Sexual identity: hormonal or genetic?

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People suffering from androgen insensitivity syndrome (AIS) are male from a genetic point of view but feel profoundly female. Mental rotation tests have shown that these people activate the same areas of the brain as women to solve these tasks. This research, led by Julie Bakker, FNRS senior research fellow and project leader at the University of Liège's GIGA Neurosciences, suggests that sex hormones are more influential than genetics on the sexual differentiation of the brain.
Changing sex in the space of a day? Many people have already expressed this wish at least once... To satisfy their curiosity, and just to feel and understand what it's like to be in the skin of a girl or a boy... However, you don't choose to be born a girl or a boy. Genetics are the deciding factor! However, the latter isn't infallible and can, in certain cases, lead to situations where the border between male and female isn't clearly distinguished.

This means that some people are born with male and female genital organs. This is referred to as intersex. This anatomical ambiguity almost inevitably leads to sexual identity issues. Furthermore, the definition of gender
isn't limited to an individual's genital organs. People with all the physical characteristics of a man can feel deeply female. That's because the differences between men and women are also located in the brain. This is what is known as the sexual differentiation of the brain. This begins when the embryo develops until puberty. FNRS senior research fellow and project leader of the *GIGA-Neurosciences*’ Research Group in Behavioural Neuroendocrinology at the University of Liège, Julie Bakker studies the mechanisms underpinning the sexual differentiation of the brain in order to better understand gender identity problems.

**Puberty, a moment of truth that is difficult to accept**

To study the sexual differentiation of the brain, Julie Bakker and her team work not only on transgenic mouse models (see the article "A male or female brain? A question of oestradiol!") but also on human models. Within the framework of a recently published study in the journal *Cerebral Cortex* (1), the researcher focused on complete androgen insensitivity syndrome (CAIS). People with the latter are genetically male but have a female sexual identity. "They have an X chromosome and a Y chromosome like men but don't have androgen receptors and are therefore insensitive to these hormones that play a key role in the masculinisation of tissues and the brain", explains Julie Bakker. Consequently, CAIS leads to a female appearance. "In general, we become aware of the problem quite late, during puberty if a girl hasn't started menstruating yet", the researcher points out. "We discover at this point that these women don't have a uterus or ovaries but have testicles in the abdominal position. In the majority of cases, it is recommended that the testicles are removed and that they follow an oestrogen treatment, i.e. female sex hormones". While this helps them to decide on their sexual identity, these women without any female genital organs can't have any children... A fact that is very difficult to accept by those who had always imagined becoming a mother one day. The work of Julie Bakker aims to better understand the mechanisms underlying the sexual differentiation of the brain in order to be better able to prevent the appearance of such problems and/or better support and orient those in question.

**Is the Y chromosome behind the masculinisation of the brain?**

"It is interesting to study individuals with CAIS in an effort to find out more about the role of sex hormones in the differentiation of the brain", emphasises the scientist. "Studies on rodents have revealed that besides sex hormones, the genes situated on the sex chromosomes play an important role in the sexual differentiation of the brain. People affected by CAIS can help us to determine whether the Y chromosome leads to a masculinisation of the brain despite the absence of the influence of androgen hormones in this process", Julie Bakker specifies. In other words, this syndrome can help scientists to ascertain whether it is the hormones or the sex chromosomes that are responsible for the masculinisation of the human brain.

To find out, Julie Bakker and her colleagues used the mental rotation technique. This particular type of imagery provides indications on the ability of those tested to mentally turn a two-dimensional or three-dimensional image. "*We used this technique because there are very clear differences between the capacities of men and women in this type of exercise*, the researcher explains. Indeed, men and women perform in a relatively characteristic manner - for instance, men are faster and make fewer mistakes - but they also use different regions of the brain during this exercise. "*Women tend to activate the frontal and temporal lobes while men activate the parietal lobe*, the specialist continues. Both sexes therefore have their own strategy to solve the task!
Typically female brain activity

Three categories of people took part in the mental rotation exercises: 'control' men and women as well as people suffering from CAIS. "The analyses confirmed the differences in the areas of the brain activated in men and women when they performed the exercise", Julie Bakker reveals. "And we noticed the same results in people suffering from CAI syndrome as the control women". Consequently, this research confirms that the differences in brain activity observed in the three categories of subjects result from the effect of sex hormones and not the presence/absence of the Y chromosome. People affected by androgen insensitivity syndrome therefore have a female reaction to mental rotation tests. Their genetic gender is less important than hormonal exposure during their development in the definition of their sexual identity. While these results already provide a good indication concerning the sexual differentiation of the brain in these people, other tests will help confirm that the overall functioning of the latter is similar to that of women. "We are also studying the volume of grey matter because it is different in men and women. We would like to see what happens in people suffering from CAIS ", Julie Bakker continues. "In addition, we are exploring the emotional responses of these three categories of people in an effort to understand to which gender CAIS individuals are similar in this respect".

Understanding the dynamics between hormones and genetics to take the best action

Although they suffer from not being able to have any children, people with androgen insensitivity syndrome generally don't have sexual identity and gender difficulties. They feel female and are attracted to men. "But there are plenty of other problems related to sexual differentiation which are more intermediary and where
things are far less clear. For instance, in the case of congenital adrenal hyperplasia, girls are subject to virilisation during embryonic development and can be born with a genital ambiguity", Julie Bakker points out. Knowing and understanding the interaction between the different hormonal and genetic protagonists leading to sexual differentiation could help people who are faced with these types of problems. "An important issue that still needs to be cleared up is to find out whether sexual differentiation is complete at birth or whether this continues until puberty", Julie Bakker explains. Recent studies suggest that the brain remains sensitive to sex hormones from an organisational point of view, until puberty (read the article A male or female brain? A question of oestradiol!).

These discoveries call into question the classic theory according to which the brain is masculinised or feminised at birth. "It's possible that the window during which sexual differentiation takes place is much bigger than the prenatal period. Organisational changes in the brain could occur up to 14 or 15 years old with perhaps a variable influence of hormones on this organisation according to age", Julie Bakker underlines. If this hypothesis turns out to be true, this could have a significant impact on how and when treatment should be given to people suffering from problems relating to the sexual differentiation of the brain. In the near future, Julie Bakker would like to study Kallmann syndrome which lead to problems concerning the neuronal migration of GnRH neurons and an absence or lack of secretion of sex hormones. "As is often the case in sexual differentiation problems, these people are treated during puberty but perhaps this is too late? Taking action earlier might give better results...", the researcher concludes.