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Sexual Differentiation of the Human Brain A Historical Perspective

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INTRODUCTION

Although Eve is supposed to have been the first to eat from the tree of wisdom, sex differences of the brain or higher functions have received only little attention in the ancient literature. It is not known whether Aristotle (384–322 B.C.) designated the period around the 9th week of gestation as the moment "upon which the fetus receives its soul" on the basis of the observation that this is the moment when rapid cerebral development begins (cf. Dobbing, 1970). This is unlikely, however, because of the sex difference that has been proposed in this process by Aristotle. The male fetus was supposed to receive its soul around the 40th day of gestation and the female around the 80th day of pregnancy. Since no such sex difference in brain development has even yet been observed, this suggests that a direct relationship between animation and the brain growth spurt was not in fact taken into consideration. Hippocrates the Greek (460–377 B.C.) estimated the moment at which the male and female become "animated" to be at 30 and 42 days of gestation, respectively (P.H. van Laer, personal communication, 1980). Thomas Aquinas (1225–1274), the Italian theologian and philosopher, adopted Aristotle's views without explicitly accounting for the remarkable sex difference as regards the moment of animation. The justification for believing that the female fetus was supposed to be animated at a later stage might, however, be deduced from his opinion that woman is a "mas occasionatus" (i.e. a man who has not reached his full destination) (*Summa Theologiae I*, 92, 1; J.A. Aertsen, personal communication, 1980).

The *mechanism* of sexual differentiation of the rest of the body has been the subject of much speculation ever since the time of Greek antiquity and was beautifully reviewed by Lesky (1950), Guthrie (1965) and Döhler and Gorski (1981). According to Democritus (± 420 B.C.) differentiation of the sexes would depend on whether the mother's or father's seed would preponderate, while Anaxagoras (± 500 B.C.) proposed that semen from the right testis produces male offspring, while semen from the left side gives rise to females. These notions have in the meantime not received any experimental support, in contrast to the option of Empedocles (± 460 B.C.), who claimed that a hot uterus would produce a male and a cold uterus a female fetus. It is now well known that the incubation temperature of the eggs in many Chelonians affects sexual differentiation. However, at higher temperatures it is the female of the species which is produced in greater abundance (Mrosovsky, 1982; Yntema and Mrosovsky, 1982; Morreale et al., 1982), just the opposite of the ancient Greek option.

Systematic observations concerning morphological sex differences in the human *brain*, on the other hand do not go back much further than a hundred years. In the course of the

19th century the interest in possible mascroscopic sex differences grew rapidly, while in the 20th century the mechanism of their possible origin received attention by an animal experimental approach. The insight that hormones were involved in the sexual differentiation of the reproductive organs, as pointed out by Bouin and Ancel (1903) was followed in the thirties by postulated sex differences in the pituitary (Pfeiffer, 1936), and at the end of the fifties by sex differences in the brain (Phoenix et al., 1959). These last authors showed that sex hormones had permanent effects upon behaviour, when given during early development. (These experiments can, however, partly be considered as a confirmation of those of Vera Dantchakoff, who reported in 1938 that prenatally androgenized guinea pigs showed increased masculine sexual behaviour in adulthood (cf. Dörner, 1981).) Until the 1960s animal experimental investigations were generally performed on male animals, so as "to avoid the troublesome variable of the female oestrous cycle" (cf. the publication "A cry for the liberation of the female rodent", Doty, 1974; De Jonge and Scholtens, 1983). However, a rapid increase in animal experimental data concerning sex differences has become noticeable in the literature over the last decades (e.g., this volume).

SEX DIFFERENCES IN MACROSCOPIC BRAIN MORPHOLOGY

The literature on macroscopic sex differences in the human brain is a remarkable mixture of scientific observations and cultural bias. The existence of comparatively minor and seemingly random morphological sex differences in the human brain, which were often used to "prove" female inferiority, has alternately been claimed and disclaimed. Thus, Huschke (1854) "showed" that the frontal lobe in the male is all of 1% larger than that of the female, leading him to the following sweeping statement: "Woman is a *Homo parietalis* and *interparietalis*, man a *Homo frontalis*, and the shape of the woman's brain is therefore more round than that of the man". * He further states that the central sulcus is straighter, more perpendicular and nearer to the front end in the female brain. Although it was admitted by Huschke that it is extremely difficult to recognize a difference in the convolutions due to sex, he nevertheless stated: "There is, however, no question that it does exist".** Mall (1909) proposed, therefore, in his critical review "that differences like those of Huschke are largely due to the personal equation of the investigator". Also the data presented by Retzius (1900) regarding proposed differences in the gyri and sulci associated with gender have been extensively criticized, e.g. by Karplus (1905), who wrote: "I will not go into the few sex differences of the brain as indicated by the authors, which after all are challenged by many. First considerably more material should also be collected here; I am so far not convinced that from the structure of the convolutions an inferiority of the female brain could be deduced". *** The observation of Meynert (1867) that in men, as contrasted with women, there is relatively more brain substance in front of the central sulcus than behind it, was discussed and criticized by anatomists such as Snell (1891) and Mall (1909). They began also to take differ-

* "Das Weib ist eine *Homo parietalis* und *interparietalis*, der Mann ein *Homo frontalis*, und das Weib hat deshalb auch ein runderes Gehirn als der Mann".

