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REVIEW

Biological studies of transgender identity: A critical review

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ABSTRACT

Introduction: There is increasing public and research interest in transgender people and communities. Coupled with this interest is a renewed pursuit of research into the possible biological origins of transgender identity. In this review, we critically examine the biological literature which explores the etiology of transgender identity, including endocrinological, behavioral, genetic, and neuroimaging studies, with the goal of identifying key trends in this literature, limitations, critical gaps, and future directions.
Methods: We searched the Pubmed database for peer reviewed original experimental research conducted since 1990, using a combination of six transgender identity-related search terms and 18 topic search terms.
Results: A total of 102 articles across the disciplines of endocrinology, genetics, cognitive function, and neuroanatomy met our review criteria. Most studies were conducted at gender identity clinics. Several approaches yielded compelling results, but where replication has been attempted, results have varied. We identified several issues in experimental design and/or interpretation that might account for this inconsistency.
Conclusion: A number of research studies have investigated biological factors that could potentially contribute to transgender identity, but results often contradict each other. Interpretation of etiological studies of transgender identity can be misunderstood and/or misused by media, politicians, and care providers, placing transgender people at risk. We question the utility of etiological studies in clinical care, given that transgender identity is not pathological. When etiological studies are undertaken, we recommend new, inclusive designs for a rigorous and compassionate approach to scientific practice in the service of transgender communities and the providers who serve them.

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Introduction

In the last decade, it has become increasingly common to see headlines in social and traditional media in which transgender identity plays a

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prominent role, most notably in the context of transgender rights and access to public facilities, employment, sports teams, and healthcare. Underlying these discussions are assumptions about the etiology of transgender identity. The purpose of this article is to provide an overview of how scientists approach the study of the biology of gender identity and to critically review current research. Our hope is to facilitate scientific literacy, so that readers can evaluate findings for themselves and contest representations of scientific research in the media that are oversimplified and/or misleading. Facilitating critical thinking about scientific studies and/or their representation in the media is particularly important for those who might be inclined to use science to affirm whether they themselves, their child, or another loved one is transgender.

Many biological studies of transgender identity are designed to evaluate whether specific biological features ("biomarkers") can be used to distinguish transgender individuals, whose gender identities do not align with the expectations of their sex assigned at birth, from cisgender people, whose gender identities align with their sex assigned at birth. An underlying assumption of this approach is that gender identity will be reflected in a difference in performance on a task or test, or in measurement or function of a part of the body, typically assumed to be somewhere in the brain. Although the concept of biomarkers is not predicated on essentialism, nearly all studies of the bodies of transgender people presume that observable differences are attributable to an inborn biological factor. Almost none of these studies engage with psychosocial contexts that may also explain their findings. In this review, we will make the argument that this ideological blind spot has resulted in major methodological and interpretive flaws and biases within the biological research on transgender identity.

Implicit in the stated purpose of the search for any transgender biomarker is the idea that identification of biological difference between transgender and cisgender people lends legitimacy to transgender identity by locating it in the structure and function of the body. This assumption is, in turn, predicated on the idea that a transgender person insisting that they are transgender is insufficient evidence for legitimacy. The impulse to medicalize transgender people is consistent with a long tradition of such practices in science and medicine, not just for transgender people, but for other marginalized groups such as cisgender people of color, disabled people, and lesbian, gay, and bisexual people.

We begin this review with a brief historical overview of the terminology used to describe transgender individuals in scientific literature to place this research in a cultural context. We will then review three major areas of scientific inquiry into biological influences on transgender identity-endocrinology, genetics, and neurobiology.

Terminology

Terminology used to describe gender identity in biological research has a different history than that used in common parlance; a brief review of this history also reveals some of the assumptions made by scientists who investigate the origins of gender identity.

The term "transsexual" is an older designation, sometimes attributed to Magnus Hirschfield, a German sexologist in the early 1900s. It was popularized by Harry Benjamin, who used it to refer to individuals who had received or were seeking medical assistance to alter their bodies to align with their gender identity (Benjamin, 1966). Benjamin labeled as "true transsexuals" those whose identity and sexual orientation aligned with social expectations. Thus, the definition of "woman" included being androphilic, or attracted solely to men. As a result, any individual who was seeking to medically transition from male to female in this era needed to state that they were attracted to men to gain access to medical transition. The legacy of these early "gatekeeping" practices is that gender identity and sexual orientation were linked in a way that persists to this day in much of the literature we review in this article. It caused a generation of scientists to focus solely on heterosexual transgender individuals (Smith et al., 2015) and caused many transgender individuals to represent themselves in a way that would give them access to treatment, which makes it difficult to evaluate the veracity of information given by participants recruited from gender identity clinics (Cohen-Kettenis & Pfäfflin, 2010; Moser, 2010; Pauly, 1998).

