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Review Article

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EVIDENCE SUPPORTING THE BIOLOGICAL NATURE OF GENDER

IDENTITY

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Running Title: Review: Gender Identity

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Abstract

Objective: To review current literature that supports gender identity having a biologic basis. .

Methods: A traditional literature review.

Results: Evidence that there is a biological basis for gender identity primarily involves 1. data on gender identity in patients with disorders of sex development along with 2. neuroanatomical differences associated with gender identity.

Conclusions: Although the mechanisms remain to be determined, there is strong support from the literature that there is a biological basis for gender identity.

Keywords: gender identity, transgender; gender dysphoria

Abbreviations:

MTF = male to female; **FTM** = female to male.

Introduction

Gender identity is a fundamental human attribute which has a profound impact on personal well-being. Transgender individuals are those whose lived and identified gender identity differs from their natal sex. Various etiologies for transgender identity have been proposed. Misconceptions which assume that gender identity can be altered still exist. However, clinical experience with treatment of transgender persons over the years has clearly demonstrated that the best outcomes with these individuals are achieved with their requested hormone therapy and surgical sexual transition, as opposed to psychiatric intervention alone (1). In this manuscript we will review the data which support a fixed, biological basis for gender identity.

Methods

This traditional literature review was conducted using a search of PubMed and Google Scholar for the following key words: gender identity, gender dysphoria, transsexual, transgender, transmen, transwomen.

Results

Disorders of Sex Development (DSD)

A seminal study by Meyer-Bahlburg et al involving outcomes of XY individuals raised as females due to severe non-hormonal, anatomic abnormalities of sex development has provided

the most convincing evidence that gender identity is fixed (2). These congenital abnormalities include penile agenesis, cloacal exstrophy, and penile ablation. For many years, female gender assignment along with surgical feminization was the dominant approach for these patients. In this study, it was observed that 78% of all female-assigned 46 XY patients were living as females. While the majority of these patients did not initiate a gender change to male, none of the 15 male-raised 46 XY patients initiated a gender change to female. Thus, risk of questioning gender identity was higher in those patients raised as females than in those raised as males among 46 XY subjects with one of these conditions. A study by the same group that examined the degree of satisfaction with surgical intervention reported by patients with 46 XY genotype also found that those subjects raised as boys were considerably more comfortable with their gender identity (3).

Another seminal study relevant to this topic was by Reiner and Gearhart (4) in their review of 16 XY genotype subjects with cloacal exstrophy who underwent female gender reassignment surgery. Out of the 14 individuals raised as girls, 4 announced they were male and 4 later chose to live as boys when they became aware of their genotype. The 2 individuals who were raised as males identified as males throughout life. The sexual behavior and attitudes of all 16 subjects ultimately reflected strong masculine characteristics regardless of gender assignment. Thus, children who were born genetically and hormonally male identified as males despite being raised as females and undergoing feminizing genitoplasty at birth. Although cohort size in these studies is small, these data provide the strongest evidence for biological underpinnings of gender identity.

In congenital adrenal hyperplasia (CAH) the adrenal glands produce excessive amounts of androgens, causing genital virilization with a spectrum of different phenotypes in 46 XX neonates. Dessens et al (5) showed that the prevalence of male gender identity in 46 XX female-raised subjects with CAH is higher than the prevalence of FTM transgender individuals

in the general population of chromosomal females. In this study, the large majority (95%) of 250 female-raised patients later maintained a female gender identity. However, 13 (5.2%) had serious problems with their gender identity. 5 alpha-reductase-2 and 17-beta-hydroxy-steroid dehydrogenase-3 deficiencies are similar conditions in which synthesis and conversion of testosterone to dihydrotosterone (DHT) is inhibited, , preventing development of external male genitalia and resulting in potential genital ambiguity. As with CAH, affected individuals are often raised as females. In a study of affected subjects, gender role changes were reported in 56-63% of cases with 5 alpha-reductase-2 and 39-64% of cases with 17-beta-hydroxy-steroid dehydrogenase-3 who were raised as girls (6). These data support the concept that gender identity might be attributed to hormone milieu during intrauterine development on some occasions.

