks, you need more white matter than is available to most women,” says Gur, “because women’s craniums are generally too small to contain enough of this type of brain tissue necessary to do well on these kinds of tests.” “But,” he continues, “in both men and women, the larger the brain, the higher the score.” However, this relationship is “steeper” in women, suggesting that women get “more performance” per increased milliliter of brain tissue volume than men do. This same correlation was not seen, in Gur’s study, between male performance and brain size.

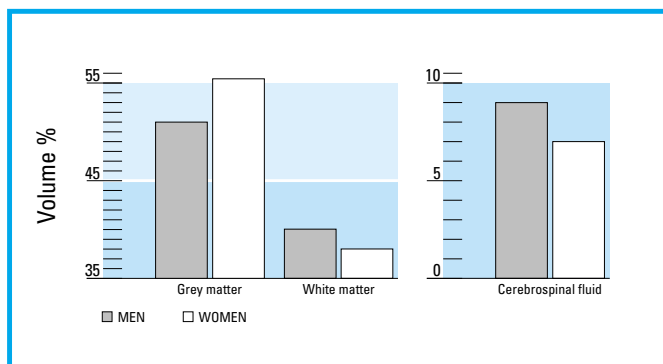
Anatomical differences are not the only thing separating men’s and women’s brains; hormonal differences may also play a part. According to research conducted by Sally Shaywitz, M.D. and colleagues at Yale University, estrogen appears to contribute to the brain’s capacity for reading, perhaps explaining why women generally perform better on language tests.

## ROLE OF ESTROGENS

In a study in the April 7 issue of JAMA, Shaywitz showed that in brain scans of postmenopausal women who were given estrogen, distinct patterns of activity were observed when the women were asked to remember a series of words or abstract figures. Compared to those of the women who took a placebo, the scans of the women who were being treated with estrogen showed more pronounced activity in the left hemisphere as they encoded either the words or figures, and more activity in the right hemisphere as they retrieved these stimuli.

Shaywitz says that this study shows that estrogen is not only altering the brain circuitry of these women, but it is doing so in a pattern that resembles that of younger people compared to older. This work may give women considering estrogen therapy even more to think about, but it also inspires one to ponder how estrogen and perhaps other sex hormones affect the brain throughout life, from puberty onward. Shaywitz is currently working on a longitudinal study of young people to try to answer those very questions.

This current research is an extension of the work that Shaywitz, who also collaborates with her husband, Bennett Shaywitz,



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M.D., and their research group at Yale have been conducting for years on dyslexia. Their goal has been to examine the neural connections responsible for reading and to understand what goes wrong with that circuitry, leading to dyslexia. Converging evidence has shown that central to the act of processing language is the breaking down of words into their most basic units of sound, called phonemes. Reading is the process of segmenting the written word into its individual phonemes that the letters represent; dyslexia is a disruption in the brain's ability to do this. An interesting finding of the current study, says Shaywitz, is that one of the regions of brain that was more active in the women being treated with estrogen – the inferior parietal lobule – was the same region that her work has shown to be involved in the storage of phonologically-coded information.

“Our hypothesis is that estrogen may be related to reading,” says Shaywitz, “and the finding that estrogen increases activation in a brain region responsible for storing phonologic information adds an important new level of support for the hypothesis.”

***So, is the battle between the sexes now being carried out in our brains?***

Men are better at some things; women are better at others, says Gur, “our job is to find out why.” One goal of examining the differences in brain between the sexes is to give researchers insights into how to treat specific brain disorders that show predominance in one sex over the other. One example is schizophrenia, which is more prevalent in males than in females.

“We need to learn how to help each other,” he says.

By **Terri Rutter**  
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