2015

The transgender brain

THE TRANS

Introduction

Despite having always existed, transgender people have recently received widespread media attention. Gender dysphoria is a condition in which an individual's physical gender conflicts with the gender they identify with. It is recognized by DSM-V [1], but its pathology is widely misunderstood. Once believed to be a psychiatric condition [2], more recent research suggests that the condition may be rooted in genetic and biological factors.

Treatment of gender dysphoria in the form of medically administered steroid sex hormones such as antiandrogen, estrogen, androgen, and testosterone have been found to have interesting neurological effects on transgender individuals. Such structural and functional changes have presented an opportunity to explore the controversial topic of sex differences in the human brain, and how sex hormones influence our behavior and function.

How the Brain Contributes

Sex and gender expression are complex, nuanced components of human biology, and understanding their neurological bases has proved itself a daunting task. "People tend to define sex in a binary way — either wholly male or wholly female — based on physical appearance or by which sex chromosomes an individual carries. But while sex and gender may seem dichotomous, there are in reality many intermediates," says Dr. Eric Vilain of UCLA's Center for Gender-based Biology [3]. In pursuing biological explanations of gender dysphoria, the scientific community has identified brain structures that are functionally and structurally sex-dependent, or sexually dimorphic, and have been studying how such areas appear in transgender individuals' brains. However, there is no switch in the brain that is flipped for one gender or the other. Current literature suggests that understanding the biological roots gender identity and expression is an evasive target to reach.

While discussing the etiology of gender dysphoria, a considerable number of studies and discussions focus on the bed nucleus of the stria terminalis (BSTc), an area implicated in sexual and anxiety-related responses. The BSTc is sexually dimorphic; in human males, the BSTc is 2.5 times larger than that of women ($p < 0.005$) [4]. It has been found to have heavy influence over sexual activity, containing both estrogen and androgen receptors. A study conducted in 1995 looked at the structure while searching for a sexually dimorphic brain area.

The postmortem brains of six male-to-female (MtF) transgender women were studied and compared to male and female control groups. While the size of participants' BSTc had no significant effect on sexual orientation, transgender people expressed the BSTc size of their preferred gender ($p < 0.005$), that is, a female-sized BSTc was found in MtF transgender women, and vice versa. Each of the participants were taking (or had taken) supplemental estrogen at some point in their lives, and this raised questions as to whether or not hormones were responsible for such size differences. For this reason, researchers looked at the brains of two non-transgender men and women who, for medical reasons, were experiencing hormone reversal. The female control had undergone menopause and expressed lowered estrogen levels, yet had the expected BSTc size for females; conversely, a man who suffered an adrenal tumor that increased his estrogen blood levels had a very large, biologically "male" BSTc.

While this information was considered a great breakthrough in understanding transgender brain structures, subsequent studies questioned the role of the BSTc. A study coming from the Netherlands Institute for Brain Research found that this structure's sexual differentiation occurs only in adulthood [5]; this conflicts with the fact that many transgender people (~67-78%) first report feeling an incongruence between their assigned gender and the gender they identify with from childhood onward [6]. Therefore, sexual differentiation of the BSTc is not a direct cause of gender dysphoria. With the BSTc having been ruled out as a cause of transsexuality, researchers directed their attention towards fetal, neonatal and pubertal hormones as a cause. However, this theory has its share of caveats as well.

Children's Hospital Los Angeles (CHLA), having the largest number transgender children and youth in the United States, conducted a study on 101 patients in an effort to develop safer and more effective treatments for transgender youth. The physiological characteristics of these patients, ages 12-24, were published in the Journal of Adolescent Health. For both male or female transgender patients, their sex hormone levels fell within the range of the sex they were assigned at birth[7]. Despite exhibiting clinically high levels of gender dysphoria, the observable physiological characteristics of the patients were consistent with their birth gender. However, certain psychological problems were found; of the 101 patients, 35% had experienced clinical levels of depression and over half had reported considering suicide. Thirty percent had already made an attempt. While grim, these statistics act as a motivating force for Johanna Olson, MD at the CHLA to find treatments that make it easier for transgender youth to grow into their preferred gender identity by providing appropriate medical attention and mental health support.

With developmental hormones having been ruled out, the search for the brain structures that influence gender expression continues. As more and more people dedicate their time to helping understand and treat people living with gender dysphoria, there are particularly interesting revelations about how cer-

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tain brain areas can influence the identities of human beings.

In 2011, two studies were conducted at the University of Barcelona that sought to discover how the white matter patterns of transgender individuals compared to the patterns of their preferred sex. White matter, glial cells, and myelinated axons that connect brain areas in the central nervous system, can be viewed with diffusion tensor imaging (DTI). Using DTI, researchers studied the white matter of transgender men and women who had not begun hormone replacement therapy. There are four areas that they found to be sexually dimorphic and possibly implicated in gender dysphoria: the anterior and posterior longitudinal fasciculus, the forceps minor, and the corticospinal tract [8].

