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The molecular mechanisms of sexual orientation and gender identity

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ABSTRACT

Differences between males and females are widely represented in nature. There are gender differences in phenotypes, personality traits, behaviors and interests, cognitive performance, and proneness to specific diseases. The most marked difference in humans is represented by sexual orientation and core gender identity, the origins of which are still controversial and far from being understood. Debates continue on whether sexual behavior and gender identity are a result of biological (nature) or cultural (nurture) factors, with biology possibly playing a major role. The main goal of this review is to summarize the studies available to date on the biological factors involved in the development of both sexual orientation and gender identity. A systematic search of published evidence was performed using Medline (from January 1948 to June 2017). Review of the relevant literature was based on authors' expertise. Indeed, different studies have documented the possible role and interaction of neuroanatomic, hormonal and genetic factors. The sexual dimorphic brain is considered the anatomical substrate of psychosexual development, on which genes and gonadal hormones may have a shaping effect. In particular, growing evidence shows that prenatal and pubertal sex hormones permanently affect human behavior. In addition, heritability studies have demonstrated a role of genetic components. However, a convincing candidate gene has not been identified. Future studies (e.i. genome wide studies) are needed to better clarify the complex interaction between genes, anatomy and hormonal influences on psychosexual development.

Contents

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1. Introduction

Differences between the two sexes are widely represented in nature. Even among humans, males and females differ in many aspects: biological phenotypes (Luders et al., 2009; Ngun et al., 2011), personality traits (Luders et al., 2009; Ngun et al., 2011; Collazzoni et al., 2017), behaviors and interests, cognitive performance and proneness to specific diseases (Berenbaum and Beltz, 2011). In the last few decades, science has focused on understanding the origins of such differences, in particular the specific influence and shaping role of genes, hormones, environment and/or socialization (Berenbaum and Beltz, 2011). Moreover, more than 50 years of empirical research have documented the sexual differentiation of the brain quite extensively, given that the existence of behavioral sex differences implies the existence of neural sex differences. However, various considerations have led to the challenging of the idea that sexual differences in behavior may depend on sexual differences within the brain. Indeed, there are some inconsistencies in literature regarding the sexual dimorphic brain areas. In addition, it is difficult to find a linear relationship between anatomy and behavior. Furthermore, sex differences in the brain may depend on life experiences (Hines, 2011a; Juraska, 1998; Maguire et al., 2006; Ming and Song, 2005). Finally, the popular view that there is a female and a male brain, mirroring the behavioral differences in the two sexes, does not have a solid scientific foundation. On the contrary, although consistent differences have been identified - including the size of the brain and of specific brain regions, the constellation of neurons, neurotransmitter content, number of receptors, etc (Cahill, 2006; Lenroot and Giedd, 2010; McCarthy et al., 2009; Sakuma, 2009). - the male and female brain are very similar. In addition, men and women present with a great variability in behavioral and psychological differences (Berenbaum and Beltz, 2016). In general, using the term “sexual dimorphic” is correct only regarding a few brain characteristics, while most do not overlap or have a minimal overlap between the two sexes (Cosgrove et al., 2007; Joel, 2011; Juraska, 1991; Koscik et al., 2009; Koscik et al., 2009; Lenroot and Giedd, 2010; McCarthy and Konkle, 2005). Moreover, the size of the brain differences is usually small (Feingold, 1994; Halpern, 1997; Hyde, 2005). Indeed, the traits that markedly differ between the two sexes are essentially two: sexual orientation and core gender identity.

2. Methods

The main methodology used in this review consisted of a careful analysis of literature focused on the role of studies available to date on the biological factors involved in the development of both sexual orientation and core gender identity. Therefore, we considered the main original studies and review articles regarding the neuroanatomical, genetic, and hormonal factors influencing sexual orientation and gender identity development. A computerized search was performed to identify all relevant studies in PubMed from January 1948 up to June 2017. The following search terms were used: (“sexual behavior“[MeSH Terms] OR (“sexual“[All Fields] AND “behavior“[All Fields]) OR “sexual behavior“[All Fields] OR (“sexual“[All Fields] AND “orientation“[All Fields]) OR “sexual orientation“[All Fields]) AND (“brain“[MeSH Terms] OR “brain“[All Fields]) AND (“genes“[MeSH Terms] OR “genes“[All Fields]) AND “hormones“[Pharmacological Action] OR “hormones“[MeSH Terms] OR “hormones“[All Fields]); (“gender identity“[MeSH Terms] OR (“gender“[All Fields] AND “identity“[All Fields]) OR “gender identity“[All Fields]) AND (“brain“[MeSH Terms] OR “brain“[All Fields]) AND (“genes“[MeSH Terms] OR “genes“[All Fields]) AND (“hormones“[Pharmacological Action] OR “hormones“[MeSH Terms] OR “hormones“[All Fields]). Each of these search terms produced a list of many significant studies that we selected on the basis of year of publication (older studies were excluded) in accordance with our aims and the clinical interest for the reader.

