Brain Research, Gender, and Sexual Orientation

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SUMMARY. Recent brain research has revealed structural differences in the hypothalamus in relation to biological sex and sexual orientation. Differences in size and cell number of various nuclei in the hypothalamus for homosexual versus heterosexual men have recently been reported in two studies. We have found that a cluster of cells in the preoptic area of the human hypothalamus contains about twice as many cells in young adult men as in women. We have called

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[Haworth co-indexing entry note]: "Brain Research, Gender, and Sexual Orientation." Swaab, D. F., L. J. G. Gooren, and M. A. Hofman. Co-published simultaneously in *Journal of Homosexuality* (The Haworth Press, Inc.) Vol. 28, No. 3/4, 1995, pp. 283-301; and: *Sex, Cells, and Same-Sex Desire: The Biology of Sexual Preference* (ed: John P. De Cecco, and David Allen Parker) The Haworth Press, Inc., 1995, pp. 283-301. Multiple copies of this article/chapter may be purchased from The Haworth Document Delivery Center [1-800-3-HAWORTH; 9:00 a.m. - 5:00 p.m. (EST)].

this cluster the sexually dimorphic nucleus (SDN). The magnitude of the difference in the SDN depends on age. In other human research, two other hypothalamic nuclei (interstitial nuclei of the anterior hypothalamus [INAH] 2 and 3) and part of the bed nucleus of the stria terminalis (BST) have been reported to be sexually dimorphic in the human.

Sexual differentiation of the human brain takes place much later than originally claimed. At birth the SDN contains only some 20% of the cells found at 2 to 4 years of age. The cell number rapidly increases in boys and girls at the same rate until 2 to 4 years of age. After that age period, a decrease in cell number takes place in girls, but not in boys. This causes the sexual differentiation of the SDN. This postnatal period of hypothalamic differentiation indicates that, in addition to genetic factors, a multitude of environmental and psychosocial factors may have profound influence on the sexual differentiation of the brain.

No difference in SDN cell number was observed between homosexual and heterosexual men. This finding refutes Dörner's hypothesis that homosexual males have a "female" hypothalamus. However, in a sample of brains of homosexual men we did find that an area of the hypothalamus called the suprachiasmatic nucleus (SCN) contains twice as many cells as the SCN of a heterosexual group. A recent report by LeVay claims that another nucleus, INAH-3, is more than twice as large in heterosexual as in homosexual men, whereas Allen and Gorski found that the anterior commissure was larger in homosexual men than in heterosexual men or women. Preliminary research on male-to-female transsexuals is also discussed.

The functional implications of these findings in determining adult sexual orientation are as yet far from clear.

FEMALE/MALE DIFFERENTIATION OF THE HUMAN HYPOTHALAMUS

Based on observations of non-human mammalian species, many researchers believe that the human brain undergoes a female/male differentiation during its prenatal stage of development, caused by genetic information (Pillard et al., 1981; Bailey & Pillard, 1991) and the organizing effects of sex hormones. However, the stage of development in which sex hormones determine sexual differentiation of the human brain and the exact influences of hormonal actions on gender and sexual orientation are, in fact, unknown.

There are three peak periods of gonadal hormone levels which

could be of importance for female/male differentiation: (1) the first half of gestation when the genitalia are formed (Reyes et al., 1974); (2) in the perinatal period; and (3) during puberty (Winter, 1978). The brain area that has been assumed to be the primary area of female/male differences in reproduction, gender identity, and sexual orientation is the hypothalamus (Dörner, 1979, 1988; Gladue et al., 1984). The supposition of Dörner and Staudt (1972) is that a structural female/male differentiation of the human hypothalamus takes place between 4 and 7 months of pregnancy. Dörner's supposition is based on two observations: (1) that during this period various hypothalamic cell groups, the supraoptic, ventromedial, and paraventricular nucleus, can be distinguished structurally; and (2) on the observation that the matrix layer around the third ventricle, in which the cells are formed, has disappeared by 7 months of gestation. Only much later did it become clear that cell death, not cell division may be the most important mechanism in female/male differentiation of the brain (Nordeen et al., 1985; Swaab & Hofman, 1988).

Sexually Dimorphic Nucleus (SDN)

The sexually dimorphic nucleus (SDN) of the preoptic area of the hypothalamus was first described in rats by Gorski et al. (1978). It is still the most conspicuous anatomical female/male difference in the mammalian brain. This cell group, which is 3 to 8 times larger in male than in female rats, is so clearly differentiated that it can even be noted with the naked eye. Lesions of the SDN affect masculine sexual behavior, i.e., mounting behavior, in the rat (Anderson et al., 1986; Turkenburg et al., 1988; De Jonge et al., 1989). However, the extent of the changes in rat sexual behavior following SDN lesions is so modest that the major function of the SDN has probably not yet been discovered.