** "Es ist aber keine Frage dasz sie existieren".

*** "Auf die von den Autoren angegebenen einzelnen Geschlechtsmerkmale der Gehirne, die ja von vielen bestritten werden, will ich hier nicht näher eingehen. Auch hier muß zunächts viel mehr Material gesammelt werden; bisher bin ich nicht davon überzeugt dasz sich aus dem Furchenbild eine Inferiorität des weiblichen Gehirns ableiten liesse".

ences in age and body size into account, as more reliable measures related to sexual differences in brain form and size. In his major study, Mall (1909) concludes: "(...) that with the methods at our disposal it is impossible to detect a relative difference in the weight or size of the frontal lobe due to (...) sex and that probably none exists". In the final paragraph Mall (1909) states: "Each claim for specific differences (in type of the brain) fails when carefully tested, and the general claim that the brain type of woman is foetal or of simian type, is largely an opinion without any scientific foundation. Until anatomists can point out specific differences which can be weighed or measured, or until they can assort a mixed collection of brains, their assertions regarding male and female types are of no scientific value".

That time may now have come, in view of the fact that Mall's opinion that "there is no variation in either genu or splenium of the corpus callosum due to (...) sex" was recently refuted by the investigation of De Lacoste-Utamsing and Holloway (1982), who by surface measurements showed the female splenium of the corpus callosum to be larger and more bulbous than its male counterpart. This is consistent with the hypothesis that the female brain is less well lateralized, such as the trend found for the left temporal planum to be larger in adult males than in females (Wada et al., 1975). In conclusion, the sex differences in macroscopic appearance of the human brain which have been reported so far are relatively small, and those which seem to be truly present are related to a sex difference in *lateralization*. This is not exactly a novel notion, since such a difference was proposed as early as 1880, by Crichton-Browne, who stated that "the tendency to symmetry in the two brain halves of the cerebrum is stronger in women than in men".

SEX DIFFERENCES IN BRAIN WEIGHT

A sex difference in brain weight is a consistent finding in the literature and has been used frequently to "prove" woman's inferiority. Although feminists of both the first wave (Suffragettes) and the second wave (Women's lib) have pointed out such malpractices with fully justifiable disapproval, distinguished women in both periods sometimes made comparable mistakes in "proving" women's superiority. An early example can be found in the handbook of *Pedagogical Anthropology* by Maria Montessori (1913). She was the first woman in Italy to be conferred a doctor's degree in medicine, became a professor of Anthropology and Hygiene at the University of Rome, and developed a pedagogical system that is still popular in The Netherlands. Montessori (1870–1952) writes in her handbook: "Because, as you know, there is a very widespread belief of long standing that is confirmed in the name of science: that woman is biologically, in other words totally, inferior, that the volume of her brain is condemned by nature to an inferiority against which nothing can prevail (...). Names as famous as that of Lombroso, which are associated with the progress of positive science, lend the weight of their authority to this form of condemnation! That the cerebral volume should be considered in its relation to the stature is a familiar principle. Accordingly we find that Manouvrier compares the brain with the mass of the whole body (...). He deduces from them (...) "the index of sexual mass", (...) and calculates how much brain man would lose if he were reduced to a mass having feminine limits. (...) Consequently the cerebral volume of woman is superior to that of man! This is an anthropological superiority which is further revealed in the more perfected form of the cranium, insomuch as woman has an absolutely erect forehead and has no remaining traces of the supra-orbital arches (characteristics of superiority in the species). Thus, we have a contradiction between existing anthropological and social conditions: woman, whom anthropology regards as a being having the cranium of an almost superior race, continues to be relegated to an unquestioned social inferiority, from which it is not easy to raise her".

Also today, sex differences in one or another brain parameter are used to "prove" female inferiority, superiority or are simply denied ("the androgyne human being"), vide infra. The coinciding attention for sex differences in on the one hand neurobiological research of the last decades and, on the other hand, the second feministic wave have once again led to an intensification of criticism by women's lib concerning research on sexual dimorphism. It has been pointed out that especially in this period of economic recession the nature-nurture aspect of this topic might be used to confirm male domination as being "a biologically determined inevitability" (De Jonge and Scholtens, 1983; Van Manen and Oudshoorn, 1983). This fear may explain — without justifying it — why a similar line of specious reasoning is employed by certain feminist writers in order to claim some sort of "female superiority".

By way of illustration for such an inversion of the traditional bias, Germaine Greer (1972) may be quoted: "It was thought that the relative lightness of the female brain argued lesser mental powers, although it was pointed out that women have a heavier brain considered relatively to the total body weight (quod not; see below). In any case, brain weight is irrelevant, as was swiftly admitted when it was found to operate to male disadvantage. If the frontal lobes are to be considered as the seat of intelligence, then it must also be pointed out that the frontal area of the brain is more developed in women". (A reference for the latter observation was not given, although Huschke (1854) came to the opposite conclusion, and Mall (1909) could not find any sex difference.)

The fact that the two most quoted authors in this subchapter are women might be not simply the result of a biased selection on our part. Studies of sections of the human experimental literature indicate that female authors analyse sex differences comparatively more frequently than do their male counterparts (Harris, 1972). A sex difference in the interest in this particular topic also became apparent from the fact that 26 participants of the current Summer School (which forms the basis for the present book, eds.) were women, while the comparable rate of the previous Summer School — entitled "Chemical Transmission in the Brain" (1981) — was only 13 ($P < 0.05$, χ^2 test).

SEX DIFFERENCES IN RELATIVE BRAIN SIZE

Since the latter half of the 19th century it has been well known that the sex difference in absolute brain weight is already present at birth (Bischoff, 1880; Pfister, 1897). The recent literature is in full agreement with earlier findings, although the reported values vary widely (Table I). Selection of material which differs with respect to cause of death, time of birth, and nutritional condition, might account for discrepancies. Although, on the average, male neonates have larger brains than do their female counterparts, differences in neonatal body weight and height between the sexes are present as well (Bayley, 1956; Tanner et al., 1966; Dekaban and Sadowsky, 1978; Voigt and Pakkenberg, 1983). One must, therefore, consider the possibility that the sexual dimorphism in neonatal brain weight is simply a result of differences in stature. Indeed, Fig. 1 demonstrates that allometric scaling explains almost all the variance in neonatal brain weight. Female neonates will have brain weights which are similar to those in males of comparable body weight. In contrast to neonatal brain weight, the head circumference values at birth reveal a consistent sex difference of approximately 2–3% (Table I), for healthy subjects. Using the data of Voigt and Pakkenberg (1983) and of

