Génétique et neurosciences du développement cognitif - TT2

Developmental mechanisms leading to cognitive disparities between men and women

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Abstract

That men and women have different cognitive profiles is becoming less and less debated ; even if some people still argue that the alleged differences between male and female cognitive aptitudes is nothing more than a cultural stereotype, accumulating scientific evidence makes a compelling case for an innate disparity between a man' and a woman's brain.

In any case, the question remains where those differences might stem from ; yet a better knowledge on mechanisms of gene transcription and the processes of sex determination are beginning to shed light on that puzzle.

Here, we first draw a picture of the main disparities between male and female cognition ; then we give a general overview of how those differences might emerge, being related to either the hormones released by sexual gonads or to the chromosomes themselves.

Contents

1 Introduction

1.1 What differences anyway ?

We give here a brief tour of cognitive differences that were reported in the literature. Pinker (Pinker & Spelke, 2005) points out that although men and women do not differ in general intelligence or g, men tend to have statistically better throwing, mental rotation and mathematical problem-solving abilities, whereas women are more dexterous and have a better visual memory and better mathematical calculation skills. He goes on to point out six differences between men and women :

1. priorities : grossly, men focus more on status and achievement, and women on personal life

2. systems vs. people : men are interested in systems whereas women are more interested in people

3. risk : men are more risk-taking than women

4. spatial rotation : findings of a difference in spatial abilities is quite noncontroversial, and men appear to have better spatial abilities than women, as reviewed in Voyer *et al.* (1995). But there are claims that these findings could as well be explained by different leasure habits and instruction history.

5. mathematical problem solving : men are better than women at problem solving.

6. greater variability among men than women : "more prodigies, more idiots", as Pinker says.

Globally, the cognitive patterns statistically associated with genders are quite consistent : even if data can seem puzzling at first with women being better at calculation and getting better grades in high school, as Spelke (Pinker & Spelke, 2005) points out, there seems to be an overall difference in cognitive focus, with women paying more attention to details while men get a more general insight into underlying structure. Roughly, women have a refined but microscopic approach and men a coarse but comprehensive one.

Baron-Cohen (Baron-Cohen *et al.*, 2005; Baron-Cohen, 2002) sums up differences between men and women by saying that men are better at *systemizing*, whereas women are better at *empathizing*. As reviewed in Baron-Cohen *et al.* (2005), males are better on the mental rotation test, spatial

navigation including map reading, targetting, are more likely to play with mechanical toys as children, and then score higher on engineering and physics problems as adults. On the other hand, females do better in tests of emotion recognition, social sensitivity and verbal fluency, start to talk earlier than boys do and are more interested in faces than objects as babies.

1.2 Nature vs. nurture

It seems unlikely that those differences might be explained by purely cultural or social factors. First, similar effects are observed in animals, as reviewed in Baron-Cohen *et al.* (2005) : male rats are better than females on the radial arm and Morris water maze, just like men are better than women at reading maps, but castrating males or treating females neonatally with testosterone makes the difference vanish. As for the fact that girls prefer dolls and boys trucks, it is also the case for young female and male vervet monkeys, so the traditional cultural explanation does not hold. Second, differences in interests (the girls-people vs. boys-systems opposition), that could allegedly be imprinted on children by their social environment, are already present in 1-day-old babies (Baron-Cohen *et al.*, 2005) . Thus, important though cultural and social influences may be, male and female brains seem to differ even without those.

1.3 Different ways to end up with different brains

Now that we have made our point that intrinsic differences (that is, independent of nurture) may exist between a male and female brain, how can we explain them ?

