ABSTRACTS
GENERATION OF SEX DIFFERENCES IN KISSPEPTIN NEURONS CONTROLLING PUBERTY AND OVULATION

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Sex differences in brain structure and function are considered to result principally from the combined effects of “organizational” and “activational” actions of gonadal steroids in the perinatal period and adulthood, respectively. The activational actions of gonadal steroids are generally considered to begin at puberty following stimulation of the hypothalamo-pituitary-gonadal axis resulting from increased gonadotropin-releasing hormone (GnRH) neuron activity. The mechanisms responsible for the increase in GnRH secretion driving puberty are currently under intense investigation. The neuropeptide kisspeptin and its receptor GPR54 have recently been shown to be an essential component of the mechanism activating GnRH neurons at puberty. Present evidence from mice suggests that a sub-population of rostral periventricular area of the third ventricle (RP3V) neurons that project directly to GnRH neurons begin to synthesize kisspeptin in the week prior to the onset of puberty [1]. As kisspeptin exerts potent stimulatory actions upon GnRH neurons [2], these data suggest that the emergence of the RP3V kisspeptin projections to GnRH neurons is a key component underlying the initiation of puberty in mammals. Although this is thought to be the same in males and females, a 10-fold, female-dominant, sex difference exists in the numbers of RP3V kisspeptin neurons in adult mice [1].

While undertaking experiments aimed at determining the mechanisms responsible for the pre-pubertal initiation of kisspeptin expression in RP3V neurons, we unexpectedly identified estradiol as being key. Female mice ovariectomized at postnatal day 15 (P15) had a >80% reduction in kisspeptin-immunoreactive RP3V neurons when examined at the time of puberty or as adults. Replacement with estradiol either from P15 or P22 onwards resulted in a complete restoration of kisspeptin expression at puberty. Finally, examination of aromatase knockout mice, that are unable to synthesize estrogens, revealed a complete absence of kisspeptin in the RP3V of adult female mice. In contrast to the RP3V, no similar changes exist for arcuate neurons expressing kisspeptin.

These findings demonstrate that estradiol acts well prior to puberty to regulate kisspeptin expression in RP3V neurons. Thus, the “activational” effects of estradiol occur unusually early in the postnatal period to help generate this sexually dimorphic neuronal population. This may reflect the pre-pubertal development of an estrogen positive feedback mechanism whereby estrogen stimulates RP3V kisspeptin neurons to enhance GnRH neuron function that, in turn, generates more estrogen. This amplification mechanism is postulated to be necessary for the initiation puberty as well as each mid-cycle ovulation in adult females [3].

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NEW TRICKS FOR AN OLD DOGMA: HOW ESTRADIOL MEDIATES MASCULINIZATION AND DEFEMINIZATION OF SEXUAL BEHAVIOR

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This year marks the 50 anniversary of an iconic paper published in Endocrinology by William Young and his trainees at the University of Kansas [1]. This elegant study of the enduring consequences of hormonal treatment of pregnant guinea pigs, brought clarity to a disparate collection of observations of hormonal effects on reproductive behavior. The authors proposed a novel hypothesis, that early hormonal actions predisposed adult behavior, now codified as the Organizational / Activational Hypothesis of hormonally mediated sexual differentiation of the brain. The predictions stemming from this hypothesis have provided a sturdy framework against which competing theories have, and continue to be tested, and as such as earned the moniker, dogma.

Sexual differentiation of the brain is a developmental process whereby gonadal steroids act during a perinatal sensitive period on the undifferentiated neural substrate to permanently alter it so that ultimately brain phenotype will match gonad phenotype. Central to the process of differentiation in rats and mice is the conversion within neurons of testicularly derived testosterone to estradiol. Treatment with testosterone, but not the nonaromatizable androgen dihydrotestosterone (DHT), mimics many of the trophic effects of estradiol, and normal masculinization of the brain is prevented subsequent to disruption of aromatase during the sensitive period [2, 3]. This basic principle, that the male brain is masculinized by local conversion of estradiol, is elucidated by the “aromatization hypothesis” first proposed by Naftolin in 1975 [4] and expanded on by others [5].

