Are the Brains of Transgender People Different from Those of Cisgender People?

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Research into the biological basis of gender identity is in its infancy, but clues are beginning to emerge.

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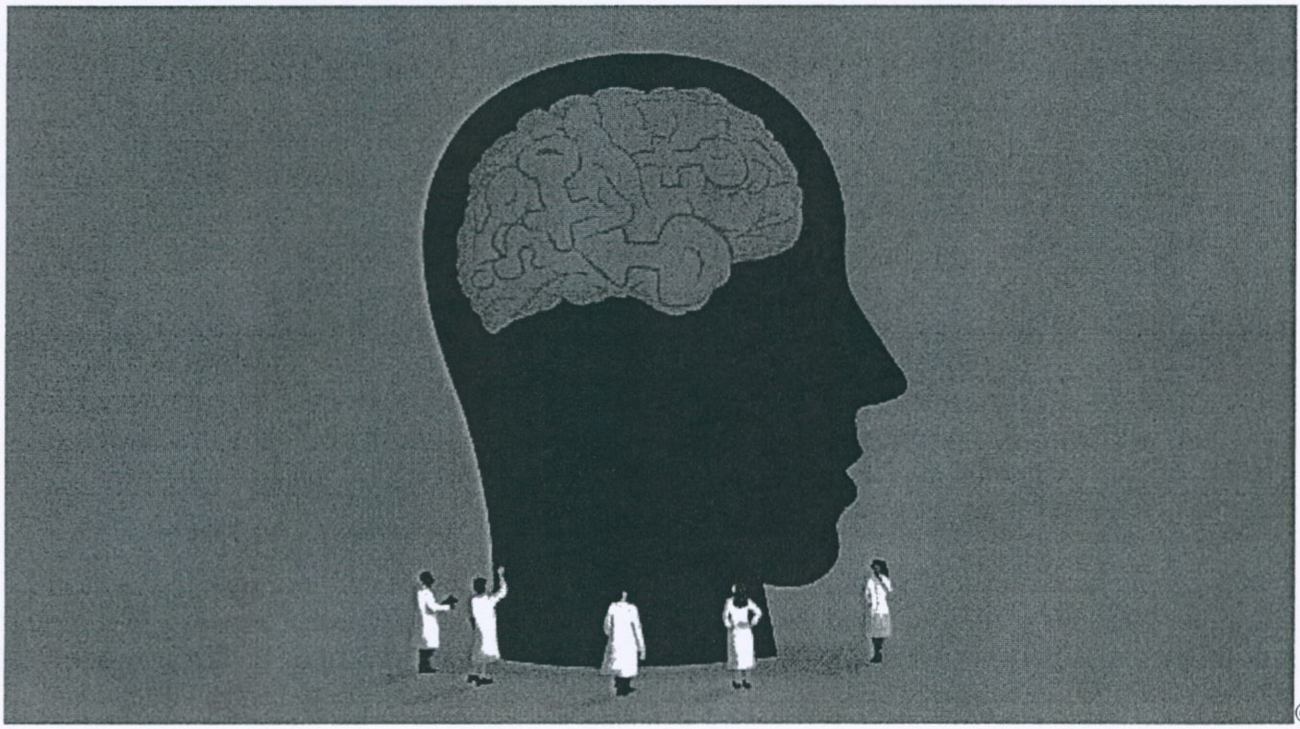

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In recent years, US society has seen a sea change in the perception of transgender people, with celebrities such as Caitlyn Jenner and Laverne Cox becoming the recognizable faces of a marginalized population. Transgender rights have also become a mainstream political issue, and the idea that people should be referred to by the names and pronouns they find most fitting—whether or not these designations match those on their birth certificates, or align with the categories of male and female—is gaining acceptance.

Yet a biological understanding of the contrast between the natal sex and the gender identity of transgender people remains elusive. In recent years, techniques such as functional magnetic resonance imaging (fMRI) have begun to yield clues to possible biological underpinnings of the condition known as gender dysphoria. In particular, researchers are identifying similarities and differences between aspects of the structure and function of the brains of trans- and cisgender individuals that could help explain the conviction that one's gender and natal sex don't match.

Techniques such as functional MRI have begun to yield clues to possible biological underpinnings of gender.

Other studies have pinpointed characteristics of the transgender brain that fall in between what is typical for either sex—results that proponents of the developmental mismatch hypothesis generally see as support for their idea. In 2014, for example, Georg Kranz, a neuroscientist at the Medical University of Vienna, used diffusion MRI data to investigate differences in white matter microstructure among trans- and cisgender subjects. Cisgender women had the highest levels of a measure of a neural property known as mean diffusivity, cisgender men the lowest, and both transgender men and women fell in between—though it's not fully understood what mean diffusivity may represent physiologically.[6] "It seems that these transgender groups were at an intermediate stage," Kranz says. Controlling for individuals' hormone levels did not alter the differences between groups, leading the authors to suggest that white matter microstructure had instead been shaped by the hormonal environment before and soon after birth—though the possibility that later life experiences also play a role cannot be ruled out, he adds.

"All available evidence points towards a biologically determined identity," Kranz says. "In [transgender] people you would say there was a mismatch in the testosterone milieu during the development of the body and then during development of the brain, so that the body was masculinized and the brain was feminized, or the other way around."

