Sexual differentiation of the human hypothalamus in relation to gender and sexual orientation

D. F. Swaab and M. A. Hofman

Recently, sex differences in the structures of the human hypothalamus and adjacent brain structures have been observed that seem to be related to gender, to gender problems such as transsexuality, and to sexual orientation, that is, heterosexuality and homosexuality. Although these observations have yet to be confirmed, and their exact functional implications are far from clear, they open up a whole new field of physiological structural-functional relationships in human brain research that has so far focused mainly on such relationships in pathology.

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SEX DIFFERENCES in relative brain size are present from the age of two years onwards¹, and it is therefore not surprising that they have been described in many brain structures and in various functions, for example, in cognition, as well as in neurological and psychiatric diseases, and in reproduction. The claims that females excel in certain tests of verbal skills, and that men have superior mathematical reasoning abilities and perform better in visuo-spatial tasks, have raised major controversies in the literature, because such sex differences are small generally and account for only a small part of the variance, and clear structural-functional relationships are absent². On the other hand, remarkably little attention has been paid so far to the possible structural basis of the often pronounced sex differences in the epidemiology of neurological and psychiatric diseases³. The proportions of cases range from more than 75% female in anorexia nervosa and bulimia to more than 75% male in dyslexia, sleep apnoea and Gilles de la Tourette's syndrome (Table 1). Not only might the number of cases of disorders show clear sex differences, but the signs and symptoms and the course of the disease might differ also. Males not only suffer from schizophrenia 2.7 times more often than females⁸, they are also prone to a more severe form of this disorder, experience an earlier onset, and exhibit more structural brain abnormalities. Relapses are more severe, and their response to neuroleptic medication is less favourable⁸. On the other hand, sex-specific prevalence can vary with age, and females apparently have a greater susceptibility to acute food deprivation during the first trimester, as was evident from the children born in the Dutch hunger winter of 1944–1945 that resulted in 2.6 times more female than male schizophrenics⁵. Another example is that, following restricted posterior left-hemisphere lesions, 41% of the males and 11% of the females developed aphasia, whereas manual apraxia was found in 6% of the females and 42% of the males¹¹. Also, in The Netherlands, the prevalence of transsexualism (see below) is strongly sex-dependent; 1:11 900 for

male-to-female transsexuals and 1:30 400 for female-to-male transsexuals¹². Finding the structural differences on which the sex differences in neurological and psychiatric disorders are based presents a challenge.

The hypothalamus

Sex differences in the hypothalamus are thought to be the basis of sex differences in (1) reproductive behaviour, that is, the menstrual cycle in women¹³, (2) gender identity, that is, the feeling that one is either male or female, and (3) sexual orientation, that is, homosexuality and heterosexuality^{2,13,14}.

Currently, no information is available about the factors that might influence gender, and cause transsexuality in humans. However, the determinants of human sexual orientation seem to be legion, as sexual orientation is influenced by a number of factors, such as genetic factors (as appeared from studies in twins and molecular genetics)^{15,16}. Hamer's group¹⁶ found a linkage between DNA markers on the X chromosome, and male sexual orientation. Sex hormones also have an influence on sexual orientation, as the increased proportion of bisexual and homosexual girls that have adrenogenital syndrome suggests¹⁷. In addition, diethylstilboestrol (DES), a compound that is related to oestrogens, increases the occurrence of bisexuality and homosexuality in girls¹⁸. Maternal stress is thought to lead to increased occurrence of homosexuality in boys¹⁹ and girls²⁰. Also, social factors are presumed to be involved²¹ in sexual orientation, although evidence in support of this effect has not yet been found. In fact, the observation that children that are raised by lesbian couples or by transsexuals generally have a heterosexual orientation^{22,23} does not support the possibility of the social environment being an important factor for determining sexual orientation. On the basis of animal experiments, it is expected that all compounds that influence metabolism of neurotransmitters in development might affect sexual differentiation of the brain also³. All these influences are supposed to affect the interaction between endogenous sex

D. F. Swaab and
M. A. Hofman are
at the Graduate
School
Neurosciences,
Amsterdam
Netherlands
Institute for Brain
Research,
Meibergdreef 33,
1105 AZ
Amsterdam, The
Netherlands.

hormones and the developing brain and thus lead to structural and functional changes of the brain. However, there is also recent experimental evidence for primary genetic control of sexual differentiation, in animals, that does not involve sex hormones. Results obtained from cultures of embryonic rat brain indicate that dopaminergic neurones might develop morphological and functional sex differences in the absence of sex steroids³.