Brain can differ in two quite different ways :

1. Connectivity and "physical properties" : that is, the network architecture of the brain. Mapping of neural projections and global connectivity play an important part in determining cognitive function, and are probably mostly determined early in development, when plasticity is still great ; any gender difference in connectivity is likely to depend more on early differences than on *instantaneous* difference between, say, circulating hormones. Thus, females seem to have more interconnections between hemispheres with the corpus callosum being more extensive ; the volumes of specific regions of male or female brains are known to differ. Moreover, the fact that women have proportionally larger language-associated regions than males (Wernicke and Broca) might underlie their superiority in verbal tasks (Craig *et al.*, 2004). Another

example is given by vasopressin neurons (vasopressin is a neuropeptide strongly implicated in attachment) : males have more vasopressin cells and denser projections than females (De Vries & Panzica, 2005). The pathway that leads to those differentiations is thought to critically involve gender-selective cell-death ; one study has shown that expression of a masculinizing gene inhibits cell death in a subset of neurons that show marked sexual difference (Kimura *et al.*, 2005).

2. Neurotransmission : more generally, chemistry as opposed to wiring. This includes, having different receptor types and concentration, or different receptor sensitivities ; e.g., in a paper studying the effect of early maternal care on vasopressin and oxytocin (neuropeptides implicated in pair-bonding and maternal affection), variations in maternal care appeared to have influenced the expression of oxytocin and vasopressin receptors in a gender-specific manner (Francis *et al.*, 2002). On the ligand part, having a different mixture of circulating hormones or released neurotransmitters obviously leads to different function.

What chemicals can influence neural developement ? They fall mainly into three categories :

1. exogenous chemicals (e.g., prenatal steroids from the mother ; no *a priori* difference between genders, but excesses of prenatal testosterone for example, are likely to cause opposite imbalances in steroid exposure in males and females. Furthermore, differences here might flatten and smooth the statistical distributions, as variability depends both on maternal and fetal hormones (e.g. a mother with high testosterone rate can masculinize the early development of her daugther's brain...)

2. endogenous hormones acting globally, e.g. circulating steroids released by the gonads.

3. endogenous proteins acting locally, i.e., expressed by the cell itself.

It is also important to recall that differences in brain function can be either *historic*, that is, the *result* of differences in the individual evolution of the brain, or *instantaneous*, e.g., a difference in circulating hormones or neurotransmitter at the moment of the test, in which case administration of hormones should be able to reverse the effects of the difference.

We will now proceed to examine how sex can be defined.

2 Gonadal sex and hormones : SRY and colleagues

Gonadal sex - that is, whether the individual has a testis or ovaries - has long been deemed the single difference between genders that could matter. And its importance should not be overlooked, even if recent findings show that chromosomal sex -whether the individual is XX or XY - matters as well.

2.1 Relevance to cognitive function

Sex steroids have a dramatic influence on cognitive processings ; estradiol has been reported to improve verbal memory in menopaused women (remember that women are found to have statistically better verbal memory than men), and testosterone has been found (in several, but not all studies) to improve cognition in older men (Wolf, 2003). Studies about the influence of circulating testosterone on spatial cognition yield conflicting results (Smith *et al.*, 2000; Liben *et al.*, 2002).

Estradiol and testosterone have been implicated in a number of developmental processes. Testosterone speeds up song development in songbirds, and appears to be critical for neural migration. To illustrate the influence of testosterone in early development, let us leave mammals and take an example in birds ; normal phrased song can be rapidly induced in very young, isolated male canaries by exposing them to adult levels of testosterone, so that with an implant of testosterone at 2 months of age, normal adult-structured song is learnt over the course of a single week instead of the usual 6 months (Gardner *et al.*, 2005).

Such experiments cannot be conducted in humans, but pathologies like dyslexia have been suggested to be associated with a slowing of left hemispheric maturation caused by a high fetal rate of testosterone, which could explain why there are more dyslexic boys than girls (Habib, 2000) (but some authors say that there is a lack of evidence for that ; see Tonnessen (1997)); this theory is part of the so-called Geschwind-Behan-Galaburda hypothesis (Geschwind & Galaburda, 1985), which relates left-handedness, verbal disorders, and some "special talents" with fetal testosterone. Even if this hypothesis is fairly controversial, correlations between traits that are thought to be associated with prenatal testosterone rates, such as 4th-2nd-digit ratio, spatial rotation abilities, less social and verbal skills, and a bunch of traits statistically associated with men (Baron-Cohen, 2002), suggest that there might be some truth in the hypothesis. Thus, early exposure to sex hormones might be critical for acquiring a male- or female-type of cognitive

profile.