Human SDN

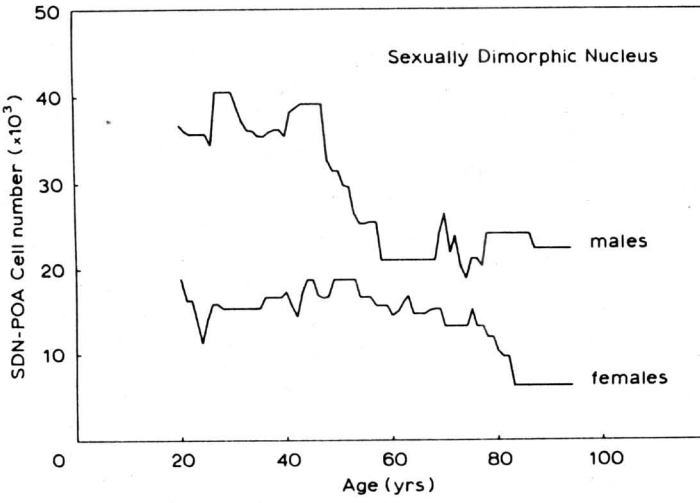
We have found an SDN in the preoptic area of the human hypothalamus that is–judged by its locale and cellular structure–probably homologous to that in the rat (Swaab & Fliers, 1985). However,

proof for such a homology is lacking at this moment. Measurements of the human SDN have revealed that the volume is more than twice as large and contains about twice as many cells in adult men as in women.

The human SDN corresponds to the intermediate nucleus as described by Braak and Braak (1987) and to the intermediate lateral hypothalamic area in early descriptions by Brockhaus (1942) and Feremutsch (1955). The sex difference which we observed in the SDN was not present in other hypothalamic nuclei. The magnitude of the sex difference was found not to remain constant throughout adulthood, but to depend on age (Figure 1). In men, a major reduction in SDN cell number was observed between the ages of 50 and 60 years, so that the female/male difference became smaller. In women over 70 years of age cell death was found to be more rapid than in men, the cell number dropping to only 10 to 15% of that found in early childhood. It appears that the sex difference in the SDN increases again in older people (Hofman & Swaab, 1989).

This effect of aging and the fact that sexual differentiation in the human SDN only occurs after the 4th year of age (Swaab & Hofman, 1988) might explain why Allen et al. (1989), who had a

FIGURE 1



sample of human adults biased for age, did not find a significant sex difference in the size of the SDN, which they called interstitial nucleus of the anterior hypothalamus 1 (INAH-1). In the study of Allen et al., 40% of the adult subjects came from the age group in which the SDN sex difference is minimal, compared to 29% in our study (Hofman & Swaab, 1989). Moreover, subjects over 70 years of age were underrepresented in Allen's study: 20% compared to the 37.5% in case of a proportional distribution of all ages. In our study, 32% of the subjects belonged to this old age group. So it seems likely that Allen et al. were unable to establish a significant sex difference in the INAH-1 (= SDN) because they used a biased sample. If we had studied only subjects within the age distribution of Allen's study, the sex difference in SDN volume would have been reduced from 2 (Hofman & Swaab, 1989) to only 1.4 times, and this difference would not have been statistically significant. The age distribution, however, does not explain why LeVay (1991) could not find a sex difference in the volume of INAH-1 either. However, only the size of the nucleus, but not its cell numbers, have been determined by this author.

Other Human Sexually Dimorphic Nuclei

Allen et al. (1989) described two other cell groups (INAH 2 and 3) in the preoptic-anterior hypothalamic area that were larger in the male than in the female human brain. LeVay (1991) could not confirm the sex difference in INAH-2, but did find such a difference in INAH-3. Since immunocytochemical characterization of the neurons was not performed, it is not clear whether the nuclei have to be considered as islands of the bed nucleus of the stria terminalis (BST), the paraventricular nucleus (PVN), of some other structure, or as separate anatomical entities. In addition, counts of the number of cells of the INAHs in the two sexes are lacking.

A clear sex difference was described by Allen and Gorski (1990) in what they called the "darkly staining posteromedial component of the bed nucleus of the stria terminalis (BNST-dspm). They found that the volume of this area was 2.5 times larger in males than in females. However, cell counts were not performed in this study either.

Another area, the suprachiasmatic nucleus (SCN) was found to

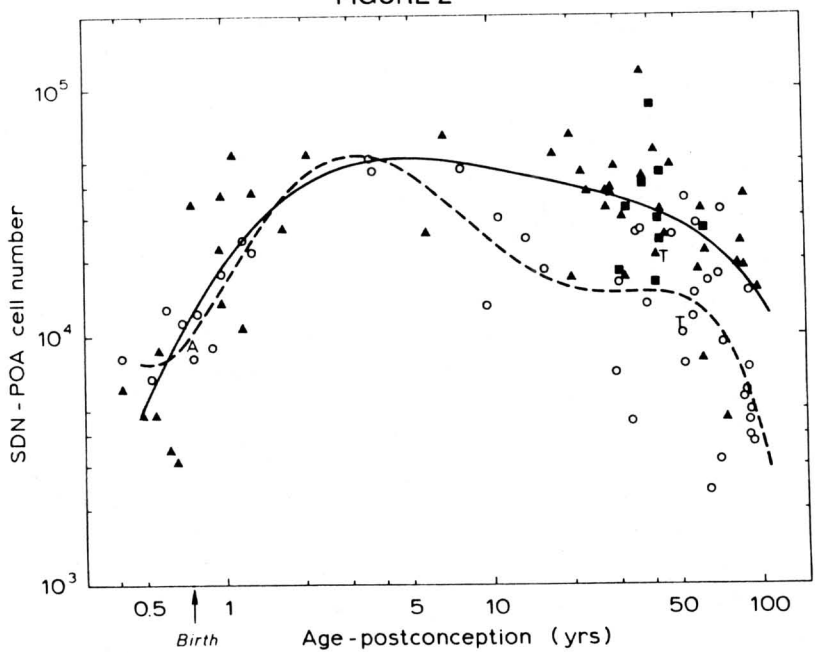
have a female/male difference in shape (Swaab et al., 1985). Though the shape of the SCN was more elongated in women and more spherical in men, no significant female/male difference was observed in volume nor total cell number of the SCN. It is not known whether this difference in shape correlates with sex differences in SCN afferent or efferent connections.