Stereotypic sexual behavior in rodents is an excellent example of an adult behavioral endpoint that is organized by neonatal hormonal exposure. The medial nucleus of the POA is a major site regulating male sexual behavior, whereas the VMN of the hypothalamus is required for the expression of female sexual behavior [6]. Of particular interest here is how steroids exert an organizational effect on developing cells in these brain regions. Males have two to three times more dendritic spines and spine synapses in the neonatal POA and VMN than females, and both these sex differences are dependent on early exposure to estradiol [2, 7]. A useful construct for investigating mechanistic questions of sexual differentiation is the operationally defined and distinct processes of masculinization, feminization and defeminization. **Masculinization** refers to an active developmental process initiated by gonadal steroids during the perinatal sensitive period followed by expression of normal male copulatory behavior in adulthood. **Feminization** is essentially what happens in the absence of masculinization, meaning it is the default pathway leading to expression of lordosis under the proper hormonal conditions in adulthood. **Defeminization** is distinct from but occurs in tandem with masculinization and refers to the process whereby the ability to express female sexual behavior is lost.

The amino acid glutamate is a fundamental building block of proteins as well as a dominant excitatory neurotransmitter in the mammalian CNS. Its actions are generally rapid and mediated via two varieties of ionotropic receptors, NMDA and AMPA, and a class of metabotropic G-protein coupled receptors referred to as the mGluR. Because it is ubiquitous and so essentially fundamental, glutamate has not generally been considered a reasonable candidate for mediating a process as specific and selective as sexual differentiation of the brain, but we have recently demonstrated that glutamate is critically...
involved in both masculinization and defeminization in the POA and VMN, respectively. In the POA, glutamate is a component of the actions of prostaglandin E2 (PGE2), as evidenced by the ability of AMPA receptor antagonists to block the induction of dendritic spines by PGE2 [2]. Activation of AMPA receptor only partly accounts for PGE2 actions, however, while a role for PKA is emerging (Wright & McCarthy, unpublished observation).

In the VMN, estradiol binds to its cognate receptor and promotes the release of glutamate from presynaptic terminals, which in turn activates postsynaptic NMDA and AMPA receptors, leading to calcium influx, activation of MAP kinase and dendritic spine formation [8]. The enhanced glutamate release requires estradiol-induced activation of PI3 Kinase, and this occurs as rapidly as within one hour after steroid exposure. Neither the activation of PI3 Kinase nor the enhanced glutamate release by estradiol requires protein synthesis, but they do require the ER. [9]. These neuroanatomical results predict that neonatal glutamate administration should be sufficient to induce defeminization and blocking glutamate should disrupt estradiol-induced defeminization. Both of these predictions have proved true[8, 10]. However, there is also a positive effect of glutamate receptor activation on organization of male sexual behavior, suggesting a functional connection between the cellular events of masculinization and defeminization.

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The seminal study by Phoenix and coworkers (1959) provided the first evidence that the capacity to display sex-specific behaviors in adulthood (and by inference, the sexual differentiation of the brain) follows the same pattern as that of the genitals. Additional evidence suggested that testosterone needs to be aromatized into estradiol to masculinize and/or defeminize the neural substrates that control sexual behavior. The results of these early studies also implied that the neural mechanisms which control later female-typical sexual behaviors normally develop perinatally in females ‘by default’, without the need for any sex steroid stimulation. However, my recent results obtained in female mice carrying a targeted mutation in the Cyp19 gene encoding the aromatase enzyme (aromatase knockout or ArKO) which is necessary for the conversion of androgens to estrogens, have shown that estradiol may be required for the development of the neural mechanisms regulating female sexual behavior. By contrast, we also obtained evidence that the principal action of prenatal estrogen exposure is to defeminize the capacity to display feminine sexual behavior later in life. Transgenic female mice that are unable to synthesize the fetal circulating estradiol binding protein, alpha-fetoprotein (AFP), due to a targeted mutation in the AFP gene, were infertile and did not show any female sexual behavior in adulthood. However, fetal exposure to an aromatase inhibitor completely rescued the capacity of female AFP-KO mice to display female sexual behaviors later in life, suggesting that AFP normally binds any estradiol circulating in the female fetus with high affinity and capacity and thereby protects the developing brain from what would otherwise be a defeminizing action of this hormone. Taken together, the results obtained in the AFP-KO mouse model clearly shows that estrogens defeminize the brain during prenatal development whereas the results obtained in the ArKO mouse model suggest that estrogens are necessary to feminize the brain at some time in development. Thus, there is an apparent paradox in estrogen action in the development of the brain.
Fifty years ago the study of sexual differentiation of brain and behavior began with the seminal publication by Phoenix, Goy, Gerall, and Young [1]. Their behavioral data, combined with anatomical data [2] established an influential new paradigm in Behavioral Neuroendocrinology. Without a doubt exposure to steroid hormones during development shapes neural development and subsequently behaviors. This paradigm has been used to examine a variety of behaviors and sex differences in a number of parts of the brain. But progress leads to paradigm shifts and less than 15 years ago the first major shift in our thinking about sexual differentiation occurred [3]. In 1996 Art Arnold proposed the then heretically idea that genes on sex chromosomes might influence sex differences in brain and behavior. Now more than a dozen papers have been published confirming this hypothesis [4]. The phenotypes affected include; autoimmune function, pain perception, social behaviors, vasopressin, habit formation and neural tube development. This second hypothesis is in complete agreement with the earlier notion; in fact for some of the phenotypes described, developmental hormones interact with sex chromosome genes. In this talk I will present unpublished data on new sexually dimorphic phenotypes influenced by sex chromosome complement. I will also describe examples in which sex chromosomes and developmental steroids act in a combinatorial manner.