TABLE I

SEXUAL DIMORPHISM IN MEAN NEONATAL BRAIN WEIGHT

Reference	Brain weight (g)		$\frac{\text{Male-female}}{\text{female}}$ (%)
	Male	Female	
Schultz et al., 1962	506	401	26.2
Chrzanowska and Kredowiecki, 1977	325	330	−1.5
Dekaban and Sadowsky, 1978	380	360	5.6
Voigt and Pakkenberg, 1983	448	372	20.4

SEXUAL DIMORPHISM IN MEAN NEONATAL HEAD CIRCUMFERENCE

Reference	Head circumference (cm)		$\frac{\text{Male-female}}{\text{female}}$ (%)
	Male	Female	
Eichorn and Bailey, 1962	35.66	34.47	3.4
Nellhaus, 1968	34.8	34.0	2.1
Meredith, 1971	34.9	34.4	1.5
Brandt, 1979	35.4	34.6	2.3

Dekaban and Sadowsky (1978), a similar degree of sexual dimorphism was found for neonatal body height (Fig. 2). When comparing differences between variables, it should be emphasized that it is important to take dimensional differences into account. Variations in linear measures, such as head circumference, simply cannot be compared directly with variations in volumetric parameters such as brain weight or volume.

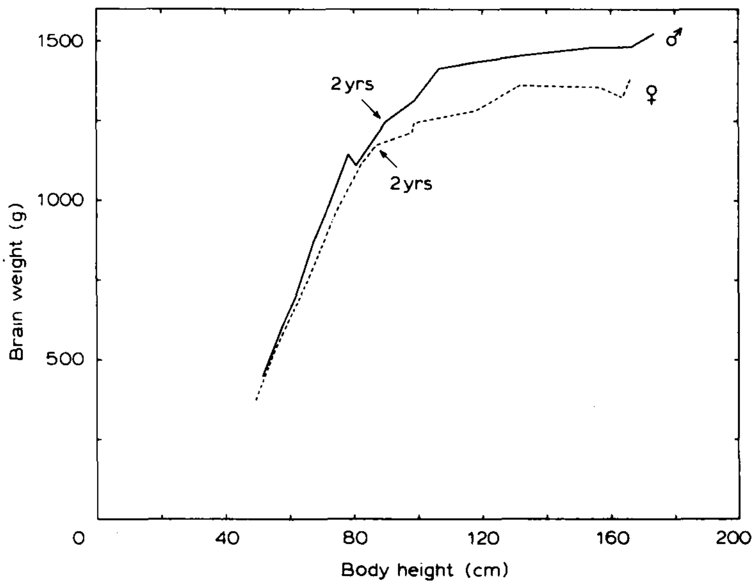

Fig. 1. Brain weight as a function of body height. Data have been compiled from Voigt and Pakkenberg (1983).

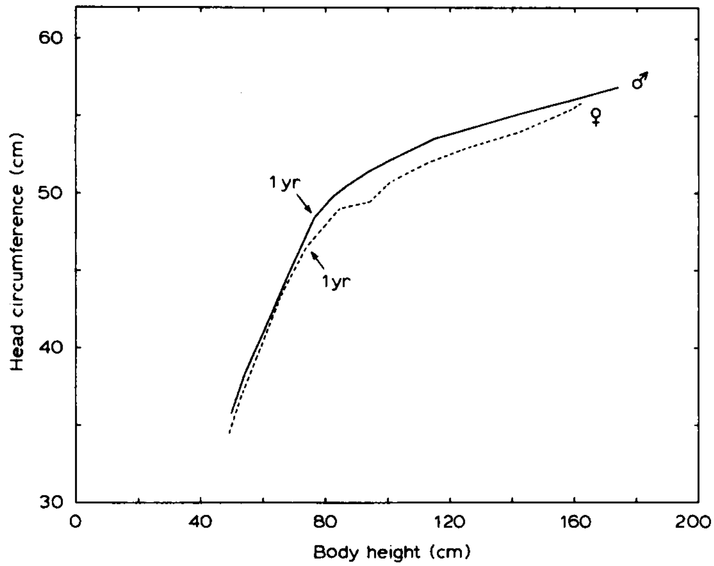

Fig. 2. Head circumference as a function of body height. Data for head circumference and body height have been compiled from Eichhorn and Bayley (1962) and Tanner et al. (1966), respectively.

TABLE II

SEXUAL DIMORPHISM IN MEAN ADULT BRAIN WEIGHT*

Reference	*Brain weight (g)*		*Male–female / female* (%)
	Male	*Female*	
Rössle and Roulet, 1938	1357	1220	11.2
Pakkenberg and Voigt, 1964	1526	1366	11.7
Chrzanowska and Beben, 1973	1463	1312	11.5
Dekaban and Sadowsky, 1978	1450	1290	12.4

* Age: $18 < t < 30$ years.

SEXUAL DIMORPHISM IN MEAN ADULT HEAD CIRCUMFERENCE*

Reference	*Head circumference (cm)*		*Male–female / female* (%)
	Male	*Female*	
Eichorn and Bailey, 1962	57.20	55.84	2.4
Nellhaus, 1968	56	55	1.8
Meredith, 1971	56.2	54.6	2.9

* Age: $t = 18$ years.