3. Sexual orientation

One of the most sexually differentiated traits in humans (with a very big effect size: sd = 6.0 to 6.7, Hines et al., 2004, 2011a), is the target of sexual arousal: the great majority of men are erotically attracted to women (i.e. gynephilic) and the great majority of women are attracted to men (i.e. androphilic) (Hines, 2011a; Hines et al., 2003, 2004; Meyer-Bahlburg et al., 2008). Sexual orientation *per se* is rather complex to study and its estimates vary depending on the method of assessment (Levant et al., 2009; Ngun et al., 2011; Meyer and Wilson, 2009; Moradi et al., 2009). Indeed, sexual orientation can be defined by sexual attraction, sexual behavior, and self-identification; therefore, results vary depending on the operationalization of sexual orientation (Berenbaum and Beltz, 2011; Savin-Williams, 2009). In addition, studying this topic may be limited by the difficulties in disclosing one's sexual orientation because of the fear of homophobic prejudice and possible internalized homophobia (Fisher et al., 2017). From the available data, approximately 3–6% of men and 1–4% of women report predominantly homosexual attractions (Diamond, 1993; Savin-Williams, 2009). According to Kinsey et al. findings, nearly half (46%) of the population reported engaging in both heterosexual and homosexual activities, or reacting to persons of both sexes, in the course of their adult lives (Kinsey et al., 1948). Thus, bisexual orientation could be considered almost as common as heterosexuality.

Sexual behavior is characterized by a variability in distribution between men and women. Indeed, in men the distribution is mostly bimodal: very few men show a similar sexual attraction to both sexes, whereas they are most frequently attracted to one sex or to the other. In contrast, compared to men, a smaller percentage of women is exclusively attracted to the same sex, but many more women than men report sexual fantasies towards both sexes (Ngun et al., 2011).

The origins of sexual orientation are still controversial and far from being well understood (Ngun et al., 2011). Debates continue on whether sexual behavior is a result of biological (nature) or cultural (nurture) factors, with biology possibly playing a major role (Jannini et al., 2010). Indeed, an impressive amount of empirical data suggests that biology is an important regulator of sexual orientation (Jannini et al., 2010; Swaab and Hofman, 1990; LeVay, 1991; Allen and Gorski, 1992; Ponseti et al., 2009; Kallmann, 1952; Bailey and Pillard, 1991; Hamer, 1999; Mustanski et al., 2005; Hu et al., 1995; Camperio Ciani et al., 2004; 2008, 2009; Iemmola and Camperio Ciani, 2009). In particular, according to several authors, sexual orientation is determined during early development, with the interaction of the gonadal hormones with the genetic background and the developing brain, and becomes evident during puberty, under the influence of sex hormones (Bao and Swaab, 2011; Hines, 2011a; Bailey and Zucker, 1995; Rivers, 2002; Balthazart, 2011; Reinisch et al., 2017). In addition, the inefficacy of reparative therapy in changing a person's sexual orientation is an important argument against the role of environment in its development (APA, 2000).

The main findings regarding the impact of specific factors on sexual orientation described below are summarized in Table 1.

Apart from the target of sexual arousal, gender differences have been reported also in mating tactics and in facial sexual preferences (Ciocca et al., 2014). Indeed, men give more importance to a mate's physical traits, whereas women give it to psychological attributions

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(Buss, 1999). In addition, despite having different targets of sexual orientation, heterosexual and homosexual males show similar mating tactics. In line, a recent study showed that facial preferences correlate with gender identity but not with sexual orientation (Ciocca et al., 2014). These findings support the theory that male homosexuality is the result of a specific change in sexual orientation that leaves other aspects of male sexual strategies unchanged (Ciocca et al., 2014).

3.1. Sexual orientation and the brain (neuroanatomic differences)

Both neuroanatomical and functional differences have been described in relation to sexual orientation variability. In particular, differences in relation to sexual orientation have been reported in three brain regions: i) the suprachiasmatic nucleus (SCN), which is larger in homosexual males as compared to heterosexual males and females (Swaab et al., 1997); ii) the anterior commissure, which is smaller in homosexual males than in heterosexual males and females (Allen and Gorski, 1992); and iii) the third interstitial nucleus of the anterior hypothalamus (INAH-3), which is smaller in homosexual males as compared to heterosexual ones and similar in size to heterosexual females (LeVay, 1991). Similarly, the ovine homolog of INAH-3 (the ovine sexually dimorphic nucleus, oSDN) is larger in female-attracted rams as compared to the male-attracted ones. In addition, oSDN is similar in size in homosexual rams and in female sheep (Ngun et al., 2011). Considering that in some mammals the differences of oSDN volume result from an early testosterone exposure, the differences in INAH-3 in humans may also be explained by variations in early testosterone exposure (Hines, 2011b; LeVay, 2011).

3.2. Sexual orientation and hormones

Historically, two different mechanisms of action of gonadal steroids on the brain and behavior have been described: organizational and activational (Cohen-Bendahan et al., 2005). Organizational effects occur during early development, in particular prenatally and neonatally, and are permanent (Cohen-Bendahan et al., 2005). Activational effects occur later in life and are associated with concurrent changes in circulating hormone levels (Cohen-Bendahan et al., 2005). The distinction between organizational and activational influences is not always clear. Indeed, research has highlighted a more complex interplay. For example, a recent study has shown a role of gonadal hormones in maintaining or increasing basic neuroanatomical differences between sexes in puberty and, maybe, later on (Raznahan et al., 2010). However, the organizational hypothesis continues to have considerable relevance in understanding sexual dimorphic traits, such as sexual orientation.

Evidence for organizational effects influencing sexual orientation come from different sources.

