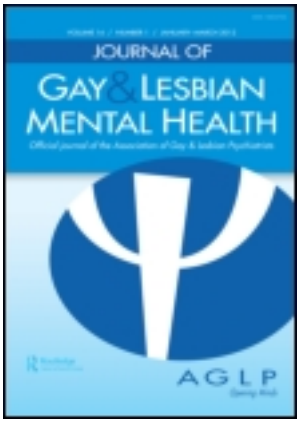

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Update on the Biology of Transgender Identity

Laura Erickson-Schroth MD MA [a]
[a] New York University, New York, New York, USA

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REVIEW ARTICLE

Update on the Biology of Transgender Identity

LAURA ERICKSON-SCHROTH, MD, MA
New York University, New York, New York, USA

Numerous studies have attempted to isolate biological factors in the development of transgender identities through research into genetics, prenatal hormone exposure, neuroanatomy, and cognitive processing. Genetic studies demonstrate that chromosomal variations are uncommon but may occur at higher rates than in the general population. Candidate genes have been investigated, with some positive results, though these have yet to be replicated. Investigations into the effects of hormone exposure on the developing fetus have focused on gender identity in intersex people, which is often unpredictable, and proxy markers for prenatal hormone exposure such as finger length ratio and birth order, which do not show clear trends in transgender groups. A few small neuroanatomical studies show distinctions in transgender people, but results are limited in their scope due to small sample sizes and confounding variables such as adult hormone exposure. Numerous studies demonstrate that male-to-female (MTF) transgender people have higher rates of left-handedness, but the theoretical basis for this difference is not well described. Accumulating evidence indicates that prenatal biology likely contributes to transgender identity, but that its role may be interactive, rather than deterministic.

KEYWORDS transgender, gender identity, biology, etiology, brain organization theory

INTRODUCTION

In recent years, we have witnessed increasing numbers of people identifying as transgender, a term used by those who see themselves as possessing a gender different from that which they were assigned at birth. A

Address correspondence to Laura Erickson-Schroth, MD, MA, 564 First Avenue, Apartment 14d, New York, NY 10016. E-mail: erickson.schroth@gmail.com

number of psychological and sociological theories address gender identity development (Kohlberg, 1966; Bem, 1981; Bussey & Bandura, 1999), though not specifically transgender identity development. The main target of biological research into transgender identity has been prenatal hormones and their organizing effects on the fetal brain (Cohen-Kettenis & Gooren, 1999; Diamond, 2006; GIRES et al., 2006; Gooren, 2006; Veale, Clarke, & Lomax, 2010a; Corsello et al., 2011; Meyer-Bahlburg, 2011; Bao & Swaab, 2011; Hines, 2010; Berenbaum & Beltz, 2011). Investigators have also begun to study earlier influences, such as genetic polymorphisms. This article gathers the biological studies of transgender identity to date and discusses the concepts important to a critical analysis of research on this topic.

Within psychiatry many transgender individuals are currently diagnosed as having Gender Dysphoria, a category of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*. Some providers view transgender identity as a normal variant, like homosexuality, while others consider it a mental disorder (Drescher, 2010). Many healthcare practitioners are adopting language that prioritizes the lived experiences and self-definitions of people with gender-variant identities in place of pathologizing terminology. Transgender people have varied experiences of their gender. They may or may not wish to take cross-gender hormones or have surgeries. They include people who identify as transsexual, an older term that usually refers to those who desire surgery, as well as genderqueer, a newer term for those who understand themselves as both or neither gender. Other terms include female-to-male (FTM) and male-to-female (MTF). The majority of the population, which is not transgender, is sometimes referred to as "cisgender." This newly created word, borrowed from classical Latin, is preferred over terms such as "biological," "genetic," or "natural," male or female, as these imply that gender identity is more real in nontransgender people than in transgender people.

When considering the research findings on culturally influenced phenomena such as gender identity and sexual orientation, it is important to evaluate not only the study methods but also the study aims and subject recruitment strategies (Byne, 1994; Erickson-Schroth, 2010). Many researchers come to this field after studying the biology of sex differences and therefore attempt to link gendered attitudes and behavior to biological processes. Other investigators are motivated to reduce the social stigma and isolation often faced by transgender people by demonstrating that the causes of transgender identity are not within an individual person's control. Either of these stances may overemphasize evidence that supports biological causes and minimize the impact of sociocultural factors. Despite scientists' best efforts at objective research, science that is closely linked to social issues is affected by its cultural surroundings, and results often reflect the dominant theories of the time (Jordan-Young, 2010).

Subject recruitment strategies are of utmost importance in studies of transgender identity. The term transgender describes a heterogeneous group

of people who identify in distinct ways. The majority of studies reviewed for this article involve research subjects who identify as transsexual, rather than transgender. This recruitment of subjects simplifies the participant pool but also limits its scope. In addition, a number of studies further subdivide transsexual participants, primarily MTFs, by sexual orientation, or recruit only those with a particular sexual orientation.