For untreated FtM participants, the white matter in these four areas appeared to be more consistent with the patterns found in biological males than it did biological females; patterns were closer to those who shared their gender identity (men) than those who shared their biological sex (females); the brain appeared masculinized. [9] As female-to-male participants were studied first, the data collected from male-to-female individuals came as a surprise. MtF participants who had not begun hormone therapy had white matter patterns that appeared to be in between male and female controls; the measured difference between the patterns in all four parts was statistically significant.

Interestingly, Ivanka Savic-Berglund from the Karolinska Institute in Sweden has a prediction as to why these specific white matter areas are dimorphic in men and women and altered in transgender individuals. One of the four regions, the superior longitudinal fascicle, could be a vital part in the development and expression of gender identity. "It connects the parietal lobe [involved in sensory processing] and frontal lobe [involved in planning movement] and may have implications in body perception" [11]. While a significant amount of the research involving gender dysphoria focused on grey matter and nuclei within the brain, this research may have found a new lead - the complexity of gender and sexual expression in the brain is too complicated for only one brain area, so focusing on what connects our brain areas may yield the best chance at demystifying the search.

How Hormones Affect the Brain

Male-to-female (MtF) or female-to-male (FtM) transgender individuals undergo a unique form of treatment which presents an opportunity to understand how our hormones influence behavioral and neurological development. The introduction of sex hormones in transgender individuals influences the development of their physical secondary sex characteristics, but also results in chemical and structural changes in the brain. The effects of administered sex hormones as a form of treatment for transgender individuals has shed light on the neurological effects of androgen, testosterone, estrogen and other sex hormones.

Women are twice as likely to be diagnosed with depression as men, a phenomenon widely believed to be a result of varying levels of sex hormones in the brain. Men experiencing hypogonadism, whose bodies produce little or no testosterone, are subject to increased chances of depression and anxiety disorders as well. Researchers at The Medical University of Vienna in Austria found a relationship between high-doses of androgen administered to transgender men and the binding of serotonin transporter (SERT) to several brain areas implicated in depression [12]. SERT is vital in the recycling and reuptake of serotonin, as it gathers serotonin from the synaptic cleft and returns it to the presynaptic neurons; for this reason, many antidepressants (including SSRIs) target this protein [13, 14]. Thirty-three transgender individuals, both male-to-female and female-to-male, underwent PET scans before beginning hormones, four weeks after going on hormones, and four months after starting.

At both the four week and the four month mark of the study, the brains of male-to-female participants undergoing androgen treatments showed an increase in SERT binding in the amygdala, caudate nucleus, putamen, and median raphe nucleus. Levels of SERT binding were positively correlated to the amount of androgen being administered. After four months of treatment, the correlation between SERT binding and testosterone became nonsignificant. Interestingly, the opposite was true for MtF participants. Anti-androgen and estrogen treatments resulted in a decrease in the levels of SERT binding in the insula, anterior, and mid-cingulate cortex. The researchers view this finding as an opportunity to create new methods of treatment for depression and anxiety disorders, as well as a way to increase the effectiveness of our current SSRI's.

Researchers conducted a longitudinal study looking at testosterone's influence on FtM transgender people's brains, and the collected data highlights an interesting possible explanation for this sex difference. The participants in the study underwent MRI scans before and during their high-dose testosterone treatment. It is understood that testosterone has a significant influence on human verbal intelligence and cognition [15]. High levels of fetal testosterone, measured by testosterone levels in amniotic fluid, correlated to weaker verbal intelligence and a smaller vocabulary [16]. However, a recent study found an interesting relationship between testosterone levels and two areas of the brain implicated in speech production and comprehension: Broca's and Wernicke's areas.

Continuous high-dose treatment of testosterone decreased the grey cortical matter in both areas. Unexpectedly, and for reasons not well understood, medically administered testosterone increased

the white matter that connected these two areas. The researchers concluded that the effects of decreased grey matter in Broca's and Wernicke's overpowered the effects strengthening of white matter between these areas. The study emphasizes the importance of hormone replacement therapy as a form of treatment for transgender individuals, as supplemental sex hormones can people to grow into their gender identity psychologically as well as physically.

Conclusion

The existence of sexually dimorphic areas in the brain is the topic of an ongoing and highly politicized debate. However, the brain is a complex and variable organ, a complex machine made of varying cogs that rarely fit into binary categories. Studying the brains of transgender people presents an opportunity to legitimize gender dysphoria even further, as well as gives the neuroscience community a unique opportunity to peek into what gender really means and how it manifests itself: with hormones, with brain structures, or the connections that bring all of the bits and pieces together.

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