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Sex differences matter: Males and females are equal but not the same

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ABSTRACT

Sex differences between males and females can be detected early in life. They are present also later even to a much greater extent affecting our life in adulthood and a wide spectrum of physical, psychological, cognitive, and behavioral characteristics. Moreover, sex differences matter also in individual's health and disease. In this article, we reviewed at first the sex differences in brain organization and function with respect to the underlying biological mechanisms. Since the individual functional differences in the brain, in turn, shape the behavior, sex-specific psychological/behavioral differences that can be observed in infants but also adults are consequently addressed. Finally, we briefly mention sex-dependent variations in susceptibility to selected disorders as well as their pathophysiology, diagnosis, and response to therapy. The understanding of biologically determined variability between males and females can have important implications, especially in gender-specific health care. We have the impression that it is very important to emphasize that sex matters. Males and females are differently programmed by nature, and it must be respected. Even though we as males and females are not the same, we would like to emphasize that we are still equal and together form a worthy colorful continuum.

1. Introduction

Males and females differ due to a combination of genetic and hormonal factors. The recognition of sex differences is possible early during development. First of all, to address properly the differences between men and women, it is necessary to distinguish between sex and gender and their respective effects on health. Gender refers to the continuum of complex psychosocial self-perceptions, attitudes, and expectations people have about members of both sexes, behavior, lifestyle, and life experience [1]. Sex refers to the biological differences between males and females. Two distinct sexes- males and females are determined by sex chromosomes and genes that form certain gonads, internal and external genitalia, and physiological hormones. Another crucial aspect that contributes to phenotypical sexual differences is epigenetics [2]. The various epigenetic modifications such as methylation, acetylation, ubiquitination, etc. regulate gene expression (activating or repressing it) without changing the DNA sequence. The inactivation of X chromosomes in females, genomic imprinting, and differential miRNAs/non-coding RNAs mapping on the X-chromosome are the main principal epigenetic mechanisms, involved in the determination of sex differences [3]. It is also important to note that some studies have demonstrated that genetic differences such as single nucleotide polymorphisms (SNPs) located on autosomes can be predictors of differentially methylated alleles. This explains why some functionally irrelevant variants can possibly be reconsidered and associated with some sex specific phenotype [4].

Many features of the brain and behavior vary by sex. Current research cannot ignore sex differences in brain anatomy, physiology, and neurochemistry, especially considering the different prevalence of many psychiatric and developmental disorders in males and females, signs, and symptoms of pathophysiology, and response to therapy.

The aim of this paper is to bring an overview of sex differences between males and females pointing out that different genetic and hormonal environment code male and female developmental trajectory. Despite the complexity, we would like to overview that due to different underlying biological forces, males and females differ not only in obvious biological aspects but also in brain activity, sex-specific cognitive and behavioral styles, and also susceptibility to illness and disorders. Despite the complexity, biology matters in studying sex differences, especially considering males' and females' different vulnerabilities to many developmental and psychiatric disorders. This review has the aim to show there is a biological basis for sex differences, and that biology plays its role. We would like to point out that sex cannot be ignored as a possible covariate in various domains and those we mentioned. In other words, this review wants to show why sex matters and regarding the aspect of biology men and women are not the same.

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On the other hand, we are aware of the fact that under certain circumstances sex differences in adult neural structure or function could be shaped through experience, practice, and neural plasticity.

Sex steroid hormones are the key regulators of sexual differentiation and development. The mechanism of their activity is complex and still not fully understood. Steroids are not the only origin of sex differences. Genetic and environmental factors modulate the expression of genes coding not only hormones but also enzymes involved in steroidogenesis and receptors for hormones. The whole mosaic is even more complicated by the nongenomic action of steroids. Environmental factors, such as diet or physical activity, education, or socialization must be also taken into consideration. It must be mentioned that under certain circumstances sex differences in adult neural structure or function could be shaped through experience, practice, and neural plasticity We are aware of the fact, that research on sex differences cannot be complete without consideration of both genetic/hormonal and social influences that fuels the development via complex nature-nurture interactions. However, here we focused more on the features of the brain and behavior that vary by sex and may be referring to different hormonal exposure [5] (Fig. 1).

