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Sexual Dimorphism of the Human Brain: Myth and Reality

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With 3 Figures

Many neuroanatomical sex differences have been identified in both animals and humans, which may form the neural bases for sex-specific behavior and reproductive as well as non-reproductive functions. The present essay gives a brief review of the findings on sex differences in the human brain.
Our observations on the human hypothalamus revealed that the shape of the suprachiasmatic nucleus (SCN) – a structure involved in the regulation of circadian rhythms and reproductive cycles – is elongated in females and more spherical in males. In addition, an extremely large SCN was observed in the brains of homosexual men who died from AIDS. Both the volume of the SCN and the number of vasopressin neurons were about twice as large as in a male reference group. In contrast to the SCN, in which only shape differences were found in relation to gender, the volume and cell number of the sexually dimorphic nucleus of the preoptic area (SDN-POA) showed a marked sexual dimorphism. The mean volume of the SDN-POA was 2.2 times larger in males than in females and contained about twice as many cells. The function of this sexually dimorphic area in humans is not known, but presumably it is involved in the control of male sexual behavior. The fact that no differences in either volume or cell number were observed between the SDN-POAs of homo- and hetersexual men indicates a selectivity of the SCN in this respect and contradicts the view that male homosexuals have a 'female' hypothalamus.

Historical Perspective

Sexual differences in the structure and functions of the human brain have been the subject of much speculation ever since the time of Greek antiquity. Aristotle, for instance, designated the moment at which the male fetus receives its 'soul' at the 40th day of gestation, whereas the female fetus was supposed to become animated only six weeks later, around the 80th day of pregnancy. In the course of the 19th century, the interest in the sexual dimorphism of the human brain grew rapidly. The first studies reported that male brains were larger and more asymmetrical than female brains, and that men had relatively more brain substance in front of the central sulcus than behind it (see Swaab and Hofman, 1984). The existence of these comparatively minor and seemingly random morphological sex differences in the human brain were often used in support of the biological view of that era, that men were intellectually superior to women and that white upperclass people were superior to other races and lower classes. Thus, Röse (1905), who investigated a number of German professors and soldiers, concluded: "Die Professoren haben bedeutend gröszere Köpfe als die Offiziere" (cited in Bolk, 1932).

A few years later, after listing the professions attainable given a particular head circumference, Bayerthal even reached the conclusion that we do not have to ask for the head size of highly-gifted women because they do not exist: "Nach der Kopfgröße genialer Weiber brauchen wir nicht zu fragen, es gibt keine" (Bayerthal, 1911; cited in Bolk, 1932)

Sex Differences in Brain Size

Although most of the early findings were not confirmed after reevaluation, the sexual dimorphism in the size of the brain or its major components still stands. At birth, the male brain is 20 per cent larger than the female brain. However, when brain size is assessed in relation to body size, the sex difference disappears. In other words, female neonates have brain weights which are similar to those in males of comparable body length. Still, if one takes the height of the subject into account, there is a difference of about 7 – 8 percent in brain weight from the second year onward (Swaab and Hofman, 1984). It seems as if the rapid growth phase of the brain in males is slightly prolonged as compared to that of females, causing a sexual difference in relative brain size. The functional significance of this sexual dimorphism in degree of encephalization is unknown.

Sex Differences in Brain Asymmetry

In addition to these findings on sex differences in the macroscopic morphology of the human brain gender related differences in lateralization of cognitive functions have been reported. The degree of functional recovery after brain injury suggests that certain cognitive abilities in males are more strongly lateralized than in females. For instance, after a left-hemisphere stroke, men are more likely than women to have a pervasive and lasting language disorder (for review see McGlone, 1980). Other studies looked for differences in performance in neurologically intact males and females. For example, Levy suggested that the differences between men and women in visual-spatial functioning (women performing more poorly than men on tests of spatial ability) are due to differences in the degree of lateralization of the brain (Levy, 1976). However, numerous contradictory findings have been reported (see e. g. Fairweather, 1976). Many studies report trends suggesting differences between the performance of men and women, but few results achieve statistical significance. Indeed, the vast majority of studies that looked for sexually dimorphic cognitive abilities found none.