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NEW VIEWS OF NEUROPLASTICITY AND SEX DIFFERENCES IN THE SONGBIRD BRAIN

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A remarkable series of observations were made about 30 years ago identifying positive correlations between brain variation and behavior in songbirds. For example, Nottebohm and Arnold [4] reported that there are profound male-biased sex differences in volume in selected nuclei in telencephalic portions of the song control system. Subsequent comparative studies revealed that in some songbird species, females sing rarely or not at all, and the brain nuclei that control song are many times larger volume in males than females. In other species, males and females sing approximately equally, and the brain nuclei that control song are approximately equal between the sexes. Statistical methods have been employed to control for phylogenetic effects while comparing the co-evolution of traits. This analysis indicates that the evolution of sex differences in song has co-evolved with the evolution of sex differences in singing behavior in songbird species [2]. Nottebohm [3] also observed marked seasonal changes in the size of song nuclei in male canaries. In this case key song nuclei were substantially larger in volume in the spring when males are singing high quality songs at high rates than in the fall when song behavior is reduced.

Both of these studies provided paradigmatic examples of how brain variation can correlate closely with behavioral variation. However, since this pioneering work, studies have focused on trying to identify more precisely what aspects of behavioral variation might be regulated by these sex and seasonal differences in the brain. The initial hypothesis proposed by Nottebohm was that this brain variation is related to the capacity to learn song. However, it was subsequently discovered that females with smaller song nuclei do learn to produce song in some cases and that males who exhibit seasonal changes in their song nuclei do so without any evidence of seasonal changes in the learning of song. Other hypotheses related to differences in the performance of song. Because song is a complex learned behavior that varies widely among songbird species it is not surprising that the nature of sex differences in singing behavior also vary widely. In the most extreme case (e.g., zebra finches, Carolina wrens) females never sing. In these species, song is a male activity only and functions to deter rivals and/or attract and court females. In other species (e.g., white-crowned sparrows) females rarely sing and when they do it is with less complexity and stereotypy than males. In yet others (e.g., some white-throated sparrows) females may sing with equal complexity to, but less often than males. Finally, females may duet with males (antiphonally or otherwise) with complexity and amount of singing almost equal to that of males. Thus, female song varies among species from being non-existent to being essentially identical to male song [see 1 for a review]. It is also apparent that singing behavior varies between the sexes in at least three dimensions: song complexity (e.g., song repertoire size), song stereotypy (reliability of song production from rendition to rendition), and amount of singing. One approach to better understand the functional significance of sex differences in the brain would be to explore sex differences in connectivity, volume and cellular properties of the song-control system in target species in which the sexes differ along only one of these dimensions. Because female song may differ in complexity, organization and timing of production from male song, detailed examination of the female song-control system may shed light on the neural and
neuroendocrine control of song. It is thus unfortunate that almost all studies of the connectivity, development, and electrophysiological properties of the song-control system have been carried out exclusively in males. Females have also been found to exhibit seasonal changes in the volume of their song control nuclei in some species such as white-winged crossbills and northern cardinals. Questions such as whether the regulation and functional significance of such adult neuroplasticity is the same in males and in females have not been addressed. As a first step to investigating these issues I studied (in collaboration with my colleague, Eric Fortune) the physiological consequences of testosterone-induced growth in the volume of the song nucleus HVC in female canaries (Canaria serinus). Canaries have relatively small volumes of HVC and rudimentary song behavior as compared to males. The application of exogenous testosterone can elicit male-like song behaviors and brain morphologies in female canaries. The functional physiological consequences of sex differences and hormone-driven