Actually, the relation between hormonal rates and cognitive abilities has been suggested to be curvilinear rather than linear, so that the best way to get an outstanding performance in a task would be to have less testosterone if you are in the high-range of testosterone concentrations (e.g., a boy), and more if you are in the low-range (e.g., a girl), as suggested by Kimura (1999. Sex and cognition. Cambridge, MA: MIT Press, cited in Liben *et al.* (2002)). Consistent with this hypothesis is the result of a statistical study that shows that better-than-average performance in both spatial and verbal tasks is associated with a "less gender-typical finger-length ratio" (Burton *et al.*, 2005)- somehow the ancient myth of the androgyne as a symbol of perfection might have some kind of scientific justification ?

Sex hormones have also been reported to be critical for the development of neuropeptidic systems, such as the vasopressinergic and oxytocinergic systems. As suggested by Pinker (Pinker & Spelke, 2005), cognitive disparities could be partly accounted for by different preferences and priorities, and those preferences might be shaped by neuropeptides ; e.g., vasopressin (Young *et al.*, 2001) has been linked to fidelity and monogamy in prairie voles (as opposed to unfaithful mountain voles), oxytocin has recently been demonstrated to increase trust in humans (Kosfeld *et al.*, 2005) and had already been largely linked to pair-bonding (Young *et al.*, 2001), and those two peptides appear to have different circulating concentrations in males and females, and to be critically influenced by gender and sex hormones (Ishunina & Swaab, 1999).

A last example of the critical influence of gonadal hormones on the development of cognitive faculties is the effect of gonadectomy on the prefrontal dopaminergic system in the male rat. Dopamine in the prefrontal cortex is critical for cognitive tasks involving planning ; gonadectomy leads to an increased dopamine axon density in prefrontal area, probably altering cognitive function (Kritzer, 2003).

So sex hormones - and, consequently, the gonadal sex - play a crucial part in cognitive function. Next section examines how gonadal sex is determined.

2.2 Determining the gonadal sex

In 1990, the long sought-after testis-determining factor, that determined gonadal sex in mammals, was identified as a sequence located on the Y chromosome, termed SRY, and coding for a transcription factor that seemed to be necessary and sufficient to lead to differentiation of the gonad into testis (Sinclair *et al.*, 1990). This SRY sequence, when introduced in female mouse embryos, induces male development (Koopman *et al.*, 1991). Yet further re-

search has demonstrated that SRY actually antagonizes DAX1, an inhibitor of male differentiation located on the X chromosome, and which can induce development of XY individuals as females when overexpressed (Swain *et al.*, 1998); actually, SRY is neither sufficient to get a male gonad (if DAX1 if overexpressed), nor necessary as there are cases of XX individuals that have a male gonad, but no SRY (McElreavey *et al.*, 1993). SRY then regulates the expression of other genes downstream the sex determination cascade (notably SOX9, a gene on the X chromosome that is sometimes thought of as being a better candidate to be a brain-determining gene, and is not found only in mammals (Koopman, 2001; Graves, 2002)), by binding to the DNA and bending it (Capel, 1998).

SRY expression stimulates the undifferentiated gonad into becoming a testis ; cells are stimulated to secrete a hormone causing the potential female duct to regress, whereas Leydig cells are stimulated to secrete testosterone (Craig *et al.*, 2004).