The considerable interest in the asymmetric functional organization of the brain, such as a left-hemisphere dominance for language (Geschwind and Levitsky, 1968), has led to the search for its anatomical substrates. Although differences have been found between males and females in the degree of asymmetry of the brain, findings vary according to the brain region studied and the method of measurement (for review see Janowsky, 1989). The results do not suggest a single mechanism, such as one that causes a larger hemisphere in one sex or the other. Instead, one would have to posit a mechanism that differentially affects males and females in different regions of the brain. Neuroanatomical asymmetries in fact may be the basis for

specializations in higher cortial function, but evidence for its sexual dimorphism is still weak.

Another controversial finding is the reported sex difference in the number of fibers crossing between the two hemispheres, which may reflect differences in interhemispheric communication and hemispheric dominance for cognitive processes in males and females. The anterior commissure is one pathway for the transfer of information between the hemispheres. A study described that it was 36 per cent larger in females than in males when adjustments were made for lower female brain weight (Allen and Gorski, 1986). Another interhemispheric pathway is the corpus callosum of which the splenium, or caudal portion, was reported by Holloway and colleagues to be more bulbous and the posterior fifth was found to be larger in female brains (Holloway and De Lacoste, 1986). The absolute area of the corpus callosum did not differentiate the male brains from the female brains. In contrast to these findings, Witelson recently found a larger corpus callosum in males and a trend for males to have a larger genu and anterior midbody (Witelson, 1989). However, a morphometric study by Weber and Weis (1986) and three studies using magnetic resonance imaging failed to find sex differences in the morphology of the corpus callosum (Kertesz et al., 1987; Oppenheim et al., 1987; Byne et al., 1988). One suggestion for these negative findings is that callosal size may not reflect the actual number of commissural fibers and, therefore, may not be an accurate indicator of hemispheric interconnection and lateralization. It should also be noted that only 2 per cent of cortical neurons are estimated to send their axons through the corpus callosum. This raises the question whether or not such a small percentage of neurons could differentially influence cognition in males and females at a detectable level. In addition, the great variation in callosal size, even within sex and handedness groups, makes it unlikely that significant sex differences can be found (see Harris et al., 1987; Byne et al., 1988). It may be that individual differences in brain morphology are more important for functional specialization and behavior than are gender differences.

It is clear that sexual dimorphism in the corpus callosum is a subtle finding, at best, and when significant differences were found they did not necessarily coincide with the gender-related differences in functional organization of the brain.

Sex Differences in the Hypothalamus

In contrast to the many controversial findings with regard to the sexual dimorphism in brain asymmetry and interhemispheric connections recent studies have described several strikingly dimorphic areas in the human hypothalamus which are possibly linked to the endocrine control of sexual behavior. Allen and Gorski, for example, found that the volume of the posteromedial region of the bed nucleus of the stria terminalis – a structure located in the basal part of the brain – was 2.5 times larger in males than in females (Allen and Gorski, 1990). This region in humans appears to correspond to an area in the bed nucleus of rodent species which concentrates gonadal steroids (Stumpf et al., 1975; Commins and Yahr, 1985; Bonsall et al., 1986) and is involved in sexually dimorphic functions including agressive behavior, sexual behavior, and gonadotropin secretion (Beltramino and Taleisnik, 1980; Shaikh et al., 1986; Powers et al., 1987). Therefore, it is possible