2. Sex differences in brain organization

Animal studies with rats pointed out that the nucleus of the preoptic area (SD-POA) implicated in male copulatory behavior exhibits sexual difference. It represents one of the most characterized sex differences and it is 2.6 times larger in males when compared to females [6]. Sexually dimorphic regions are not always larger in males. The anteroventral periventricular nucleus (AVPV), part of the hypothalamus associated with the regulation of ovulatory cycles, is larger in females with a higher cell density in both mice and rats [7]. Other volumetric sex differences were also reported (for review see [8]). However, there are some concerns about the lack of internal consistency within a single brain in the animal literature. Human MRI studies allow the simultaneous assessment of multiple brain features in many individuals. The largest single-sample study of neuroanatomical sex differences to date performed on 2750 female and 2466 male participants from a UK biobank (mean age 61.7 years, range 44–77 years) showed males having higher raw volumes, raw surface areas, and white matter fractional anisotropy; females had on the other side higher raw cortical thickness and higher white matter tract complexity. In other words, sex differences were reported, sometimes in favor of women and sometimes in favor of men. However, there was considerable distributional overlap between the sexes [9]. Another MRI study of more than 1,400 human brains (♂: mean age of 31.5, range 18–79; ♀: mean age 28.9, range 18-75) similarly demonstrates that, although there are sex differences in the brain, human brains do not belong to one of two distinct categories: male brain/female brain. Most human brains have a mixture of characteristics, such as tissue structure belonging generally to both men and women [10,11].

Previously mentioned studies looked only at the brain structure but not the function. However, functional connectome organization showed stronger connectivity for males in unimodal sensorimotor cortices, and stronger connectivity for females in the default mode network [9]. The connectivity profiles showed an early separation between the developmental trajectories of the two sexes, with males displaying higher intra-hemispheric connectivity and females of the same age displaying higher interhemispheric connectivity. This implies that the average male brain is designed for better connecting sensory perception with motor activity and the female brain is predisposed to linking analytic and intuitive processing [12]. These observations support the formerly postulated callosal theory according to which prenatal testosterone mediates early axon pruning in callosal tissue, and thus the more testosterone a brain is exposed to *in the uterus,* the more lateralized the functions are [13]. It is also in line with one of the first works in this field that already in 1959 showed that prenatal testosterone affects the brain architecture. [14]. Authors back then assumed that these effects were more likely subtle, as they were reflected in function rather than invisible structure. Organizational effects possibly produce permanent changes in the wiring and sensitivity of the brain areas [15–17]. This theory was later proved by more recent research [18–22] demonstrating for instance, how males' and females' brains worked differently during solving the same language tasks [23]. It can be speculated then that our brain might work differently in order to compensate for a different hormonal influence, caused by gonadal steroids. In other words, sex differences exist to enable more similar performance in certain tasks considering the different hormonal environment in males and females

