Sexual differentiation in the human brain
D.F. Swaab1, A-M. Bao1, T. Ishunina1,2
1Netherlands Institute for Neuroscience, Amsterdam, The Netherlands, 2Department of Histology, Kursk State Medical University, Kursk, Russia

Functional sex differences are expressed from early childhood onwards, e.g. in our playing behaviour and drawings. Sex differences in cognition, reproduction, gender identity (the feeling to be male or female) and sexual orientation, and in the incidence of neurological and psychiatric disorders in adulthood are presumed to be based upon structural and functional sex differences in the brain. Many of such sex differences have now been described in the human brain. They arise during development by an interaction of sex hormones and the developing neurons, although direct genetic effects are probably also involved [1]. Factors influencing structural [2] and functional [1, 3] sex differences in the brain are genetic factors like mutations or polymorphisms in the sex hormone receptors, abnormal prenatal hormone levels and compounds such as anticonvulsants, Diethylstilbestrol (an estrogen-like compound) and environmental endocrine disrupters. When given during pregnancy they interact with the action of sex hormones on the fetal brain. An influence of postnatal social factors on gender or sexual orientation has not been established. In rodents, masculinization of the brain in development is due to estrogens that are formed by aromatization of testosterone. In sexual differentiation of the human brain direct effects of testosterone seem to be of primary importance based upon evidence shown e.g. from subjects with mutations in the androgen receptor, estrogen receptor or in the aromatase gene [3].

In transsexuals we observed a reversal of the sex difference in the central nucleus of the bed nucleus of the stria terminalis. The size, type of innervation and neuron number agreed with their gender identity and not with their genetic sex [4,5]. Various structural and functional brain differences related to sexual orientation have now also been reported [1,6,7].

There is a clear sex difference in psychiatric disorders such as depression: the prevalence, incidence and morbidity risk is higher in females than in males, which may be due to both organizing and activating effects of sex hormones on the hypothalamo-pituitary-adrenal-axis. Fluctuations in sex hormone levels are considered to be involved in the susceptibility to depression, seen e.g. in the premenstrual, ante- and postpartum period, during the transition phase to the menopause and during oral contraceptives treatment. It was found that about 40% of the activated corticotropin releasing hormone (CRH) neurons in the hypothalamic paraventricular nucleus in mood disorders expresses also the estrogen receptor (ER)-α [8]. Estrogen-responsive elements are found in the CRH gene promoter region, while estrogens stimulate CRH expression in animal studies. An androgen-responsive element in the CRH gene promoter region has also been identified recently, which initiates a suppressing effect on CRH expression [9].

In addition, there are sex differences present in the way the brain ages and in Alzheimer neuropathology [3, 7]. The field is becoming extra complex by the presence of splice variants (and isoforms) of ER-α and the local production of steroid hormones in the brain. In the human medial mamillary nucleus and hippocampus we detected, using RT-PCR, ERα splice forms skipping entire exons 7, 4 and 2 and we identified two novel variants: 1) MB1 that is lacking 168 nucleotides in exon 1, and 2) TADDI, in which 31bp are missing in between exons 3 and 4, while 13bp are inserted from the middle of exon 2 [10,11]. In our recent work we investigated whether canonical and alternatively spliced ERα-mRNA and protein are affected by age, menopause and Alzheimer disease (AD) in the hippocampus that is essential for declarative memory. Experimental and clinical studies indeed suggested beneficial effects of estrogens on hippocampus-dependent cognitive functions. Such positive effects have, however, not been obtained in late AD stages. Interestingly, nuclear ERα immunocytochemical expression was prominently higher in young women (34-50 years of age) than in young men (31-64 years of age), possibly due to higher plasma estrogen levels. Moreover, nuclear ERα, aromatase and the Golgi complex size which is indicative of neuronal metabolic activity, enhanced during aging in women. Our data suggested that the elevated expression of nuclear ERα in postmenopausal women versus pre- and perimenopausal women is due to a drop in circulating estrogen levels that seems to cause an increase in the local estrogen production in the hippocampus, which may subsequently up-regulate ERα. Furthermore, locally synthesized estrogens may stimulate hippocampal neuronal metabolic rate in postmenopausal women via rapid non-genomic mechanisms. In AD cases canonical and alternatively spliced ERα-mRNA, and aromatase gene transcripts were down-regulated, suggesting reduced local estrogen levels and diminished signaling through ERα. Whether this
finding may be related to a general genetic shut-down in the AD hippocampus remains to be elucidated. Concluding, structural and functional sex differences in the brain are present in all stages of life, and are involved in many functions in health as well as in diseases.

References