changes in HVC volume have not been thoroughly investigated. However, if brain variation is to have behavioral meaning, it must result in physiological variation. Here we show that HVC neurons in female canaries exhibit selectivity for testosterone-induced autogenous songs. Remarkably, this selectivity persists in females in which the concentrations of circulating testosterone have returned to nominal levels and HVC volumes have been dramatically reduced. Adult female canaries were given exogenous testosterone which elicited singing. Songs were recorded. Subsequently, in half of the birds, the testosterone implants were removed. Three weeks later, singing in these birds was dramatically reduced whereas birds with the testosterone implants continued to sing. These songs were recorded as well. Finally, we recorded the extracellular responses of single units in HVC of urethane anesthetized these two groups of birds: high testosterone and low testosterone. Testosterone titers were measured through the experiment and HVC volumes were measured after the electrophysiology. Neurons were probed with three types of auditory stimuli. These included the bird's own learned songs (BOS), reversed BOS (REV), and conspecific songs (CON). REV stimuli have identical spectral and amplitude properties as BOS, but are dramatically altered in the time domain. All neurons in both groups exhibited the characteristic 'bursty' spontaneous activity that has been observed in previous studies. Neurons also exhibited strong preferential responses to BOS stimuli over all other stimuli used. The patterns of spiking elicited by BOS stimuli were similar to those reported earlier. Selectivity for song appears to be equivalent in both low and high testosterone groups. This suggests that the underlying circuitry for selectivity for BOS is present in low testosterone birds. The neural representation of song appears to be, therefore, independent of the marked changes in HVC volume. This study illustrates that very precise connections must be made between seasonal and sex differences in brain and behavior if we are going to be able to identify clearly the nature of brain variation in relation to behavioral variation.

Reference list
A SECOND LOOK AT THE FUNCTION OF SEXUAL DIFFERENTIATION OF THE BRAIN

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The main factors in sexual differentiation of brain and behavior are well understood. Differences are caused by different exposure to gonadal hormones during development (organizational effects) (Bakker and Baum, 2007; Schwarz and McCarthy, 2008), in adulthood (activational effects) (Cooke et al., 1998), and by direct effects of sex chromosomes. Hundreds of sex differences have been found in the brain in almost any parameter imaginable. Remarkably, in most cases we do not understand how these sex differences contribute to sex differences in brain function. At least two factors make resolving this issue difficult. The first is that sex differences in behavior are often overstated (Södersten, 1984). The second is that the function of sex differences are too narrowly interpreted. Intuitively, such differences are thought to underlie sex differences in behavior or other overt functions controlled by the brain. Other options are typically not considered.

Studying the sexually dimorphic vasopressin/vasotocin (AVP/AVT) projections from the bed nucleus of the stria terminalis (BST) and the medial amygdala (MeA) offers some answers. In most vertebrates studied, these projections are much denser in males than in females (De Vries and Panzica, 2006). The widespread presence of this sex difference among vertebrates suggest that it was important enough to conserve it through vertebrate evolution. These projections have been especially well studied in rats, where they have been implicated in social and reproductive behaviors as well as in autonomic functions. Comparative studies, however, suggest that AVP/AVT may have different roles in males and females. For example, in virgin voles, AVP stimulate parental behavior in males but may inhibit it in females as treatment AVP receptor antagonists inhibits parental behavior in males but stimulates it in females. These and similar behavioral data obtained in different species suggest that sex differences in neuropeptide pathways do not always induce sex differences in function, but may also prevent them by compensating for differences in hormonal and physiological conditions that may otherwise cause undesirable sex differences in certain functions (De Vries, 2004). Such dual function may be a general phenomenon for sex differences in the brain. This implies that the neural substrate of functions that show no obvious sex differences may nonetheless differ between males and females. Functional imaging studies suggest that this is true for humans as well.