Hormones and brain development

In analogy with observations in many mammalian species, the human brain might well undergo sexual differentiation during its development as a result of an organizing effect of sex hormones, and such a structural organization might be the basis for functional sex differences^{3,24}. In experimental animals, sex hormones affect the developing brain mainly through testosterone that has been transformed into oestrogens by aromatase during a crucial period in development. The crucial period in the rat occurs during late pregnancy and the first two weeks of neonatal life and is thought to be initiated by the surge of plasma testosterone that occurs in the male fetus around embryonic day 17 and 18. Activity of aromatase is high in the medial preoptic hypothalamic region of most mammals, including human fetuses, especially in the prenatal and neonatal period²⁵. The presence of aromatase in the developing brain explains the extraordinary ability of oestrogens to mimic, at least partly, the organizing actions of androgens²⁵. In addition, not only oestrogen receptors but also testosterone receptors have been observed in the mammalian limbic system and, therefore, male differentiation of some brain regions might be under direct control of testosterone (for reviews, see Refs 3, 25 and 26). In the human brain, neither sex hormone receptors nor aromatase have, as yet, been localized on a cellular level. The stages of development at which sex steroids determine sexual differentiation of the human brain are most probably the three periods during which sexually dimorphic peaks in gonadal hormone levels are found, namely during the first half of gestation (when the genitalia are formed), during the perinatal period, and during puberty²⁷. In human neonates of 34–41 weeks of gestation, the level of testosterone is tenfold higher in males than in females²⁸. Although the peak of testosterone during puberty is thought generally to be involved in activation rather than organization, the number of neurones of the hypothalamus of the domestic pig, to our surprise, showed a twofold increase in a sexually dimorphic hypothalamic nucleus around puberty²⁹ – thus, late organizational effects cannot be excluded. Few data are available on the exact period in development when the human brain differentiates according to sex. Brain weight is sexually dimorphic from two years postnatally onwards, taking differences in body size between boys and girls into account¹. The supposition of Dörner³⁰ that structural sexual differentiation of the human hypothalamus would take place between four and seven months of gestation was based only on the observation that the matrix layer around the third ventricle, in which the hypothalamic cells are presumed to have been formed, has disappeared by seven months of gestation. Yet,

Table 1. Ratios for females over males suffering from particular neurological and psychiatric diseases

Disease	% Female : male	Refs
Anorexia nervosa	93 : 7	4
Bulimia	75 : 25	4
Schizophrenia following Dutch hunger winter	72 : 28	5
Anxiety disorder	67 : 33	6
Depression	63 : 37	6
Multiple sclerosis	58 : 42	7
Severe mental retardation	38 : 62	8
Autism	29 : 71	8
Stuttering	29 : 71	8
Schizophrenia	27 : 73	8
Dyslexia	23 : 77	8
Sleep apnoea	18 : 82	9
Gilles de la Tourette	10 : 90	10

about 80% of the cells of the sexually dimorphic nucleus appeared to be formed postnatally²⁷ (Fig. 1). In addition, it has also become clear that cell death, rather than cell division, might be the most important mechanism in sexual differentiation of the nervous system^{27,31}. This mechanism takes place in the human sexually dimorphic nucleus between four years of age and puberty²⁷ (Fig. 1). It might be said that the evidence that is currently available suggests that sexual differentiation of the human hypothalamus becomes apparent between two years of age and puberty, although this might, of course, be based upon processes that were programmed much earlier, that is, in mid-pregnancy or during the neonatal period.