The current generation of investigations into biological influences on the origin of transgender identity owes much of its foundational assumptions to the work of Ray Blanchard and colleagues at the Gender Identity Clinic in Toronto. In his now classic study, Blanchard interviewed 163 transgender women who were seeking approval for medical transition (Blanchard, 1985). Blanchard suggested that his subjects fell into two groups. One group recalled an awareness of their female identity in early childhood and an attraction solely to men, while the other indicated a more gradual development of gender dysphoria, prolonged episodes of cross-dressing, and an early orientation that was not exclusively toward men (e.g., an orientation toward women, toward both men and women, or asexuality). Blanchard additionally reported that individuals in the latter group typically were "autogynephilic," i.e., they experienced sexual arousal with the thought or image of themselves as women. Blanchard labeled these two groups "homosexual transsexuals" and "non-homosexual transsexuals," respectively, describing their sexual orientation relative to their sex assigned at birth.

Many now recognize a number of concerns with Blanchard's typology, including questions about the basis on which sexual orientation was determined and the problematic statistical approach used in the analyses (e.g. Baldinger-Melich et al., 2020; Veale, 2014). In addition, the labels used by Blanchard are now considered disrespectful and confusing since they reference the sexual orientation of a transgender individual relative to their sex assigned at birth rather than their gender identity. Including sexual orientation of participants in research related to gender identity could potentially be useful, but assuming this is the most important variable with which to divide groups or including only those participants with particular sexual orientations has no basis in science.

More recently, many scientists have shifted away from using the term transsexual, with a preference instead for "transgender," a term promoted by Virginia Prince (Stryker, 2017) to refer to those whose gender identity is not consistent with cultural expectations of their sex assigned at birth, regardless of their surgical status. Thus, in recent scientific research papers, participants are referred to as transgender (or trans) women (male-to-female, "MTFs") or transgender (or trans) men (female-to-male, "FTMs"). At the same time, men and women whose gender identity aligns with the social expectations of their sex assigned at birth are referred to as cisgender (or cis) men and women. In the last five to six years, a growing number of studies now include individuals whose identities do not fall within the "gender binary," meaning that they do not have either or only a masculine or feminine gender identity. These individuals use different terms to describe their identities, among them nonbinary, genderqueer, genderfluid, bigender, and agender (Matsuno & Budge, 2017; Beemyn & Rankin, 2011; Bornstein, 1998). Finally, the phrase "sex assigned at birth," e.g. assigned female or male at birth, ("AFAB" and "AMAB" respectively), is used to differentiate aspects of an individual's body when born from their identity.

Because of the changes in terminology over time, as well as differences across disciplines in how transgender people are referred to in the scientific literature, we opted to include a range of terms in our search strategy (see Methods).

Biological background: The sexual differentiation process

Most attempts to understand the development of gender identity rely heavily on the organizational-activational theory of mammalian sexual differentiation (Phoenix et al., 1959; Young et al., 1964; see review by Arnold, 2009). Under this theory, many sex differences such as external genitalia were originally presumed to be the result of the presence (XY, male) or absence (XX, female) of *in utero* exposure to testosterone or one of its metabolites. Sexual differentiation of the brain also follows this pattern; for example, female guinea pigs exposed to testosterone during brain development (e.g. Phoenix et al., 1959) and perinatally castrated male rats (e.g. Young et al., 1964) later exhibit sexual behavior more typical of the other sex as adults. Studies of the behavior of people who have had atypical patterns of *in utero* hormone exposure, such as in intersex conditions of congenital adrenal hyperplasia (CAH) or androgen insensitivity syndrome (AIS) have been used to support the extension of the organizational-activational theory to humans (for a review, see Hines et al., 2015).

Under the organizational-activational theory of mammalian sexual differentiation, the origin of the difference in the exposure of XX and XY developing fetuses to sex steroid hormones is assumed to be primarily the result of the action of a single gene on the Y chromosome, *SRY*, which signals the originally gender-neutral gonad to develop into testes capable of secreting androgens (Rosenfeld, 2017). In the absence of a signal from the *SRY* gene, the gonad develops into ovaries and is quiescent until the onset of puberty. Thus, an activated *SRY* gene results in the presence of testosterone (or, in some cases, one of its metabolites) during early development, permanently defeminizing development (preventing female-typical developmental pathways) and masculinizing (promoting male-typical) development. In the absence of *SRY*, and thus no exposure to steroid hormones, tissues are feminized.

The organizational-activational theory has been updated to include additional independent, non-hormonally based genetic effects on the process of sexual differentiation, the acknowledgement that the brain, itself, can synthesize hormones, and the understanding that maternal hormones can play a role, but the basic tenets of the original theory have remained an influential factor in studies of sex differences in behavior (Arnold, 2020).

Armed with this understanding and keeping the historical context and cultural assumptions of biologically based research of transgender people in mind, we conducted a literature review to identify common themes and findings of studies designed to assess for the biological origins of transgender identity.