Groupings based on sexual orientation derive from a typology developed by Kurt Freund and Ray Blanchard, which has created significant controversy in the field (Blanchard, 1985; Lawrence, 2010; Veale, Clark, & Lomax, 2008; Dreger, 2008; Serano, 2008; Nuttbrock et al., 2011). The debate surrounding the legitimacy of dividing MTFs by sexual orientation revolves around the implied motivations of those categorized. In Blanchard's typology, MTFs are believed to fall into one of two categories: "autogynephilic," sexually attracted to females and desiring sex change due to the eroticism of imaging themselves as women, or "homosexual," sexually attracted to males and desiring sex change in order to appeal to men. Many transgender individuals take offense to their identities being described as motivated by their sexual orientation rather than their own sense of their gender identity. Of note is that researchers have not generally divided FTMs by sexual orientation. This brings up a number of questions about the types of sexuality researchers find compelling and the ways in which different groups of individuals find their sexualities under scrutiny. Without conclusive evidence that typology by sexual orientation reflects a real difference, or delineates the only two categories of MTF transsexual identity, recruiting study participants in this way creates a challenge to making inferences about the population as a whole. It also introduces the confounding factor of sexual orientation into biological studies of transgender identity development, as those studies that recruit transgender individuals with one particular sexual orientation may produce results related more to the individual's sexual orientation than gender identity. Unfortunately, given the broad scope of this review and limited space available, it is not possible to classify each study reviewed by whether sexual orientation was a factor in subject recruitment.

METHOD

A PubMed search was conducted for English language articles relevant to the topic and published between January 1, 1950, and May 15, 2012. The initial search terms included "transsexual," "transgender," and "gender identity" combined with "review," "brain," "biology," and "etiology." Subsequent searches included the term "gender identity" combined with "twin," "chromosome," "gene," "animal models," "intersex," "congenital adrenal hyperplasia," "5-alpha-reductase," "cloacal exstrophy," "androgen insensitivity," "micropenis," "polycystic ovary syndrome," "prenatal," "diethylstilbestrol," "finger

length," "birth order," "MRI," "handedness," and "spatial ability." The author also investigated works cited that were of interest in the articles returned by the search. Due to the relatively specific nature of the topic, multiple study designs were included in the review, including cohort studies, case control studies, surveys, case reports, and previous literature reviews.

GENETICS

A number of studies examine the effects of genetics on the development of transgender identity. These include twin studies and other family studies that capture heritability, as well as studies of gender identity in people with chromosomal variations and direct studies of genes related to sex hormones. Overall, genetic studies suggest a possible heritable component to aspects of gender identity, but no specific genes have been identified and the role of any genetic factor is uncertain (Ngun, Ghahramani, Sánchez, Bocklandt, & Vilain, 2011).

Family Studies

Recent studies suggest that family members of transgender people are more likely to be transgender, although the shared family environments make it difficult to disentangle genetic and environmental explanations, and the overwhelming majority of those with transgender siblings are cisgender. There are a number of case reports of family members concordant for transgender identity (Green, 2000b). In a recent large Internet-based survey, transgender and other gender-variant people reported significantly more gender-variant relatives than others (Veale, Clarke, & Lomax, 2010b). Another large study demonstrated an increase in the prevalence of transgender identity in siblings of transgender subjects and also showed a difference in concordance for MTFs versus FTMs, suggesting disparate mechanisms for the development of transgender identity in the two (Gómez-Gil et al., 2010). There is some recent thought that genomic imprinting, through X chromosome inactivation, may play a role in some cases of MTF identity, as a sample of MTFs had more maternal aunts than uncles, but the FTMs did not have a similar aunt to uncle ratio (Green & Keverne, 2000). The internet-based survey noted above did not find increased rates of maternal aunts to uncles in MTFs (Veale et al., 2010b).

Twin Studies

Multiple case reports show concordance in transgender identity between identical twins. However, there are similar numbers of reports of discordance

(Segal, 2006; Heylens et al., 2012). Coolidge, Thede, and Young (2002) conducted the only twin study that attempted to analyze the heritability of GID specifically and not simply gender-atypical behavior. Parents of 96 monozygotic and 61 dizygotic same-sex twin pairs provided information to assess the presence of GID in their children. Symptoms were clinically significant in 2.3% of the sample, with an estimated heritability of 0.62. While interesting, the study is quite limited. It was a small sample based on parental information, and it assessed gender identity in children and adolescents. Children diagnosed with GID do not invariably become transgender adults (Drummond, Bradley, Peterson-Badali, & Zucker, 2008; Green, 1985; Wallien & Cohen-Kettenis, 2008).