3.2.1. Animal models

Studies on animals, in particular rodents and ferrets, showed that an early hormonal milieu can influence partner preference and sexual behavior (Domínguez-Salazar et al., 2002; Stockman et al., 1985). In particular, male rats castrated at birth show a lower female partner preference, as compared to those not castrated during early life, indicating a possible role of testosterone in organizing a male-typical partner preference. However, there is strong evidence that, in rats, testosterone conversion into estradiol by the brain enzyme aromatase represents a pivotal step in sexual differentiation of the male brain (Naftolin et al., 1975). Indeed, in rats, estradiol seems to have a crucial role in organizing male sexual behavior. In addition, results from alpha-fetoprotein and aromatase-knockout (AFP-KO and Ar-KO) mice suggest a possible difference in the timing of estradiol actions (Bakker et al., 2004; Bakker, 2014). In particular, the defeminizing action of estradiol in males occurs prenatally and it is avoided in females by the protective role of AFP. On the other hand, the feminizing action of estradiol occurs in natal females when ovaries start their activity, and AFP have diminished.

3.2.2. Studies in clinical populations

Another analytical method to solve this dilemma is to observe clinical populations that have abnormal hormonal levels. The most studied condition is congenital adrenal hyperplasia (CAH), which exposes female fetuses to abnormally high levels of androgens. Several studies have reported a masculinized behavior, in particular more same-sex experience, and self-identification as homosexual than in the general population, suggesting the fundamental role of prenatal androgens (Hines et al., 2004; Fisher et al., 2016a,b). Although not all studies are consistent, this is mainly due to methodological issues. However, it is important to note that females with CAH do not offer a perfect model to study organizational effects on behavior. In fact, social response to masculinized genitalia may cause the behavioral changes (Cohen-Bendahan et al., 2005; Burri et al., 2011). Moreover, behavioral changes in CAH women may also be caused by high post-natal androgens (Cohen-Bendahan et al., 2005). Furthermore, the size of the difference in sexual orientation between women with and without CAH is moderate. In fact, even if women with CAH, as compared to their sisters or other typical women, have more frequently gynephilic sexual interest (i.e. arousal and fantasy towards women), the majority of them report an exclusively heterosexual orientation (Hines et al., 2004; Zucker et al., 1996). In summary, research on CAH supports a fundamental role of pre-natal androgens in influencing sexual orientation, although many inconsistencies have yet to be clarified.

Another clinical population providing a sort of “natural experiment” on the behavioral role of hormones is represented by complete androgen insensitivity syndrome (CAIS), which affects only 46, XY individuals (Cohen-Bendahan et al., 2005). In fact, if oestrogens are involved - as in rodents - in sexual differentiation of the male human brain, persons with CAIS should have typical male behavior, because, through the brain aromatase, their testosterone is indeed actively converted into oestrogens. In contrast, if the human brain is masculinized by androgens (instead of by the aromatized oestrogens), individuals with CAIS should have typical female behavior, because they do not have a functioning androgen receptor. Available evidence shows that CAIS individuals report stereotypical female sexual behavior, including heterosexual orientation (Hines et al., 2003; Wisniewski et al., 2000), supporting a major role of androgens in the development of typical male behavior.

3.2.3. Studies in typical populations

While hormonal manipulation in humans is unethical, studies on typical populations are performed both through direct measures of prenatal hormones, or through index that mirror the prenatal androgen level.

3.2.3.1. Direct measures. Where direct measures are concerned, the only method considered reliable is measuring hormonal levels within the amniotic fluid. However, results regarding associations between testosterone in amniotic fluid and childhood behavior was, until now, inconsistent, mainly due to methodological issues. Therefore, research in this field is promising and needs to be implemented (Cohen-Bendahan et al., 2005).

3.2.3.2. Indirect measures. Indirect measures of prenatal hormonal

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Table 1
The table summarizes the main findings regarding the impact of specific factors on sexual orientation and gender identity.