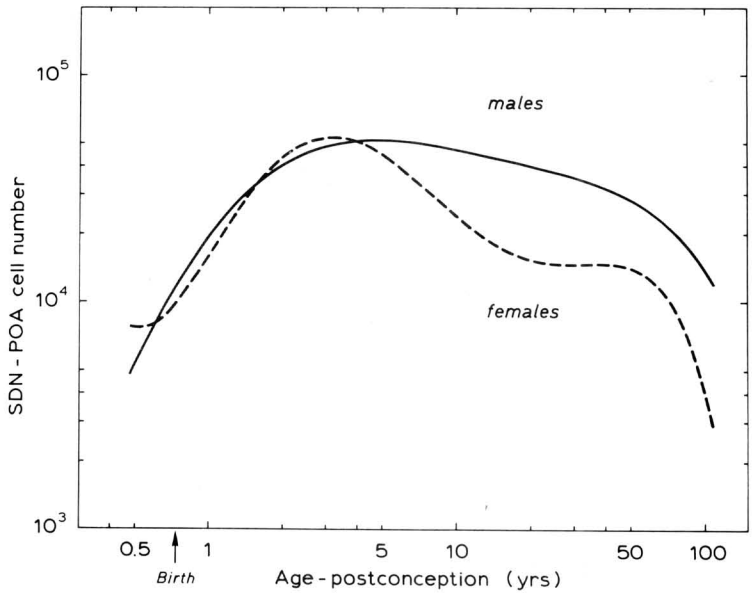

Fig. 1 Development and sexual differentiation of the human sexually dimorphic nucleus of the preoptic area (SDN-POA). Cell numbers reach a peak value around 2–4 years postnatally, after which a sexual differentiation occurs due to a reduction in cell number in the SDN-POA in females, whereas the cell number in males remains approximately unchanged up to the age of 50 years. These growth curves demonstrate that the SDN-POA in the human brain has a non-linear, sex dependent pattern of growth and decay. From Hofman and Swaab (1989), reprinted with permission

that in human beings as well, gonadal hormones influence the sexual dimorphism in the bed nucleus of the stria terminalis and that this morphological difference, in part, underlies sexually dimorphic functions.

Our own observations on the human hypothalamus revealed a marked sex difference in an intensely staining cell group in the medial preoptic area (Swaab and Fliers, 1985; Hofmann and Swaab, 1989). The volume of this sexually dimorphic nucleus (SDN-POA), which corresponds to the intermediate nucleus as described by Braak and Braak (1987), was 2.2 times larger in males than in females and contained about twice as many cells. No sex differences were observed in either cell density or mean diameter of the cell nuclei.

The sexual differentiation of the SDN-POA becomes manifest only after the age of about four years, as a result of a decrease in cell number in females, whereas the cell number remains unaltered up to the age of about 50 years in males (Swaab and Hofman, 1988). In females, cell death was found to be more prominent than in males, especially among aged people, dropping to values which were only 10–15 per cent of the cell number found in early childhood (Fig. 1). In males, a major reduction in the cell number of the SDN-POA was found between the age of 50–60 years. In conclusion, we can say that the sexually dimorphic nucleus of the preoptic area in the human brain has a sex dependent pattern of growth and decay. In other words, the sexual differentation of the SDN-POA cell number is

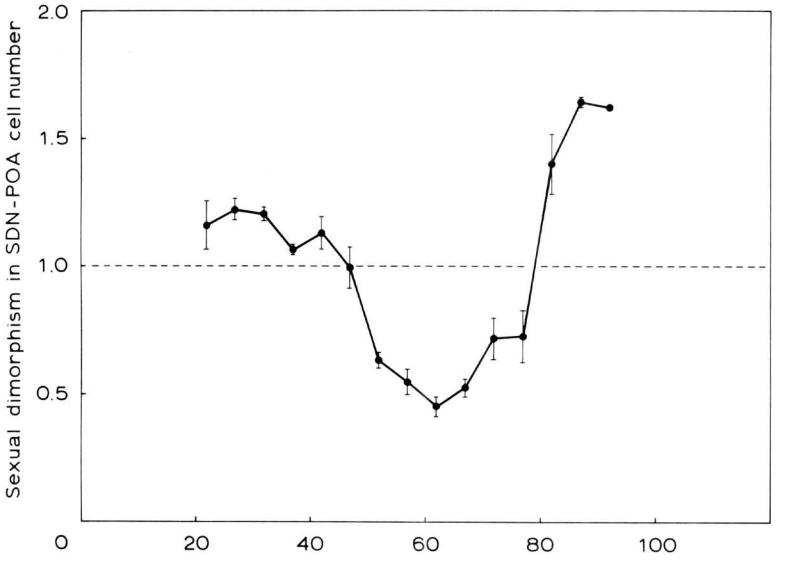

Fig. 2 Sexual dimorphism in the total cell number of the sexually dimorphic nucleus of the preoptic area (SDN-POA) in human adults as a function of age. Values are means ± S.E.M. and based on normalized five-year averages of smoothed data. The dashed line is the normalized mean dimorphism for adults, with males having, on average, 2.1 times as many cells as females. Notice that the sexual differentiation in SDN-POA cell number is not constant throughout adult life, but varies with age. From Hofman and Swaab (1989), reprinted with permission