Methods

A keyword search was conducted using the Pubmed database on February 5, 2021. Transgender-related search terms included transgender OR transsexual OR transexual OR gender identity OR gender nonconforming OR gender non-conforming. Topic search terms included gene OR genetic OR chromosome OR twin OR monozygotic OR digit ratio OR finger ratio OR mental rotation OR spatial rotation OR brain OR histology OR MRI OR fMRI OR DTI OR cortical thickness OR functional connectivity OR BOLD OR postmortem OR hypothalamus. Search was limited to peer reviewed original research articles published since 1990 with an experimental design (i.e., no reviews or case reports were included). We then reviewed identified abstracts to ensure they concerned the etiology of transgender identity.

Results

Our search returned a total of eight postmortem tissue studies, 49 neuroimaging studies, 22 genetic studies, 11 studies of digit ratio, and 12 studies of cognitive function meeting our criteria for review. Of note, the search terms "gender nonconforming" and "gender non-conforming" did not return any search results; gender non-conformity per se has not been examined in this literature.

Discussion

Proxy markers for prenatal androgen levels

Because prenatal hormone exposure plays a powerful role in the early sexual differentiation of the brain, it is an attractive starting point for many scientists seeking to explore the development of different gender and sexual identities. As the development of genitalia precedes that of the brain (Cowan, 1979), it has been proposed that female gender identity in XY individuals might be due to an absence or lower level of androgens during brain development and/or a lack of effective androgen receptors in the brain relative to that seen during genital development (Zhou et al., 1995). By similar logic, it is argued that individuals who are XX and have a male gender identity might have been exposed to atypical levels of androgens during brain development (Sadr et al., 2020). Together, these are referred to as the prenatal androgen hypothesis. It is difficult to test this hypothesis directly, both because measurement procedures might be damaging to a fetus and because the gender identity of the developing fetus will not be known for a number of years. Thus, scientists have developed proxy markers that can be assessed in adults, serving as representations of likely prenatal hormone exposure. To date, two noninvasive measures, digit ratio and mental rotation tests, have been used to test the possibility that transgender identity is linked to intrauterine hormone exposure.

Digit ratio

In 1875, Ecker first discovered that the ratio of the length of the index finger to that of the fourth finger differs between cisgender men and women. He found that, on average, females have a slightly higher 2:4 finger ratio than males (Ecker, 1875). Sex differences in this ratio are quite small, with significant in-group variation and between-group overlap; a large sample size and careful, consistent measurement are required to reveal these differences (Ribeiro et al., 2016; Voracek et al., 2007).

In 1998, Manning et al. suggested that the 2:4 ratio was correlated with prenatal androgen levels and, as such, might serve as an indirect measure of prenatal androgen exposure (Manning et al., 1998). This hypothesis was supported by a study which found a negative correlation between amniotic hormone levels and fetal digit ratio (Lutchmaya et al., 2004; but see Richards et al., 2020), and others which found a lower digit ratio in XX individuals with CAH, a condition which causes elevated levels of prenatal androgens (Brown et al., 2002; but see Richards et al., 2020). Part of the appeal of this hypothesis is its suggestion of a quantitative, rather than qualitative, marker of prenatal androgen exposure. However, others have called into question the utility of digit ratio in this context citing the lack of sensitivity of the measure (see below), the limited statistical approach used by many studies (Au Yeung & Tse, 2017), the lack of support by studies of androgen receptor variability (Voracek, 2014; Hampson & Sankar, 2012), and data suggesting that digit ratios may not reflect fetal testosterone (de Sanctis et al., 2017) and/or are an artifact of hand size (Lolli et al., 2017). Nonetheless, use of the measure continues, and hundreds of studies have been published in which digit ratio has been correlated with many behavioral traits (Leslie, 2019; Voracek & Loibl, 2009; Manning & Fink, 2008).

Several researchers have used digit ratio to explore the possibility that differences in prenatal androgen levels lead to transgender identity. The prenatal androgen hypothesis of gender identity development rests on the assumption either that digit ratio and the development of gender identity in the brain occur at the same time, a possibility that seems highly unlikely (Galis et al., 2010; Cowan, 1979), or that prenatal androgen levels shift in transgender individuals after the genitals form but before digit ratio is determined, and subsequently remain at this new level during development of gender identity.

Results of individual digit ratio studies in transgender people are inconclusive. The first such study found that transgender women had higher digit ratios that cisgender men, but only in right-handed individuals, and there was no difference between the digit ratios of transgender men and cisgender women (Schneider et al., 2006). Two other studies reported effects for trans women but not trans men (Sadr et al., 2020; Siegmann et al., 2020). Other studies found an effect for trans men, but not trans women (Leinung & Wu, 2017; Wallien et al., 2008), trans women but not trans men (Sadr et al., 2020), an effect for both trans men and trans women, but not in the predicted direction (Kraemer et al., 2010), no difference in finger ratio between groups (Veale et al., 2010). It is possible that these discrepancies in results are due to differences in measurement techniques across studies, differences in the criteria used to assign participants into gender identity groups, and/or the different racial composition of their participant base (Manning, 2017).