Fig. 1. Development and sexual differentiation of the human sexually dimorphic nucleus of the preoptic area (SDN-POA) of the hypothalamus. Log-log scale. Note that, at the moment of birth, the SDN-POA is equally small in boys (triangles) and girls (circles) and contains only about 20% of the cell number found at 2–4 years of age. Cell numbers reach a peak value around 2–4 years postnatally, after which a sexual differentiation occurs in the SDN-POA as a result of a decrease in cell number in the SDN-POA of women, whereas the cell number in men remains approximately unchanged up to the age of 50. The SDN-POA cell number in homosexual men (squares) does not differ from that in the male reference group (see also Fig. 4). The curves are quintic polynomial functions that are fitted to the original data for males (solid line) and females (broken line). Reproduced, with permission, from Ref. 27.

Fig. 2. Topography of the sexually dimorphic structures in the human hypothalamus. A is a more rostral view than B. Abbreviations: III, third ventricle; AC, anterior commissure; BNST-dspm, darkly staining posteromedial component of the bed nucleus of the stria terminalis; Fx, fornix; I, infundibulum; INAH1–4, interstitial nucleus of the anterior hypothalamus 1–4; LV, lateral ventricle; OC, optic chiasm; Ot, optic tract; PVN, paraventricular nucleus; SCN, suprachiasmatic nucleus; SDN, sexually dimorphic nucleus of the preoptic area; and SON, supraoptic nucleus. Scale bar, 5 mm.

Sexually dimorphic nucleus of the preoptic area

The sexually dimorphic nucleus of the preoptic area (SDN-POA) of the hypothalamus, as first described in the rat by Gorski and colleagues³², is still

the most conspicuous morphological sex difference in the mammalian brain. The cytoarchitectonic sex difference of this cell group, which is three to eight times larger in male rats than in female rats, is so evident that it can even be observed with the naked eye in Nissl-stained sections. Lesions of the SDN-POA affect masculine components of sexual behaviour in rat^{33,34}, and the positive correlations between the volume of the SDN-POA, and both testosterone levels and male sexual activity in rat studies, suggest a similar relationship²⁴. On the other hand, the extent of the changes in sexual behaviour following lesions to the SDN-POA is so small^{33,34} that it is quite likely that the major function of the SDN-POA has not yet been established. We have found a SDN-POA in the human hypothalamus that is – judging by its sex difference in size and cell number, localization and cytoarchitecture – probably homologous to the SDN-POA in the rat²⁷ (Fig. 2). The presence of galanin-containing neurones in the human SDN-POA (Ref. 35), and in the same area in rat³⁶, is consistent with this. Recent support for such a similarity comes from the observation that the human SDN-POA contains thyrotropin-releasing hormone (TRH)-containing neurones³⁷ similar to what has been reported in rat³⁸. The human SDN-POA is identical to the intermediate nucleus as described by Braak and Braak³⁹. Morphometric analysis of the human SDN-POA revealed that the volume is more than twice as large in young adult men as it is in women, and contains about twice as many cells in men⁴⁰ (Fig. 3). The magnitude of the SDN-POA sex difference was found not to remain constant throughout adulthood, but to depend on age (Fig. 3). In males, a major reduction in SDN-POA cell number was observed between the ages of 50 and 60 years. This change resulted in a much less pronounced sex difference in cell numbers. In females of over 70 years of age, cell death was found to be prominent, dropping to values that were only 10–15% of the cell number found in early childhood, so that the sex difference in the SDN-POA increases again in old people⁴⁰ (Fig. 3). This sex difference in the pattern of aging, together with the fact that sexual differentiation in the human SDN-POA occurs only after the fourth year of age²⁷, might explain why Allen and colleagues⁴¹, who worked with a sample of human adults that contained a large number of middle-aged subjects, did not find a significant sex difference in the size of the SDN-POA (Ref. 27). Since there was more than one sexually dimorphic nucleus in the hypothalamus, Allen and colleagues⁴¹ did not want to conform to the name SDN-POA. Unfortunately, they did not go back to the original name of ‘intermediate nucleus’³⁹ but called it the ‘interstitial nucleus of the anterior hypothalamus 1 (INAH1)’, confusing the nomenclature even further. The age distribution, however, does not explain why LeVay⁴² was also unable to find a sex difference in the volume of the INAH1. However, it should be noted that LeVay⁴² and Allen and colleagues⁴¹ measured only the volume of hypothalamic structures. Volume is susceptible to various pre- and post-mortem factors, such as differences in agonal state and fixation time^{27,43} but also to histological procedures and methods, such as section thickness. Therefore, it is essential to include data on