not constant throughout adult life, but varies with age (Fig. 2). It means that the age distribution of the subjects is even more important than the problem whether or not the subjects are strictly age-matched. This might explain, in part, why in another study on the human hypothalamus (Allen et al., 1989) the SDN-POA was reported to be only 1.2 fold larger in males than in females, whereas we found this nucleus to be 2.2–2.5 times larger in the male brain (Swaab and Fliers, 1985; Hofman and Swaab, 1989). In fact it should be possible to obtain an even larger sexual dimorphism in this nucleus than the 2.5 of Swaab and Fliers' study by comparing either very young or extremely old individuals. Therefore, it seems appropriate in further studies on the sexual dimorphism of this and other hypothalamic nuclei with sex dependent patterns of development and aging to use brain material derived from subjects within a narrow age-range or to emphasize that the gender differences may depend on the (mean) age of the subjects.

In addition to changes in the hypothalamus, increasing age is accompanied by decreased sexual activity and deterioration of gonadal function (for reviews see Riegle and Miller, 1981; Sonntag, 1987). A substantial decrease in free testosterone concentrations, for example, has been observed in healthy men between 45–65 years, as well as a reduced ovarian oestradiol and progesterone secretion in postmenopausal women (Vermeulen, 1976; Deslypere and Vermeulen, 1984). Whether the reduction in cell number with aging is a direct consequence of these age-related alterations in gonadal function, or vice versa, is not clear.

A time-course relationship between aging effects on the cellular morphology of the sexually dimorphic nucleus and age-related deterioration of reproductive functions might give a clue as to the putative role of this nucleus in the neural circuitry underlying sexual behavior and reproductive processes in man. Lesion experiments in rats (De Jonge et al., 1989) and correlative studies relating sexual activity, plasma testosterone levels and SDN-POA volume (Anderson et al., 1986; Turkenburg et al., 1988) seem to indicate that the SDN-POA is involved in the regulation of masculine sexual behavior.

In addition to the sexually dimorphic nucleus in the preoptic area we also investigated the suprachiasmatic nucleus in the human hypothalamus for the possible presence of morphological sex differences. The suprachiasmatic nucleus (SCN) is considered to be the biological clock involved in the regulation of circadian rhythms, such as the sleep-wake cycle and longer periodic processes, such as the ovulation cycle. These considerations, together with the sex differences in rhythmicity (Wollnik, 1985; Wollnik and Turek, 1988) make this structure of special interest for the study of sex differences. We found that the shape of the suprachiasmatic nucleus is elongated in females and more spherical in males (Swaab et al., 1985; Hofman et al., 1988). The overall volume, cell density and total cell number of the SCN turned out to be virtually identical in both sexes so that the difference is basically one of shape. One hypothesis is that the shape of the SCN may influence the pattern of its connectivity to other hypothalamic regions. It is also possible that the feminization of the shape of the SCN occurs not until the onset of puberty with its attendant hormonal changes, and that once influenced by female hormones it retains its shape. Since various observations indicate that the suprachiasmatic nucleus might be involved in the process of reproduction and sexual behavior (for review see Swaab et al., 1987) we may expect to find a link between the endocrine system and the sexual differentiation of this hypothalamic nucleus. In fact, there are indications that during development the difference in plasma levels of sex hormones causes sexual differentiation of the brain.