A sexual dimorphism in brain weight and head circumference is present also in adulthood (Table II); the quoted sources all show a lower brain weight and a smaller head circumference in adult females compared with adult males. This sexual dimorphism has often given rise to vehement and emotional reactions, that might be related to the direct relationship set forth in the literature between brain size and intellectual capacity. Thus Röse (1905), who investigated a number of German professors and soldiers concluded: "The professors have considerably larger heads than the officers. The regular professors have the largest heads, followed at only a very short distance by the other university teachers; extraordinary professors..." *. Bayerthal (1911) followed up these observations by the remarks: "One can at least become an ordinary professor of surgery and obstetrics with a minimum head circumference of 52–53 cm (...), but with a head circumference under 52 cm you cannot expect an intellectual performance of any significance, while under 50.5 cm no normal intelligence can be expected" **. In this connection he also makes the remark: "We do not have to ask for the head circumference of women of genius — they do not exist" ***.

In spite of such sweeping statements, it seems plausible to suppose that intelligence is determined in part by the amount of brain tissue in excess of that required for receiving sensory information and controlling muscle movements (Passingham, 1979; Hofman, 1982). The absolute brain size is, however, not the whole story since differences in body size must also be taken into account (Tobias, 1970; Jerison, 1973; Hofman, 1983). This means that the 11–12% difference in average adult human brain weights between the sexes might be a purely allometric phenomenon, as in neonates. However, a graphic representation (Figs. 1 and 2) reveals that this is not the case and that the sexual dimorphism in both brain weight and head circumference in postnatal life cannot be explained by differences in height. The sex difference in relative head circumference seems to disappear after the puberal growth spurt (Fig. 2). The sexual dimorphism in relative brain size, on the other hand, which does not appear until the brain has reached about 85% of its adult value, i.e., around the 2nd year of life, persists throughout life. It seems as if the rapid growth phase of the brain in males is slightly prolonged as compared with that of females, causing a larger brain weight relative to height. Whether or not this minor sexual dimorphism in average degree of encephalization in humans has any analogue in neural function cannot be answered at the moment.

FUNCTIONAL AND MICROSCOPICAL SEX DIFFERENCES

Evidence for the presence of functional sex differences in the human has accumulated over the last decades, e.g., for female superiority in certain verbal tasks and male superiority in spatial functioning (McGlone, 1980; Inglis and Lawson, 1981). Differences in sleep (Webb, 1982), lateralization e.g. of language (McGlone, 1980; Inglis and Lawson, 1981) have also been reported. A sex difference in lateralization of visual field accuracy was found already in 3- and 4-year-old children (Jones and Anuza, 1982). In addition, sex differences in cerebral organization for speech and praxic functions have emerged from retrospective studies of aphasic and apraxic patients (Kimura, 1983). In spite of such studies the possibility of a "hardware" basis in the brain for such functional sex differences has often been rejected vigorously throughout the years. The starting point and ideal of the author Couperus (1904–05) was the "androgynous human being", who supposedly possesses both male and female

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* "Die Professoren haben bedeutend grössere Köpfe als die Offiziere. Die ordentlichen Professoren haben die grössten Köpfe mit ganz geringen Abständen folgen die übrigen Universitätslehrer: ausserordentliche Professoren...".

** "Man kan wenigstens bei einem Umfang des Kopfes von 52–53 cm noch ordentlicher Professor der Chirurgie und Geburtshilfe werden". (...) "doch werden wir beim erwachsenen Mann unter 52 cm keine bedeutende geistige Leistungen mehr zu erwarten haben, und unter 50.5 cm keine normale Intelligenz".

*** "Nach der Kopfgrösse genialer Weiber brauchen wir nicht zu fragen es gibt keine...".

characteristics in equal measure. This concept has been revived by the women's liberation movement during the few last decades, sometimes to the point of dogmatism, by which the very possibility of any sexual dimorphism whatsoever (even in the face of available experimental data and psychological observations) is flatly denied as far as brain function is concerned. Germaine Greer (1972), for example, states "(...) although sex hormones do enter the brain, (...) no correlation between that physiological fact and mental capacity or behaviour has ever been established". Indeed, macroscopically the similarities and not the differences between male and female human brains are the most striking, but functional sex differences do exist. Recent biochemical and microscopical observations throughout the animal kingdom, however, show that in the brain similar macroscopical structures may be built up from sexually dimorphic neurotransmitter systems, and may contain differences in synaptic termination patterns, regional cell size, density and number, and dendritic trees. Such differences could easily serve as the basis for functional sex differences (Ayoub et al., 1982; Swaab and Ter Borg, 1981; De Vries et al., 1981, 1983). Studies on the microscopical and chemical differentiation of the human brain have only recently been started, but the sex difference reported for the hypothalamic LHRH content in the human fetus (Siler-Khodr and Khodr, 1978) already supports the possible presence of such differences in the human brain.

A SEX DIFFERENCE IN THE HUMAN SUPRACHIASMATIC NUCLEUS?