total cell numbers of hypothalamic nuclei, since this parameter is not influenced by such factors.

Other hypothalamic sexually dimorphic structures

Allen and colleagues⁴¹ described two other cell groups (INAH2 and INAH3) in the preoptic-anterior hypothalamic area of humans that were larger in the male brain than in the female brain. It is unclear which nuclei in the rat are homologous to the INAH2 and INAH3 and so far nothing is known about their neurotransmitter content. LeVay⁴² could not confirm the sex difference in the INAH2 but did find such a difference in the INAH3. Since no immunocytochemistry was performed, it is not clear whether the nuclei should be considered as, for example, islands of the paraventricular nucleus (PVN) or bed nucleus of the stria terminalis, or as separate anatomical entities.

Another sex difference was described by Allen and Gorski⁴⁴ in what they called the 'darkly staining posteromedial component of the bed nucleus of the stria terminalis' (BNST-dspm). The volume of the BNST-dspm was found to be 2.5 times larger in males than in females.

The vasopressin-containing subnucleus of the suprachiasmatic nucleus (SCN) showed a sex difference in shape but not in volume or vasopressin-cell number. The shape of the SCN was elongated in women and more spherical in men²⁷. However, the vasoactive intestinal polypeptide (VIP)-containing subnucleus of the human SCN was found to be twice as large in young men (ten to 30 years) as in young women, and contained twice as many cells⁴⁵. In the age group of 41 to 65 years, this sex difference was reversed, and it disappeared altogether after the age of 65 (Refs 45 and 46). These observations show again how important age is in the case of sexual dimorphism of the human brain.

The anterior commissure was found to be 12% larger in females⁴⁷, and the interthalamic adhesion, a grey structure that crosses the third ventricle between the two thalami, was present in more females (78%) than males (68%)⁴⁷, confirming the old study of Morel⁶¹ of 1947 (compare Ref. 47). The two latter observations suggest a greater connectivity between the cerebral hemispheres of women as compared with men.

Development of the human SDN-POA

In mid-pregnancy, the SDN-POA can already be distinguished in the human fetal brain²⁷, yet the SDN-POA cell number and volume at full-term birth are only 22% and 18%, respectively, of the values found between two and four years of postnatal age. During the first postnatal years, up to the age of two to four years, the SDN-POA cell number increases rapidly at the same rate in both boys and girls, and only after this age does the human SDN-POA differentiate according to sex, owing to a decrease in both SDN-POA volume and cell number in women. In men, these parameters remain unaltered up to the age of about 50 (Fig. 1)²⁷. The surprisingly late postnatal sexual differentiation of the human SDN-POA might be a general phenomenon in the human brain, as it seems as if the sex difference in the volume of the BNST-dspm does not occur until

Fig. 3. Age-related changes in the total cell number of the sexually dimorphic nucleus of the preoptic area (SDN-POA) in the human hypothalamus. The general trend in the data is enhanced by using smoothed growth curves. Note that in males, SDN-POA cell number declines steeply between the age of 50 and 60 years, whereas in females, from the age of about 50 years, a more gradual cell loss is observed, which continues up to old age. These growth curves demonstrate that the reduction in cell number in the human SDN-POA in senescence is a non-linear, sex-dependent process. Reproduced, with permission, from Ref. 40.

adulthood⁴⁴. Together, these data support the notion that sexual differentiation of the human hypothalamus takes place after the perinatal period and before adulthood, rather than during mid-gestation, although it is possible that the pre- or perinatal peak of testosterone programmes cell death a few years later.