The Suprachiasmatic Nucleus in Homosexual Men

In this respect it is interesting that we recently observed an extremely large suprachiasmatic nucleus in the brains of homosexual men who died from AIDS (Swaab and Hofman, 1990). Both the volume (Fig. 3) and the number of vasopressin neurons were about twice as large as in a male reference group. The fact that no differences in either volume or cell number were observed between the sexually dimorphic nucleus of the preoptic area of homo- and heterosexual men indicates a selectivity of the suprachiasmatic nucleus in this respect and contradicts the view that male homosexuals have a 'female' hypothalamus. The explanation for the large SCN in homosexual men most likely may be found in an early stage of brain development due to a disturbance of programmed cell death in this nucleus, which normally occurs around the first year after birth (Swaab et al., 1990). The difference in the SCN cell number in relation to sexual orientation cannot be directly related to sexual differentiation of the brain since no differences in the volume or cell number of this nucleus were found between males and females. The possibility cannot be excluded, however, that sex hormone levels during brain development

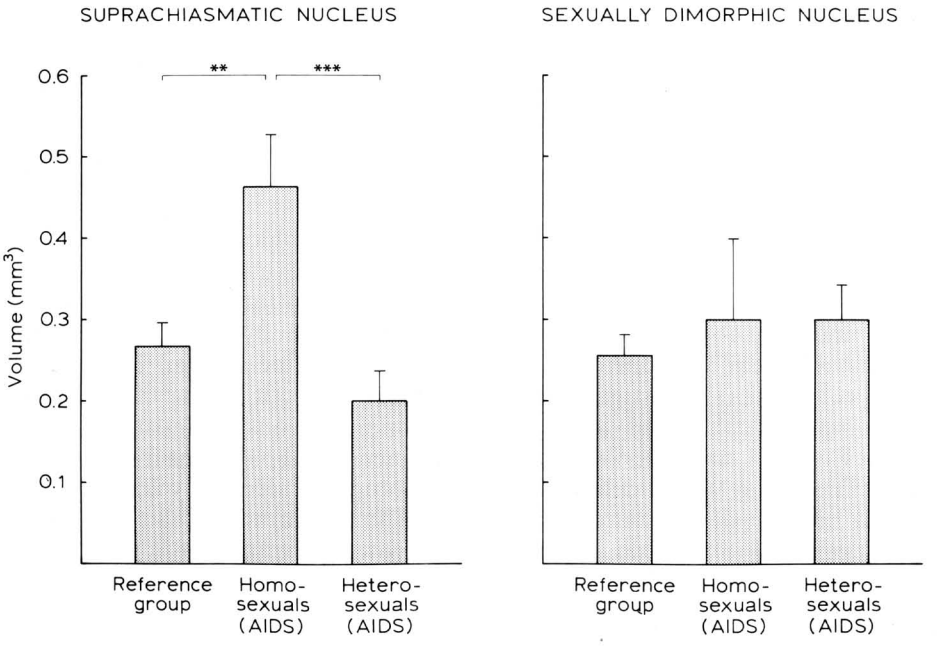

Fig. 3 Volume of the human suprachiasmatic nucleus (SCN) and sexually dimorphic nucleus of the preoptic area (SDN-POA) as measured in three groups of adult subjects: 1.) a male reference group, 2.) homosexual males who died from AIDS, and 3.) heterosexuals who died from AIDS. The values indicate medians and the standard deviation of the median. The differences in the volume of the SCN between groups are statistically signficant (** $p < 0.01$; *** $p < 0.001$). Note that none of the parameters measured in the SDN showed significant differences among the three groups. From Swaab and Hofman (1990), reprinted with permission

do play some part in this phenomenon. In fact, the observation that a similarly enlarged suprachiasmatic nucleus was present in a woman with Prader-Willi-syndrome, a congenital LHRH deficiency in which sex hormone levels are very low throughout life, suggests that the interaction with sex hormones during the early phase of development might be essential for the postnatal cell death in the SCN. Animal studies have to reveal whether or not the suprachiasmatic nucleus is causally implicated in sexual orientation, or whether or not the size of this nucleus and sexual preference are influenced by a common factor during development.

Concluding Remarks

In this article we have tried to give a brief review of the findings on sex differences in the human brain. It may be clear that in humans a correspondence between sexually dimorphic behaviors or gender-specific behaviors and their neural bases is still elusive. Some studies suggest that there are sexually dimorphic regions in the human brain, which can be related to functional differences, whereas numerous other studies failed to replicate these findings. In addition, the differences in cog-

nitive abilities between males and females are sometimes so fragile that they disappear with minor procedural changes. In most cases, individual brain differences are more remarkable than the sex differences that have been described (see Janowsky, 1989). It may be that our individual cognitive abilities and personalities are more different than differences in cognition and personality between the sexes. This would make it extremely hard to find neural evidence of functional sex differences in cognition.