We are currently investigating the human suprachiasmatic nucleus (SCN) for the possible presence of microscopical and chemical sex differences. The SCN is considered to be the "endogenous hypothalamic clock" (Mosko and Moore, 1978) which controls circadian rhythms such as the sleep-wake cycles (Bethea and Neill, 1980; Moore, 1982). In addition, the SCN plays an essential role in longer rhythmic phenomena such as the ovulation cycle (Brown-Grant and Raisman, 1977). These considerations together with the sex differences in rhythms (Davis, 1982; Webb, 1982) make this structure of special interest for the study of sex differences. Such differences have in fact been reported for the rat with respect to the size of the SCN (Gorski et al., 1978) and its synaptology (Güldner, 1982). Until recently, the very existence of the SCN in the *human* brain was questioned because it was difficult to visualize (e.g., Defendini and Zimmerman, 1978; for references see Lydic et al., 1980). The SCN contains vasopressinergic neurones, not only in the rat (Swaab et al., 1975) but also in the human brain (Dierickx and Vandesande, 1977), which now makes it much easier to visualize this structure. Such cells are present already at birth (Swaab and Ter Borg, 1981) and have been shown in the rat to innervate the periventricular nucleus, the organum vasculosum laminae terminalis (OVLT) and the dorsomedial hypothalamic nucleus (DMH) (Hoorneman and Buijs, 1982). These last two structures are implicated in the regulation of the oestrous cycle (Szentágothai et al., 1968; Wenger et al., 1979; Piva et al., 1982). Studies on the Brattleboro rat, which is homozygous for vasopressin deficiency, suggest that the vasopressinergic neurones of the SCN might be essential for a regular ovarian cycle (Boer et al., 1981). Interesting in this respect is also the observation that vasopressin inhibits sexual behaviour (Bohus, 1977; see reviews Södersten et al., 1983). The observation that homozygous Brattleboro rats maintain normal circadian rhythmicity (Peterson et al., 1980) does not mean that the vasopressinergic cells of the SCN are not normally essential in this respect. Plasticity in the developing brain is sometimes very impressive, so that other neuronal systems might take over the function of the absent vasopressin cells. This makes the Brattleboro rat not the ideal model for investigating the possible functions of vasopressinergic cells in adulthood (Swaab, 1980). T. Partiman in our group was struck by a sex difference in the rostro-caudal diameter of this nucleus in the human brain. The diameter of the nucleus in women was 43% larger than that of men. The maximal area covered by vasopressinergic cells in the middle of the SCN was, however, 35% smaller in women. 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 (D.F. Swaab, E. Fliers and T. Partiman, unpublished observation). This is — to our knowledge — the first transmitter-characterized system in the *human* brain for which a clear sex difference has been demonstrated. The functional implication of the SCN shape difference is still obscure.

EXOGENOUS SEX STEROIDS AND FURTHER RESEARCH

Although research on the possible effects of endogenous steroids on the developing brain is just starting, it is clear from psychometric studies that such substances, when administered during development, may cause permanent changes in human brain function. This is illustrated by the behavioral changes observed in children of pregnant women who were treated for impending abortion by the administration of sex hormones. Although this treatment is not effective in preventing abortion, it has nevertheless been used extensively, and appears to have induced behavioral changes in the children of these mothers (Reinisch and Karow, 1977; Reinisch, 1981; Reinisch and Sanders, 1984). In The Netherlands, DES (diethylstilboestrol, an estrogen compound) turns out even to have been dispensed by mail order as a sex-stimulating compound! Developmental sequelae of such an abuse cannot easily be traced for obvious reasons.

If permanent morphological alterations in the human brain are indeed induced by sex hormones during development in a similar fashion as has been observed in animal experiments, the morphometric determination in later life of lasting changes in immunocytochemically identified neural systems might give information concerning the exposure of the fetus to steroids or other potentially deleterious chemicals. If this turns out to be the case, it would be all the more important to test, by means of similar methodology, the hypothesis that prenatal hormonal influences upon brain differentiation underlie such conditions as homosexuality, the Imperato–McGinley syndrome and transsexuality (e.g., Gooren, 1984; Meyer-Bahlburg, 1984). The next decades will tell us if this is a fruitful course to pursue.

SUMMARY AND CONCLUSIONS

Although Aristotle designated the moment at which the male fetus receives its "soul" as the 40th day of pregnancy as compared with day 80 for the female fetus, very little attention was paid in the ancient literature to the possibility that there existed gender differences either in structure or in functions of the brain.

In the course of the 19th century the interest in this topic grew rapidly. However, the literature on macroscopic sex differences of the human brain, was, and still is, a remarkable mixture of scientific observations and cultural bias. Those sex differences which seem to be really present, i.e. the larger splenium of the corpus callosum in women and the larger left temporal planum in men, involve sex differences in brain *lateralization*. Recent allometric calculations have revealed that the sex difference in average neonatal brain weight can be largely if not entirely explained by differences in body size. The lower brain weight of females as compared to males, particularly after the 2nd year of life, however, cannot be explained by differences in mean height. Whether or not this sexual dimorphism in encephalization during the postnatal life of humans has an analogue in neural function is not known.

Evidence for sex differences in brain function has accumulated over the last 30 years. From the animal experimental literature it can be extrapolated that similar appearing macroscopic brain structures may be built up from sexually dimorphic neurotransmitter systems. Differences between the sexes might also be present in synaptic termination patterns, regional cell size, density or number, and in dendritic arborization.

By way of example, some of our own observations on the human suprachiasmatic nucleus (SCN) are mentioned. Staining with antibodies raised to vasopressin enables morphometric studies on this "hypothalamic clock". These studies revealed that the SCN in women tends to be larger in its cranio-caudal diameter, while in men it has a larger maximal diameter in the middle of the nucleus. On the whole, however, neither the total volume nor the cell number of the SCN turned out to differ. This sexual dimorphism in the SCN shape is to our knowledge the first gender-linked difference in an identified neurotransmitter system that has been reported within the human brain.

The next decade will hopefully tell us whether or not the careful study of such transmitter systems is a fruitful way of obtaining information concerning the effects of endogenous or exogenous steroid hormones on the developing human brain.

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REFERENCES

Ayoub, D.M., Greenough, W.T. and Juraska, J.M. (1982) Sex differences in dendritic structure in the preoptic area of the juvenile macaque monkey brain. *Science*, 219: 197–198.

Bayerthal (1911) *Arch. Rassen- u. Gesellschaftsbiol.*, VIII.

Bayley, N. (1956) Growth curves of height and weight by age for boys and girls, scaled according to physical maturity. *J. Pediat.*, 48: 187–194.

Bethea, C.L. and Neill, J.D. (1980) Lesions of the suprachiasmatic nuclei abolish the cervically stimulated prolactin surges in the rat. *Endocrinology*, 107: 1–5.

Bischoff, T.L. (1880) *Das Hirngewicht des Menschen*, Neusser, Bonn, pp. 46–64.