Since only few human brain structures in the two sexes have been investigated and a sex difference in relative human brain size exists (Swaab & Hofman, 1984), we expect that many more female/male differences in the human brain will be found.

Development of the Human SDN

As early as mid-pregnancy the origins of the SDN can be observed in the human fetal brain (Swaab & Hofman, 1988; Polzovic et al., 1988). Yet the SDN cell number (Figure 2) and volume at

FIGURE 2



birth are only 22% and 18%, respectively, of the values found between 2 and 4 years of age. In the second half of pregnancy and during the first postnatal years there is no significant female/male difference in the size of the SDN. During the first postnatal years the SDN cell number rapidly increases in both boys and girls up to the age of 2 to 4 years. Only after this period does the human SDN differentiate according to sex. In women there is a decrease in both SDN volume and cell number, whereas in men, these remain unaltered up to the age of about 50 (Swaab & Hofman, 1988).

Our results do not support the proposition that gonadal hormones stimulate the formation of cells of the SCN during the fetal or perinatal period. In mid and later pregnancy, the levels of sex hormones are much higher in boys than in girls (Reyes et al., 1974; Winter, 1978). Yet, the SDN size and cell number have the same magnitude in boys and girls up to the age of 2 to 4 years. The discovery of the late postnatal female/male differentiation of the human hypothalamus is consistent with the observation that neither estrogen, androgen, nor progestin receptors are found in the human fetal brain at mid-pregnancy (Abramovich et al., 1987). The sex difference in the volume of the BNST-dspm seems to occur only in adulthood, although there is reason for caution in accepting these conclusions. The sample size of subjects between 10 and 20 years of age was small in the study of Allen and Gorski (1990); and it may be that the sexual dimorphism of the BST is already present in adolescents.

In general, these data support the notion that female/male differentiation of the human hypothalamus takes place after birth and before adulthood, rather than during mid-pregnancy. The observation that sexual differentiation of the human SDN does not take place earlier than 4 years after birth, calls for a reevaluation of the possible relationship between the sex dimorphism of the SDN and the perinatal testosterone peak in boys, which lasts only some 90 days (Forest & Cathiard, 1975). It is possible that this testosterone peak prevents SDN cell death which normally occurs in females. A similar mechanism is supposed to take place in the spinal cords of rats (Nordeen et al., 1985).

In addition, one may speculate that not only hormones, but also other factors (such as stress) might be involved in sexual differenti-

ation of the brain in early childhood (cf. Swaab & Hofman, 1988; Gooren et al., 1990). A case in point is the history of a 20½-year-old man who had suffered a complete loss of testes at birth, but showed the conventional gender identity, gender role, and sexual functioning (Gooren & Cohen-Kettenis, 1988). This case may support the idea that factors other than hormones may be involved in sexual differentiation of the brain, or, conversely, that the hormonal factors in development of gender and sexual orientation exert their effects before birth.