On the other hand, several studies have described dimorphic areas in the hypothalamus which may be linked to endocrine control of sexual behavior, both in humans and animals. Animal studies have been more fruitful in their search for behavioral and neurobiological differences between sexes by studying well described behaviors that are controlled by a known endocrine system. These have not been the behaviors investigated in humans. However, it seems that investigations linking dimorphic behavior to dimorphic brain regions are most successful when the behavior is circumscribed, carefully defined, and consistent from animal to animal. These may be guidelines for constraining the seemingly limitless behaviors and brain systems that could be studied in the future. Meanwhile, it is evident that now anatomical sex differences are known to be present in the human brain, Freud's statement "Die Anatomie ist das Schicksal" will cause even more confusion.

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Buchbesprechung

Steroid Hormone Action. Hrsg. RINGOLD, G.; 308 S., 118 Abb., 10 Tab., 18 × 26 cm. New York: Alan R. Riss. Inc. 1988. (UCLA Symposia on Molecular and Cellular Biology, Vol. 75), Leinen, 96,– $.

Unsere Kenntnisse der Mechanismen, über die Steroidhormone ihre Wirkung entfalten, sind durch die enormen Fortschritte auf dem Gebiet der Molekularbiologie in den letzten Jahren wesentlich bereichert worden. Für alle Steroidhormone, einschließlich der Vitamin D-Metaboliten, ist nachgewiesen, daß ihre stereospezifische Bindung mit hoher Affinität an Rezeptorproteine eine konformationelle Änderung der Proteinstruktur bewirkt, die zu einer erhöhten Affinität des Rezeptorkomplexes an die DNA des Zellkerns führt. Im Zellkern verändert der an die DNA gebundene Rezeptorkomplex die Transkription von spezifischen Genen, die über eine Modulation der RNA-Synthese sich letztlich in einem bestimmten Hormonresponse der Zelle äußert.
Der vorliegende Band stellt in 25 Beiträgen eines Symposiums in Park City (Utah/USA) unter Beteiligung international namhafter Wissenschaftler neue Ergebnisse und Erkenntnisse bei der Aufklärung der eukaryotischen Genexpression dar. Die Vorträge sind in 4 Sektionen: 1. Steroid Structure and Function; 2. Hormonal Activation of Receptor Activity; 3. Regulation of Steroid-Responsive Genes; und 4. Complex Regulation of and by Steroids, gegliedert. Auf der Grundlage von experimentellen Arbeiten bzw. von zusammenfassenden Übersichten werden neue Erkenntnisse über die Struktur der Rezeptorproteine, über deren funktionell unterschiedlichen Domainen, über die Prozesse der Rezeptoraktivierung und über die Antihormonwirkung auf Rezeptorebene vermittelt. Ein großer Fortschritt stellt die Insertion der genetischen Information in prokaryotische Expressionssysteme dar, die es ermöglicht, größere Mengen von Steroidrezeptoren für eingehendere Untersuchungen in die Hand zu bekommen. Durch den Nachweis von steroidbindenden Proteinen in Pilzen sind jetzt Objekte zugänglich, die es ermöglichen, Mechanismen der Steroidhormonwirkung in weniger komplexen Systemen zu untersuchen.
Die Beiträge über die Struktur der rezeptorbindenden DNA-Abschnitte (HRE) und über die biochemischen bzw. molekularen Ereignisse bei der Aktivierung der Transkription zeigen auf, wie komplex sich diese Prozesse darstellen und wie weit wir von einem umfassenden Einblick noch entfernt sind.
Durch die vielseitige Behandlung der komplexen Materie vermittelt der vorliegende Band einen fundierten Eindruck über den internationalen Stand auf diesem aktuellen Gebiet der Forschung. Biochemiker, Biophysiker, Biologen und Endokrinologen, die auf diesem Gebiet arbeiten bzw. an ihm interessiert sind, werden wertvolle Anregungen für ihre eigenen Arbeiten bzw. neue Erkenntnisse aus diesem sorgfältig abgefaßten Buch entnehmen können. G. HOBE (Jena)