Data from disorders of sexual development highlight the potential influence of abnormal hormone exposure on development of transgender identity in some individuals. However, it is important to note that most transgender individuals develop a gender identity which cannot be explained by atypical sexual differentiation. It is possible for individuals with normal sexual differentiation to develop transgender identity later in life.

Neuroanatomical Differences

Many of the current hypotheses for the biological origin of transgender identity are based on atypical sexual differentiation of the brain. The perception of one's own gender is linked to sexual differentiation of the brain, which, in transgender individuals, differs from the body phenotype (7). Regarding transgender identity, Swaab et al have proposed that this discrepancy could be due to the fact that sexual differentiation of the brain takes place only after sexual

differentiation of gonads in early fetal life (8). Along these lines, the degree of masculinization of the genitals may not reflect that of the brain .

The notion of transgender-specific cerebral phenotypes has been further supported by postmortem brain studies investigating the underlying neuroanatomical correlates of gender identity (9,10,12). The vast majority of these studies have compared particular regions of interest only in MTF transgender individuals (13,14,15). These studies support the hypothesis that atypical cerebral networks in transgender individuals have a neuroanatomical basis. Studies have examined both grey and white matter areas of the brain, as follows:

Grey Matter Studies

Studies involving grey matter in transgender individuals have provided the strongest neuroanatomical case for transgender gender identity. Postmortem brain studies suggest that some subcortical structures are feminized in MTF transgender individuals. One of the earliest and most influential studies in this area involved the bed nucleus of the stria terminalis (BSTc), which was reported to be a sexually dimorphic nucleus in humans with a larger volume in males than in females. In 1995, Zhou et al found that the size and the number of neurons in the BSTc of 6 MTF estrogen-treated transgender individuals was typical for the size and neuron numbers found generally in control females (9).The authors further reported that these findings could not be explained by differences in adult sex hormone levels.

A similar study by Kruijver et al provided further data supporting the role of the BSTc in transgender identity (10). They examined tissue from the same 6 MTF estrogen-treated transgender persons studied by Zhou et al and found that the number of neurons in the BSTc was

more similar to genetic XX female controls. BSTc neuron number was also in the male range in the 1 FTM androgen-treated transgender individual studied.

Most transgender individuals have feelings of gender dysphoria which begin in childhood. However, in a study of BSTc volume in postmortem brains of 50 control subjects, Chung et al reported that sexual dimorphism in the BSTc did not develop until adulthood (11). Yet, the same group remarked that changes in fetal hormone levels could have delayed effects on BSTc volume and neuron in adulthood, thereby suggesting a role for BSTc as a marker for gender identity. Still, delayed development of sexual dimorphism in the BSTc would not explain the early development of gender dysphoria or gender identity discrepancy in childhood.

In 2008, Garcia-Falgueras and Swaab were the first to report a sex reversal in the uncinate nucleus as part of brain networks involved in gender identity. They examined the interstitial nucleus of the anterior hypothalamus (INAH 3), which is a sexually dimorphic component of the uncinate nucleus, in relation to brains of transgender individuals (12). They reported that INAH3 volume and neuron number in 11 MTF transgender persons was in the female range.

The above studies are limited by the fact that they involved post-mortem examinations of a small number of MTF transgender individual brains, some of whom had either received hormone treatment or surgery. Therefore, study findings may represent confounding effects from exogenous hormones in a small group of transgender individuals. Nevertheless despite their small sample size, these studies provide valuable evidence that gender identity has a link to neuroanatomy.

Studies by Luders et al provided further evidence that transgender identity is associated with distinct cerebral patterns (13,14). In 2009, the group analyzed MRI data of 24 MTF

transgender individuals who had not yet begun hormone treatment. These subjects were shown to have a pattern that was more similar to control men. However, they also revealed a significantly larger, more “feminized” volume of regional grey matter in the right putamen in these subjects. In 2012, the same group observed thicker cortices in 24 MTF transgender individuals who had not yet received exogenous hormones compared with 24 age-matched control men in a number of regions across the lateral and medial cortical surfaces. The data supported a dichotomy between MTF transgender individuals and gender congruent males with regard to brain structure.