Boer, K., Boer, G.J. and Swaab, D.F. (1981) Reproduction in Brattleboro rats with diabetes insipidus. *J. Reprod. Fertil.*, 61: 273–280.

Bohus, B. (1977) The influence of pituitary peptides on sexual behavior. In: H.-P. Klotz (Ed.), *Hormones et Sexualité, Problèmes Actuels d'Endocrinologie et de Nutrition*, Expansion Scientifique Française, Paris, pp. 235–246.

Bolk, L. (1918) *Hersenen en Cultuur*, 2nd Edn., Scheltema en Holkema, Amsterdam.

Bouin, P. and Ancel, P. (1903) Sur la signification de la glande interstitielle du testicule embryonnaire. *C.R. Soc. Biol.*, 55: 1682–1684.

Brandt, I. (1979) Perzentilkurven für das Kopfumfangswachstum. *Kinderarzt*, 2: 185–188.

Brown-Grant, K. and Raisman, G. (1977) Abnormalities in reproductive function associated with the destruction of the suprachiasmatic nuclei in female rats. *Proc. Roy. Soc. Lond. B*, 198: 279–296.

Chrzanowska, G. and Beben, A. (1973) Weight of the brain and body height in man between the ages of 20 and 89 years. *Folia Morphol. (Warsz.)*, 32: 391–406.

Chrzanowska, G. and Kredowiecki, A. (1977) Analyse der Frischgewichte 993 menschlicher Gehirne, *Ergebn. Exp. Med.*, 25: 161–172.

Couperus, L. (1904–05) *De Berg van Licht*, L.J. Veens Uitgeversmaatschappij, Amsterdam, 1973, pp. 26–27.

Crichton-Browne, J. (1880) On the weight of the brain and its component parts in the insane. *Brain*, 2: 42–67.

Dantchakoff, V. (1938) Rôles des hormones dans les manifestations des instincts sexuels. *C.R. Acad. Sci. (Paris)*, 206: 945–947.

Davis, F.C. (1982) Development of the suprachiasmatic nuclei and other circadian pacemakers. In: D.C. Klein (Ed.), *Melatonin Rhythm Generating System*, Karger, Basel, pp. 1–19.

Defendini, R. and Zimmerman, E.A. (1978) The magnocellular neurosecretory system of the mammalian hypothalamus. In: S. Reichlin, R.J. Baldessarini and J.B. Martin (Eds.), *The Hippocampus*, Raven Press, New York, pp. 137–154.

De Jonge, F. and Scholtens, J. (1983) Aangeboren of aangeleerd. *Wetensch. Samenl.*, 2: 13–21.

Dekaban, A.S. and Sadowsky, D. (1978) Changes in brain weights during the span of human life: relation of brain weights to body heights and body weights. *Ann. Neurol.*, 4: 345–356.

De Lacoste-Utamsing, C. and Holloway, R.L. (1982) Sexual dimorphism in the human corpus callosum. *Science*, 216: 1431–1432.

De Vries, G.J., Buijs, R.M. and Swaab, D.F. (1981) Ontogeny of the vasopressinergic neurons of the suprachiasmatic nucleus and their extrahypothalamic projections in the rat brain — presence of a sex difference in the lateral septum. *Brain Res.*, 218: 67–78.

De Vries, G.J., Best, W. and Sluiter, A.A. (1983) The influence of androgens on the development of a sex difference in the vasopressinergic innervation of the rat lateral septum. *Brain Res.*, 8: 377–380.

Dierickx, K. and Vandesande, F. (1977) Immunocytochemical localization of the vasopressinergic and the oxytocinergic neurons in the human hypothalamus. *Cell Tissue Res.*, 184: 15–27.

Dobbing, J. (1970) Undernutrition and the developing brain. The relevance of animal models to the human problem. *Am. J. Dis. Child.*, 120: 411–415.

Döhler, K.-D. and Gorski, R.A. (1981) Sexual differentiation of the brain: past, present and future. *BRI Bull.*, 5: 5–9.

Dörner, G. (1981) Sex hormones and neurotransmitters as mediators for sexual differentiation of the brain. *Endokrinologie*, 78: 129–138.

Doty, R.L. (1974) A cry for the liberation of the female rodent: courtship and copulation in rodentia. *Psychol. Bull.*, 81: 159–172.

Eichorn, D.H. and Bayley, N. (1962) Growth in head circumference from birth through young adulthood. *Child Develop.*, 33: 257–271.

Geschwind, N. and Levitsky, W. (1968) Human brain: left–right asymmetries in temporal speech region. *Science*, 161: 186–187.

Gooren, L. (1984) Sexual dimorphism and transsexuality: clinical observations. In: G.J. De Vries, J.P.C. De Bruin, H.B.M. Uylings and M.A. Corner (Eds.), *Sex Differences in the Brain. The Relation between Structure and Function. Progress in Brain Research*, this volume, Ch. 24.

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

Greer, G. (1972) *The Female Eunuch*, Paladin, London, p. 99.

Gruenwald, P. and Minh, H.N. (1960) Evaluation of body and organ weights in perinatal pathology. I. Normal standards derived from autopsies. *Am. J. Clin. Pathol.*, 34: 247–253.

Güldner, F.-H. (1982) Sexual dimorphisms of axo-spine synapses and postsynaptic density material in the suprachiasmatic nucleus of the rat. *Neurosci. Lett.*, 28: 145–150.

Guthrie, W.K.C. (1965) *A History of Greek Philosophy, Vol. 2*, Cambridge University Press, Cambridge.

Harris, S.L. (1972) Who studies sex differences? *Am. Psychol.*, 27: 1077–1078.

Hofman, M.A. (1982) Encephalization in mammals in relation to the size of the cerebral cortex. *Brain Behav. Evol.*, 20: 84–96.

Hofman, M.A. (1983) Evolution of brain size in neonatal and adult placental mammals. A theoretical approach. *J. Theor. Biol.*, 105: 317–332.