Chromosomal Variations

Like cisgender people, most transgender people have XX or XY chromosomes. Some intersex conditions appear to predispose people to gender dysphoria, but this is thought to be due to hormonal variations rather than direct effects of chromosomes (Gooren, 2006; Corsello et al., 2011; Bao & Swaab, 2011; Hines, 2010; Berenbaum & Beltz, 2011). Gender dysphoria is extremely rare in those raised female with Complete Androgen Insensitivity Syndrome (CAIS), a condition in which there are XY chromosomes but the body is unresponsive to androgens (T'Sjoen et al., 2011). Case reports have documented the existence of transgender individuals with a number of chromosomal variations, including XXY, XXXY, XYY, XXX, and mosaicism, but more systematic studies reveal that variations are uncommon. In the largest systematic study to date, which included 251 MTFs and 117 FTMs, 97.55% had the expected karyotypes based on the gender assigned to them at birth. Still, the 2.45% of transgender individuals with chromosomal variations was higher than the 0.53% found in large studies of the general population. In this study, MTFs had a higher rate (3.19%) of variations than FTMs (0.85%), although the difference was not significant given the sample size. The authors also reviewed similar studies by others and concluded that karyotyping provides limited information (Inoubli et al., 2011).

Candidate Genes

To date, no studies have conclusively linked genes to transgender identity. Recently, a number of research groups have investigated genes for hormones that are involved in prenatal sexual differentiation of the brain, including androgen, estrogen, and progesterone receptor genes as well as genes for aromatase and other enzymes. The positive findings were for differences in repeat length polymorphisms in the androgen and estrogen receptor genes, as well as a single nucleotide polymorphism in the CYP17 gene. Though statistically significant, these differences were small, and the findings are not

replicated in other studies (Henningsson et al., 2005; Hare et al., 2009; Ujike et al., 2009; Bentz et al., 2007; Bentz et al., 2008) (see Table 1). Together, genetic studies provide some support that genetic variations in hormones could play a role in shaping gender identity in some people.

HORMONE LEVELS

Early in the study of transgender identity, scientists speculated that adult hormones might differ between transgender and cisgender people. At the same time, researchers were also investigating adult hormone levels in homosexual men and women. Neither of these groups has shown any consistent differences in adult hormone levels from heterosexual cisgender people (Baba et al., 2007).

Testosterone level in FTMs remains the only current subject of research in adult hormone levels and gender identity. There is continued debate about whether this group has increased rates of Polycystic Ovary Syndrome (PCOS) and other hyperandrogenic conditions compared with cisgender women (Baba et al., 2007; Balen, Schachter, Montgomery, Reid, & Jacobs, 1993; Bosinski et al., 1997; Futterweit, Weiss, & Fagerstrom, 1986; Mueller et al., 2008; Pache & Fauser, 1993; Spinder, Spijkstra, Gooren, & Burger, 1989). The most comprehensive study to date showed no increased rate of PCOS, but a significant increase in androgen levels (Mueller et al., 2008) (see Table 2).

The target of the majority of current research relates to the effects of hormones on the developing fetus. Prenatal hormones are implicated in sex differences between cisgender people using the same models, and there remains considerable debate about the scientific evidence for what is termed brain organization theory (Cohen-Kettenis & Gooren, 1999; Diamond, 2006; GIRES et al., 2006; Gooren, 2006; Veale et al., 2010a; Corsello et al., 2011; Meyer-Bahlburg, 2011; Bao & Swaab, 2011; Hines, 2010; Berenbaum & Beltz, 2011; Jordan-Young, 2010).

In the first study of its kind, Phoenix, Goy, Gerall, and Young (1959) showed a change in the adult behavior of animals after prenatal administration of hormones. Female guinea pigs administered testosterone prenatally demonstrated more male-typical mounting behaviors. Multiple research groups went on to demonstrate that mating behaviors and tendency toward aggression or domination could be altered in other animals, including primates, with androgen administration prenatally (Diamond, 2006; Hines, 2011). Since then, a number of researchers have attempted to link prenatal androgens to transgender identity in humans. One of the main issues of contention is that transgender is an identity rather than a behavior, and as such it is historically and culturally bound, making it much more complicated than mating behavior in animals. Animals may act in particular ways that are typical of one sex or the other, but cannot convey a gender