Three recent studies conducted meta-analyses of all studies of transgender identity and digit ratio to address mixed findings across studies (Sadr et al., 2020; Siegmann et al., 2020; Voracek et al., 2018). All note the small difference in digit ratios between groups and the relatively small number of transgender participants, and thus advocate for meta-analyses as the most powerful way to evaluate a relationship between digit ratio and gender identity. All report higher digit ratios in trans women than in cisgender men and no significant difference between digit ratios of transgender men and cisgender women, although one reported a non-significant difference in digit ratios of trans men (Sadr et al., 2020). The authors of one of the three meta-analyses conclude by discussing the limited scope of the data published thus far.

While the results of meta-analyses are of interest, there remain concerns about the ability of digit ratio to accurately reflect prenatal androgens, as well as general utility of this marker and its relationship to personality traits (Wong & Hines, 2016; Hines et al., 2015). In addition, the impact of factors such as race that have a demonstrated effect on digit ratio (Manning et al., 2007) are not controlled for in any study of digit ratio in transgender populations. This is a particular concern for studies of transgender individuals, since many studies collect data from gender clinic patients, who, due to race, socioeconomic status, and other factors, are more likely to be White (Galupo et al., 2016; Kuper et al., 2011; Puckett et al., 2021), whereas control populations from more general clinics or other sources, are less likely to be so.

Mental rotation tests

A second noninvasive approach employed to test the prenatal androgen hypothesis of gender identity is mental rotation tests. Mental rotation tests examine the ability of an individual to quickly identify two-dimensional representations of three-dimensional objects as being the same or different. They are the most robust cognitive tests that shows sex differences regardless of age and culture (Voyer & Bryden, 1990; Peters et al., 2006), but distributions of male and female test scores still overlap, making the predictive ability of these tests negligible. However, findings related to sex differences have not gone unchallenged. Terlecki and colleagues found that computer experience contributed to gender differences in spatial ability Terlecki & Newcombe, 2005; Terlecki et al., 2008), and Feng et al. demonstrated that playing action video games can decrease the gender gap in spatial ability (Feng et al., 2007). In addition, priming of subjects about their expected results based on gender prior to testing can have an impact on test results (Leiner et al., 2018).

Like digit ratio, spatial ability has been linked to prenatal androgens, a hypothesis supported by studies showing higher scores on mental rotation tests in girls with CAH (Karalexi et al., 2020; Hines et al., 2015; Puts et al., 2008). As a result, several studies have compared the performance on mental rotation tests of transgender and cisgender people to determine if hormone exposure plays a role in transgender identity. As in digit ratio research, there is no consensus among studies. Some authors report an effect of gender identity on test performance in participants who were not receiving hormone therapy (Van Goozen et al., 2002), but others do not (Cohen-Kettenis & Klink, 2015; Haraldsen et al., 2003; Schöning et al., 2010). This lack of consensus may be the result of methodological factors. In addition, it is noteworthy that in all these studies comparisons were performed according to sex assigned at birth. That is, transgender men were compared to cisgender women, and transgender women were compared to cisgender men. There were no comparisons between participants with the same gender identities (e.g., cisgender versus transgender men).

The prenatal androgen theory of gender identity development suggests that transgender identity is related to differences in hormonal exposure that lead to differences in cognition between transgender and cisgender people with the same sex assigned at birth. Research studies have failed to find a consistent influence of gender identity on the putative prenatal hormone proxy marker of mental rotation task performance. There are nuanced ways to view these results. First, it is important to remember that prenatal hormones are not the only possible influence on these tests. Individuals can be trained to enhance their spatial abilities, and it is likely that the early childhood experiences of most transgender individuals influenced their abilities consistent with the expectations of their sex assigned at birth. Thus, test scores could reflect early childhood education and toy access, rather than gender identity. Second, it is important to recognize that functionally, the brain is not a single entity; rather, different brain regions may have differing exposure or sensitivity to prenatal hormones (Joel et al., 2020; Smith et al., 2015). This possibility can be explored by studies of the genes controlling hormone receptor development and distribution in different parts of the brain.

Genetics

Information on a potential role for genetics in gender identity is limited, but family and twin studies indicate a possible hereditary contribution. In a 2011 study in Spain, researchers asked 995 trans people about gender identity in their families and found that 1/211 non-twin siblings were also transgender. This number was significantly higher than the documented rate of transgender identity in the population overall (Gómez-Gil et al., 2011). However, estimates of the proportion of transgender people in the public have been steadily increasing, likely due to improved survey techniques and the impact of a broader awareness of diversity, and thus possibility, in gender identities. In the United States, for example, recent studies show that 0.6% of people—higher than 1/200—identify as transgender (Flores et al., 2016), suggesting that the 1/211 rate found in the Spanish study may not actually differ much from the general population.