Hoorneman, E.M.D. and Buijs, R.M. (1982) Vasopressin fiber pathways in the rat brain following suprachiasmatic nucleus lesioning. *Brain Res.*, 243: 235–241.

Huschke (1854) *Schädel, Hirn und Seele*, Jena, 1854 (cited in: Mall, 1909).

Inglis, J. and Lawson, J.S. (1981) Sex differences in the effects of unilateral brain damage on intelligence. *Science*, 212: 693–695.

Jerison, H.J. (1973) *Evolution of the Brain and Intelligence*, Academic Press, New York.

Jones, B. and Anuza, T. (1982) Sex differences in cerebral lateralization in 3- and 4-year-old children. *Neuropsychology*, 20: 347–350.

Karplus (1905) *Obersteiner's Arbeiten aus d. Neurol. Inst. XII*, Wien.

Kimura, D. (1983) Sex differences in cerebral organization for speech and praxic functions. *Can. J. Psychol.*, 37: 19–35.

Lesky, E. (1950) Die Zeugungs- und Vererbungslehren der Antike und ihr Nachwirken. In: *Abhandlungen der Geistes- und Sozialwissenschaftlichen Klasse, Vol. 19*, Akademie der Wissenschaften und der Literatur in Mainz, Wiesbaden, pp. 1225–1425.

Lydic, R., Schoene, W.C., Czeisler, C.A. and Moore-Ede, M.C. (1980) Suprachiasmatic region of the human hypothalamus: homolog to the primate circadian pacemaker? *Sleep*, 2: 355–361.

Mall, F.P. (1909) On several anatomical characters of the human brain, said to vary according to race and sex, with special reference to the weight of the frontal lobe. *Am. J. Anat.*, 9: 1–32.

McGlone, J. (1980) Sex differences in human brain asymmetry: a critical survey. *Behav. Brain Sci.*, 3: 215–263.

Meredith, H.V. (1971) Human head circumference from birth to early adulthood: racial, regional and sex comparisons. *Growth*, 35: 233–251.

Meyer-Bahlburg, H.F.L. (1984) Psychoendocrine research on sexual orientation. Current status and future options. In: G.J. De Vries, J.P.C. De Bruin, H.B.M. Uylings and M.A. Corner (Eds.), *Sex Differences in the Brain. The Relation between Structure and Function. Progress in Brain Research*, this volume, Ch. 23.

Meynert (1867) Das Gesamtgewicht und die Teilgewichte des Gehirns, etc., *Viertaljahrsschr. Psychiat.*, 1.

Montessori, M. (1913) *Pedagogical Anthropology*, William Heinemann, London.

Moore, R.Y. (1982) The suprachiasmatic nucleus and the organization of a circadian system. *Trends Neurosci.*, 5: 404–407.

Morreale, S.J., Ruiz, G.J., Spotila, J.R. and Standora, E.A. (1982) Temperature-dependent sex determination: current practices threaten conservation of sea turtles. *Science*, 216: 1245–1247.

Mosko, S. and Moore, R.Y. (1978) Neonatal suprachiasmatic nucleus ablation: absence of functional and morphological plasticity. *Proc. Natl. Acad. Sci. (U.S.A.)*, 75: 6243–6246.

Mrosovsky, N. (1982) Sex ratio bias in hatching sea turtles from artificially incubated eggs. *Biol. Conserv.*, 23: 309–314.

Nellhaus, G. (1968) Head circumference from birth to eighteen years. *Pediatrics*, 41: 106–114.

Pakkenberg, H. and Voigt, J. (1964) Brain weight of the Danes. *Acta Anat.*, 59: 297–307.

Passingham, R.E. (1979) Brain size and intelligence in man. *Brain Behav. Evol.*, 16: 253–270.

Peterson, G.M., Watkins, W.B. and Moore, R.Y. (1980) The suprachiasmatic hypothalamic nuclei of the rat. VI. Vasopressin neurons and circadian rhythmicity. *Behav. Neur. Biol.*, 29: 236–245.

Pfeiffer, C.A. (1936) Sexual differences of the hypophyses and their determination by the gonads. *Am. J. Anat.*, 58: 195–225.

Pfister, H. (1897) Das Hirngewicht im Kindesalter. *Arch. Kinderheilk.*, 23: 164–192.

Phoenix, Ch.H., Goy, R.W., Gerall, A.A. and Young, W.C. (1959) Organizing action of prenatally administered testosterone propionate on the tissues mediating mating behavior in the female guinea pig. *Endocrinology*, 65: 369–382.

Piva, F., Limonta, P. and Martini, L. (1982) Role of the organum vasculosum laminae terminalis in the control of gonadotrophin secretion in rats. *J. Endocrinol.*, 93: 355–364.

Reinisch, J.M. and Sanders, S.A. (1984) Prenatal gonadal steroidal influences on gender-related behavior. In: G.J. De Vries, J.P.C. De Bruin, H.B.M. Uylings and M.A Corner (Eds.), *Sex Differences in the Brain. The Relation between Structure and Function. Progress in Brain Research*, this volume, Ch. 25.

Reinisch, J.M. (1981) Prenatal exposure to synthetic progestins increases potential for aggression in humans. *Science*, 211: 1171–1173.

Reinisch, J.M. and Karow, W.G. (1977) Prenatal exposure to synthetic progestins and estrogens: effects on human development. *Arch. Sex. Behav.*, 6: 257–288.

Retzius (1900) *Biol. Untersuch.*, 9 (cited in: Mall, 1909).

Röse (1905) Archiv für Rassen- und Gesellschaftsbiologie, Vol. II. In: L. Bolk (Ed.), *Hersenen en Cultuur*, Scheltema en Holkema, Amsterdam, 1918, p. 19.

Rössle, R. and Roulet, F. (1938) *Mass und Zahl in der Pathologie*, Springer, Berlin.