2.3 A glimpse on how gonadal hormones induce downstream organization

A study on mutant Bax knockout mice (Forger *et al.*, 2004) illustrates an intermediate step between gonadal hormone and differences in brain architectures of male and female brains. In the principal nucleus of the bed nucleus of the stria terminalis, males have more neurons than do females, whereas in the anteroventral periventricular nucleus (AVPV), females have more neurons overall and many more dopaminergic neurons than do males. These sex differences are due to testosterone or its metabolites.

The study shows that a null mutation of the Bax gene (Bax is a gene crucially implicated in apoptosis) completely eliminated sex differences in overall cell number in both the principal nucleus of the bed nucleus of the stria terminalis and AVPV, without altering the sex difference in AVPV dopaminergic cell number.

Thus, testosterone appears to use different pathways to influence neural architecture, even within a single nucleus, and one important pathway is cell death.

Gonadal sex has thus a tremendous importance on cognitive function. Yet direct genetic influences of sex chromosomes are increasingly recognized, as we will now see.

3 Beyond gonadal hormones : direct genetic influences

3.1 Evidence that gonadal sex fails to account for all disparities

Three lines of evidence reviewed in Erickson (1997), showing that male and female embryo display differences long before the start of hormonal release by the gonads, suggest that sex determination may start shortly after conception:

- the XY preimplantation embryo usually develops more rapidly than the XX preimplantation embryo
- SRY is already transcribed in the preimplantation embryo
- male and female preimplantation embryos are antigenically distinguishable, which proves that genes are already differently expressed

As reviewed in Rinn & Snyder (2005), many genes are expressed differently in males and females in the mouse brain before exposure to hormonal differences, and neurons differentiate differently according to sex before fetal synthesis of sex hormones.

Further evidence is given by an analysis of the sex phenotype of a gynandromorphic finch (Agate *et al.*, 2003), whose right half of the brain is genetically male, whereas the left half is genetically female (see fig.1). Both halves of the brain are exposed to a single gonadal hormone environment ; however, the neural song circuit on the right is found to have a more masculine phenotype than that on the left. Thus, direct genetic influences of chromosomes within cells could be quite important to create sex differences in cell function.

Finally, administration of exogenous steroids cannot induce cross-sex development (Craig *et al.*, 2004).

Recent reviews have collected a number of facts that give more importance to chromosomal sex than in earlier studies (Arnold, 2004; Arnold *et al.*, 2003, 2004; Arnold, 1996; Xu *et al.*, 2002). We will now examine how chromosome differences may lead to gender-related differences in individual cells.

3.2 From chromosomal to functional disparity

Not only are cells influenced by hormonal signal, but they have their own local pool of chemical signals too : the nucleus with its unique pattern of gene

This half-male, half-female zebra finch was divided down the middle, with male feathers on the right and female feathers on the left. The brain was more masculine on the right side.

Agate, Grisham, et al., 2003.

Figure 1: Half male, half female

expression. Patterns of gene expression vary widely across cells, and differential expression of proteins might directly contribute to cognitive differences between men and women.

A woman has two X chromosomes, whereas a man has an X and a Y. Hence, there are a number of possibility for genes situated on sex chromosomes : they can be either on X or Y with no homologue on the other kind of chromosome, or present on both X and Y, as a pseudo-autosomal pair or only homologous pair. Y being so ridiculously short compared to X, there is an obvious need for more refined regulation of expression to avoid XX cells being overwhelmed with proteins on the X with no homologue on the Y.

As a result, usually, only one copy of X is expressed in each cell, and that copy is randomly selected between the two copies of a female cell. That regulation type has a number of consequences (Craig *et al.*, 2004) :

- overall, two different X are expressed in the female organism (one per cell), instead of only one in the male organism ; this might result in a smoothing of variability (grossly, phenotype is averaged over the two copies), so that any "extreme" cannot be as sharp as in male. This might be an explanation to the greater variability observed in men comparatively to women.