The SDN-POA and sexual orientation

A prominent theory about the development of heterosexual-homosexual orientation is that it develops as a result of an interaction between the developing brain and sex hormones. According to Dörner's hypothesis⁴⁸, male homosexuals would have a female differentiation of the hypothalamus.

Once it had been found that the SDN-POA of the hypothalamus of young male adults contains twice as many cells as that of females, Dörner's hypothesis of sexual orientation could be put to the test. In contrast to this hypothesis, neither the SDN-POA volume nor its cell number in the hypothalamus of homosexual men differed from that of the male reference group in the same age range or from that of a heterosexual control group of subjects that also suffered from AIDS (Ref. 49) (Fig. 4). The fact that no difference in SDN-POA cell number was observed between homosexual and heterosexual men did not agree with the global formulation of Dörner's hypothesis that male homosexuals have 'a female hypothalamus'. A similar conclusion can be drawn from the observations on the SCN and anterior commissure in homosexual men (see below).

The SCN and sexual orientation and reproduction

The first difference in the human brain that relates to sexual orientation was found in the vasopressin-containing subnucleus of the SCN that was found to be twice as large in homosexual men⁴⁹. Our observation that the volume of the vasopressin subnucleus of the SCN in homosexual men was 1.7

Fig. 4. Volume and cell number of the human suprachiasmatic nucleus (SCN) and sexually dimorphic nucleus (SDN). (A) Volume of the human SCN and SDN as measured in three groups of adult subjects: (1) a male reference group ($n = 18$); (2) male homosexuals who died of AIDS ($n = 10$) and (3) heterosexuals who died of AIDS ($n = 6$; four males and two females).

The values indicate medians and the standard deviation of the median. The differences in the volume of the SCN between homosexuals and the subjects from both other groups, are significant statistically. (Kruskal–Wallis multiple comparison test, * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.) Note that none of the parameters measured in the SDN (A and B) showed significant differences among the three groups (P always greater than 0.4). (B) Total number of cells in the human SCN and SDN. The SCN in homosexual men contains 2.1 times as many cells as in the reference group of male subjects, and 2.4 times as many cells as the SCN in heterosexual AIDS patients. (C) The number of vasopressin (VP)-containing neurones in the human SCN (the human SDN does not contain VP-producing cells). The SCN in homosexual men contains, on average, 1.9 times as many VP-producing neurones as the reference group of male subjects and 3.6 times as many VP neurones as the SCN in heterosexual AIDS patients. The SCN of heterosexual individuals who died of AIDS contains less VP cells than the subjects from the reference group. Reproduced, with permission, from Ref. 49.