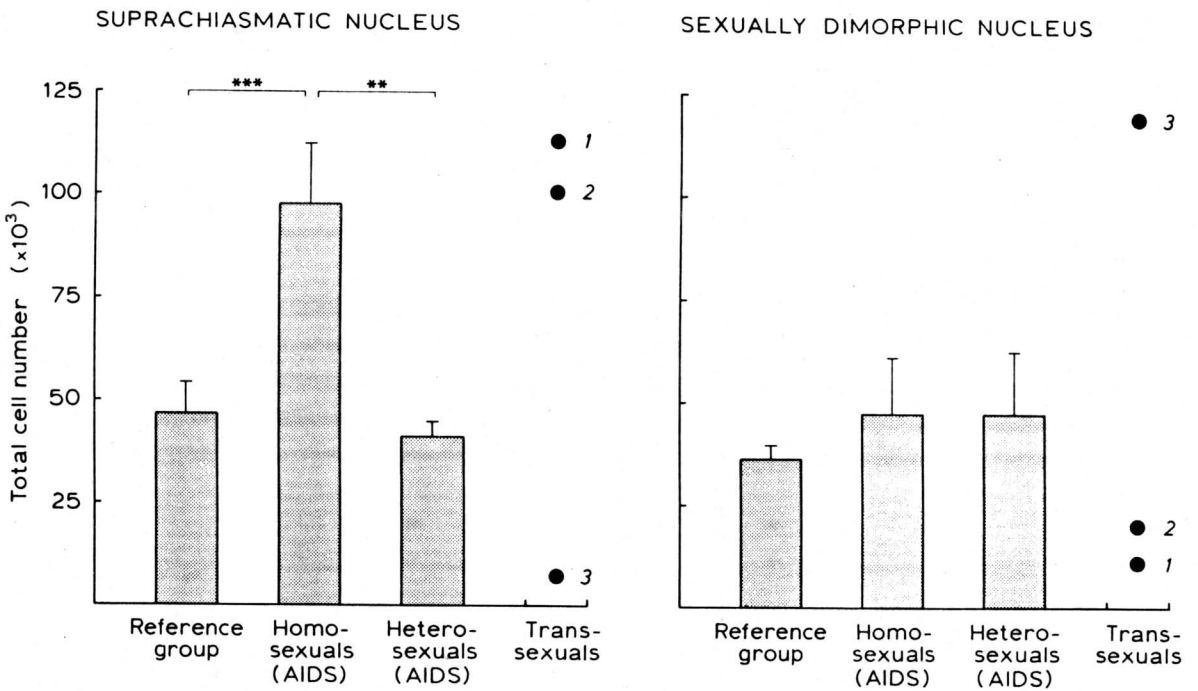
THE HUMAN HYPOTHALAMUS, SEXUAL ORIENTATION, AND GENDER IDENTITY

We had the opportunity to study the structure of the anterior hypothalamus in relation to sexual orientation. We investigated 34 subjects; eighteen males from 22 to 74 years of age, the sexual orientation of whom was generally not known, served as a comparison group. The homosexual male group consisted of 10 non-demented AIDS subjects aged 25 to 43. Six non-demented heterosexuals, 4 males, 2 females, aged 21 to 73 years, who had also died of AIDS, served as a control group. Two areas of the hypothalamus were studied; the SDN (see before) and the suprachiasmatic nucleus (SCN). The main results were as follows: cell numbers in the SDN of the reference group, the male homosexuals, and the heterosexual subjects did not differ. However, the SCN volume in homosexual men was 1.7 times as large as that of the reference group of male subjects and contained 2.1 times as many cells (Figure 3).

The SCN is considered to be the principal component of the biological clock generating and coordinating hormonal, physiological, and behavioral circadian rhythms (i.e., day-night rhythms with a period length of nearly 24 hours) (Moore, 1978; Rusak & Zucker, 1979; Moore-Ede et al., 1982). In addition, the SCN is thought to be involved in reproduction, at least in laboratory animals (Södersten et al., 1981; Swaab et al., 1987).

A prominent theory on the causes of human sexual orientation is that it develops as a result of an interaction between the prenatal brain and sex hormones (Gladue et al., 1984; Erhardt et al. 1985; Dörner, 1988; McCormick et al. 1990). A multitude of factors,

FIGURE 3


SUPRACHIASMATIC NUCLEUS
SEXUALLY DIMORPHIC NUCLEUS
Total cell number (x10³)
125
100
75
50
25
***
**
1
2
3
Reference group
Homo-sexuals (AIDS)
Hetero-sexuals (AIDS)
Trans-sexuals

including genetic information (Pillard et al., 1981; Bailey & Pillard, 1991), maternal stress (Dörner et al., 1980; Anderson et al., 1986; Ellis et al., 1988), and chemicals (Swaab & Mirmiran, 1986) are thought to influence the process of female/male differentiation of the brain and sexual orientation. Recent *in vitro* observations suggest that sexual differentiation of some neuronal systems may even take place in the absence of sex hormones (Reisert & Pilgrim, 1991).

According to Dörner's hypothesis, male homosexuals would have a female differentiation of the hypothalamus. Dörner's hypothesis concerning sexual orientation became testable immediately after we had found that the SDN of the preoptic area of the human hypothalamus contains twice as many cells in men as in women (Swaab & Fliers, 1985; Swaab & Hofman, 1988; Hofman & Swaab, 1989). In contrast to this hypothesis, neither the SDN volume nor the cell number in the hypothalamus of homosexual men (who died of AIDS), however, differed from that of the male reference group in the same age range (Figure 2; Swaab & Hofman, 1988). More recent data (Figure 3) confirmed and extended this observation with a heterosexual control group of subjects also suffering from AIDS (Swaab & Hofman, 1990). The fact that no difference in SDN cell number was observed between homo- and heterosexual men who died of AIDS refutes Dörner's hypothesis that male homosexuals have a "female" hypothalamus.

The SCN and Sexual Orientation

Swaab and Hofman (1990) observed that the SCN in homosexual men contains 2.1 times as many cells as the SCN of the reference group (Figure 3). This finding cannot be attributed to differences in technical errors such as shrinkage of hypothalamic tissue during the experimental procedure. The difference in SCN cell number in relation to sexual orientation cannot, however, be directly related to female/male differentiation of the brain since no differences in SCN volume or cell number were found between males and females (Swaab et al., 1985; Hofman et al., 1988).

The larger SCN (and, in particular, an increase in the number of neurons) in homosexual men raises a number of questions about the way this difference may have developed. It appears very unlikely

that homosexual behavior as such would increase the neuronal number in any brain structure. Yet the development of SCN cell numbers (Swaab et al., 1990) suggests that the explanation for the larger SCN in homosexual men most likely may be found in early brain development. At birth, the SCN contains only 13-20% of the adult number of cells, but in the postnatal period development is rapid. Cell counts reach a peak around 13-16 months after birth (Swaab et al., 1990). The SCN cell numbers found in adult homosexual men were in the same order of magnitude as found around 13-16 months after birth. The normal pattern is that the cell numbers decline to the adult value of about 35% of the peak values. In homosexual men, therefore, this postnatal cell death in the SCN seems to have been curtailed.

The possibility that sex hormones play some role in SCN development is also reinforced by an observation of Södersten et al. (1981). They showed that the amplitude of the circadian rhythm in sexual behavior, of which the SCN is the basis, is enhanced in male rats which were treated neonatally with anti-estrogens. This observation makes it more likely that a larger SCN, as reported here for homosexual men, may relate to a difference in the interaction with sex hormones during development. This possibility should be tested in animal experiments and further explored in human subjects.

One might argue that the present finding of an enlarged SCN in male homosexuals who died of AIDS only holds for a particular subset of homosexual men (i.e., those likely to acquire AIDS through contact with a high number of frequently changing sexual partners with whom receptive anal intercourse was performed [Curran et al., 1985; Van Griensven et al., 1987]). The possibility that an enlarged SCN may be related to the level of sexual activity rather than to sexual preference certainly warrants further study. Experiments in rats, however, have shown a close correlation between sexual activity and SDN size (Anderson et al., 1986). Our observation that the size of the SDN in homosexual men did not differ from that of the male reference group nor from that of the heterosexual men that died of AIDS, does not support this possibility.