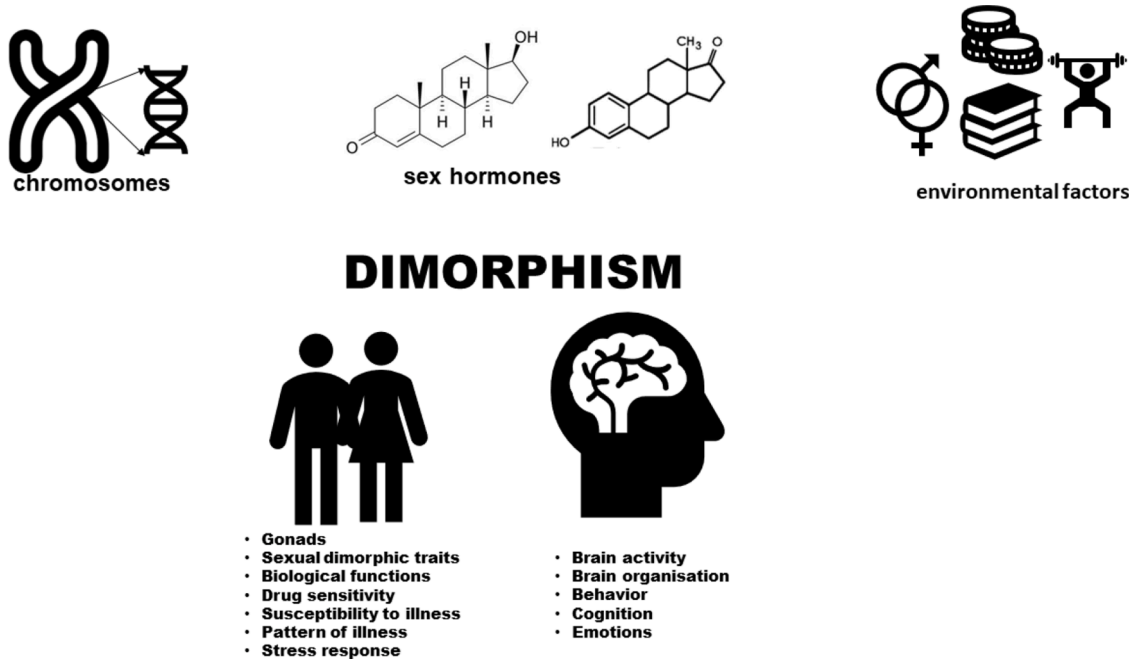

Fig. 1. Factors contributing to sex differences. Genetic and environmental factors such as diet, physical activity, education, socioeconomic status, or socialization modulate the expression of genes coding not only sex hormones but also enzymes involved in steroidogenesis and receptors for hormones.

[24].

Despite the intense research in this field, it remains challenging to precisely understand when sexual differentiation begins. Animal research reveals valuable information that helps to shed more light on the understanding of critical periods in brain development and their impact on further functioning [25]. Sexual differentiation of the brain is a unique critical window that corresponds with the onset of endogenous testosterone production from fetal testes. In rodents, the window starts to be open on embryonic days 16–18 [26]. Circulating testosterone levels fall within hours of birth and the critical period closes shortly thereafter as the process of masculinization irrevocably proceeds. Females are not exposed to endogenous testosterone as the ovaries are quiescent; therefore, gonadally derived hormone exposure is limited to the testosterone exposure from their littermates. During this window, the brain sex of a female can be converted to that of a male by the administration of exogenous steroids. Females remain sensitive to exogenous testosterone treatment for up to a week after birth, afterward female becomes insensitive to the masculinizing effects of exogenous testosterone indicating the end of the sensitive period [27–29]. Because of the unique synthesis of testosterone in males but the shared sensitivity of both sexes to this steroid hormone, males have a short critical period whereas females have a longer sensitive period [30]. Interestingly, at the time of birth, there is no visible difference in POA between males and females. The process is completed by ten days of age [30].

In humans, a critical period for the organization of the brain is thought to be between weak 8 and 24 of gestation [31]. During this period, testosterone levels are high. Testosterone levels become increased from the 7th week of gestation, reaching the peak in the fetal serum between weeks 12 and 18 of pregnancy [32]. This developmental period is essential for normal CNS function, brain masculinization in male fetuses, and neurological health [33,34]. It appears that brains undergo different developmental trajectory prenatally during which activity of hemispheres is set up [35].

However, studies on human newborns and infants have limitations and bring puzzling information. There is some research pointing out the sex differences in brain volume and cortical thickness [36], while other papers found no significant effect in 1 to 6 years of age [37]. After birth, specifically from 4 to 12 weeks of postnatal life, there is a second peak of testosterone in male infants, sometimes called mini-puberty [24]. According to some authors, this time is of particular interest since it is presumed to be another critical period for the development of sex differences in the human brain [38]. This time is of particular interest since it is presumed to be another critical period for the development of sex differences in the human brain. Moreover, it provides the opportunity to directly measure parameters of interest with minimal impact on the social environment [24]. However, this is just a speculation at this moment, since to date, no evidence suggests the postnatal period is sensitive to sexual differentiation. Based on the current state of knowledge, the process seems to be entirely prenatal [30]. Future studies on primate models might answer this question, whether there is a second and later sensitive period for differentiation of the primate brain [39].

Before any physical signs of puberty, there is a quiescence period when endogenous gonadal steroids remain in relatively stable low concentrations [40]. A wide spectrum of endocrine changes is associated with the maturation of the reproductive functions during the adolescent period [41,42]. We now know that also brain structures can be modified during this time of puberty [43]. Steroid hormones activate specific processes such as the production of new cells, dendritic growth, spine density, myelination, and brain plasticity and also contribute to the activation of sex-specific behavior [44–47]. Sex steroids were found to change gene expression in neurons, modulating their possible responses to incoming signals [48].