times as large and contained 2.1 times as many cells as the SCN of the male reference group (Fig. 4)⁴⁹ also implied that the difference in SCN volume could not be attributed to differences in shrinkage of hypothalamic tissue during the histological procedure. The difference in the vasopressin-containing cells of the SCN in relation to sexual orientation seems to be rather specific, since the number of VIP neurones in the SCN of homosexual and heterosexual men was not different⁵⁰. The SCN is, indeed, the clock of the human brain, and regulates circadian and circannual changes⁵¹. Differences in the SCN between homosexual and heterosexual men might thus go together with differences in circadian rhythms. Recently, it was found that gay men arise and retire earlier each day than heterosexual men⁵² (see also Ref. 53 – although not interpreted by the authors in this way). This does not imply that the SCN, apart from its circadian function, could not also be involved in sexual behaviour as was suggested by LeVay⁴². On the contrary, there are many observations that suggest an involvement of the SCN in reproductive processes. As long as 20 years ago, post-coital ultrastructural changes that indicate neuronal activation were observed in the SCN of the female rabbit. It is also important that the activity of neurones of the SCN increases suddenly around puberty. This is indicative of the addition of a reproductive function to the already matured circadian functions of the rat SCN. In addition, efferents of the rat SCN innervate several regions that are involved in reproductive behaviours, for example, the preoptic area, medial amygdala and bed nucleus of the stria terminalis. The rat ovarian reproductive cycle is controlled by the SCN, possibly by VIP fibres via direct innervation of luteinizing hormone releasing hormone (LHRH)-containing neurones. Several morphological sex differences have been reported that support putative reproductive functions of the SCN. The SCN of male rats contains a larger amount of axo–spine synapses, postsynaptic density material and asymmetrical synapses compared with that of female rats. Their neurones also contain more nucleoli. The sex difference in the shape of the vasopressin-containing subdivision of the human SCN, and the sex difference in the number of VIP-containing neurones in the human SCN (see above), is also consistent with sexually dimorphic functions. In seasonal breeders, immunoreactivity to VIP in the SCN fluctuates in relation to seasonal fluctuations in sexual activity. The recently observed activation of *c-fos* in the SCN by sexual stimulation also points to a role of the SCN in reproduction (for references to this paragraph, see Ref. 45). An interesting analogy to our observations on the enlarged SCN in homosexual men and sexual orientation was found recently by Bakker and colleagues⁵⁴ who found that rats treated with the aromatase inhibitor 1,4,6-androstatriene-3,17-dione (ATD) showed a partner preference for female rats when tested in the late dark phase, and a preference for male rats when tested in the early dark phase. This is the first indication of the involvement of the SCN in sexual orientation. In the same ATD-treated ‘bisexual’ rats, we have found recently an increased number of vasopressin-expressing neurones in the SCN (Ref. 55). This supports the hypothesis that the increased number of vasopressin-containing neurones

that was observed in the SCN of homosexual men⁴⁹ might be caused by a difference in the interaction of testosterone, aromatase, oestrogens, sex hormone receptors and the developing brain. The possibility of sex hormones playing a role in the development of the SCN is reinforced by an observation of Södersten and colleagues⁵⁶ who showed that the amplitude of the circadian rhythm in sexual behaviour, for which the SCN is the substrate, is enhanced by anti-oestrogen treatment of the neonatal animal.

Other hypothalamic differences in relation to sexual orientation

The second anatomical difference in the hypothalamus, according to sexual orientation, was found by LeVay in the INAH3 (Ref. 42). This nucleus was twice as large in heterosexual men as in homosexual men. There is no evidence for LeVay's assumption that the INAH3 would be homologous to the SDN-POA in the rat. Recently, Fliers and colleagues³⁷ found no TRH-containing neurones in the INAH3, whereas they were present in the SDN-POA/INAH1. This supports the possibility that the human SDN-POA and INAH1 is homologous to the rat SDN-POA (see above). Since no homology to hypothalamic structures in experimental animals is known for the INAH3, it is concluded that the functional consequences, also of LeVay's finding, are currently far from clear.

A third idiosyncrasy that concerns sexual orientation was described by Allen and Gorski⁵⁷ who found that the anterior commissure was larger in homosexual men than in (presumed) heterosexual men and women. Although LeVay's finding of a smaller INAH3 in homosexual men and heterosexual women agrees with Dörner's hypothesis⁴⁸ that homosexual men would have a female hypothalamus, the observations in the SDN-POA, the SCN (Ref. 49) and the anterior commissure⁵⁷ do not support this idea but support the idea of a 'third sex', that is, a 'different' hypothalamus in homosexual men that is neither similar to that in females, nor to that in male heterosexuals.

A recent abstract reported that the isthmus of the corpus callosum of gay men was 13% larger than that of heterosexual men⁵⁸, a similar result to the one reported for the anterior commissure⁵⁷.

Transsexuality

Transsexuals have, often from childhood onwards, the strong feeling of having been born the wrong sex. Their desire to resemble the opposite sex is so strong that they are even willing to undergo surgery to achieve this.