An alternative explanation for the enlarged SCN found in homosexual men who died of AIDS is that it might be related to the

disturbed function of the gonads in adulthood that has been found in AIDS patients (Croxson et al., 1989). Our observation that the SCN in heterosexual male AIDS patients is not enlarged seems to exclude this possible explanation. Certainly homosexual men who had not died of AIDS should be studied in the future. In this respect, it is interesting that we observed an enlarged SCN in two (primary) male-to-female transsexuals who did not suffer from AIDS (Swaab et al., 1987; Figure 3).

The functional association between sexual orientation in men and SCN size is not clear at this moment. Various observations in animals suggest that the SCN, apart from being the biological clock, may be involved in reproductive processes (Södersten et al., 1981; Swaab et al., 1987). Judged from its nucleolar size, the SCN is also activated around puberty in rats (Anderson, 1981). In addition, lesions of the SCN area in the female rat reduced the positive feedback response of gonadotropic hormones to estrogens (Gray et al., 1978; Wiegand et al., 1980). However, recently it was observed that lesions in the adult male rat SCN did not alter sexual orientation (F. H. De Jonge, F. Kruyver, & W. van de Broek, unpubl. results). This observation argues in favour of the possibility that sexual orientation and the size of the SCN are not causally related but may be subject to the same influences in development.

The relationship between a large SCN and homosexuality is unexpected and, for the time being, difficult to interpret. The relationship need not be causal in the sense that it is a necessary and sufficient condition for developing a homosexual orientation. It is imperative to study more material before definitive conclusions can be drawn. We have no information on the size of the SCN in female homosexuals, for instance, or in bisexuals. Until more data have been collected our finding is open to various interpretations. It is particularly pertinent to study the SDN and SCN in subjects whose prenatal/postnatal history has been atypical (an excess of androgens in females/a deficiency or insensitivity to androgens in males) as has been done in earlier work on sexual orientation (e.g., Money et al., 1984). Also the finding of LeVay (1991) of a larger INAH-3 and that of Allen and Gorski (1992) of a larger anterior commissure in homosexual men, can at present not be interpreted in functional terms.

Gender Identity and Transsexuality

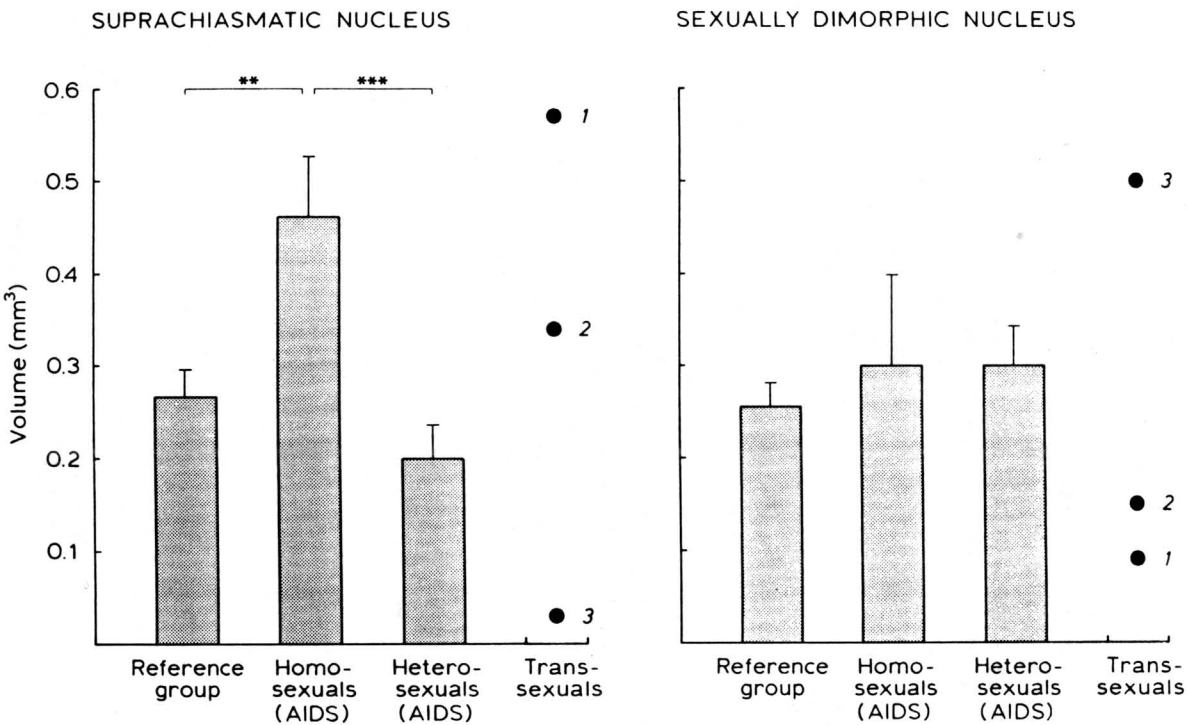
It has been proposed that one's self-identification as a man or as a woman, like sexual orientation, develops as a result of an interaction between the developing brain and sex hormones. Transsexuality is considered to be the result of a disturbance of this interaction (Gladue et al., 1984; Dörner, 1988). In view of the similarity between the hypotheses on the development of gender identity and sexual orientation, it is of interest that 60% of the male-to-female transsexuals are androphile and that some 10% are biphile. In no less than 95% of the cases, female-to-male transsexuals are gynaecophilic (Coleman, Bockting, & Gooren, 1992). These data indicate that indeed similar (but as yet unknown) mechanisms may play a role in the development of both gender identity and sexual orientation.