Differences in brain volume and cerebral activation patterns have been implicated as potential explanations for transgender identity. In 2011, Savic et al examined brains of 24 living MTF transgender individuals and found significant volume reductions of the putamen in MTF transgender individuals in addition to significant increases in grey matter volumes compared with male and female controls (15). Although these findings differ from the previous findings of a smaller, “feminized,” putamen in MTF transgender individuals, they still reported that certain brain areas showed characteristic structural features in the transgender group compared with controls.

The same group investigated 12 living MTF transgender individuals who smelled two steroid compounds: the progesterone derivative 4,16-androstadien3-one (AND) and the estrogen-like compound estra-1,3,5(10),16-tetraen-3-ol (EST). These compounds have been reported to activate the hypothalamic networks in a sex-differentiated way. MTF transgender individuals who had not received hormone treatment were found to respond similarly to female controls with activation of the anterior hypothalamus in response to AND (16). Another study by Gizewski et al showed a similar cerebral activation in MTF transgender individuals relative to female controls during viewing of erotic stimuli (17). While the above studies also only

involved MTF transgender individuals, they nonetheless suggested altered neuroanatomical pathways as an explanation for transgender identity.

The following two studies were unique from the aforementioned ones because they included both MTF and FTM transgender individuals who had not received hormone treatment. Zubiaurre et al reported that FTM transgender individuals showed evidence of subcortical gray matter masculinization in the right putamen, while MTF transgender individuals had feminized cortical thickness (18). In 2013, a study by Simon et al found differences in grey matter in 17 living transgender subjects compared with controls (19). Differences were seen in transgender patients in the cerebellum, angular gyrus, and parietal lobe compared with controls, independent of their biological gender.

White Matter Studies

Although an early study by Emory et al (20) found no difference in the whole corpus callosum or the splenium region between MTF and FTM transgender individuals, the following MRI studies of white matter brain characteristics of transgender individuals have suggested a strong neuroanatomical explanation for transgender identity . Yokota et al reported that the pattern of corpus callosum shape in both FTM and MTF transgender individuals was closer to subjects with shared gender identities than to subjects who shared the same natal sex (21). Among FTM transgender individuals who had not received hormone treatment, certain white matter fasciculi involved in higher cognitive functions were closer to the pattern of control males than to control females (22). Among MTF transgender individuals who had not received

treatment, diffusion tensor imaging revealed an intermediate white matter pattern that was between male and female controls (23).

Genetic Factors and Exposures

Although limited in size and scope, the involvement of genetic factors in transgender identity is supported by small studies of gene abnormalities associated with steroid hormones, twin case studies, neuroproteins, and prenatal exposures.

Steroid Hormone Genetics

Select genes have been associated with transgender identity. Although these studies have been small, they represent the most convincing findings to date linking atypical genes with transgender identity among both MTF and FTM transgender individuals. The CYP17 gene encodes the 17-alpha hydroxylase enzyme and is associated with elevated serum levels of estradiol, progesterone, and testosterone. In a case-control study of 151 transgender individuals, Bentz et al reported a significant association between the CYP17 gene and FTM transgender individuals but not in MTF transgender individuals (24). Another study by the same group examined a polymorphism in the gene coding for 5-alpha reductase and found no association in a sample of both MTF and FTM transgender individuals (25).

Various groups have investigated steroid hormone receptor gene variants to determine if they confer likelihood of an individual developing transgender identity. Steroid hormones exert profound influences on fetal sexual development and act via specific receptors. It is therefore plausible that abnormal development of sex hormone receptor function may predispose to

transgender identity. The above studies to date on this topic, however, have been contradictory, and require replication to completely support this hypothesis. Henningson et al found an association between MTF transgender individuals and a dinucleotide CA polymorphism in the estrogen receptor beta gene (ERb) (26). However, two subsequent studies by separate groups showed different results. Hare et al performed a larger study of MTF transgender individuals and found no relationship with the ERb, but instead found a significant association with the androgen receptor repeat (27). In a similar study of 242 MTF and FTM transgender individuals, Ujike et al examined sex steroid receptor genes and found no association with transgender identity (28).

There have been several small case reports of atypical sex chromosomes in transgender individuals. The most common association reported was with disomy-Y (47, XXY), however no statistically significant association between particular genes has been noted (29).. Two recent studies of MTF and FTM transgender individuals reported that aneuploidies are slightly more common in transgender individuals than in the general population but neither was controlled. In the first, karyotype abnormalities were found in 2.5% of the 368 transgender individuals studied (30). A second study of 302 transgender individuals also showed a low overall incidence (1.5%) of chromosomal abnormalities (31).