- then, the inactivation process is actually not that simple : as many as 1/5 genes located on the X-chromosome have been estimated to escape inactivation ; among those, some have lost their Y homologue (resulting in the female having two active copies instead of one in the male), others do have a homologue on the Y, but the contribution of the Y-linked gene is often smaller than that of the X-linked one (Xu *et al.*, 2002), thus giving way to an inhomogeneity in quantities.

- there might also be a *temporal* inhomogeneity, in that X and Y homologues may not be expressed at the same stages of brain development, and *spatial* inhomogeneity as well, as they may not be expressed in the same tissues (Xu *et al.*, 2002)

- there have been reports that a gene for social cognition on the X could be parentally imprinted, that is, it would be expressed only when located on the X chromosome that was inherited from the father (Xu *et al.*, 2002).

Thus, chromosomal transcription of genes located on sex genes can be quite different between males and females.

4 Non-linear amplification

4.1 A small difference might alter the whole transcriptome : transcriptional amplification

A crucial point when it comes to understanding how a mere 25,000 genes can lead to such tremendous variability and functionality, is that regulation of expression is extremely complex and involves a series of interwoven cascades. Thus, differential expression of one single transcription factor leads to an alteration of the expression of all the genes whose transcription is controlled by it, which in turn alters expression of still other genes further downstream, so that one inevitably loses track of some consequences of a tiny mutation.

Differences in expression of gonadal hormones may lead to dramatically different protein expression patterns ; as for the other diferentially expressed proteins (e.g. those on the X chromosome that do not undergo X inactivation), they might alter a number of downstream processes as well. With all the autosomal genome being identical, two transcriptomes can differ dramatically because of the difference of sex chromosomes. Thus, gene expression differs not only in reproductive tissues, but in somatic tissues as well (Rinn & Snyder, 2005), leading to differences in reaction to diseases such as kidney diseases that progress faster in men than women.

Given that early neural development relies on chemical gradients, initially small differences in the expression of one protein might lead to slightly different organizations of brain areas, and neural migration. Those differences mean functional differences as well, in that two differentially organized brains will process input information differently, thus leading to still further differences. There seem to be few gene expression differences between the male and female adult brain, while there are much more in the prenatal brain (Rinn & Snyder, 2005) ; this might imply that the crucial influence of sex chromosomes on brain is mainly concentrated on the early developmental period.

4.2 From low-level to high-level disparities : functional amplification

Once the brain has been structured differently, the whole response to external input may be different. A difference in low-level processes inevitably spreads to high-level cognitive processes in the absence of compensation. High-level processes build on the information provided by low-level ones, so that there is a second type of amplification of differences : any purely sensory difference is likely to spread into a cognitive difference, which in turn leads to cognitive

differences of higher level. Thus, even assuming that differences between a male and a female brain are not that obvious at birth, it is inevitable that the two brains will evolve quite differently, even when they get exactly the same input, as they are adapting to the world with different learning rules : a "same" external input might indeed be a "different" internal input, because of those small initial differences. Weighting input features differently gives a different perception of the world, different criteria, and so different learning rules.

5 Conclusion

Female and male brains have an initial chromosomal difference that unfolds into a cognitive difference throughout brain development ; be it through global release of sex steroids by the gonads, or by local transcription of genes located on sexual chromosomes, sex determines two different transcriptome profiles. Having different transcriptomes means following different rules, and evolving to be more and more different, if there is no evolutionary pressure to keep a functional homogeneity, which would restore unity by imposing functional constraints from the outside. We have not mentionned evolutionary considerations so far, as they were outside the scope of that mini-review ; but traditional roles devoted to genders, with woman breeding children and man "hunting and gathering" might have acted to stabilize rather than play against gender disparities. Yet you shouldn't forget that what we're speaking of here is : widely overlapping distributions, the significance of which is only statistical. Individual variability is overwhelming when compared to gender variability. Statistics apply to large numbers, not individuals ; so don't try to predict your little brother's IQ by looking at his finger lengths.

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