Sexual Dimorphism in the Human Brain

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Abstract

In this paper I explpore what is currently known about sexual dimorphisms of the human brain and the developmental processes that produce them. Specifically, I focus on how genetic information brings about changes in the prenatal and neonatal hormonal environment, how that hormonal environment affects developing neural structures, and what the ultimate results of those changes are.

1 Introduction

For ages humanity has speculated as to whether or not and to what extent the brains of women and men differ. Various groups have given their answer, usually to further their own ends by starting out with an a priori assumption of masculine (or feminine) superiority and manipulating or selectively viewing available data to fit that presumption, all in the name of science [4]. But after years of hopefully more unbiased scientific research, we still know comparatively little about what exactly is the difference between a male brain and a female brain. We know even less about what developmental processes create those differences, but one thing we do know, is that sexual dimorphisms in the human brain tend to be very small. It's difficult to detect differences between female and male brains because, quite frankly, the the observable physical magnitude of those differences is very small. In fact, a widely held belief among scientists studying sexual dimorphisms of the nervous system is that the differences between a male and female brain are far less than those encountered between a right handed and left handed brain. In addition, it's very difficult to do the kind of research that needs to be done in order to understand sexual dimorphisms of the human brain. For example, in order to understand how steroid hormones mediate neural development, scientists would have to expose many fetuses to abnormally high levels of androgens and estrogens, a completely unethical methodology. Although this type of research has been done on animal models, brain structure and behavior studies don't seem to correlate very well with humans, or, for that matter, other primates. Nevertheless, progress has been made in this area cumulatively resulting in the idea that sexual dimorphisms in the human brain results from genetic determination of the prenatal and neonatal hormonal environment which in turn causes sexually differential changes in brain structure. The methods by which these processes occur and their ultimate results are the subject of this paper.

2 How genetics determine the prenatal and neonatal hormonal environment

Human development proceeds along two different lines: a female and a male developmental pathway. If a developing individual possesses a Y-chromosome, then it will proceed along the male developmental pathway; otherwise, it defaults to the female developmental pathway. The Y-chromosome's primary influence seems to be the production of a recently decoded protein called testes determining factor, or TDF. The synthesis of TDF in undifferentiated fetal gonadal cells induces them to develop into testes; in its absence, the gonadal tissues develop into ovaries. Once this process of gonadal differentiation occurs, the development of sexual dimorphisms is driven not by the presence or absence of a Y-chromosome directly, but rather by testicular secretions [2, pp. 42–43]. The primary secretions are the steroid hormone testosterone and the peptide hormone known as Mullerian Regression Factor (MRF). MRF serves to inhibit the development of the internal female reproductive tract, while testosterone effects changes in the neural structure of the fetus, and directs masculinization of the entire body including primary and secondary sexual characteristics. The presence of testosterone determines neural sexual dimorphisms since female ovaries synthesize only minute quantities of estrogen during development and what little is produced cannot directly influence the brain for reasons that will soon become clear [5, pp. 304–305]. Thus, both the body and brain proceed along a female developmental path unless outside masculine modifications are made to the default female design by the Y-chromosome.

According to Breedlove [2], the best explanation posed so far as to how the sexual differentiation of the brain occurs is the Organizational hypothesis, which states that sex hormones administered during narrow windows of time during development direct neural structure formation into divergent male and female morphs. It was soon discovered, however, was that not only will testosterone masculanize the developing brain, but so will estrogen! The two substances are in fact very similar chemically, and the process that converts testosterone to estrogen, known as aromatization, is rather simple, while the reverse process is very costly in terms of energy and therefore occurs so rarely as to be insignificant for our purposes. Shortly after estrogen's masculanizing effects on the fetal brain were noticed, it was experimentally demonstrated by use of radioactive tracers that testosterone was being converted into estrogen by the hypothalamus, an important region of the brain. This all raises the question: if human brains can be emasculated by circulating estrogen, why aren't females emasculated by the small amount of estrogen they produce and more importantly, by maternal estrogen? It turns out that pre- and neonatal humans have a substance known as alpha-fetoprotein (AFP) circulating in their blood which binds selectively to natural, but not synthetic, estrogen. The net effect is that estrogen cannot affect the fetal brain since it is already bound to AFP. When testosterone is converted to estrogen in the hypothalmus of human males it does not bind to AFP because AFP is unable to cross the blood-brain barrier and enter the brain where aromitization occurs. The fact that AFP does not bind to synthetic estrogens proved very useful in the design of human experiments on prenatal hormonal mediation of sexual dimorphisms in the brain. Recent studies indicate that AFP serves to regulate, rather than completely inhibit the role of estrogen on brain development [2, p. 52]. Jacobson indicates that receptors for estradiol, the form of estrogen that testosterone is converted to, exist in

nerve cells of both sexes. He further claims that the estradiol-receptor complex moves from the nerve cell membrane into the cell nucleus where it regulates expression of genes that direct male brain development [5, pp. 304–305]. I will discuss the mechanisms by which it does so in the next section.