Reference list

SEX DIFFERENCES IN SOCIAL AND EMOTIONAL BEHAVIOR IN MICE: HOW, WHY AND WHEN.

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Sexual selection theory [5] predicts that the behavioral strategies in coping with social and environment challenges would differ in males and females when a discrepancy in parental investment exists - as it is in all mammalian species. The intertwined but separate issues addressing proximate and evolutionary questions should always be considered in biological research; thus, when addressing the question of sex differences in emotional and defensive behavior we should consider the proximate mechanisms (e.g., genetic and hormonal basis) and the adaptive significance of such behavioral diversity (i.e., ultimate causation). I address here three main issues on sex-related differences in social and emotional behavior in mice: 1) basic sex differences in house mice; 2) proximate and ultimate causes of such differences, and 3) the interfering effects of hormonally active chemicals.

Although strain differences exist, male and female house mice show clear differences in their social behavior and emotional responses [9]. Male mice are indeed territorial and aggressive to other males, while females are generally tolerant and socially oriented to other females. However, our studies in wild-trapped mice have shown that the timing and context of aggression and its targets appear to differ in females and males and the social organization of female mice appears to be more complex and variable than the clear-cut territorial dominance observed among males. Females appear to become aggressive after short periods of cohabitation with a male and direct attacks mostly towards other females, except during lactation when males are also attacked [8]. A number of studies have revealed higher levels of locomotor activity, sometimes associated by lower anxiety, in female relative to male mice, which show higher levels of novelty seeking, though many factors (such as strain, housing procedures, age, experience, reproductive state) can affect these behaviors. Different housing procedures, as means to provide different social environment, differentially affect male and female mice. We have shown that living alone for a short period or with same-sex siblings (brothers or sisters) may have a different psychosocial relevance for the two genders while not affecting any physiological indexes of stress in male and female mice [6]. Common developmental manipulations may have differential carry-over effects in adult males or females; establishing unisexual groups of mice at different age (before or after puberty) induced several behavioral and physiological alterations in males but not in females, with the exception of lower corticosterone level in both male and female housed together with unrelated conspecifics after weaning or as subadults [3].

In mice, as in other mammals, non reproductive behaviors have been described to show sex differences in quantity of performance expressed rather than being present in one sex and absent in the other [1]. Although some of these sex differences reflect activational effects of estradiol and testosterone in the blood of adult males and females, differential actions of gonadal steroids during the perinatal period play a crucial role in organizing the sexual dimorphism in behavior and its underlaying neural substrates [4]. However, gonadal hormones are not the only mechanism mediating the development of sexual dimorphism; genetic mechanisms, independent by hormonal action, may trigger sexual differentiation of brain and behavior [2]. The environment also (e.g., maternal behavior) appears to have an important impact on the dimorphism and differentiation of the CNS, thus influencing
behavior.
As steroid hormones are a critical element of the process of sexual differentiation of brain and behavior in higher vertebrates, exposure to endocrine active compounds (EACs) that mimic, antagonize or in other ways interfere with these hormonal signals at sensitive developmental stages in the life cycle is likely to impact subsequent neuroendocrine and behavioral functions. Results from our and other laboratories indicate that developmental exposure to low doses of EACs affect the sexual differentiation of non reproductive behavioral systems in mice, such as explorative, emotional and cognitive behaviors. Here I present our ethological investigations of the effects of maternal exposure during pregnancy and/or lactation to the estrogenic chemical bisphenol A (BPA) at a concentration within the range of human exposure and not patently teratogenic (10-40 ug/kg), on behavior and neural circuits of male and female offspring [7]. A consistent effect of the maternal exposure to BPA is that in different experimental settings, while a sex difference was observed in the control group, exposure to BPA decreased sex differences of several behavioral responses. Males and females showed differing sensitivities to the estrogenic chemical exposure. More specifically, maternal exposure to BPA mostly affected female mice on exploration, emotional and cognitive behaviors, and maternal behavior, while males were more sensitive to BPA as far as the development of aggression and social interactions. Post-natal exposure appears sometimes produce wider effects than fetal (pre-natal) exposure on several responses, though possible confounding effects of cross fostering procedure should be considered. In the conceptual frame of evolutionary theory, sex-differences in behavior are thought to reflect adaptive differences of behavioral strategies in coping as resulting from sexual selection. Longitudinal studies on effects of endocrine disrupting chemicals should be carried out in order to evaluate in which contexts, and with what intensity, eliminating or reversing sex differences could have relevance to population dynamics, and whether behavioral alterations occur in systems influencing reproductive success and thus individual fitness.