TABLE 1 Direct Genetic Studies of Transgender Identity Grouped by Gene

Gene studied	Paper	Participants	P-Value	Findings
Androgen receptor	Henningsson et al. (2005)	29 MTFs, 229 cisgender men		No difference between MTFs and cisgender men.
	Hare et al. (2009)	112 MTFs, 258 cisgender men	0.04	**MTFs had longer CAG repeat lengths than cisgender men (243.2 vs. 245.1 base pairs).**
	Ujike et al. (2009)	74 MTFs, 168 FTMs, 106 cisgender men, 169 cisgender women		No differences between MTFs and cisgender men or FTMs and cisgender women.
Estrogen receptor beta	Henningsson et al. (2005)	29 MTFs, 229 cisgender men	0.03	**MTFs had longer CA repeat lengths than cisgender men (159.9 vs. 158.6 base pairs).**
	Hare et al. (2009)	112 MTFs, 258 cisgender men		No difference between MTFs and cisgender men.
	Ujike et al. (2009)	74 MTFs, 168 FTMs, 106 cisgender men, 169 cisgender women		No differences between MTFs and cisgender men or FTMs and cisgender women.
Aromatase (CYP19)	Henningsson et al. (2005)	29 MTFs, 229 cisgender men		No difference between MTFs and cisgender men.
	Hare et al. (2009)	112 MTFs, 258 cisgender men		No difference between MTFs and cisgender men.
	Ujike et al. (2009)	74 MTFs, 168 FTMs, 106 cisgender men, 169 cisgender women		No differences between MTFs and cisgender men or FTMs and cisgender women.
5-Alpha reductase	Bentz et al. (2007)	100 MTFs, 47 FTMs, 755 cisgender men, 915 cisgender women		No differences between MTFs and cisgender men or FTMs and cisgender women.
CYP17	Bentz et al. (2008)	104 MTFs, 49 FTMs, 756 cisgender men, 915 cisgender women	0.03 to 0.06, depending on genotype model	**Single nucleotide polymorphism (SNP) frequencies differed between FTMs (T allele 56%, C allele 44%) and cisgender women (T allele 69%, C allele 31%).** MTFs did not differ from cisgender men.
Estrogen receptor alpha	Ujike et al. (2009)	74 MTFs, 168 FTMs, 106 cisgender men, 169 cisgender women		No differences between MTFs and cisgender men or FTMs and cisgender women.
Progesterone receptor	Ujike et al. (2009)	74 MTFs, 168 FTMs, 106 cisgender men, 169 cisgender women		No differences between MTFs and cisgender men or FTMs and cisgender women.

Significant findings are in boldface.

TABLE 2 Polycystic Ovary Syndrome in FTMs

Paper	Participants	Prior Treatment	PCOS Criteria	Significance	Findings
Baba et al. (2007)	69 FTMs, no controls	No prior hormonal or surgical treatment	Rotterdam		58% of FTMs diagnosed with PCOS, 39.1% with hyperandrogenemia.
Balen et al. (1993)	16 FTMs, 1 cisgender identical twin	No prior hormonal treatment	Not named		47% of FTMs diagnosed with PCOS.
Bosinski et al. (1997)	12 FTMs, 15 cisgender women	No prior hormonal treatment	Not named		81.7% of FTMs and none of the cisgender women had oligomenorrhea or menstrual dysregularities. 56.2% of FTMs versus 13.3% of cisgender women had hirsutism. 83.3% of FTMs versus 33.3% of cisgender women had increased levels of at least one measured androgen. 8/9 FTMs who received ultrasounds had polycystic ovaries. Ultrasounds were not performed on cisgender women.
Futterweit et al. (1986)	40 FTMs, 30 cisgender women	No prior hormonal treatment, however 10/40 were evaluated endocrinologically after gonadectomy.	Definite diagnosis: multifollicular ovaries on laparotomy plus hirsutism or oligomenorrhea. Probable diagnosis: polycystic ovaries on ultrasound plus hirsutism or oligomenorrhea with increased testosterone or LH/FSH ratio		27.5% of FTMs with probable PCOS. No mention of whether PCOS was diagnosed in any of the cisgender women.

(*Continued on next page*)

TABLE 2 Polycystic Ovary Syndrome in FTMs (*Continued*)

Paper	Participants	Prior Treatment	PCOS Criteria	Significance	Findings
Mueller et al. (2008)	61 FTMs, 94 cisgender women	No prior hormonal treatment	Both Rotterdam and NIH	$p = 0.002$	44.3% of FTMs versus 20.2% of cisgender women had elevated androgen levels (significant difference). No increased rates of PCOS in FTMs.
Pache & Fauser (1993)	17 FTMs, no controls	No prior hormonal treatment	Not named		23.5% of FTMs likely had PCOS based on oligomenorrhea and serum androgen levels.
Spinder et al. (1989)	16 FTMs, 8 cisgender women	No prior hormonal treatment	Hirsutism or oligomenorrhea plus elevated testosterone or LH/FSH ratio		None of the FTMs met the criteria for PCOS.

National Institutes of Health (NIH) Criteria (1990): ALL of the following: (1) Irregular ovulation (2) Clinical or biochemical signs of androgen excess (3) Other causes are ruled out.
Rotterdam Criteria (2003): 2 out of 3 of the following: (1) Irregular or absent ovulation (2) Signs of androgen excess (3) Polycystic ovaries on ultrasound.

identity (Herbert, 2008). In addition, prenatal androgens are linked not only to gender identity but also to sexual orientation, though the two are different constructs (Corsello et al., 2011; Bao & Swaab, 2011). It is yet unclear how the prenatal hormone theory might apply differently to gender identity and sexual orientation, though feasible that the timing or amount of hormone exposure could play some role.