3 How sex hormones modulate neural structure in the fetal brain

According to Jacobson [5, pp. 305–307], the primary method by which sex hormones bring about sexual dimorphisms in the human brain is differential cell death. He points to research showing that in mammals, androgens rescue cells in the bulbocavernous nucleus of the lumbar spinal cord from apoptosis, or programmed cell death. Pilgrim and Hutchison liken the process of development for sexually dimorphic brain structures to sculpting away at rock to reveal a final shape. Thus, the brain is built by amassing vast amounts of cells and synapses and then by the killing of those that aren't needed, at least in terms of the sexual dimorphic regions [3, p. 845]. This sculpting process is believed to occur in the first 2 years of life whereas puberty is considered to be more of an activation of already existing cellular machinery that has been dormant for several years. They further speculate as to by what mechanism sex hormones cause differential cell death, believing it to occur by either the initiation of a cell death program or by the removal of a necessary nerve growth factor. Some evidence is provided for the concept of sex-specific nerve cell death programs by the fact that a protooncogene product known as Raf-1 that is inhibited by testosterone has been experimentally determined to be present in much higher concentrations in sexually dimorphic areas of female rat brains than in male rat brains during development. Raf-1 is a key component in the chemical process that initiates apoptosis in nerve cells. In addition, oestrogen enhances the transcription of c-fos and c-myc, two genes that also play important roles in initiating programmed cell death [3, p. 845].

Although differential cell death is the primary mechanism by which sexual dimorphism of the human brain comes about, it is not the only one, nor does it always result in greater male neural specialization or quantity. For example, Pilgrim and Hutchison caution us that not all types of sexual dimorphism involving numbers of specific types of brain cells in specific areas that vary with gender are based a completely male-specific survival enhancement [3, p. 845]. Other means by which steroid hormones mediate sexual dimorphisms in the developing brain include the soma size of nerve cells, patterns of synaptic reorganization, and cell to cell interactions. Soma size is often related to the amount of connections a neuron can make. In humans, soma size is at least partially under the control of testosterone or its estradiol metabolite. Animal studies indicate that enhanced soma and dendritic tree size in males is related to much faster growth during the early postnatal period. In addition, sex steroids appear to modulate synaptic plasticity in adults, although they have different roles depending on the region. In some regions, estrogens have been shown to promote synaptogenesis while in others, androgens prove necessary for the maintenance of synaptic connectivity. Finally, sex hormones can cause changes in neural structure by indirectly acting on nearby cells and thereby inducing local environmental changes. One possible cell-cell interaction could involve

a steroid-insensitive neuron being affected transsynaptically by a nearby steroid-sensitive neuron that releases a growth inhibitor. Another possible interaction involves a domino effect of sorts, where the survival of a high level steroid-insensitive nucleus (collection of highly interconnected neurons) is dependent upon the survival of lower level steroid sensitive nuclei. Lastly, steroid modification of glial (neural support) cells has also been observed. That is, sex hormone mediation of glial cell synthesis and secretion of neurotrophic or cell growth factors would have a great effect on neural composition since glial cells are responsible for guiding migrating neurons and growing axons through direct surface contact in addition to chemical secretion (Englele, Schubert, Bohn, 1991 and Beyer, Epp, Fassberg, Reisert, Pilgrim, 1990 and others cited in [3, pp. 846–849]).