	Author	Study design	Sample	Main findings
Sexual orientation				
Brain	Swaab et al., 1997	Post mortem	n = 34	The suprachiasmatic nucleus (SCN) is larger in homosexual males as compared to heterosexual males and females.
	Allen and Gorski, 1992	Post mortem	N = 90	The anterior commissure is smaller in homosexual males than in heterosexual males and females.
	LeVay, 1991	Post mortem	N = 41	The third interstitial nucleus of the anterior hypothalamus (INAH-3) is smaller in homosexual males as compared to heterosexual ones and similar in size to heterosexual females.
Hormones	Domínguez-Salazar et al., 2002	Animal models (rats)	n = 33	Male rats neonatally treated with aromatase inhibitor (1,4,6-androstatriene-3,17-dione, AT) showed feminine sexual behaviors while manifesting a preference for a sexually active male over an estrous female.
	Meyer-Bahlburg et al., 2008	Case-control	N = 143	Women with Congenital adrenal hyperplasia (CAH), compared to typical women, more frequently have gynephilic sexual interests, supporting the role of pre-natal androgens in influencing human sexual orientation.
	Hines et al., 2003	Case-control	N = 22	Complete androgen insensitivity syndrome (CAIS) individuals report stereotypical female sexual behavior, including androphilic sexual orientation, supporting a major role of androgens in the development of typical male behavior.
	Kraemer et al., 2006	Case-control	N = 409	Homosexual women have a more masculine digit ratio (lower 2D:4D ratio) compared to heterosexual ones, suggesting a role of prenatal androgens in influencing sexual orientation in females. No differences were found between homosexual and heterosexual men.
	McFadden and Pasanen, 1998	Case-control	N = 237	The click-evoked otoacoustic emissions (OAE) are stronger in females than in males. OAE of homosexual and bisexual females were found to be intermediate to those of heterosexual females and heterosexual males. An explanation is that the auditory systems of homosexual and bisexual females, and the brain structures responsible for their sexual orientation, have been partially masculinized by exposure to high levels of androgens prenatally.
Genes	Camperio-Ciani et al, 2004	Case-control	N = 198	Ascendant females in the maternal line of homosexual males were found to be significantly more fecund that the ones in the maternal line of heterosexual males, solving the Darwinian paradox (genes of homosexuality should not survive or diffuse in a population as they promote non-reproductive behaviors).
	Camperio Ciani et al., 2009	Case-control	N = 239	As in the previous study on homosexuals (Camperio-Ciani et al, 2004), mothers of bisexuals show significantly higher fecundity, as do females in the maternal line (cumulated fecundity of mothers, maternal grandparents, and maternal aunts), compared to the corresponding relatives of heterosexual controls.
	Sanders et al., 2015	Genome-wide linkage scan	N = 908	Results support the existence of genes on pericentromeric chromosome 8 and chromosome Xq28, influencing development of male sexual orientation.
Immunology	Blanchard, 2017	Meta-analysis	N = 19.977	The fraternal birth order effect is the tendency for older brothers to increase the odds of homosexuality in later-born males. The present meta-analyses confirmed that fraternal birth order is the most broadly established factor influencing sexual orientation in men.
Core gender identity				
Brain[a]	Zhou et al., 1995	Post- mortem	N = 7	Bed nucleus of the stria terminalis (BSTc) is smaller and with lower somatostatin neurons in women and in MtF transsexuals than in non-transsexual men. In contrast, the only FtM studied, (biological female with a male gender identity) showed a BSTc with male characteristics.
	Garcia-Falgueras and Swaab, 2008	Post- mortem	N = 42	MtF transsexuals have a smaller INAH-3 and with a lower number of neurons than non-transsexual men.
Hormones	Burke et al., 2014a,b	Case-control	N = 47	Female-typical OAE has been reported in MtF transsexuals.
	Pasterski et al., 2015	Case-control	N = 153	Girls with CAH had more cross-gender responses than female controls on all three measures of cross-gender identification. Furthermore, parent report indicated that girls with CAH exhibited more cross-gender compared to girls without CAH and to boys with and without CAH. These data suggest that girls exposed to high concentrations of androgens prenatally are more likely to show cross-gender identification than controls.
	Meyer-Bahlburg et al., 2006.	Case-control	N = 145	Non-classical variant CAH women showed a few signs of gender shifts in the expected direction, simple virilizing (SV) women were intermediate, and salt wasting (SW) women most severely affected. In terms of gender identity, two SW women were gender-dysphoric, and a third had changed to male in adulthood. All others identified as women. Authors conclude that behavioral masculinization/de-feminization is pronounced in SW-CAH women, slight but still clearly demonstrable in SV women, and probable, but still in need of replication in NC women. This study supports the role of prenatal hormones in gender identity development.
Genes	Bentz et al., 2008	Case-control	N = 1822	An increased prevalence of the A2 allele of the CYP17 MspA1 polymorphism (which encodes the 17alpha-hydroxilase) has been reported in FtM subjects, but not in MtF ones.
	Fernández et al., 2015	Case-control	N = 628	A2 allele of CYP17 MspA1 polymorphism frequency was higher in the FtM than the female control and male control groups, or the MtF group. This FtM > MtF pattern reached statistical significance ($p = 0.041$), although allele frequencies were not gender specific in the general population ($p = 0.887$). This data confirm a sex-dependent allele distribution of the CYP17 MspA1 polymorphism in the transsexual population.
	Hare et al., 2009	Case-control	N = 370	A significant association was identified between MtF transsexualism and the androgen receptor (AR) allele, with transsexuals having longer AR repeat lengths than non-transsexual male control subjects. No associations for transsexualism were evident in repeat lengths for aromatase (CYP19) or oestrogen receptor beta (ERbeta) genes. This study provides evidence that male gender identity might be partly mediated through the androgen receptor.
	Henningsson et al., 2005	Case-control	N = 258	MtF transsexuals differed from controls with respect to the mean length of the ERbeta repeat polymorphism, but not with respect to the length of the other two studied polymorphisms. A significant partial effect for all three polymorphisms (a tetra nucleotide repeat polymorphism in the aromatase gene, CA repeat in the ERbeta gene and CAG repeats in the androgen receptor gene), as well as for the interaction between the AR and aromatase gene polymorphisms, on the risk of developing transsexualism was reported.

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Table 1 (*continued*)

Author	Study design	Sample	Main findings
Fernández et al., 2014b	Case-control	N = 915	No significant difference in allelic or genotypic distribution of the genes examined between MtFs and controls were found. Moreover, molecular findings presented no evidence of an association between the sex hormone-related genes (ERβ, AR, and CYP19A1) and MtF transsexualism.
Ujike et al., 2009	Case-control	N = 517	No significant differences in allelic or genotypic distribution of any gene examined were found between MtFs and control males or between FtMs and control females. Thus, this does not provide any evidence that genetic variants of sex hormone-related genes confer individual susceptibility to MtF or FtM transsexualism.

MtF = male to female transsexuals; FtM = female to male transsexuals; AR = androgen receptor; ER = estrogen receptor.

[a] Neuroimaging studies in transgender people are not included, as they have been addressed in the recent review by Kreukels and Guillamon (2016).

levels was more often employed in clinical research as a proxy on the role of hormones in sexual orientation and/or identity.