Twin studies also suggest a possible genetic contribution to gender identity. A 2012 review of the case report literature on gender identity in twins found that nine of 23 monozygotic twin pairs were concordant for transgender identity, while none of the 21 dizygotic twins of transgender people who shared a sex assigned at birth identified as transgender themselves (Heylens et al., 2012). In earlier research conducted by Coolidge et al., parents of 96 monozygotic and 61 dizygotic twins ages four to 17 rated their children on traits related to the diagnosis of Gender Identity Disorder, and estimated a heritability of 62% (Coolidge et al., 2002).

Because family and twin studies suggest that there are possible genetic components to gender identity, researchers have investigated the chromosomal makeup of transgender people. Chromosomal research has been largely unproductive, with most studies showing no differences compared with cisgender people assigned the same sex at birth (Fernández et al., 2018b; Auer et al., 2013; Inoubli et al., 2011). Some, but not all, studies suggest that there may be a higher frequency of Klinefelter syndrome (XXY chromosomes) in transgender women than in cisgender men (Fernández et al., 2018a).

Other studies have examined specific genes that might be linked to gender identity. Genes of interest have included those that code for hormone receptors and enzymes involved in hormone production pathways. However, so far there have been no replicated studies linking specific genes to gender identity. Studies of transgender women have yielded all negative results for differences in genes for estrogen receptor beta, progesterone receptors, and SOX9 (involved in embryonic sex development; Lombardo et al., 2013) and majority negative results for estrogen receptor alpha, androgen receptor (Fernández et al., 2018a; Hare et al., 2009), and

CYP19 (aromatase, which converts androgens to estrogens; Fernández et al., 2014; Sosa et al., 2004). Research with transgender men has yielded all negative results for differences in genes for androgen receptors, progesterone receptors, and CYP19 (Ujike et al., 2009), and conflicting results for estrogen receptors alpha and beta (Fernández et al., 2015). Researchers have also begun preliminary studies using whole genome sequencing, though these studies are still in their infancy.

There has been little attempt to explore or resolve the differences in findings among genetic studies of transgender identity. However, possible explanations for discrepancies in results include heterogeneity of samples and/or small sample sizes that are underpowered for the purpose of genetic studies. Furthermore, there is a broader conceptual issue of the large logical leap from a single gene variant to a complex social identity. Indeed, in the broader neuroscientific literature, there has been a move away from assessing single gene variants and their relationships to behavioral, cognitive or mental health differences. This is due to the problem of an approach that tries to equate complex social phenomena to a single gene mechanism, as well as the problem of attempting to find a gene associated with behavior in the absence of evidence for a biological mechanism linking a gene to behavior (Collins et al., 2012; Sanders et al., 2008; Cooper, 2001).

Studies of the brain

Neuroscientific studies of transgender people have included postmortem tissue studies and multimodal neuroimaging studies, including structural magnetic resonance imaging (MRI) studies of brain volume or cortical thickness, resting state and task-based functional MRI (fMRI), and diffusion tensor imaging (DTI). Many brain regions have been implicated in this literature; few findings have been replicated. The authors of these studies attribute their findings to altered exposure to hormones in utero. However, studies of adult human brains are not designed to assess the prenatal hormonal milieu and there is no direct evidence for this interpretation. As with much of human neuroscientific research, these studies are not designed to demonstrate causal effects, but instead show correlations between brain structure/function and transgender identity.

Postmortem studies

The first postmortem study of transgender people reported that the volume of the bed nucleus of the stria terminalis in transgender women was consistent with those of cisgender women (Zhou et al., 1995). The postmortem studies that have followed, all from Swaab and his associates, characterize hypothalamic structure and typically find receptor and cell type distributions in transgender women to be consistent with those of cisgender women (Taziaux et al., 2012; Taziaux et al., 2016; Garcia-Falgueras & Swaab, 2008; Kruijver et al., 2001; Kruijver et al., 2000). One study of cell count and volume in the hypothalamus found that transgender women had intermediate values between those of cisgender men and women (Garcia-Falgueras et al., 2011). Importantly, these studies are not designed to assess potential effects of cross gender hormone therapy.

Structural morphometry

The first magnetic resonance imaging (MRI) study of transgender people assessed corpus callosum volume, reporting a null finding (Emory et al., 1991). Since then, 11 studies have characterized regional brain volumes in transgender men and women (Matsuno & Budge, 2017; Mueller et al., 2017; Kim et al., 2016; Seiger et al., 2016; Hoekzema et al., 2015; Simon et al., 2013; Savic & Arver, 2011; Luders et al., 2009). Volumetric differences in nearly every brain region have been implicated, including many regions that are not known to be sexually dimorphic in cisgender people. Few findings have been replicated, and several regions (i.e., occipital and parietal cortices, insula, and cerebellum), show contradictory findings across studies that cannot be explained by hormone use.