3. Sex differences in temperament and cognition

To a certain degree, previously mentioned brain differences translate to behavioral differences. Many of these cognitive and behavioral differences appear early in life, and they are biologically determined rather than learned (see below). On the contrary, one can argue that observed sex-associated differences in cognition and behavior in humans are due to the effects of cultural influences. However, there is a large body of research pointing to the biological basis of sex-based cognitive differences that cannot be ignored. Prenatal and neonatal testosterone exposures, together with genetic factors affecting androgen signaling, are strong candidates for having a causal role in shaping human behavior [49]. Moreover, many cognitive processes were proved to be influenced by circulating hormones throughout life [50–52].

Remarkably, sex differences in behavior are detected very early, at an age when children show few if any signs of recognizing either their own or other children's sex. A study of rhesus monkeys, for example, showed that males strongly preferred toys with wheels over plush toys, whereas females found plush toys more likable [53]. A much more recent study found that boys and girls 9 to 17 months old showed marked differences in their preference for stereotypically male versus stereotypically female toys [54]. Girls that are affected by higher fetal testosterone levels displayed a typical male pattern of play [55,56]. The sex-typed play has been intensively studied and many research groups have reported links to prenatal testosterone exposure [57–60]. While the complex involvement of social influences on toy preference of human subjects is always a factor, a primary role for organizational hormones in toy preference seems likely.

There are also sex differences in the motif, color choice, figure composition, and use of motion in children's pictures (age from 5 to 9 years) [61,62]. Girls draw flowers, butterflies, the sun, and human motifs significantly more often than do boys, who more often draw mobile objects such as trains and cars. Girls use color more often and more diffusely; they tend to arrange their figures in a row and draw each figure equally. Boys tend to use blue and gray; draw three-dimensionally, and magnify or emphasize a central figure or theme more often than girls [63]. The masculine index was significantly higher in girls with congenital adrenal hyperplasia producing a higher amount of testosterone due to enzymatic disturbance. This indicates that androgen exposure during fetal life may contribute to shaping masculine characteristics in children's free drawings [63].

Sex differences in spatial-visualization ability were detected as early as in 3 and 5-month-old infants [64,65]. Male infants showed an advantage in mental rotation performance and also exhibited greater visual attention to the object [66]. Sex differences in young infants were further demonstrated in multiple age groups during infancy [67]. Boys also react earlier in infancy to experimentally induced perceptual discrepancies in their visual environment [68]. Infant girls, even newborns respond more readily to faces. In adulthood, women remain more oriented to faces, while men to objects [69,70]. Sex differences in visuospatial skills are well documented mainly in the adult population, generally favoring men [71]. Visual information processing relies on at least two separate abilities [72,73] Firstly, coordinate processing specifies precise spatial locations of objects in terms of metric units and gives exact distances, particularly useful for guiding actions and navigation. Secondly, a robust description of the shape that would rely on categories of spatial relations (e.g., above/below, etc.) is useful for recognizing objects [74]. Men are better at visualizing what happens when a complicated two- or three-dimensional shape is rotated in space and may be biased towards a coordinate processing approach while females to categorical judgments [75]. Due to different spatial processing, in navigation tasks, male and female brains use different strategies to solve the same problem. Females tend to rely on landmarks, while males more typically rely on more effective strategies of "dead reckoning": calculating one's position by estimating the direction and distance traveled [76,77]. Functional MRI studies identified consistent differences in activation patterns during visuospatial tasks reflect a true sex-based difference in visuospatial processing. A study on a young population (7 and 15 years of age) showed that males may engage regions that are

associated with a visuomotor network, and females utilize areas indicated in spatial attention and working memory [78]. Adult studies are in line with data published on younger populations suggesting gender-specific differences in the neuropsychological processes involved in mental rotation tasks [79,80]. Studies have shown that gender differences in mathematics performance (493,495 students 14-16 years of age) are non-existent or that male or female advantage relates mainly to certain subskills [81]. In this regard, there are evident culture-dependent differences; for example, although males seem on average to outperform females in mathematics across all OECD countries, females score better than males in Finland [82]. But the truth is that males overrepresent females at the highest performance levels [83].