Mixed results for studies of the transgender brain

It's unlikely that gender identity has such a straightforward biological explanation, however, and some studies have identified features of the transgender brain that appear closer to the natal sex, casting doubt on the developmental mismatch hypothesis. In a 2015 study from the Netherlands Institute for Neuroscience, a comparison of the distribution of gray matter in 55 female-to-male and 38 male-to-female transgender adolescents with cisgender controls in the same age group found broad similarities in the hypothalami and the cerebellums of the transgender subjects and cisgender participants of the same natal sex.[7] There were, however, some differences in specific subregions.

A 2013 study that focused on cortical thickness, which tends to be slightly greater in women than in men, also yielded mixed results. Led by Antonio Guillamon, a neuroscientist at the National Distance Education University in Spain, researchers analyzed the MRI scans of 94 subjects and found that the total cortical thickness of both transgender women and men was more similar to that of cis women than that of cis men. But this finding did not hold true across the entire brain: in a structure in the forebrain known as the right putamen, which is involved in motor tasks and learning, cortical thickness in transgender men was more similar to that in cisgender men, and transgender women showed no significant differences from either cisgender control group.[8]

"What we found is that, in several regions, cis women, male-to-female trans, and female-to-male trans have thicker cortex than cis males, but not in the same regions," says Guillamon, who hypothesized in a 2016 review article that the brains of cisgender women, transgender women, transgender men, and cisgender men may each have a distinct phenotype.[9] "The cortex is vital for gender."

In another study that yielded mixed results with regard to the developmental mismatch hypothesis, researchers at RWTH Aachen University in Germany tested how cisgender people and transgender women discriminate between men's and women's voices. The team found that in some respects, such as the level of activation of a brain area called the right superior frontal gyrus, trans and cis women were similar, while cisgender men showed higher activity, possibly reflecting greater cognitive effort on the task.[10] Despite similar levels of activation between trans and cis women, however, the transgender women were equally good at identifying male and female voices, while both cisgender groups found it easier to identify voices of the opposite sex.

"Overall, we see in some measures that [transgender people] actually do show these similarities with people [who] share their gender identity, but not for all measures," says Kreukels. Researchers are "still trying to unravel" those similarities and differences in the brain, she says.

More research could further clarify the basis not just of gender dysphoria, but also of gender itself, Guillamon suggests—with implications far beyond the pronouns with which we identify. "Phylogenetically, and with respect to evolution . . . it is important to know whether one is a male or a female," and with whom to copulate, he says. "It is one of the pivotal points in biology, and the biology of humans."

Savic says she hopes the results of studies on transgender people will help make gender identity a less-charged issue. "This is just part of the biology, the same way as I have black hair and somebody has red hair."

For now, as is the case for many aspects of human experience, the neural mechanisms underlying gender remain largely mysterious. While researchers have documented some differences between cis- and transgender people's brains, a definitive neural signature of gender has yet to be found—and perhaps it never will be. But with the availability of an increasingly powerful arsenal of neuroimaging, genomic, and other tools, researchers are bound to gain more insight into this fundamental facet of identity.

THE EFFECT OF HORMONE TREATMENT ON THE BRAIN

In order to avoid confounding effects, many studies comparing the brains of trans- and cisgender people only include transgender subjects who have not yet begun treatments to bring levels of key sex hormones in line with those of their experienced genders. But some groups are specifically exploring the effects that these treatments might have on the brain. "There is an ongoing debate over whether hormonal administration in adult individuals changes the brain or not," says Sven Müller, a psychologist at Ghent University in Belgium. If cross-sex hormone treatment can shape the adult brain, he notes, it's important to find out "what happens to the brain, and what are the implications for certain cognitive functions."

Only a handful of studies have addressed the question of how these hormone treatments affect the brain. In one led by Antonio Guillamon of National Distance Education University in Madrid, researchers found that testosterone thickened the cortex of transgender men, while six months or more of estrogen and antiandrogen treatment led to a thinning of the cortex in transgender women (*J Sex Med*, 11:1248-61, 2014). A Dutch study similarly concluded that the overall brain volumes of transgender women dropped as a result of treatment, while those of transgender men increased, particularly in the hypothalamus (*Eur J Endocrinol*, 155:S107-14, 2006). And last year, Karolinska Institute neuroscientist Ivanka Savic found that the brains of transgender men taking testosterone showed several changes, including increases in connectivity between the temporoparietal junction (involved in own-body perception) and other brain areas (*Cereb Cortex*, doi:10.1093/cercor/bhx054, 2017).

In another study published last year, of 18 transgender men and 17 transgender women who'd undergone at least two years of hormone therapy, and 57 cisgender controls of both sexes, Müller and colleagues found indications that such hormone treatments might even affect regions the brain that are not commonly considered to be among those sensitive to sex steroids—specifically, the fusiform gyrus, involved in the recognition of faces and bodies, and the cerebellum, known in part for its role in motor control (*Neuroendocrinology*, 105:123-30, 2017). Moreover, he notes, the changes in the cerebellum were linked to treatment duration. "People might need to broaden the scope as to where in the brain they are looking for effects [of hormone treatments]."

In addition to shedding light on the brain networks controlling gender perception and dysphoria, the results of these studies will add to what's known about the effects of hormone treatment on transgender individuals, says Savic. "If we potentially provide treatment with sex hormones, which we should do for persons who need that, it is very important to know what sex hormones do to the brain."