3.2.3.2.1. Twin studies. One interesting method is to consider co-twin sex as an indirect indicator of prenatal hormones. In fact, as observed in animal models (Even et al., 1992), it has been suggested that, also in humans, the female member of an opposite-sex twin pair may be exposed to higher levels of testosterone during prenatal development than is a female member of a same-sex twin pair (Miller, 1994; Resnick et al., 1993). Conversely, a male member of an opposite-sex twin may be exposed to lower levels of testosterone (Miller, 1994; Resnick et al., 1993). Therefore, the female member should be masculinized, while the male member should display more feminine traits. Results are mixed, with some evidence for female subjects and no evidence for the male ones. In particular, although these findings need to be replicated, females show a male pattern of tooth size, spontaneous otoacoustic emissions, lateralization, and spatial ability (Berenbaum et al., 2012; Cohen-Bendahan et al., 2005). However, it has to be considered that twins also share the same post-natal environment (McHale et al., 2001; Stoneman et al., 1986).

3.2.3.2.2. Biological markers. Different biological markers have been considered as an indirect indicator of prenatal hormones. Associations between these markers and sexually differentiated behaviors are interpreted as mirroring the influences of prenatal sex hormones on these behaviors. (Cohen-Bendahan et al., 2005).

(i) Finger ratio

In 1998, Manning et al. observed a sex difference in the ratio of the length of the index finger to that of the ring finger (2D:4D, Manning et al., 2007). In particular, the 2D:4D ratio is greater in females compared to males, also in childhood and in intrauterine life (Galis et al., 2010; Malas et al., 2006; Branas-Garza et al., 2013; Grimbos et al., 2010; Honekopp and Watson, 2010; Manning et al., 2000; Manning and Fink, 2011). Indeed, various evidence suggests that finger ratio is a possible marker of prenatal androgen levels, with low 2D:4D indicating high prenatal testosterone and low oestrogens, while high 2D:4D indicates low prenatal testosterone and high oestrogens (Manning et al., 1998). In line with this, analysis of samples from routine amniocentesis showed that a low 2D:4D ratio was associated with high fetal testosterone (FT) in relation to fetal estradiol (FE), and high values of 2D:4D with low FT and high FE (Lutchmaya et al., 2004). In addition, digit ratio correlates with the distribution of a common polymorphism of the androgen receptor (number of CAG repeat in the exon 1, Manning et al., 2004a,b). In particular, a low 2D:4D digit ratio (i.e. more masculine) was associated with a low number of CAG repeat, which indicates a high activation of androgen receptor (Manning et al., 2004a). Moreover, women with CAH showed a lower 2D:4D compared to healthy control females, supporting the role of androgens on finger ratio (Brown et al., 2002a; Honekopp and Watson, 2010, 2010; Okten et al., 2002; Rivas et al., 2014). Many other human behaviors displaying an apparent sex difference (such as aggressive behavior and risk taking) are correlated with digit ratio (Benderlioglu and Nelson, 2004; Götestam et al., 1992; Hampson, 1990; Schwerdtfeger et al., 2010). Furthermore, other syndromes, which are more represented in males, show an apparent relationship with finger ratio: ADHD symptoms (Martel et al., 2008; McFadden et al., 2005a,b; Stevenson et al., 2007), autism symptoms (De Bruin et al., 2009; Manning et al., 2001; Noipayak, 2009), disorders of eating behavior risk (Klump et al., 2006; Smith et al., 2009).

Since both human sexual orientation and finger ratio are associated with prenatal androgen levels, some studies have focused on the relationship between sexual orientation and finger ratio. Indeed, different Authors have reported a more masculine (lower) digit ratio in homosexual than in heterosexual women (Brown et al., 2002b; Hall and Love, 2003; Kraemer et al., 2006; McFadden and Shubel, 2002; McFadden et al., 2005a,b; Puts et al., 2004; Rahman and Wilson, 2003; Totorice, 2002; M. S. Wallien et al., 2008; Williams et al., 2000), suggesting a fundamental role of prenatal hormones in influencing sexual orientation in females. Furthermore, this relationship also suggests that the critical period for the development of sexual orientation and sexual differentiation in finger ratio overlap (between 6 and 9 weeks of gestation, Puts et al., 2008). These results have been recently confirmed in a meta-analysis (Grimbos et al., 2010). However, studies on homosexual male populations found inconsistent results. In fact, some do not find significant differences in finger ratio between homosexual and heterosexual men (e.g. Miller et al., 2008; Voracek et al., 2005; M.S. Wallien et al., 2008), whereas others found significantly higher (e.g. Hiraishi et al., 2012; Kangassalo et al., 2011; Manning et al., 2001) or lower 2D:4D ratios (e.g. Rahman, 2005; Rahman and Wilson, 2003; Robinson and Manning, 2000) in homosexual men compared to heterosexual ones. To explain this incongruence it has been suggested that a “ceiling effect” occurs: all men are exposed to a prenatal androgen stimulation enough to receive the maximum effect of androgens on sexual orientation (Breedlove, 2010).

However, it is important to note that the finger ratio is related to ethnicity, and also to latitude related environmental variables (Lippa, 2003; Manning et al., 2004b; Manning and Robinson, 2003).