Studies on early language development were mostly conducted on children of various ethnicity and race in the first three years of life, in heterogeneous socioeconomic environment and countries. Study on Croatian toddlers showed that girls acquire language faster than boys. Boys represent more than 70% of late talkers and just 30% of early talkers [84]. Girls on average have a larger vocabulary. For example, at 16 months, girls have a vocabulary of 95 words, while boys have a vocabulary of 25 words [85]. The differences are not observed only in the development of the language system but also in the development of overall social communication skills. Independently on race, ethnicity, or socioeconomic status, boys lag behind girls in the development of many communication features – eye contact, gesture use, gesture imitation, joint attention, social referencing, etc. perhaps due to different roles they have had in social groups during evolution (for review see [84]). Some research showed that adult females (aged from 20 to 30) outperformed men on the verbal fluency task [86]. A meta-analysis of 98 studies ($N = 11{,}528$) assessed verbal fluency through narrative writing, and a robust female advantage became evident. It was associated with the reproductive life stage and variations in current estradiol concentrations [87] However, some papers raises also doubts. Verbal abilities in adult populations differ by just 0.1 standard deviation between males and females so it becomes rather difficult to replicate the sporadic findings of significant sex difference [88] Moreover it was shown that the results must be interpreted with caution [89]. In more selected samples, female advantage can disappear because of greater male variability.

Traditionally, men have shown a prevalence in gross motor performance and women in fine motor performance, due to gender roles and the work they are accustomed to carrying out more frequently [90]. However, with time, these differences have become more insignificant due to changes in male/female roles in some societies (especially in western societies) [91]. Recent research on fine motor tasks performed by 220 Spanish participants (ages: 12–95) reported sex differences in precision. However, more effects were observed according to age groups rather than sex. [90]. Moreover, it can be argued that sex differences in motor behavior could reflect the existing differences in personality [92] and individual cultural differences [91].

Individual differences in cognitive abilities can be generally measured by the intelligence quotient (IQ). No differences were found in the mean IQ of males and females. However, males´ performance is more variable, they form a higher percentage in intellectually gifted but also in mentally challenged individuals [93,94].

Notably, investigations of visuospatial or verbal variability between males and females also have practical importance in the interest of particular occupations. Spatial abilities and mathematical reasoning skills are both strong domains typical for males. They are relevant to science, technology, engineering, and general mathematical competence [95,96]. Those are likely to be necessitated in various professional fields, for instance, architecture, engineering, navigation, science, and medicine [97]. It is proved that teenagers who excel in the tasks requiring high mathematical and spatial demands are more likely to major in technical disciplines in college and are over-represented in technical positions [98]. Studies have found a disproportionately higher number of males scoring in the extreme right tail of the distribution, from which many talented technical professionals are sourced [99].

Apart from cognitive differences, males and females differ in temperament and personality. Large sex differences were documented for empathy (for review see [100]). It is noteworthy, that a recent study with over 10,000 participants concluded that sex differences in empathy were all due to sex-stereotyped norms and expectations [101]. However, several behavioral studies with infants and young children provide objective evidence that females experience greater empathy than males [102–104]. Studies with children are especially valuable in this field since they point towards the biological origin of the sex differences due to the fact that socialization pressure and social expectations had less time to exert their influence. Also, females generally tend to display more of social competence than males inside as well as outside of the family. They are more caring, sensitive to the needs of others, and prosocial [105,106]. Published literature provides evidence that there are sex differences in caregiving emerging early in development. Studies investigated how infants manipulate objects, such as dolls, that traditionally are handled differently by boys and girls [107]. Female play more often involves caring for another individual (e.g., pretended baby), male play does not [108]. This was shown not only in humans but also in primates [109,110]. Regarding the animal kingdom, there are also other studies that reported sex differences in behavior whether the individuals come to the aid of others in need. For example, female mice were more likely than male mice to approach mates who were restrained and in pain [111]. In another study, females rats were shown to behave in prosocial ways without training or reward and act intentionally even when prosociality decreases food intake [112] According Cordoni et al., who studied behavior of western gorillas, providing comfort to victims of aggression or individuals who are otherwise upset is a domain of females [113]. Studies in nonhuman animals and younger human populations (infants/children) offer converging evidence that sex differences in prosocial behavior have phylogenetic and ontogenetic roots in biology and are not merely cultural by-products driven by socialization (for review see [114]. It can be explained by a lower potential rate of reproduction, larger certainty about biological relatedness to their offspring, and a larger investment from the start of gestation in their evolutionary trajectory [114]. These traits of females are reflected in more careful and protective parental behavior and also in their occupational interests [115].