Gender Identity in Intersex People

Intersex people, or those with Disorders of Sex Development (DSDs), are born with anatomy that is not traditionally male or female. Two intersex syndromes of special interest in gender identity research are Congenital Adrenal Hyperplasia (CAH) and 5-Alpha Reductase Deficiency (5-ARD). In the relevant CAH syndrome, excess fetal androgens masculinize the genitalia of the XX female fetus. In Western countries, these children are typically raised as girls, though some who have extremely masculinized genitalia may be brought up as boys (Lee, Houk, & Husmann, 2010). The literature on sex-typed behaviors in CAH females is quite complex. Recent reviews demonstrate that they do not differ from other girls in spatial ability, verbal ability, language lateralization, handedness, or aggression, but may prefer "boy toys" as children and later have decreased sexual interest in men, lower marriage rates, and increased sexual fantasy about other women (Jordan-Young, 2010). These behaviors may be confounded by having distinct genitalia, receiving steroid treatments, and experiencing life as an intersex person. The vast majority of CAH females who are reared as females develop stable adult female identities (Jordan-Young, 2010), with a review showing that only 5.2% had "serious problems with their gender identity" (Dessens, Slijper, & Drop, 2005). In those reared male, usually because of severe genital masculinization, a larger number (12.1%) reported gender identity issues.

In 5-Alpha Reductase Deficiency the normal conversion of testosterone to dihydrotestosterone (DHT) is disrupted, decreasing the masculinization of genitalia in those with XY chromosomes. These children are often reared as girls, but at puberty may experience testicular descent, facial and body hair growth, deepening of the voice, and clitoral/phallic enlargement, leading them to appear more like men. A review of the literature indicates that 56–63% of those with 5-ARD reared as girls later changed their gender to male (Cohen-Kettenis, 2005). While the development of male gender identity could conceivably be related to prenatal hormone exposure, there are also a number of other possibilities (Corsello et al., 2011). In many societies, the male role provides considerable status that is not afforded the female role. There are also many places where living as a hirsute woman with a deep voice and enlarged clitoris could be extremely uncomfortable and shameful. In some locations, where 5-ARD is a well-known syndrome due to its frequency, families may be aware ahead of time that their child is likely

to experience a male typical puberty, and may adjust the child's upbringing accordingly. In two of the most studied locations, the Dominican Republic and New Guinea, there are specific words for people with 5-ARD, and in New Guinea they are considered a third sex (Herdt & Davidson, 1988; Imperato-McGinley, Peterson, Gautier, & Sturla, 1979). Among those raised female who later develop a male gender identity, there does not seem to be much literature on gender dysphoria in childhood. This could indicate that these children do not have trouble accepting a female gender role early on, but the absence of literature does not necessarily indicate the absence of the issue.

Despite efforts by some researchers to divide intersex conditions by syndrome and assist families in choosing a gender for their child based on empirical evidence (Diamond & Sigmundson, 1997; Diamond & Watson, 2004; Meyer-Bahlburg, 2005; Meyer-Bahlburg, Dolezal, Baker, Ehrhardt, & New, 2006), some reviews point out that, in general, gender of rearing is currently our best overall predictor of adult gender identity (Cohen-Kettenis, 2005; De Vries, Doreleijers, & Cohen-Kettenis, 2007). One major exception is in genetic males with presumed male typical prenatal hormone exposure who are reared as girls. Genetic males may be raised female for a variety of reasons, including penile agenesis, penile ablation, or cloacal exstrophy. It has been the view of many physicians that XY infants without the possibility of a functioning penis should be raised as girls due to the social stigma. A review indicates that in as many as half of published reports, those with these conditions who are raised female choose to change their gender by adulthood. This evidence suggests that prenatal hormones may play a part in adult gender identity, but that the social factors related to gender of rearing also seem to be very important, given that as many as half of the initial assignments as female are accepted (Meyer-Bahlburg, 2005; Reiner & Gearhart, 2004).

Environmental Exposures

Our environment is rife with chemicals and hormones, some of which we purposefully ingest in food or medications. Since the 1970s, scientists have investigated the effects of the synthetic estrogen Diethylstilbestrol (DES) on the developing fetus. In addition, there have been follow-up studies of other medications taken during pregnancy and their effects on the gender identity of the child. More recently, there has been increasing discussion about hormones in the environment, and the effects they may have on sex, gender, and sexual orientation.

DES was prescribed from the 1940s to 1970s to prevent miscarriages until it was found to be associated with vaginal and cervical cancer in female offspring. Since then, "DES daughters," women born to mothers who took DES during pregnancy, have been a closely followed group with their

own medical registries. Although an estrogen, DES is proposed to have brain masculinizing effects (Hines, 2011). Nonetheless, outcomes are mixed; studies of verbal and spatial ability in DES daughters do not yield positive results, reports of sex-typed behavior and sexual orientation studies are very mixed, and the only large-scale study showed no effect on sexual orientation (Jordan-Young, 2010; Titus-Ernstoff et al., 2003). There has been little research into the gender identity of DES daughters. This author is unaware of any published literature on gender change in this population. A few studies have compared DES daughters with controls on a sex role inventory, and found no significant differences in masculinity or femininity in the DES exposed group (Bekker, Van Heck, & Vingerhoets, 1996). In addition to DES, anti-epileptic medications taken during pregnancy have been investigated for their effects on the gender identity of the developing fetus due to their potential to cause changes in hormone levels. However, these medications have not been shown to increase the rate of transgender identity (Dessens et al., 1999).