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NAKED MOLE-RATS: WHO NEEDS SEX DIFFERENCES?

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Sex differences are nearly ubiquitous among mammals; they presumably evolved, and are maintained, to support sex differences in physiology and behavior. Most of what we know about sex differences in the nervous system, however, comes from studying a small number of relatively non-social species (e.g., rats and mice). Many species live socially and exhibit some form of cooperative breeding. Sexual differentiation in such species might differ from that in common lab models, in terms of the timing, extent, or cellular mechanisms. We are testing this hypothesis by examining naked mole-rats (*Heterocephalus glaber*).

Naked mole-rats are eusocial rodents that exhibit the strictest reproductive hierarchy of any mammal. They are native to Africa and live in large colonies containing up to 250 individuals; only one female in each colony breeds (the queen), and she mates with one, two, or at most three males. The remaining colony members are non-reproductive subordinates, who show no sexual behaviors, but help with pup care, foraging, maintaining the burrow system, and colony defense. Subordinates are not sterile, however, and can become reproductive if removed from their natal colony. It is estimated that, in nature, < 1% of all naked mole-rats ever become breeders.

We find a striking lack of sex differences in naked mole-rats. The external genitalia are remarkably monomorphic, as are the striated muscles associated with the genitals. We also find no sex differences in breeders or subordinates in cell size, cell number, or volume of the principal nucleus of the bed nucleus of the stria terminalis (BNST), paraventricular nucleus (PVN), ventromedial nucleus (VMH), medial amygdala (MeA), or Onuf’s nucleus in the spinal cord (a homologue of the rat spinal nucleus of the bulbocavernosus). Vasopressin innervation of the brain also does not differ between the sexes. However, we do find several breeding status-related changes: breeders, regardless of sex, have more neurons in Onuf’s nucleus and the VMH, and a larger volume of the BNST, MeA, and PVN than subordinates. Breeders also have more vasopressin than subordinates in the dorsomedial hypothalamus and (unexpectedly) fewer androgen-receptor expressing cells in every brain region examined. This suggests that a change in social status triggers considerable neural remodeling in naked mole-rats and indicates that status, rather than sex, has a predominant role in determining neural structure.

We reason that the relative reduction in sex differences in naked mole-rats is related to their social structure. Sexual differentiation during perinatal life (as in rats and mice) may not be necessary for the large majority of animals that will never reproduce, and neural sex differences may even be detrimental in a society where males and female helpers perform identical functions. We are currently testing this hypothesis by examining sex differences in mole-rat species with different social structures.

But what about the lack of sex differences among breeding naked mole-rats? Male and female breeders show sex differences in sexual behavior, and only the females lactate. Our results suggest that gross morphological sex differences are not necessary for these sex differences in behavior and remind us how little we actually know about what those “extra” cells or larger volumes buy males (or females, depending on brain region) in other species.

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SEXUAL DIFFERENTIATION OF THE HUMAN BRAIN IN RELATION TO GENDER IDENTITY AND SEXUAL ORIENTATION.

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During the intrauterine period the brain develops in a male direction through direct action of testosterone on the developing nerve cells, and in a female direction through the absence of this hormone. In this way gender identity (the feeling of being a man or a woman) and our sexual orientation are programmed into our brain structures when we are still in the womb. As the sexual differentiation of the genitals takes places much earlier in development (in the first 2 months of pregnancy) than the sexual differentiation of the brain (starting in the second half of pregnancy and becoming overt in adulthood), these two processes may be influenced independently of each other, which may result in people with male sexual organs who feel female and vice versa (a phenomenon called transsexuality). This also means that in the case of an ambiguous sex at birth, the degree of masculinization of the genitals may not reflect the same degree of masculinization of the brain. Sex differences are not only found in relation to gender and sexual orientation, i.e. to homo/heterosexuality and pedophilia, but also in cognition, aggression, and many other behaviors. Gender and sexual orientation are programmed during intra-uterine development under the influence of a number of biological factors. There is no proof that social environment after birth has an effect on the development of gender identity or sexual orientation. Differences in brain structures, sex hormone receptors and brain functions are discussed that are related to gender and sexual orientation.

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