Regarding the process of evolution, males adopted different reproductive strategies compared to females. Males (young adults, from western societies) are more focused on finding mates which more strongly enhances male-male competition to gain access to females [116]. A metanalysis of 150 studies (analyzing participants from age 9 to 21) showed males are expected to be more prone to risk-taking than females but this difference was decreased by age [117]. Males also more often engage in dominant behavior intended to non-aggressively achieve or maintain power, status, and resources. Even though males are not face orientated, interestingly, they show a stronger response to angry facial expressions. The angry face is possibly perceived as a challenge [118]. Males are more utilitarian than females in moral dilemmas. They make decisions that are viewed as more rational and are aimed at maximizing overall welfare. They act according to the proverb: “The ends justify the means”. Females are driven by emotions, making more deontological decisions according to the phrase: “The means are more important than ends” [119]. Males and females also differ in the ability to produce humor. Men’s humor output was rated as funnier than women’s more due to evolutionary and cultural factors rather than biology [120].

4. Sex differences in pathology

Sex and gender are increasingly recognized as major influencing factors in literally all disorders (Fig. 2). It is beyond the scope of this review to discuss all differences. We will point out some of the main fields in which gender plays a significant role. Sex differences must be considered and be included as the main topics in the development of

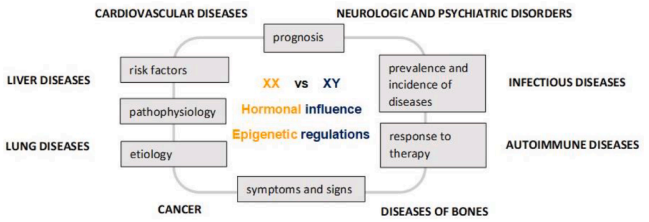

Fig. 2. Sex differences in disease. Sex and gender are increasingly recognized as major influencing factors in many disorders. The complex interplay between sex chromosomes, sex hormones, and epigenetic factors can influence incidence/prevalence, etiopathogenesis, response to therapy, and/or prognosis of the diseases.

guidelines. However, compared to other fields, guidelines in neuropsychiatry are lagging behind. A growing body of evidence (for review see [121]) clearly indicates the need to integrate sex and gender in clinical guidelines since those are potential drivers of much of patient diversity, affecting disease etiopathogenesis, presentation, diagnosis, and treatment. Taking such diversity into consideration might help improve preventive measures, increase diagnosis efficacy, enable more effective and targeted patient therapy, and/or reduce complications and related disability [1,121].

One of the neurodevelopmental diseases in which sex difference matters are autism spectrum disorders (ASD). ASD is a set of heterogeneous neurodevelopmental conditions, characterized by difficulties in social interaction and communication (both verbal and non-verbal), repetitive behavior, and unusually narrow interests that appear during early childhood. The worldwide population prevalence is about 1 %, however, the male-to-female ratio is about 3:1 (and even more than 10:1 in ASD individuals without intellectual deficits) [122–125]. The male bias might be partly explained by the fact that the most widely used diagnostic tools for ASD also present a certain male bias when assessing ASD traits in girls, who may perform slightly differently from boys [126, 127]. Especially, girls with autism spectrum disorder who are verbally fluent and with average or above-average intelligence may be camouflaging their deficits, which could result in them being underdiagnosed [128] and, therefore, girls may receive other diagnoses such as personality disorder, anxiety disorders, or anorexia nervosa instead of ASD. This delays proper diagnosis and therapy [122,129]. Another hypothesis suggests that fetal testosterone (fT) and other factors (for review see [125]) might possibly lead to extreme expression of the psychological and physiological attributes that are on average more typical for the male brain, particularly with respect to systemizing (so-called extreme male brain theory). Since positive correlations between fT levels and the number of autistic traits such as systemizing, attention to detail, or narrow interests as well as inverse correlations between fT and eye contact, language development, or quality of social relationships were shown, the boys (at least partly due to the higher fT exposure) would be more at risk than girls [125].