(ii) otoacustic emission

It has been observed that the otoacustic emissions (weak sounds produced by the auditory transduction apparatus of the inner ear, OAEs) of newborn males are weaker than those of newborn females, and these sex differences persist throughout the lifespan. Moreover, homosexual women exhibit fewer and weaker OAEs than heterosexual ones, displaying a male shifted pattern (McFadden and Pasanen, 1998). In addition, bisexual women showed an intermediate figure between homosexual and heterosexual ones (McFadden and Pasanen, 1998; Breedlove, 2017). This finding suggests that bisexual and lesbian women are exposed to higher prenatal androgen levels than normal (McFadden, 2011). This hypothesis is supported also by animal studies using hormonal

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manipulation: OAEs are masculinized by prenatal exposure to androgens later on in gestation. However, no differences in OAEs have been found between heterosexual and non-heterosexual males.

In summary, some evidence supports a role of prenatal androgens in influencing human sexual orientation. However, it is clear that, during pregnancy, other unknown factors – most probably genetic and/or maternal – play a role in moderating androgen influences on sexual orientation.

3.3. Sexual orientation and genes

Homosexual behavior may also raise a *Darwinian paradox*: genes for homosexuality should not survive or diffuse in a population as they promote nonreproductive behaviors. However, various research has tried to offer a convincing solution to the possible paradox, providing evidence of an important genetic component in the development of sexual orientation (Mustanski et al., 2005; Camperio Ciani et al., 2008; 2009; 2004; 2012; Iemmola and Camperio Ciani, 2009; Hu et al., 1995; Sanders and Dawood, 2003).

Even though early research failed to find evidence for genetic factors influencing homosexuality (Rice et al., 1999; Mustanski et al., 2005), Camperio Ciani laboratory showed first in 2004 a genetic maternal effect influencing both sexual orientation in males and fecundity in females (Camperio-Ciani et al., 2004). Indeed, ascendant females in the maternal line (and not in the paternal one) of homosexual males were found to be significantly more fecund than the ones in the maternal line of heterosexual males (Camperio-Ciani et al., 2004). The ascendants of homosexuals generated in fact up to one-third more offspring than those of heterosexuals (Camperio-Ciani et al., 2004), balancing the fitness detrimental effect. The “maternal fertile female hypothesis” was then replicated several times across countries (Camperio Ciani et al., 2012; Camperio Ciani and Pellizzari, 2012; Iemmola and Camperio Ciani, 2009; Rahman et al., 2008), and confirmed in bisexual males (Camperio Ciani et al., 2009). In 2008, a seminal paper showed for the first time a sexually antagonistic genetic mechanism constituted of two polymorphisms (at least one in the X chromosome and the other in the autosomes), solving *de facto* the Darwinian paradox (Camperio Ciani et al., 2008). This result confirmed previous data suggesting the importance of the q28 region on the X chromosome (Hamer et al., 1993).

After several years, the mathematical prediction of Camperio Ciani (Camperio Ciani et al., 2008; Camperio Ciani et al., 2012) was empirically supported by a large population genome-wide association study by Sanders et al. (2015), confirming the signal in chromosome 8 and in the X chromosome. Recently, a few studies have emerged suggesting an epigenetic canalization effect as a possible way to influence homosexuality especially in lesbians (Rice et al., 2012, 2013). An additional important line of research, even if criticized by different authors (Camperio Ciani et al., 2016a; b), is the avuncularity and kin selection hypothesis for genetic maintenance of homosexuality by some Authors (VanderLaan and Vasey, 2011; Vasey and VanderLaan, 2007). In particular, an exceptional avuncular behavior was found in androphilic transgenders in Samoa that could help via kin selection the genetic maintenance of the homosexual trait.

3.4. Sexual orientation and immunology

Different studies have shown that older brothers increase the odds of homosexuality in later-born human males, whereas older sisters, younger brothers and sisters have no effect (Schwartz et al., 2010; Bailey and Zucker, 1995; Blanchard, 2001, 2008, 2012, 2017; Blanchard and Lippa, 2007;). This phenomenon, called the *birth order effect,* has been explained by a progressive maternal immune reaction (Blanchard, 2008). Indeed, this effect may be triggered when male fetal cells enter the maternal circulation (usually during childbirth of a male newborn). Thus, the mother's immune system recognizes these male-specific molecules as foreign and starts producing antibodies. The maternal anti-male antibodies may cross the placental barrier during a subsequent pregnancy and interfere with the brain differentiation (and sexual orientation) of a male fetus. The maternal immunization strength increases with each male fetus, leading to an increased probability of homosexuality with each older brother (Blanchard, 2008). Despite the fraternal birth order effect being the most broadly established causal factor in the entire research field of human homosexuality, the maternal immune hypothesis has no empirical support.

4. Core gender identity

Gender identity is defined as an inner sense of self as a female or a male or, occasionally, some categories different from male and female (APA, 2013). Usually, gender identity is congruent with the assigned sex and is stable throughout life (Wood and Eagly, 2002).

Core gender identity, together with sexual orientation, is the human trait with the largest sex difference: the vast majority of girls and women have a female self-identification, whereas the vast majority of boys and men have a male self-identification. However, some individuals (defined as *transgender*) persistently or transiently identify with a gender different from their natal sex. Only in some transgender people, the incongruence between the experienced or expressed gender and the assigned one leads to a significant psychological discomfort (APA, 2013; Fisher et al., 2013). This distress, called *Gender Dysphoria,* represents a dimensional phenomenon that can occur with different degrees of intensity, of which the most extreme form (i.e. *transsexualism*) is accompanied by a desire for social or somatic transition, aimed at aligning, as much as possible, the body with the gender identity (APA, 2013; Fisher et al., 2010, 2014, 2016a,b).