Two brain regions, the caudate and putamen, are densely populated with sex steroid receptors (Giedd et al., 2012) and thus are of relevance to the prenatal androgen hypothesis. However, there is mixed evidence for differences between cisgender and transgender people in these areas (Matsuno & Budge, 2017; Mueller et al., 2017; Kim et al., 2016; Savic & Arver, 2011; Luders et al., 2009). One study found no differences in caudate volume when comparing transgender women to cisgender men and women and a smaller putamen in transgender women compared to both cisgender men and women (Savic & Arver, 2011). However, other studies found a larger putamen in transgender women relative to cisgender women (Flint et al., 2020; Khorashad et al., 2021); again, contradictory findings cannot be explained by hormone therapy. Two studies found that transgender men, regardless of testosterone use, had a larger caudate/putamen than cisgender women. However, this finding is not consistent with what would be expected based on the broader cisgender sex differences literature in this region (Lenroot et al., 2007) and is also not consistent with a more recent study (Khorashad et al., 2021).

Another area of interest in the study of gender identity is the precentral gyrus, the site of somatotopic representation of the body. Manzouri et al. reported that the volume of this region was similar between transgender men not taking testosterone and cisgender women (Manzouri et al., 2017) and others report smaller precentral gyrus volume in transgender men than in cisgender men (Khorashad et al., 2021). There is also evidence for volumetric differences in the precentral gyrus between transgender and cisgender women (Khorashad et al., 2021). The precentral gyrus is notable because studies using different imaging modalities have also highlighted this region (see functional MRI section).

Cortical thickness

Some studies of cortical thickness, though not all, have found differences between transgender and cisgender people (Khorashad et al., 2021). These findings have been distributed over most of the cortex, showing little regional specificity (Burke et al., 2018; Matsuno & Budge, 2017; Zubiaurre-Elorza et al., 2014; Zubiaurre-Elorza et al., 2013; Luders et al., 2009). Furthermore, studies have shown contradictory effects of testosterone therapy on prefrontal cortical thickness in transgender men, which may be due to differences in modeling total brain volume (Kilpatrick et al., 2019; Burke et al., 2018; Matsuno & Budge, 2017). A recent study identified differences between cisgender heterosexual men and women and transgender men and women in regions comprising the default mode network, which is thought to subserve self-referential processing (Zhou et al., 2020). However, when a cisgender gay and lesbian group was included in the analyses and sexual orientation was included as a covariate in the model, these findings were no longer significant, suggesting that previous cortical thickness findings could be related to sexual orientation (Manzouri & Savic, 2019), or, perhaps more likely, increased rates of depression and anxiety that occur in both cisgender gay and transgender communities that also impact the default mode network (Karstens et al., 2017; Ducharme et al., 2014).

Diffusion tensor imaging

Diffusion tensor imaging (DTI) is an MRI technique used to assess the integrity of brain white matter tracts. One DTI metric is fractional anisotropy (FA), an indirect measure of the number and size of axons, as well as their degree of myelination. Thus, FA is a measure of the integrity of brain structural connections (Beaulieu, 2002).

Some studies have found that the brains of transgender people have white matter microstructural properties intermediate to those of cisgender men and women (Kranz et al., 2014; Rametti, Carrillo, Gómez-Gil, Junque, Segovia et al., 2011; Rametti, Carrillo, Gómez-Gil, Junque, Zubiarre-Elorza et al., 2011; but see also Hahn et al., 2015; Manzouri & Savic, 2019). However, no specific regional findings have been replicated.

Of note, one DTI study found increased FA in the somatosensory cortex of transgender people relative to cisgender people, which, coupled with findings in other imaging modalities in this region, could indicate alterations in brain regions related to body self-perception among transgender people (Case et al., 2017). Future studies using dimensional assessment of dysphoria symptoms could help to elucidate the relationship between this region and its possible role in gender dysphoria.

Functional MRI (fMRI) studies

Most fMRI studies of transgender people employ cognitive tasks that show performance differences between cisgender men and women, such as verbal fluency (Soleman et al., 2013) and mental rotation tasks (Burke et al., 2016; Carrillo et al., 2010; Schöning et al., 2010). These findings are framed as affirming the prenatal androgen hypothesis as well as supporting biological sex differences in cognition between cisgender men and women. A longitudinal fMRI study designed to assess for the effects of hormone therapy on brain activity during a mental rotation task found that transgender boys showed reduced prefrontal activation relative to cisgender girls prior to initiation of testosterone therapy, and, following therapy, they showed patterns of task-related activation similar to cisgender boys (Burke et al., 2016). There is some evidence for blood oxygen level dependent (BOLD) signal consistent with gender identity during mental rotation tasks, although more longitudinal studies are needed (Burke et al., 2016; Carrillo et al., 2010; Schöning et al., 2010).