Twin studies

Twin literature supports the potential contribution of genetic factors to the development of transgender identity. In two separate retrospective studies of twin pairs, Bailey et al and Coolidge et al demonstrated a strong heritable component among twins with transgender identity (32,33). A similar study by Hylens et al of 23 twin pairs showed that 9 out of 23 monozygotic twin pairs were concordant for transgender identity, in contrast to no concordance among the

dizygotic twin pairs (34). Two small studies or studies (35,36) have also demonstrated a higher concordance for transgender identity among monozygotic twins versus dizygotic twins. Nevertheless, the overall prevalence of monozygotic twins discordant for transgender identity still outnumbers those who are concordant.

Neuroproteins

Brain-derived neurotrophic factor (BDNF) is a member of the growth factor family which is involved in synaptic plasticity and neuronal development. Altered BDNF signaling is thought to be a contributor to psychiatric conditions. Fontanari et al (37) reported that serum BDNF levels were 15% lower in an uncontrolled study of 45 MTF transgender individuals. However, all study subjects were treated with hormones and no female subjects were included.

Neurokinin B (NKB) is a potent regulator of GnRH secretion, which is essential for reproductive function. A postmortem brain study of 4 MTF transgender individuals by Taziaux et al (38) showed an infundibular NKB volume similar to control females. The feminization observed may have been explained either by medical estrogen therapy or lack of androgens due to orchectomy.

Prenatal Exposures

Dessens et al (39) reported that 3 prenatally anticonvulsant-exposed subjects were transgender individuals. For many years, researchers have been assessing the impact of prenatal exposure to the estrogenic anti-miscarriage drug DES (diethylstilbestrol) on development of gender dysphoria in affected offspring. While the vast majority of DES-exposed children have not developed transgender identity, a 5 year online study of DES-exposed sons by Kerlin et al reported at least 150 cases of moderate to severe gender dysphoria among 500 sons with confirmed or suspected prenatal DES exposure (40).

Conclusion

Current data suggest a biological etiology for transgender identity. Studies of DSD patients and neuroanatomical studies provide the strongest evidence for the organic basis of transgender identity. Sample sizes of the majority of studies to date on this subject are small, and conclusions must be interpreted with caution. Further research is required to assign specific biological mechanisms for gender identity.

Table 1. Evidence for a Biologic Basis of Gender Identity

Although no studies to date demonstrate mechanism, multiple studies demonstrate associations with gender identity that support it being a biological phenomenon. The table below organizes areas studied by type of study and lists the associations that have been made.

Studies showing rigid gender identity in patients with disorders of sexual development (DSD)

- Congenital, non-hormonal conditions
 - Penile ablation/agenesis, cloacal exstrophy

Studies showing that gender identity may be associated with prenatal hormone exposure in some (perhaps otherwise predisposed) individuals

- Congenital Adrenal Hyperplasia
 - Hormone deficiencies
 - 5 alpha-reductase-2,
 - 17-beta-hydroxy-steroid dehydrogenase-3

Studies with gender identity associated with neuroanatomical differences

- Grey Matter Studies
 - Bed nucleus of stria terminalis (BSTc)
 - Uncinate nucleus
 - Putamen volumes
 - Cortical thickness
 - Hypothalamic response to odorous steroids
 - White Matter Studies
 - Corpus callosum
 - Microstructure differences

Studies with gender identity associated with genetic factors and exposures

- Steroid Hormone Genetics Genes: CYP17, SRD5A2, ER β , androgen receptor
 - Sex Chromosome Aneuploidy Disomy-Y
 - Twin case studies

- Neuroproteins BDNF, NKB
- Prenatal exposures Anticonvulsants, DES

Legend:

CYP17: Cytochrome P-450 17 alpha gene

BDNF: Brain-derived neurotropic factor

SRD5A2: Steroid-5-alpha-reductase, alpha polypeptide 2 gene

NKB: Neurokinin B

ER_b: Estrogen receptor beta gene

DES: Diethylstilbestrol

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