A theory of transsexualism's origin is based on the fact that the differentiation of the genitals takes place much earlier in development (i.e., in the first 2 months of pregnancy) than sexual differentiation of the brain (the second half of pregnancy). Thus, according to some Authors, these two processes may be influenced independently by different interaction among genes, sex hormones, and developing brain cells (Bao and Swaab, 2011; Fisher et al., 2016a,b).

The main findings regarding molecular mechanisms influencing core gender identity development described below are summarized in Table 1.

4.1. Core gender identity and the brain (neuroanatomic differences)

Many brain structural differences between males and females have been reported. For instance, total brain volume is larger in males than females. Moreover, in many regions, cortical thickness is greater in women (Luders et al., 2006). Furthermore, while the amygdala is larger in males, the hippocampus is larger in females (Goldstein et al., 2001). However, many of these findings have not been replicated; in addition, only very few brain sex differences have been linked to behavioral sex differences.

Post-mortem studies by Zhou et al. reported that, in humans, the central subdivision of the bed nucleus of the stria terminalis (BSTc) may be a potential biological marker for gender identity (Zhou et al., 1995). In fact, it is smaller and with low somatostatin neurons in women and in male-to-female transsexuals (biological male with a female gender identity, MtF) than in non-transsexual men (Zhou et al., 1995). In contrast, the only female-to-male transsexual studied (a biological female with a male gender

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identity, FtM) showed a BSTc with male characteristics. However, the interpretation of these findings is complicated by many factors. First, small sample size (six MtF and one FtM transsexuals); second, all the transsexuals studied underwent hormonal treatment; third, sex difference in BNSTc does not appear before puberty (Chung et al., 2002), while many transsexuals reported a cross gender identity since childhood. Therefore, it has been suggested that difference in BNSTc may be due to life experience (Hines, 2010) and/or to exogenous hormonal therapy (Lawrence, 2009). Another study reported that MtF transsexuals have a smaller INAH-3 than non-transsexual men and also the number of neurons contained in this nucleus was smaller (Garcia-Falgueras and Swaab, 2008).

Apart from post-mortem studies, brain structure in transsexual individuals has also been investigated *in vivo* trough magnetic resonance imaging (MRI). However, MRI studies have shown conflicting results, some reporting a grey matter volume in transsexuals in line with the gender identity, others in line with the natal sex (Hoekzema et al., 2015; Luders et al., 2009; Savic and Arver, 2011; Simon et al., 2013; Zubiaurre-Elorza et al., 2012). Studies examining white matter in both MtF and FtM transsexuals by diffusion tensor imaging have shown a matter microstructure pattern statistically different from the natal sex (i.e. demasculinized in androphilic MtF and masculinized in gynephilic FtM, Kranz et al., 2014; Rametti et al., 2011a, 2011b). In addition, differences in performance and regional brain activity during visuospatial and verbal fluency task have been reported, possibly reflecting the organizational and activational effects of sex hormones (Burke et al., 2016; Schöning et al., 2010). Also, a sex-atypical hypothalamic activation while smelling putative pheromones in MtF transsexual has been demonstrated (Berglund et al., 2008; Burke et al., 2014a,b).

In summary, the number of post-mortem and *in vivo* studies focused on the development of core gender identity is rather low and limited by the use of mixed samples. However, they provide some evidence for the role of prenatal organization of the brain in the development of transsexualism (Kreukels and Guillamon, 2016).

4.2. Core gender identity and hormones

The extent of the effect of prenatal hormones on gender identity development is still under debate (Ciocca et al., 2016).

The most interesting observation comes from clinical population studies. Indeed, research on the relationship between finger ratio and gender identity has produced inconsistent results (Hisasue et al., 2012; Kraemer et al., 2009; Wallien et al., 2008) and the use of digit ratio as a marker of prenatal androgens has been criticized (Hines, 2010). In addition, a more female-typical OAE has been reported in MtF transsexuals, supporting the idea that they have been exposed to lower amounts of androgen during early development in comparison to control boys (Burke et al., 2014a,b). However, the possible influence of sexual orientation was not taken into account by the authors. In summary, studies from typical populations focusing on the development of core gender identity suffer from different methodological limitations and did not show homogenous results.

More interesting observations come from girls with CAH. In fact, different studies have demonstrated that CAH women, compared to controls, report more cross-gender role behavior and patterns during childhood (Berembaum and Resnick, 1997; Ercan et al., 2013; Meyer-Bahlburg et al., 2006; Meyer-Bahlburg, 2013; Pasterski et al., 2015), with a preference for typically male toys (Berenbaum and Hines, 1992; Berembaum and Resnick, 1997; Berenbaum and Snyder, 1995; Dittmann et al., 1990; Jürgensen et al., 2012; Meyer-Bahlburg et al., 2006; Slijper, 1984) and playmates (Berenbaum and Snyder, 1995; Meyer-Bahlburg, 2013). However, even if there is strong evidence (40.9%) of more typical male behaviours (Ercan et al., 2013), the majority (95%) of 46,XX CAH patients were raised as females, developing a female gender identity later on. Indeed, only a few cases of gender dysphoria have been described, with some changes from female-to male gender (Gupta et al., 2006; Kuhnle and Bullinger, 1997; Meyer-Bahlburg et al., 1996; Warne et al., 2005). Although this rate far exceeds gender dysphoria in the general population (3% vs. 0.002–0.003% in CAH vs. female general population, respectively, APA, 2013), the absolute proportion is quite low and it cannot be predicted from genital virilisation (Arlt and Krone, 2007; Dessens et al., 2005). Accordingly, evidence from 46,XY individuals with high sex-typical androgen levels, reared as girls because of congenital or acquired genital defects (e.g. micropenis, cloacal exstrophy, accidental ablation penis), show a variability in gender identity, with some of them identifying as male and some as female (Berenbaum and Beltz, 2011). Thus, the social environment of these children may have had an influence, indicating that prenatal androgen exposure is not an exclusive determinant of gender identity development. Some clinical conditions also suggest a role of pubertal hormones in this regard. Indeed, a gender identity change from female to male during puberty has been reported in 56–63% of 5alfa-reductase deficiency subjects (Cohen-Kettenis, 2005), without any correlation with the degree of genitalia masculinization. This observation suggests a role for pubertal hormones in influencing gender identity; however, cultural or other environmental pressures (such as family) should also be considered. In addition, gender identity change is accompanied by bodily changes, particularly impressive in 5alfa-reductase deficiency subjects. Finally, two cases of CAIS with gender dysphoria have been reported, one of which led to a complete male gender reassignment. Also these report cases question the role of the androgen receptor pathway in the development of male gender identity (Kulshreshtha et al., 2009; T'Sjoen et al., 2011).