More recent fMRI studies using gendered faces, bodies, or voice stimuli have found that transgender people show reduced BOLD signal when perceiving stimuli associated with their sex assigned at birth (Fisher et al., 2020; Majid et al., 2020; Smith et al., 2018; Case et al., 2017). For example, cisgender people show greater activity in the somatosensory cortex than transgender people when viewing images of their own bodies, as well as greater activity in the medial prefrontal cortex, a region associated with self-referential processing, when viewing stimuli associated with their birth-assigned sex. Transgender people, in contrast, showed greater activity in this region when viewing bodies of their lived gender (Clemens et al., 2017). There is also evidence to suggest that BOLD signal in visual cortex during perception of gendered faces correlates with self-reported gender dysphoria among transgender women (Ku et al., 2013), suggesting that gender dysphoria may be related to the perception or salience of gendered stimuli. A study of embodiment among transgender men exposed participants to tactile stimulation to the chest and, as a control condition, the hand. Transgender men showed reduced somatosensory cortical activity during the chest condition relative to the hand condition, while a control group of cisgender women did not show this difference (Case et al., 2017). This indicates altered representation of a body part associated with gender dysphoria and is consistent with somatosensory cortex findings in the structural, resting state, and DTI literatures.

These studies are representative of the recent shift to a focus on the neural correlates of embodied processing and gender dysphoria, as opposed to the use of transgender people as case-controls for the study of cisgender sex differences. These studies generally confirm functional alterations in regions comprising the default mode network, such as the medial prefrontal cortex, as well as sensory cortices, consistent with the hypotheses that there are differences in regions associated with perceptual and self-referential processing. Importantly, these studies do not differentiate between transgender identity and gender dysphoria, which is distress associated with a mismatch between the body and/or gender role and sense of self. A critical future direction for this line of inquiry will be to assess for gender dysphoria as a continuous variable, as it is a more proximal marker of interoceptive function than transgender identity per se.

Resting state MRI (rsMRI) studies

Resting state MRI methods assess brain activity in the absence of a specific task and correlate the activity of regions across time to identify brain functional networks. The rsMRI literature has shown that transgender people have functional connectivity patterns that differ from cisgender people (Burke et al., 2018; Clemens et al., 2017; Mueller et al., 2016; Spies et al., 2016; Lin et al., 2014; Ku et al., 2013) with some exceptions (Nota, Burke et al., 2017a; Nota, Kreukels et al., 2017b). This, coupled with the somewhat consistent negative finding of a relationship with sex hormones (Nota, Burke et al., 2017a; Nota, Kreukels et al., 2017b; Mueller et al., 2016; Spies et al., 2016), could indicate that rsMRI findings are related to the experience of gender dysphoria, not gender identity. Indeed, more recent studies have used rsMRI to test hypotheses related to the neural correlates of body representation among transgender people. These studies have found altered network connectivity of brain regions related to body sensation and self-monitoring (Uribe et al., 2020; Manzouri & Savic, 2019; Schneider et al., 2019; Burke et al., 2018; Spies et al., 2016; Lin et al., 2014). Two longitudinal studies found increases in resting state functional connectivity of these regions following initiation of hormone therapy (Burke et al., 2018; Clemens et al., 2017; Spies et al., 2016). We speculate that this could be related to normalization of internalized bodily representation following hormone therapy.

Most recently, three studies have used machine learning or support vector machine techniques to predict the gender of and categorize transgender people based on a training set of cisgender neuroimaging data (Baldinger-Melich et al., 2020; Flint et al., 2020; Clemens et al., 2020). These studies have concluded that transgender brains are intermediately sexed between those of cisgender men and women. The machine learning approach is predicated on the use of cisgender brains as a standard by which transgender people's brains must be compared. We caution against machine learning approaches designed to categorize social identities on the basis of a biological feature as they can run into similar issues as other research in this area, such as assuming that biological features can serve as a simple proxy for social and cultural identities. Other scholars have thoroughly critiqued the use of machine learning regarding race and ethnicity (Koenecke et al., 2020; Zou & Schiebinger, 2018).

Future directions

In this review, we have identified a number of issues with experimental design, analysis, and interpretation in studies of biological influences on the development of transgender identity which limit their utility and potentially misdirect their interpretation, potentially harming transgender individuals. Below, we review the issues we have identified and make specific recommendations for improvement. We make these recommendations both in hopes of affecting the practice of science as well as providing a context from which clinicians and members of the transgender community can view conclusions drawn by scientists and media reports of their work.

Future directions: Sample recruitment and selection

As biological research into transgender identity matures, researchers must use thoughtful recruitment strategies to achieve representative sampling. Most studies recruit participants from gender identity clinics as they begin seeking transition-related care. Those who receive care at gender clinics are not representative of transgender populations. Recruitment from gender clinics can result in samples with an underrepresentation of individuals who are nonbinary, who have less access to medical care, and people of color (Galupo et al., 2016; Puckett et al., 2021). Individuals from different races and cultures have different lived experiences which can challenge assumptions of studies based only on those with socioeconomic and cultural access to medical care (Galupo et al., 2016).

It is also possible that the information gathered in the recruitment process is inaccurate if recruitment is limited to gender identity clinics. For example, patients recruited at gender clinics may underreport mental health conditions to gain access to medical transition. Trauma, stress, and psychiatric illness are alarmingly high in transgender populations and inclusion and consideration of accurate mental health information is vital to representative community portrayal and to the well-being of the transgender community (James et al., 2016). A second concern is that clinic patients may also routinely state that they are heterosexual relative to their gender identity in order to align with cultural perceptions of masculine and feminine identities (Cohen-Kettenis & Pfäfflin, 2010; Moser, 2010; Pauly, 1998). All these issues could be addressed by using community-based recruitment strategies.