Finally, we were given the opportunity to study the hypothalami of 3 male-to-female transsexuals (Figure 4). Two of them appeared to have a large SCN with high cell numbers and a small SDN with low cell numbers. The third transsexual subject, however, had a small SCN and a large SDN. These two different patterns could not be related to sexual orientation of these three subjects in any simple way. These findings suggest, however, that a relationship might exist between (1) a large SCN and small SDN and primary transsexuality (i.e., awareness of gender problems from early childhood onwards) on the one hand, and (2) a small SCN and large SDN and secondary transsexuality (i.e., awareness of transsexuality later in life) on the other. It is obvious that more data are necessary in order to establish whether such a relationship indeed exists.

CONCLUSIONS

In keeping with observations in many mammalian species the human hypothalamus has been hypothesized to undergo sexual differentiation during development due to an organizing effect of sex hormones. We have found a sexually dimorphic nucleus (SDN) in the preoptic area of the human hypothalamus that contains about twice as many cells in young adult men as in women. The magnitude of the sex difference in the SDN depends on age. In the litera-

FIGURE 4


SUPRACHIASMATIC NUCLEUS
SEXUALLY DIMORPHIC NUCLEUS
Volume (mm³)
0.6
0.5
0.4
0.3
0.2
0.1
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***
1
2
3
Reference group
Homo-sexuals (AIDS)
Hetero-sexuals (AIDS)
Trans-sexuals

ture two other hypothalamic nuclei (INAH 2 and 3) and a part of the bed nucleus of the stria terminalis (BST) have been reported to be sexually dimorphic in humans.

At birth, the SDN contains only some 20% of the cell number found at 2 to 4 years of age. The cell number rapidly increases in boys and girls at the same rate until 2 to 4 years of age, after which the SDN differentiates according to sex due to a decrease in cell numbers in girls. This period of sexual differentiation of the human hypothalamus is much later than formerly presumed. This offers the possibility that, in addition to genetic information, a multitude of postnatal factors may interact with the process of sexual differentiation of the brain, e.g., hormones, other chemical compounds, and psycho-social factors.

No difference in SDN cell number was observed between homosexual and heterosexual men. This refutes the most global formulation of Dörner's hypothesis that male homosexuals would have a "female" hypothalamus. However, in a sample of brains of homosexual men we found that the suprachiasmatic nucleus (SCN) contained twice as many cells as in the brains of the reference group. The observation that a similarly enlarged SCN was present in a woman with Prader-Willi syndrome suggests that (sex) hormones and SCN development might be interrelated. Recent reports claimed INAH-3 to be more than twice as large in heterosexual men as in homosexual men (LeVay, 1991) and the anterior commissure to be larger in homosexual men (Allen & Gorski, 1992). Preliminary data suggest that the SCN is large and the SDN small in primary male-to-female transsexuals and that the SCN is small and the SDN large in secondary male-to-female transsexuals.

In conclusion: differences in size and cell number have been reported in a number of hypothalamic nuclei in relation to sexual orientation and gender identity. However, the functional implications of these findings are far from clear.

AUTHOR NOTE

Brain material was obtained from the Netherlands Brain Bank (coordinator Dr. R. Ravid) and from Dr. L. J. G. Gooren (Dept. of Endocrinology, Free University, Amsterdam, The Netherlands), Dr. R. S. Williams (Neuropathology Laboratory, Shriver Center, Walton, USA), Dr. L. Mrzljak and Dr. I. Kostovic (Dept. of

Anatomy, Univ. of Zagreb, Yugoslavia), Dr. P. G. Barth (Dept. of Pediatrics and Neurology, AMC, Univ. of Amsterdam, The Netherlands), and Dr. H. P. H. Kremer (Dept. Neurology, Univ. of Leyden, The Netherlands). General pathology and neuropathology were performed either at the Free University of Amsterdam (Dr. W. Kamphorst) or at the AMC, Univ. of Amsterdam (Dr. D. Troost). We want to thank Mr. B. Fisser for his technical assistance and Ms. W. T. P. Verweij for her secretarial help.

REFERENCES

Abramovich, D. R., Davidson, I. A., Longstaff, A., & Pearson, C. K. (1987). Sexual differentiation of the human midtrimester brain. *European Journal of Obstetrics, Gynecology and Reproductive Biology, 25*, 7-14.

Allen, L. S., Hines, M., Shryne, J. E., & Gorski, R. A. (1989). Two sexually dimorphic cell groups in the human brain. *Journal of Neuroscience, 9*, 497-506.

Allen, L. S., & Gorski, R. A. (1990). Sex difference in the bed nucleus of the stria terminalis of the human brain. *J. Comp. Neurol., 302*, 697-706.

Allen, L. S., & Gorski, R. A. (1992). Sexual orientation and the size of the anterior commissure in the human brain. *Proc. Natl. Acad. Sci. USA, 89*, 7199-7202.

Anderson, C. H. (1981). Nucleolus: Changes at puberty in neurons of the suprachiasmatic nucleus and the preoptic area. *Exp. Neurol., 74*, 780-786.