Schultz, D.M., Giordano, D.A. and Schulz, D.H. (1962) Weights of organs of fetuses and infants. *Arch. Pathol.*, 74: 80–86.

Siler-Khodr, T.M. and Khodr, G.S. (1978) Studies in human fetal endocrinology. I. Luteinizing hormone-releasing factor content of the hypothalamus. *Am. J. Obstet. Gynecol.*, 130: 795–800.

Snell, O. (1891) Die Abhängigkeit des Hirngewichtes von dem Körpergewicht und den geistigen Fähigkeiten. *Arch. Psychiat. Nervenkr.*, 23: 436–446.

Södersten, P., Henning, M., Melin, P. and Ludin, S. (1983) Vasopressin alters female sexual behaviour by acting on the brain independently of alterations in blood pressure. *Nature (London)*, 301: 608–610.

Swaab, D.F. (1980) Neurohypophyseal hormones and their distribution in the brain. In: D. de Wied and P.A. van Keep (Eds.), *Hormones and the Brain*, MTP Press, Lancaster, pp. 87–100.

Swaab, D.F. and Ter Borg, J.P. (1981) Development of peptidergic systems in the rat brain. In: K. Elliott and J. Whelan (Eds.), *The Fetus and Independent Life, Ciba Foundation Symp. No. 86*, Pitman, London, pp. 271–294.

Swaab, D.F., Pool, C.W. and Nijveldt, F. (1975) Immunofluorescence of vasopressin and oxytocin in the rat hypothalamo-neurohypophyseal system. *J. Neur. Transm.*, 36: 195–215.

Szentágothai, J. Flerko, B., Mess, B. and Halasz, B. (1968) *Hypothalamic Control of the Anterior Pituitary.* Akadémiai Kiadó, Budapest.

Tanner, J.M., Whitehouse, R.H. and Takaishi, M. (1966) Standards from birth to maturity for height, weight, height velocity and weight velocity: British Children, 1965. *Arch. Dis. Childh.*, 41: 613–635.

Tobias, P.V. (1970) Brain size, grey matter and race — fact or fiction? *Am. J. Phys. Anthrop.*, 32: 3–26.

Van Manen, S. and Oudshoorn, N. (1983) Sociobiologie en feminisme. *Wetensch. Samenl.*, 2: 22–26.

Voigt, J. and Pakkenberg, H. (1983) Brain weight of Danish children: a forensic material. *Acta Anat.*, 116: 290–301.

Wada, J.A., Clarke, R.A. and Hamm, A. (1975) Cerebral hemisphere asymmetry in humans. Cortical speech zones in 100 adult and 100 infant brains. *Arch. Neurol.*, 32: 239–246.

Webb, W.B. (1982) Sleep in older persons: sleep structures of 50- to 60-year-old men and women. *J. Gerontol.*, 37: 581–586.

Wenger, T., Kerdelhue, B. and Halázs, B. (1979) Short-term effect of the lesion of the organum vasculosum of the lamina terminalis on hypothalamic LH-RH and serum LH, FSH and prolactin in adult female rats. *Neuroendocrinology*, 29: 276–280.

Yntema, C.L. and Mrosovsky, N. (1982) Critical periods and pivotal temperatures for sexual differentiation in loggerhead sea turtles. *Can. J. Zool.*, 60: 1012–1016.

DISCUSSION

M.A. CORNER: To what extent have individual differences *within* each sex been studied through the years, vis à vis the supposed sexually dimorphic brain measures?

D.F. SWAAB: In the more recent literature this is, of course, not such a problem because the statistics that are generally applied include manners for variation within the sex. But also in the old literature attention has been paid to this problem. Mall (1909) plotted all the individual data in his graphs. He failed to find sex differences and stated: "It is found, however, that portions of the brain vary greatly in different brains and that a very large number of records must be obtained before the norm will be found. For the present the crudeness of our method will not permit us to determine anatomical characters due to race, sex or genius and which, if they exist, are completely masked by the large number of individual variations".

J.C. KING: The outline of vasopressin-positive cells corresponds well with that of tissue stained with cresyl violet?

D.F. SWAAB: In this (6-μm) sections it is impossible to see the boundaries of the SCN by means of a conventional staining (we used thionine for this purpose). Using cryostat (40-μm) sections, the anti-vasopressin staining appeared to coincide very well with the cytoarchitectural boundaries of the SCN.

J.C. KING: You are equating the SCN nucleus with that of vasopressin-immunopositive cells in the nucleus. Yet there is a ventral cell group that contains vasoactive intestinal polypeptide (VIP)-positive cells. Might not the relationship between VIP and vasopressin be different between the sexes rather than the shape of the SCN?

D.F. SWAAB: Indeed, the SCN contains many more transmitters than vasopressin alone, and it would be most interesting to study also the other peptides in this nucleus in relation to e.g. sex, age and dementia. However, we have not done that until now.

C.D. TORAN-ALLERAND: Studying gross anatomical differences is problematic, and without microscopical correlates such cases as the observed differences in the splenum of the corpus callosum are difficult to evaluate, since differences in fixation and length of fixation may produce significant differences in gross appearance.

D.F. SWAAB: Gross morphological sex differences can, of course, not be considered as the final answer to all questions. It should serve as a start to indicate those areas which might be of interest for further detailed and more sophisticated research (scanning the entire human brain, e.g. with an electron microscope, would be a less efficient procedure!). A sex difference appearing only after fixation, as hypothesized by you, is still a difference which could be due to physio-chemical sex differences in the brain. Also such differences have, of course, to be worked out by a multi-disciplinary approach.

REFERENCE

Mall, F.P. (1909) On several anatomical characters of the human brain, said to vary according to race and sex, with special reference to the weight of the frontal lobe. *Am. J. Anat.*, 9: 1–32.