The selection of a suitable comparison group is also a challenge. Many studies of transgender people in the biological literature opt to compare transgender people to cisgender people with the same assigned sex at birth. One of the most striking examples of this tendency is in studies of cognitive function, where comparisons between groups with the same gender identity (e.g. cis men versus trans men) might provide useful insights. Comparing cisgender and transgender people with the same assigned sex is not sufficient to make inferences about transgender identity. Differences between transgender men and cisgender women could also be due to simple gender differences that exist between cisgender men and women. We recommend as best practice recruitment of a cisgender comparison sample that includes a group matched for sex assigned at birth and a group matched for gender identity. Furthermore, a cisgender sample matched for anxiety and depression diagnoses or symptoms may also be warranted to rule out confounds of psychiatric illness while still recruiting a representative transgender sample.

Future directions: Statistical concerns

Another methodological concern is the lack of rigorous statistical standards in much of the biological literature on transgender identity. For example, of the 49 neuroimaging papers we reviewed, 14 either report only uncorrected statistics or provide no information on correction for multiple comparisons. Because of the large number of statistical tests performed in neuroimaging analyses, this approach causes a significant risk of Type I error and is not consistent with the standards of modern neuroimaging research (Woo et al., 2014). This lack of rigorous statistical standards, coupled with small sample sizes, likely contributes to the lack of replications and even contradictory findings that plague most of this literature. By building trusting and equitable relationships with local transgender communities, researchers will be more likely to recruit appropriately powered samples.

Future directions: Interpretation of results

It is not possible to prove causation from observational studies that identify group differences or correlations. Findings that demonstrate differences between transgender and cisgender people may represent differences in the brains of people with and without, for example, depression, rather than signifying anything about gender identity. Indeed, many of the neuroimaging studies of transgender people implicate regions associated with anxiety and depression. Most of these studies either do not assess these conditions in their samples or exclude them. At best, this results in a nonrepresentative sample of transgender people; at worst, we have a sample of transgender people with a history of depression and anxiety who did not report it because they were recruited for participation in the study while attempting to access transition-related care. This tendency to overlook potential mediators of primary findings is also seen in studies involving cognitive tests and/or measurement of digit ratio. As discussed above, there is reason to call into question the utility of either of these measures in studies of identity. Regardless, a finding of, for example, a correlation between performance on spatial rotation tests and gender identity is often used to infer an innate difference in brain structure or function, when these differences might be due to shared psychosocial factors.

Clinical significance

Individuals who are seeking therapy and/or identity-related medical assistance for themselves or a child/minor often are exposed to scientific studies on transgender identity or (over)simplified and/or inaccurate representations of them by the media. For those untrained in critically evaluating scientific research, this experience can be especially powerful and potentially dangerous. Some might take author conclusions at face value and worry over whether results apply to them. Parents and guardians might read studies in search of a clear way to confirm or deny their child's transgender identity. Clinicians are also exposed to media representations of scientific studies, regardless of whether they can invest the time to critically review the literature themselves. It is therefore of critical importance that medical and mental health clinicians be aware of the issues that we have raised in this review, most notably the goals of the researchers, and limitations in study design and interpretation so that they might help allay the fears, concerns, and misunderstandings of their clients.

Limitations

Cultural understanding and discussion of transgender identity is rapidly evolving. In turn, terminology is rapidly evolving. We made every attempt in this review to locate and carefully evaluate every recently published scientific inquiry into the origins of transgender identity. Often this meant conducting parallel searches using the terms transgender and transsexual, reflecting differential terminology usage in strictly medical journals versus those that are broader in their readership. While we are confident that we have captured all relevant studies, we are also aware of the implicit limitation in literature reviews in a rapidly evolving field. We urge readers to consider the time frame in which this review was written and published. Similarly, we hope that subsequent reviews will be increasingly inclusive in their use of keywords and terminology.

Conclusions

Most research on transgender identity is designed and conducted by cisgender individuals and, as a result, is necessarily prone to implicit bias that influences recruitment, design, analysis, and interpretation of data. Inclusion of transgender people at all stages of research will address many of the challenges that we have identified that face this literature, while also reducing the disparity between community-based and medicalized understandings of transgender identity. Community inclusion in research is also essential for ethical reasons. In the interest of science and the community affected by its practice, we recommend that those invested in conducting research with transgender people review and enact the recently proposed best practices for community-based participatory research in transgender communities (Reisner et al., 2016; Veale et al., 2022).

Ethics statement

No institutional ethics review was required for this review paper. However, we adhered to the recommendations of Reisner et al. (2016) and Veale et al. (2022) in conducting this research.

Disclosure statement

The authors have no conflicts of interest to disclose.

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Data availability statement

The data on which we based this literature review can be found in the articles cited in the References section.

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