Anderson, R. H., Fleming, D. E., Rhees, R. W., & Kinghorn, E. (1986). Relationship between sexual activity, plasma testosterone and the volume of the sexually dimorphic nucleus of the preoptic area in prenatally stressed and nonstressed rats. *Brain Res., 370*, 1-10.

Bailey, J. M., & Pillard, R. C. (1991). A genetic study of male sexual orientation. *Arch. Gen. Psychiatry, 48*, 1089-1096.

Bailey, J. M., Willerman, L., & Parks, C. (1991). A test of the maternal stress theory of human male homosexuality. *Arch. Sex. Behav., 20*, 277-293.

Braak, H., & Braak, E. (1987). The hypothalamus of the human adult: Chiasmatic region. *Anat. Embryol., 176*, 315-330.

Brockhaus, H. (1942). Beitrag zur normalen Anatomie des Hypothalamus und der Zona incerta bei Menschen. *J. Psychol. Neurol., 51*, 96-196.

Coleman, E., Bockting, W. O., & Gooren, L. J. G. (1993). Homosexual and bisexual identity in sex-reassigned female-to-male transsexuals. *Arch. Sex. Behav., 22*, 37-50.

Croxson, T. S., Chapman, W. E., Miller, L. K., Levit, C. D., Senie, R., & Zumoff, B. (1989). Changes in the hypothalamic-pituitary-gonadal axis in human immunodeficiency virus-infected homosexual men. *J. Clin. Endocrinol. Metab., 68*, 317-321.

Curran, J. W., Meade Morgan, W., Hardy, A. M., Joffe, H. W., Darrow, W. W., & Dowdle, W. R. (1985). The epidemiology of AIDS: Current status and future prospects. *Science, 229*, 1352-1357.

De Jonge, F. H., Louwerse, A. L., Ooms, M. P., Evers, P., & Van de Poll, N. E.

(1989). Lesions of the SDN-POA inhibit sexual behavior of male Wistar rats. *Brain Res. Bull., 23*, 483-492.

Dörner, G. (1979). Psychoneuroendocrine aspects of brain development and reproduction: In L. Zichella & P. Pancheri (Eds.), *Psychoneuroendocrinology in reproduction: An interdisciplinary approach* (pp. 239-252). Amsterdam: Elsevier.

Dörner, G. (1988). Neuroendocrine response to estrogen and brain differentiation in heterosexuals, homosexuals, and transsexuals. *Arch. Sexual Behav., 17*, 57-75.

Dörner, G., Geiser, T., Ahrens, L., Krell, L., Munz, G., Sieler, H., Kittner, E., & Muller, H. (1980). Prenatal stress and possible aetiogenetic factor homosexuality in human males. *Endokrinologie, 75*, 365-368.

Dörner, G., & Staudt, J. (1972). Vergleichende morphologische Untersuchungen der Hypothalamusdifferenzierung bei Ratte und Mensch. *Endokrinologie, 59*, 152-155.

Ehrhardt, A. A., Meyer-Bahlburg, H. F. L., Rosen, L. R., Feldman, J. F., Veridiano, N. P., Zimmerman, I., & McEwen, B. S. (1985). Sexual orientation after prenatal exposure to exogenous estrogen. *Arch. Sex. Behav., 14*, 57-75.

Ellis, L., Ames, M. A., Peckham, W., & Burk, D. (1988). Sexual orientation of human offspring may be altered by severe maternal stress during pregnancy. *J. Sex. Res., 25*, 152-157.

Feremutsch, K. (1955). Strukturanalyse des menschlichen Hypothalamus. *Monatschr. Psychiatr. Neurol., 121*, 87-113.

Forest, M., & Cathiard, A. M. (1975). Patterns of plasma testosterone and Δ-4-androstenedione in normal newborns: Evidence for testicular activity at birth. *J. Clin. Endocrinol. Metab., 41*, 977-981.

Gladue, B. A., Green, R., & Helleman, R. E. (1984). Neuroendocrine response to estrogen and sexual orientation. *Science, 225*, 1496-1499.

Gooren, L. J. G., & Cohen-Kettenis, P. (1988). Erotosexuality in a man lacking physiological postnatal androgen exposure. *J. Psychol. Hum. Sexuality, 1*, 129-135.

Gooren, L. J. G., Fliers, E., & Courtney, K. (1990). Biological determinants of sexual orientation. *Ann. Rev. Sex. Res., 1*, 175-196.

Gorski, R. A., Gordon, J. H., Shryne, J. E., & Southam, A. M. (1978). Evidence for a morphological sex difference within the medial preoptic area of the rat brain. *Brain Res., 148*, 333-346.

Gray, G. D., Södersten, P., Tallentrie, D., & Davidson, J. M. (1978). Effects of lesions in various structures of the suprachiasmatic-preoptic region on LH regulation and sexual behavior in female rats. *Neuroendocrinology, 25*, 174-191.

Hofman, M. A., Fliers, E., Goudsmit, E., & Swaab, D. F. (1988). Morphometric analysis of the suprachiasmatic and paraventricular nuclei in the human brain. *J. Anat., 160*, 127-143.

Hofman, M. A., & Swaab, D. F. (1989). The sexually dimorphic nucleus of the

preoptic area in the human brain: A comparative morphometric study. *J. Anat., 164*, 55-72.

LeVay, S. (1991). A difference in hypothalamic structure between heterosexual and homosexual men. *Science, 253*, 1034-1037.

McCormick, C. M., Witelson, S. F., & Kingstone, E. (1990). Left-handedness in homosexual men and women: Neuroendocrine implications. *Psychoneuroendocrinology, 15*, 69-76.