Other chemicals of interest are "environmental estrogens" or "endocrine disrupters," which are present in many plastics and insecticides. Groups concerned over the presence of these chemicals have pointed out that there seem to be increasing numbers of intersex animals and people as well as transgender people (Dörner et al., 2001). A few small studies have investigated the effect of exposures on childhood play behavior (Swan et al., 2010; Vreugdenhil, Slijper, Mulder, & Weisglas-Kuperus, 2002). At present there is only correlational evidence for an effect of environmental estrogens on human gender identity, and many people believe that the increasing rates of transgender identity are instead a result of more open cultural stances toward gender variance.

PROXY MARKERS FOR PRENATAL HORMONE EXPOSURE

Finger Length Ratio

Finger length ratio is hypothesized to relate to prenatal hormone exposure. Cisgender men have been shown, on average, to have shorter index compared to ring fingers than cisgender women. This is termed the second-to-fourth digit ratio (2D:4D). However, there is considerable overlap between male and female ratios, so much so that this ratio cannot be used to predict sex in a study participant (Breedlove, 2010). There are also significant measurement problems, as there is no standard method of finger length evaluation.

Some researchers studying sexual orientation have found differences in finger length ratios between heterosexual and homosexual people (Grimbos, Dawood, Burriss, Zucker, & Puts, 2010). Among MTFs, two studies have demonstrated a feminized finger ratio compared with cisgender men,

although one of these was in the right hand only (Kraemer et al., 2009), and the other was in the right hand of right-handed people only (Schneider, Pickel, & Stalla, 2006). Another study showed no difference between MTFs and cisgender men (Wallien, Zucker, Steensma, & Cohen-Kettenis, 2008). In FTMs, the results have been even more mixed, with one study showing a more masculinized ratio (Wallien et al., 2008), another showing a more feminized ratio, but only in the right hands of right-handed people (Kraemer et al., 2009), and one demonstrating no difference compared with cisgender women (Schneider et al., 2006). A large Internet-based survey of self-measured finger length showed no significant differences in finger length ratio between MTFs and cisgender men or FTMs and cisgender women (Veale et al., 2010b). Some of the studies fail to find the expected difference between cisgender men and women, which is relied upon to indicate that a study has been conducted properly.

Fraternal Birth Order and Sibling Sex Ratio

In the wake of a series of studies on fraternal birth order and sibling sex ratio in gay men, researchers have conducted similar studies with MTFs. A hypothesis for the finding that gay men have more older brothers is that prior male pregnancies lead to maternal immunization against H-Y antigens or to protein-bound testosterone that diminish their effects. It has also been hypothesized that the social environment in certain cultures leads boys with older brothers to have more homosexual feelings (Blanchard, 2008).

Several studies have examined fraternal birth order and sibling sex ratio in MTFs with varying results. Two studies of gender variant male children and adolescents demonstrated high ratios of brothers to sisters compared with an estimate of the general population (Zucker et al., 1997; Schagen, Delemarre-van de Waal, Blanchard, & Cohen-Kettenis, 2012), but studies of adults have shown no differences in number of older brothers between MTFs and cisgender men (Veale et al., 2010b) or between MTFs and the expected population mean (Green, 2000a). In many of these studies, estimates of general population are used in place of controls, which can be limiting. In addition, each study uses a different method to count siblings (e.g., some include half-siblings, others do not), making it difficult to compare results.

Some researchers postulate that androphilia alone, and not gender variance, is influenced by fraternal birth order, a view that is supported by findings in studies of gay men (Blanchard, 2008). Studies comparing birth order in androphilic versus nonandrophilic MTFs seem to point toward a role for birth order in sexual orientation but not necessarily gender identity (Green, 2000a; Blanchard, Zucker, Cohen-Kettenis, Gooren, & Bailey, 1996; Blanchard & Sheridan, 1992; Gómez-Gil et al., 2011).

In contrast to studies of MTFs, results of studies of birth order and sibling sex ratio in FTMs have been extremely mixed, with no clear trend and no real theoretical basis (Schagen et al., 2012; Green, 2000a; Gómez-Gil et al., 2011; Zucker, Lightbody, Pecore, Bradley, & Blanchard, 1998).

Proxy markers for hormonal exposure, such as finger length ratio and fraternal birth order, are attractive to researchers because they are easily measured, but so far there are no clear trends in this research that would explain transgender identity. It is of interest that sexual orientation may also relate in some way to these markers.

NEUROANATOMY AND FUNCTIONAL IMAGING

Increasing numbers of studies have investigated possible differences in brain morphology between transgender and cisgender people using histological or structural imaging techniques. It is implicit (and sometimes explicit) in these studies that morphological differences, if they are discovered, are believed to be caused by differential prenatal hormone exposure (Zhou, Hofman, Gooren, & Swaab, 1995; Garcia-Falgueras, Ligtenberg, Kruijver, & Swaab, 2011).