This problem of gender identity has been proposed to develop as a result of a disturbed interaction between the developing brain and sex hormones⁴⁸. In view of the relationship between the hypotheses on the development of gender and sexual orientation, it is interesting to note that 60% of the male-to-female transsexuals are orientated sexually towards males, and that 10% are bisexual. In no less than 95% of the cases are female-to-male transsexuals orientated sexually towards women⁵⁹. The high proportion of transsexuals that are orientated sexually towards their own genetic sex indicates that indeed similar (but as yet unknown) mechanisms

might play a role in the development of both gender and sexual orientation. We have studied the hypothalami of five male-to-female transsexuals, and have found a remarkable inverse relationship between the cell number in the SDN-POA, and the number of vasopressin-containing neurones in the SCN (Ref. 27). When the SDN-POA was small in a male-to-female transsexual, the number of vasopressin-containing neurones in the SCN was high, and vice versa. This might point to the possibility that the developing brain of these transsexuals was exposed to different amounts of oestrogens, since it was found that, in rats, inhibition of aromatase by ATD caused the size of the SDN-POA to decrease⁶⁰, and the number of vasopressin-containing neurones caused it to increase⁵⁵. Since the size of the SDN-POA, and the number of vasopressin-containing neurones in the SCN, was extremely variable between the five male-to-female transsexuals, the size of these two structures does not seem to be related to their problem of gender identity. The search for structures that might be related directly to problems of gender identity, that is, structures whose anatomy is 'female' in genetically male transsexuals, is in progress.

Concluding remarks and summary

Functional sex differences in reproduction, gender and sexual orientation might be based on anatomical differences in the hypothalamus. Differences in structure in the human hypothalamus that are related to gender or sexual orientation were indeed reported recently. The magnitude of such differences depends strongly on age, and replication of these data is certainly necessary. Since the size of brain structures might be influenced by pre-mortem factors (for example, by agonal state) and post-mortem factors (for example, by fixation time), not only should measurements of volume be performed, but also a parameter that is not dependent on such factors as, for example, total cell number of the brain structure in question should be estimated.

The period of overt sexual differentiation of the human hypothalamus occurs between approximately four years of age and puberty, thus, much later than is presumed generally. In principle, it offers the possibility of interaction of a multitude of postnatal factors that act on sexual differentiation of the brain, not only of a genetic or hormonal, but also of a chemical and psycho-social nature.

The mechanisms that cause sexual differentiation of hypothalamic nuclei, the prenatal and postnatal factors that influence this process, and the exact functional consequences of the morphological hypothalamic differences await further elucidation.

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Neural networks that co-ordinate locomotion and body orientation in lamprey

S. Grillner, T. Deliagina, Ö. Ekeberg, A. El Manira, R. H. Hill, A. Lansner, G. N. Orlovsky and P. Wallén

S. Grillner,
T. Deliagina,
A. El Manira,
R.H. Hill,
G.N. Orlovsky and
P. Wallén are at
the Nobel
Institute for
Neurophysiology,
and Dept of
Neuroscience,
Karolinska
Institute, S-17177
Stockholm,
Sweden, and
Ö. Ekeberg and
A. Lansner are at
NADA, Royal
Institute of
Technology,
Stockholm,
Sweden.

The networks of the brainstem and spinal cord that co-ordinate locomotion and body orientation in lamprey are described. The cycle-to-cycle pattern generation of these networks is produced by interacting glutamatergic and glycinergic neurones, with NMDA receptor-channels playing an important role at lower rates of locomotion. The fine tuning of the networks produced by 5-HT, dopamine and GABA systems involves a modulation of Ca^{2+} -dependent K^+ channels, high- and low-threshold voltage-activated Ca^{2+} channels and presynaptic inhibitory mechanisms. Mathematical modelling has been used to explore the capacity of these biological networks. The vestibular control of body orientation during swimming is exerted via reticulospinal neurones located in different reticular nuclei. These neurones become activated maximally at different angles of tilt.

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THE NERVOUS SYSTEM can be studied at many different levels from ion channels, single cells and synapses to neural networks and global cognitive functions. Individual neural networks represent an important category of functional modules that are at an intermediary level of complexity in the nervous

system. Different specialized networks are used in sensory systems, as well as in the co-ordination of a host of different movement patterns from swallowing to skilled movements. One of the most complex movement patterns that any nervous system can co-ordinate, and recruit at will, is that producing