Money, J., Schwartz, M., & Lewis, V. G. (1984). Adult erotosexual status and fetal hormonal masculinization: 46,XX congenital virilizing adrenal hyperplasia and 46,XY androgen-insensitivity syndrome compared. *Psychoneuroendocrinology, 9*, 405-414.

Moore, R. Y. (1978). Central neural control of circadian rhythms. In W. F. Ganong & L. Martini (Eds.), *Frontiers in neuroendocrinology* (pp. 185-206), Vol. 5. New York: Raven Press.

Moore-Ede, M. C., Sulzman, F. M., & Fuller, C. A. (1982). *The clocks that time us: Physiology of the circadian timing system.* Cambridge, MA: Harvard University Press.

Nordeen, E. J., Nordeen, K. W., Sengelaub, P. R., & Arnold, A. P. (1985). Androgens prevent normally occurring cell death in a sexually dimorphic spinal nucleus. *Science, 229*, 671-673.

Pillard, R. C., Poumadere, J., & Carretta, R. A. (1981). Is homosexuality familial? A review, some data, and a suggestion. *Arch. Sex. Behavior, 10*, 465-475.

Polzovic, A., Marinkovic, R., Gudovic, R., Mihic, N., & Grkovic, D. (1988). Vascularization of the preoptic area in the human fetus. In M. Bajic (Ed.), *Advances in the biosciences* (pp. 143-146), Vol. 70. Neuron, Brain and Behaviour. Oxford: Pergamon Press.

Reisert, I., & Pilgrim, C. (1991). Sexual differentiation of monoaminergic neurons–genetic or epigenetic? *TINS, 14*, 468-473.

Reyes, F. I., Boroditsky, R. S., Winter, J. S. D., & Faiman, C. (1974). Studies on human sexual development. II. Fetal and maternal serum gonadotropin and sex steroid concentrations. *J. Clin. Endocrinol. Metab., 38*, 612-617.

Rusak, B., & Zucker, I. (1979). Neural regulation of circadian rhythms. *Physiol. Rev., 59*, 449-526.

Södersten, P., Hansen, S., & Srebro, B. (1981). Suprachiasmatic lesions disrupt the daily rhythmicity in the sexual behaviour of normal male rats and of male rats treated neonatally with anti-estrogen. *J. Endocrinol., 88*, 125-130.

Swaab, D. F., & Fliers, E. (1985). A sexually dimorphic nucleus in the human brain. *Science, 228*, 1112-1115.

Swaab, D. F., & Hofman, M. A. (1984). Sexual differentiation of the human brain. A historical perspective. In G. J. De Vries, J. P. C. De Bruin, H. B. M. Uylings, & M. A. Corner (Eds.), *Sex differences in the brain. Progress in brain research* (pp. 361-374), Vol. 61. Amsterdam: Elsevier.

Swaab, D. F., & Hofman, M. A. (1988). Sexual differentiation of the human hypothalamus: Ontogeny of the sexually dimorphic nucleus of the preoptic area. *Dev. Brain Res., 44*, 314-318.

Swaab, D. F., & Hofman, M. A. (1990). An enlarged suprachiasmatic nucleus in homosexual men. *Brain Res., 537*, 141-148.

Swaab, D. F., & Mirmiran, M. (1986). Functional teratogenic effects of chemicals on the developing brain. In M. M. Cohen (Ed.), *Monographs in Neural Sciences* (pp. 45-57), Vol. 12. Basel: S. Karger.

Swaab, D. F., Fliers, E., & Partiman, T. S. (1985). The suprachiasmatic nucleus of the human brain in relation to sex, age and senile dementia. *Brain Res., 342*, 37-44.

Swaab, D. F., Roozendaal, B., Ravid, R., Velis, D. N., Gooren, L. J. G., & Williams, R. S. (1987). Suprachiasmatic nucleus in aging, Alzheimer's disease, transsexuality and Prader-Willi syndrome. In E. R. de Kloet, V. M. Wiegant, & D. De Wied (Eds.), *Neuropeptides and brain function. Progress in brain research* (pp. 301-311), Vol. 72. Amsterdam: Elsevier.

Swaab, D. F., Hofman, M. A., & Honnebier, M. B. O. M. (1990), Development of vasopressin neurons in the human suprachiasmatic nucleus in relation to birth. *Devel. Brain Res., 52*, 289-293.

Turkenburg, J. L., Swaab, D. F., Endert, E., Louwerse, A. L., & Van de Poll, N. E. (1988). Effects of lesions of the sexually dimorphic nucleus on sexual behavior of testosterone-treated female Wistar rats. *Brain Res. Bull., 22*, 215-224.

Van Griensven, G. J. P., Tielman, R. A. P., Goudsmit, J., V. d. Noordaa, J., De Wolf, F., De Vroome, E. M. M., & Coutinho, R. A. (1987). Risk factors and prevalence of HIV antibodies in homosexual men in The Netherlands. *Am. J. Epidem., 125*, 1048-1057.

Wiegand, S. J., Terasawa, E., Bridson, W. E., & Gray, R. W. (1980). Effects of discrete lesions of preoptic and suprachiasmatic structures in the female rat: Alterations in the feedback regulation of gonadotropin secretion. *Neuroendocrinology, 31*, 147-157.

Winter, J. S. D. (1978). Prepubertal and pubertal endocrinology. In F. Falkner & J. M. Tanner (Eds.), *Human Growth. I. Principles and Prenatal Growth* (pp. 183-213), Vol. 2. London: Baillière Tindall.