A small number of histological studies conducted postmortem on transgender subjects have explored the size of various brain structures. The first of its kind focused on the neuronal volume of a sexually dimorphic area of the hypothalamus called the bed nucleus of the stria terminalis (BSTc). Two separate analyses of the same MTF subjects indicated that the neuronal number in this area of the brain was higher in men than women and that MTFs fit into the female group (Zhou et al., 1995; Kruijver et al., 2000). These studies had a small sample size of only six MTFs. All of the participants had been taking estrogen prior to their deaths, and five of the six had undergone orchiectomies and were taking anti-androgens. It was unclear at the time of the study whether their neuronal numbers were the result of prenatal differences or had been affected by taking exogenous hormones as adults. Indeed, in a follow-up study, it was shown that post-mortem histological volumes of the BSTc do not seem to be different between men and women until puberty at the earliest and are not statistically different until adulthood (Chung, De Vries, & Swaab, 2002), indicating that we are either programmed early on to diverge at a later time or that circulating hormones in puberty and adulthood affect this area of the brain.

In another study, the volume and number of neurons in the interstitial nucleus of the anterior hypothalamus nucleus 3 (INAH-3) in 11 MTFs was found to be similar to that of cisgender females. Most of the MTFs had taken estrogen before their deaths and the majority had also had orchiectomies (Garcia-Falgueras & Swaab, 2008). In addition, the same area of the brain was shown previously to have been sex-atypical in gay men (Byne et al.,

2001; LeVay, 1991), which introduces sexual orientation as a confounder. A few years later, the same group investigated a nearby area, INAH-1, and found that the MTFs in their study had neuronal numbers in that area that were between cisgender men and women (Garcia-Falgueras et al., 2011). Important to note is that there was considerable overlap between subjects in the histologic studies of INAH-1, INAH-3, and BSTc. In fact, the INAH-1 and INAH-3 studies used exactly the same MTF subjects, and these overlapped with all six MTF subjects in the BSTc study.

In addition to histologic studies, recent progress in structural imaging has led to the use of MRI and other modalities in research on possible neuroanatomical correlates of transgender identity. One group found that the volume of the putamen in MTFs was similar to cisgender women on MRI (Luders et al., 2009). Two groups have employed MRI to investigate the corpus callosum in transgender participants, with one finding no difference in the size of the corpus callosum of MTFs compared to cisgender men (Emory, Williams, Cole, Amparo, & Meyer, 1991), and another reporting that the shape seems to match the gender identity rather than the assigned sex of the participant (Yokota, Kawamura, & Kameya, 2005). Research into gender identity and the corpus callosum, however, is complicated by the fact that there is inconsistent data on the presence of morphological or size differences in this structure between cisgender men and women (Luders & Toga, 2010). The authors of a recent study that examined multiple areas of the brain in MTFs by MRI concluded that there was not sufficient evidence for feminization of the brain in this population (Savic & Arver, 2011).

Another set of researchers has employed diffusion tensor imaging (DTI) to measure white matter tracts in transgender participants. Rametti et al. (2010) reported that untreated FTMs showed more similarities to cisgender men than cisgender women. Hormone-treated FTMs grew even more similar to cisgender men (Rametti et al., 2012). In untreated MTFs, the same research group found that the white matter tracts appeared to fall "halfway between the pattern of male and female controls" (Rametti et al., 2011).

Functional imaging with transgender participants is still in early stages and its application has been varied. Using single-photon emission computed tomography (SPECT), Nawata et al. (2010) demonstrated an increase in blood flow in the left anterior cingulate cortex and right insula in FTMs compared with cisgender women. An fMRI study reported that MTFs showed similar cerebral activation patterns to cisgender women when shown erotic films (Gizewski et al., 2009).

In sum, studies of brain morphology and functional imaging in transgender versus cisgender subjects suggest there may be measurable differences. However, most of the studies have been small and there has been a considerable amount of overlap between subjects in the studies, which makes it difficult to draw conclusions from the present data. Imaging studies of

transgender populations are still in early stages, and pending replication of findings.

COGNITIVE PROCESSES

Recent studies have explored a number of areas of neurocognition in relation to gender identity. Developments in imaging have allowed researchers to visualize what they once could test only through psychological and motor skills exams. As with neuroanatomy, researchers have, for the most part, seen cognitive processes that may differ between genders as related to prenatal hormone exposure, although this causative view is hotly debated.

Cerebral Lateralization

Laterality of the brain describes a person's use of one or the other side of the brain to carry out cognitive or physical tasks. There is currently considerable debate about sex differences in lateralization, with some studies showing that men's brains are more strongly lateralized (i.e., processes are confined to one hemisphere rather than both), while other studies show no difference or demonstrate the opposite (Bourne & Maxwell, 2010).