In summary, evidence from different disorders of sexual development indicate that core gender identity is only modestly affected by prenatal androgens and that also sex-typical pubertal hormones may have an influence (Berenbaum and Beltz, 2011).

4.3. Core gender identity and genes

Twins studies represent a good model to assess if a certain trait is heritable. In fact, if a trait is more concordant in monozygotic twins compared to dizygotic ones, this provides good evidence that the trait is heritable. Most of the available studies have reported a substantial heritability of gender-related traits within each sex. For example, Lippa and Hershberger (1999) showed a moderate to high measure of heritability of gender-related interests. Bailey and colleagues reported a heritability pattern for gender non-conformity during childhood in a large sample of adult twins (Bailey et al., 2000). However, recall bias should be considered as well. More recently, a small heritability for adult gender identity was demonstrated by different Authors who analyzed a sample of 4426 British female twins by using a non-validated scale (Burri et al., 2011). The only study focused on gender dysphoria diagnosis - instead of gender related traits - showed a strong heritable component (62% of the variance, Coolidge et al., 2002; APA, 2013). However, gender dysphoria symptoms were reported by mothers and thus might have affected the results of the study.

Some reported cases of more than one transsexual within the same family (Green, 2000), as well as of a few twin cases (Sadeghi and Fakhrai, 2000; Garden and Rothery, 1992; Hyde and Kenna, 1977; Segal, 2006) have also been described. Indeed, a recent literature review on case studies of twins showed a higher concordance for gender dysphoria in monozygotic twins than in

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dizygotic ones, suggesting a role for genetic factors in gender dysphoria development (Heylens et al., 2012). However, it should be considered that it was not possible in these cases to separate the genetic influences from the environmental ones (Ngun et al., 2011).

A number of candidate genes have also been studied for core gender identity. In particular, assuming the crucial role of sex hormones in brain sexual differentiation, sex hormone-related genes have been considered to be possibly implicated. If mutations in sex hormones-related genes may lead to disorders of sexual development (i.e. a misalignment between chromosomal, gonadal and phenotype sex), polymorphism in steroidogenic enzymes or in steroids receptors may have a less marked effect and be possibly involved in core gender identity development. In particular, an increased prevalence of the A2 allele of the CYP17 MspA1 polymorphism (which encodes the 17alpha-hydroxilase) has been reported in FtM transsexuals, but not in MtF ones (Bentz et al., 2008; Fernández et al., 2015). No associations were found in the gene polymorphism of the 5-alpha reductase in both MtF and FtM transsexuals (Bentz et al., 2007).

The androgen receptor has also been considered an attractive candidate gene to study, because a complete loss of function (i.e. CAIS) usually results in a female gender identity. In addition, a longer (CAG)nCAA-repeat polymorphism confers a less efficient functioning. Accordingly, an increased number of trinucleotide CAG repeats in the androgen receptor gene in MtF transsexuals has been reported (Hare et al., 2009; Henningsson et al., 2005). However, this result has not been replicated by different Authors (Fernández et al., 2014b; Ujike et al., 2009). Studies on polymorphism of the oestrogen receptor beta (ERb) and aromatase (CYP19A1) genes have also yielded conflicting results. In particular, Henningsson and colleagues found that the risk of developing MtF transsexualism was influenced by the polymorphisms in the aromatase gene and in the ERb gene. In addition, they observed that the contributions from these genes were much larger for subjects carrying relatively few CAG repeats in the androgen receptor gene, presumably leading to a more active androgen receptor (Henningsson et al., 2005). However, these results were not confirmed by more recent studies (Fernández et al., 2014b; Hare et al., 2009). Different Authors found a repeat number in ERb significantly higher in FtM individuals compared to controls. These data may suggest that a functioning ERb receptor is directly proportional to the size of the polymorphism, therefore a greater number of repeats implies greater transcription activation, possibly leading to an increase in defeminilization in natal females (Fernández et al., 2014a).

Overall, the significance of these genetics studies remains unclear and future studies (e.i. genome wide studies) are needed to better clarify the role of genetics in core gender identity development.

5. Conclusions

Differences between males and females are over-represented, of which the most marked in humans are represented by sexual orientation and core gender identity. Even if several research studies have documented the possible role (and interaction) of neuroanatomic, hormonal and genetic factors in their development, many questions remain and need to be addressed.

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