4 Known sexual dimorphisms of the human brain and their implications

The most striking and easily observed dimorphism of the human brain is weight. Male brains outweigh female brains by 15that differential is due to the fact that males are often heavier and physically larger than females, brain weight to height ratios and brain weight to body weight ratios still favor males, albeit by a less significant factor. However, research to date has failed to determine what cognitive or behavioral differences follow from having a slightly larger brain [7, p. 135]. Besides brain weight as a whole, there are certain regions of the human brain that are sexually dimorphic, i.e., they differ between genders. One such area is the sexually dimorphic nucleus (SDN) of the preoptic area of the human hypothalamus, which is approximately 2.5 times larger in men than women (Swaab and Fliers, 1985 cited in [7]). Recent research suggests this area may be significant for purposes of sex identity. Other areas of known divergence include the suprachiasmatic nucleus of the hypothalamus, which is responsible for coordinating hormonal and behavioral circadian rhythms, the massa intermedia, a band of tissue connecting the two halves of the thymus which is more likely to be absent in men than women, and certain regions of the neocortex [7, pp. 136–137]. However, the most significant sexual dimorphism of all is not a localized phenomona in the brain. Rather, the question of brain lateralization and cerebral dominance, which deals with how the brain divides its processing ability among the two hemispheres and how much intercommunication occurs between them seems to be the most significant sexual dimorphism in the human brain.

Experimental evidence to date indicates that women are more funcitonally symmetric than men are with regard to cerebral hemispheres. In other words, women distribute their brain processing more equally between the two hemispheres of their brain while men tend to localize processing more. This may account for why men exhibit, on average, higher scores on tests of spatial ability than women. At the same time, women, on average, tend to have higher scores on verbal aand speech processing [1]. Additional evidence for less lateralization in women comes from the fact that women are far less likely to suffer aphasia (inability ot speak) if they have a stroke restricted to one hemisphere. Also, both men and women tend to understand more when information is presented to their right hemisphere but the discrepancy in women is less than that found in men. Recenly, much has been made

about the purported sexual dimorphism of the corpus collosum, a region of the brain the connects the two hemispheres. In reality, most of the studies conducted to date have found little if any sexual dimorphism. What little may be there seems to be of a rather subtle and difficult to detect variety since many of the aforementioned studies contradict each other [1].

5 Conclusions

There is a deeper question underlying the entire puzzle of sexual dimorphisms in the human brain. You see, there are two methods of asessing sexual dimorphisms in the human brain. The first relies on comparing and dissecting real human brains and looking for differences, while the second involves comparing differences among living humans' behavior and performance. The conundrum so far has been the lack of correlation between the two. Presumably, fundeamental gender specific cross-cultural behavior differences would necessitate sexual dimorphisms in the brain, but neurologists have had trouble corroborating some of the gender specific differences that psychologists have observed in the field and vice-versa. The solution may lie in understanding how much gross brain structure correlates to function. Even if we have irrefutable evidence as to the nature and extent of human suxual dimorphisms in the brain, or even their lack, does that knowledge amount to any practical, useful information? Pinker argues that the answer is no. He points out that, in general, humans vary mentally not because they're brains are physically hardwired in a different way, but because differences in the information and programs encoded in the same neural configuration results in individual variation. By analogy, Pinker indicates that while books do have basically the same structure, the difference between, say, Catch-22 and Developmental Psychobiology follows from the different patters of information encoded in them [6]. What this means for sexual dimorphism research is unclear, but it seems that the impact of sexually dimorphic structures in the human brain can be mediated by extremely subtle patterns of neural activity in the brain as a whole. What Pinker is saying is that structure often plays second fiddle to internal data represented by structure. Thus, two structurally different computers could be running the same software or two structurally identical computers could be running completely different hardware. The conclusion is the same, however: we cannot determine, using only first order tecniques, whether two systems differ in their structural arrangement or in the information encoded in a common structure. Thus, in order to really understand sexual dimorphisms in the human brain, we have to look more closely than we looked to date and examine brain structure and developmental patterns at much finer resolutions than we have traditionally been using.

In conclusion, I would like to point out a few not so obvious details. First of all, the brunt of research to date indicates that sexual differentiation of the brain is not dichotomous, but rather continuous. Thus, it is not strictly correct to speak of a brain as belonging to the male type or the female type, but rather to speak as to the degree to which it has been "masculinized" or "feminized." Secondly, no amount of developmental psychoneurobiological research can tell us what the role of sexes in society should be, how they should be educated, what type of laws we should pass, etc. Far too often, research into this subject area has been used inappropriately in defense of some bizarre political agenda. Science can only give us additional pieces of information on which to base our decisions; it cannot by itself decide

policy. This is a point too often glazed over as scientists rush to make social conclusions out of the latest research. Finally, I remind the reader that what exists under the microscope of advanced statistics doesn't necessarily mean anything in everyday life. The generalizations we are learning about how men and women differ are enormously small compared to the wide range of individual variance. Considerable overlap exists between the two sexes, and generally statistical differences turn out to be so small as to have no effective meaning in reality.

References

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