Sex differences can also be seen in the domain of drug abuse It has been established that females are more vulnerable than males to alcohol and most illicit drugs (such as cocaine, morphine or amphetamine, or opioids [130,131]. Clinical reports indicate that women are more likely than men to initiate drug abuse at an earlier age, engage in binge-like patterns of drug intake, report greater difficulty in quitting, exhibit greater vulnerability to drug craving and relapse, and resume higher levels of drug use following relapse. During the phase of drug withdrawal, however, males experience more severe withdrawal effects than females, suggesting that males are more sensitive to the negative effects of drugs, while females are more responsive to the rewarding effects. Thus, elevated sensitivity to the drug abuse in females may not only be due to their greater sensitivity to rewarding effects but also to their resilience to the negative effects of drugs. It has been proved that estrogens may facilitate the drug abuse in women [132].

Epidemiological data show that, in the majority of psychiatric disorders, rates of illness, clinical presentation, and treatment response may differ between men and women. Some of the diseases are more common in males (such as attention deficit hyperactivity disorder (ADHD), Tourette's syndrome, and Parkinson's disease), whereas in others, female prevalence is higher (e.g. multiple sclerosis, Alzheimer's disease, anxiety, or depression) [133,134], even though this might differ in different countries (e.g. in Alzheimer's disease) [135]. As already mentioned, sex difference plays a role in the symptomatic presentation, e.g., females more frequently exhibit depressive symptoms [136], while males tend to have a greater vulnerability to negative symptoms in schizophrenia (based on the Positive and Negative Symptoms Scale, negative symptoms include symptoms such as blunted affect, apathetic social withdrawal, lack of spontaneity, etc.) [137]. Alzheimer's disease (AD) also exhibits divergence in the clinical pattern of the disease with studies showing greater having greater cognitive decline for female patients in the areas of verbal processing, semantic and episodic memory than male AD patients [138,139]. Other diseases where sex bias can be observed are reviewed in [134]. The above-mentioned differences might be explained by the complex interactions between sex hormones, sex chromosomes, and epigenetic factors [134].

Even though we mainly discussed and emphasized the human brain, highlighting the developmental, behavioral, emotional, and cognitive differences between males and females, sex-specific differences in other somatic illnesses should also be mentioned. Many diseases, such as cardiovascular diseases (CVDs), liver diseases, osteoporosis, infectious and autoimmune diseases, and cancer show a differential susceptibility between males and females [139,140]. Sex is an important factor that influences immune system response to multiple antigens. On average, females have stronger innate and adaptive immune responses than males [141]. The risk of malignancy is higher for males (such as the esophagus, lung and bronchial, hepatocellular, or colorectal cancer) [142,143] and males are generally more susceptible to the infections than females (e.g. bacterial such as Legionella pneumophila, Campylobacter jejuni or fungal such as Cryptococcus neoformans) [144,145]. Antibody responses to bacterial and viral vaccines are often higher in females than males [146,147]. This could mean that the effective vaccine dose is lower for females than for males [147]. However, increased immunity may also lead to a predisposition of women for the loss of tolerance to their own antigens and the development of autoimmune disease [148]. The overall prevalence of autoimmunity is approximately 3–5% in the general population [149], with some diseases having more than 85% of patients females [150]. Women possess a double dosage of genes associated with X-chromosome compared to men. One copy of the X chromosome is randomly deactivated to equalize gene expression between males and females. However, it is thought that up to 23% of X-linked genes escape deactivation, including those that affect immune functions. Thus, the X-chromosome inactivation escape may cause immune responses to be amplified in women [152].

Estrogens also show protective effects on bone and cardiovascular system physiology and disease. The rapid decline in their synthesis after menopause is manifested in the faster loss of bone density and strength than in men of the same age [140,151]. Women aged 50 years and older are thus diagnosed with osteoporosis at four times the rate of men, and osteoporotic fractures are more frequent in women than men [152]. However, the literature indicates that male osteoporosis is underestimated, underscreened, underdiagnosed, and undertreated [153]. Furthermore, estrogen has the potency to decrease the risk of cardiovascular diseases because of its antioxidant, vasodilatatory, and anti-inflammatory properties, and the ability to enhance lipid profile [154]. Population studies show that there are lower rates of stroke in premenopausal women. Women also have better outcomes in ischemic stroke than men. There is also a lower prevalence of hypertension in women compared to age-matched men, and males have a significantly higher risk of developing coronary artery disease with a higher mortality rate than females, particularly at younger ages. Differences seem to be

dependent, at least partly on hormonal levels because of the rapid rise in stroke after menopause, as estrogen levels decline. The same trajectory can be observed in atherosclerosis and hypertension [154–157].