Handedness, a person's dexterity with one hand versus the other, is one measure of laterality of the brain. Mechanisms leading to handedness remain unclear, but studies have tied left-handedness to genetics, prenatal hormone levels, and developmental instability. Increased prenatal androgens may increase left-handedness, which could explain why men are more likely to be left-handed than women (Green & Young, 2001). Due to these factors, it is difficult to predict the results of handedness in transgender people. Watson and Coren (1992) argued that MTFs would have a decreased propensity towards left-handedness if they had lower levels of prenatal androgens than cisgender men, but that their likelihood of left-handedness could increase if their transgender identity was linked to developmental instability. Numerous studies have shown higher rates of left-handedness in MTFs compared to cisgender men (Veale et al., 2010b; Green & Young, 2001; Watson & Coren, 1992; Govier, Diamond, Wolowiec, & Slade, 2010; Orlebeke, Boomsma, Gooren, Verschoor, & Vanden Bree, 1992; Slabbekoorn, van Goozen, Sanders, Gooren, & Cohen-Kettenis, 2000), indicating that MTF transgender identity likely does not result from uncomplicated changes in the prenatal hormonal milieu because a simple decrease in prenatal androgens would lead to a decreased incidence of left-handedness. Research has also assessed handedness in FTMs, and seems to show that, similarly to MTFs, they have increased rates of left-handedness (Veale et al., 2010b; Green & Young, 2001; Govier et al., 2010; Orlebeke et al., 1992; Slabbekoorn et al., 2000; Herman-Jeglinska, Duklo, & Grabowska, 1997).

Theories involving increased prenatal androgens as well as developmental instability both predict this outcome, so these results are not particularly helpful in narrowing down etiologies for FTM transgender identity.

Spatial Ability

Spatial ability, especially on mental rotation tests, is one of the most sexually dimorphic cognitive tasks that has been studied, with men on average scoring higher. Although average scores on mental rotation tasks differ between cisgender men and women, individual scores remain poor predictors of a person's gender because of significant overlap in abilities (Jordan-Young, 2010). In addition, while many scientists view spatial ability as biologically determined, studies have shown that mental rotation can be improved with training or with changes in expectations (Fine, 2010). One group demonstrated that playing action video games reduced the gender gap in mental rotation ability (Feng, Spence, & Pratt, 2007). Another found that cisgender women's scores matched those of men when they were primed to believe that women were better at the task than men (Moè, 2009).

Two groups of researchers have reported differences in spatial abilities between MTFs and cisgender men (La Torre, Gossman, & Piper, 1976; van Goozen, Slabbekoorn, Gooren, Sanders, & Cohen-Kettenis, 2002). However, the first was a very small study, and the second noted a linear relationship between aptitude on spatial tasks and the perceived masculinity of subjects, but differences between the groups were not statistically significant. In contrast to these findings, other studies have demonstrated no difference in spatial abilities between MTFs and cisgender men in hormone treated (Wisniewski, Prendeville, & Dobs, 2005) or untreated (Cohen-Kettenis, van Goozen, Doorn, & Gooren, 1998; Haraldsen, Opjordsmoen, Egeland, & Finset, 2003) populations. In general, FTMs have not been shown to differ in their spatial abilities from cisgender women (Cohen-Kettenis et al., 1998; Haraldsen et al., 2003).

Cognition remains an exciting field in the study of transgender identity, though at this time there is not conclusive evidence of cognitive differences. In addition, while the etiology of differences in cognitive styles is often implied to be prenatal hormone exposure, there are certainly other possibilities, including those in the social realm.

CONCLUSIONS

A review of the biological studies to date on the etiology of transgender identity hints that genetics and prenatal hormone exposure may play some role in transgender identity development, although a biological model does not appear to account for the entirety of transgender experience. As an

alternative, a biopsychosocial model such as the Biased-Interaction Theory (proposed by Diamond, 2006) may explain how biological features set the stage for subsequent psychosocial molding of gender identity.

Crucial to understanding the possible biological contributions to transgender identity is a critical stance toward the goals of the researchers as well as the evidence behind conclusions that have been drawn. Support for a brain organization theory of transgender identity and studies defending this theory often come from researchers who are also engaged in work that attributes biological causes to gendered behavior and attitudes amongst cisgender men and women. Because of the ability to manipulate hormone levels exogenously, animal studies of prenatal androgen administration are the most direct evidence available for brain organization theory. However, human gender identity and sexual orientation are complicated phenomena whose mechanisms cannot necessarily be inferred from animal models. In addition, brain organization theories for gender identity and sexual orientation have yet to be delineated, and are currently very similar. Finally, a recent explosion of individuals identifying as transgender or gender-variant demonstrates that transgender communities are diverse. There are likely many distinct reasons for each person to identify as transgender, a fact which mandates a biopsychosocial approach to this topic.

This article gathers significant research related to the biology of transgender identity. It is limited in scope by its use of a single database and study language (English), as well as its inclusion of heterogenous study designs without sufficient space to discuss the detailed merits and limitations of each study. However, it is the author's hope that creating a central resource for beginning research on this topic will provide a starting point for those interested in learning more, as well as propel forward scientific work that considers the many ways in which human beings organize their lives and identities.

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