Moreover, men and women may differ in the symptoms, clinical evolution, and/or prognosis of a disease [1,140]. Pertaining to coronary heart disease (CHD), it was found out that women are less likely to have typical angina and are more likely to have atypical or non-anginal pain than men. Consequently, CHD in women is very often underdiagnosed [140,158]. Women also experience aphasia as a consequence of a stroke more frequently than men, which can be explained by the fact that women tend to suffer embolic strokes more often, and those are more likely to cause aphasia than lacunar strokes (which are more frequent in men) [155]. Sex can also determine the course of the disease and its prognosis, such as in atrial fibrillation where, women, compared to men, have a more functional impairment, greater limitation in their daily activities, and lower quality of life scores [159].

Lastly, one's response to the therapy might fluctuate based on sex. It has been estimated that women have nearly a twofold greater risk than men for exhibiting adverse drug reactions (ADRs) across all drug classes and are significantly more likely to be hospitalized secondary to an ADR [160]. In general, this might be the result of anatomical and physiological differences, which influence pharmacokinetics (e.g. absorption, distribution, metabolism, or elimination), and/or pharmacodynamics (e.g. enhanced sensitivity) of drugs. Other factors such as variability of immune system response and polypharmacy (higher rate in women), possibly leading to drug interactions, might also contribute to the differences [1, 160–162]. It is known that females have longer drug elimination times than males (women have relatively lower glomerular filtration rate compared to men), and/or enhanced sensitivity to some drugs [140,160,162]. Most drugs in adults are not administered based on weight but as a "one size fits all" dose, leading to higher exposures in women [160]. It should be noted that plasma concentrations of some drugs might undergo variations in relation to the different phases of the menstrual cycle: higher concentrations in the follicular phase with a higher risk of side effects, and lower concentrations in the luteal phase, resulting in minor therapeutic efficacy [1]. Despite the need for studies to address the impact of sex differences on the adverse effects of drugs, the female sex still remains underrepresented in clinical studies [163, 164].

5. Conclusion

This review aims to summarize the sex differences between males and females reported from an early age until adult life. Males and females differ not only in obvious biological aspects but also in brain activity, sex-specific cognitive and behavioral styles as well as susceptibility to illness and disorders. Trying to assign the relative contributions of "nature" versus "nurture" is tough at best. Human individuals are very complex, and the role of culture is definitely not zero. It must be also mentioned that many sex differences are not rigid and resistant to change. They are affected by numerous factors interacting over time, including socialization by parents, siblings, and teachers as well as education, lifestyle, environmental factors, and self-socialization based on an individual's understanding of sex and gender. But the whole story cannot be explained without taking the biologically affected sex differences into consideration, the emphasis of which is the main task of this review. The biological differences originating from different genes on the sex chromosomes, together with hormonal influences prenatally, during mini-puberty or adolescence cannot be disregarded. The period of mini-puberty is particularly of interest and can bring more light to this topic in the future. The understanding of the biologically determined variability between males and females can have important implications. To give a complex overview of the sex differences, we discussed not only the differences in the human brain, emphasizing the developmental, behavioral, emotional, and cognitive differences between males and females but also sex-specific differences in somatic illnesses. The biologically programmed sex differences between males and females affect the epidemiology, manifestation, pathophysiology of many widespread diseases, and the approach to health care. The knowledge of these differences has crucial clinical implications. Gender-specific health care, prevention, management, and treatment of many common diseases should reflect the most obvious and most important risk factors for the patient: sex and gender. This still remains underestimated and a challenge for the future [1,153,165]. There is a limited amount of papers that bring a complex summary of the sex differences in the physiology and pathophysiology of the brain and other somatic systems of our body. We would like to point out that sex cannot be ignored as a possible covariate in various domains and those we mentioned. However, the findings on sex differences need caution in the interpretation. It would also be incorrect to doubt the role of the social environment and other types of influences not discussed here. We are aware of the fact that under certain circumstances sex differences in adult neural structure or function could be shaped through experience, practice, and neural plasticity. Research on sex differences cannot be complete without consideration of both genetic/hormonal and social influences that fuels the development via complex nature-nurture interactions.

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Ivan Szadvári: Writing – original draft, Writing – review & editing. **Daniela Ostatníková:** Funding acquisition, Writing – review & editing. **Jaroslava Babková Durdiaková:** Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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