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COMMENTARY

Hormonal, Genetic, Immunological: An Array of Mechanisms but How Do They Interact, If at All?

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In their Target Article, Vanderlaan et al. (2022) clearly distinguish what they call "direct" versus "indirect" evidence in their review of biodevelopmental mechanisms influencing sexual orientation. Direct evidence includes studies measuring variables that are thought to influence sexual orientation such as fetal hormones, genes or maternal antibodies potentially affecting brain development. In contrast, indirect studies refer to biomarkers of developmental processes that provide circumstantial evidence for a differential biological influence during development leading to same-sex versus other-sex orientation.

This presentation rarely discusses the limitations of the supporting studies. It must be acknowledged that all studies that are reviewed, even those providing the so-called "direct" evidence are, in fact, only correlational in nature. Since deliberate manipulation of these processes is impossible for obvious ethical reasons in humans, only animal studies can provide true causal evidence for a role of biological factors in the determination of sexual orientation or as it is more often called sexual partner preference. Animal studies have, however, other limitations (Baum, 2006).

Sexual orientation is obviously controlled by the brain and the mechanisms affecting this orientation should thus affect brain development. VanderLaan et al. (2022) summarize the evidence supporting this assertion. Available data are far from conclusive, but they largely support the existence of differentiated mechanisms related to sexual orientation that, in turn, relate to basic endocrine or genetic developmental processes (Balthazart, 2020; Roselli, 2018). Similarly, cross-cultural studies in non-Western populations provide support for all types of biological influences (genetic, hormonal, and immunological) on sexual orientation even if there are major gaps in knowledge at this level (Bailey et al., 2016; Vanderlaan & Vasey, 2011).

Independence or Additivity?

Altogether, the first part in the review makes a strong case for the existence of biological factors that influence the development of sexual orientation whereas there is very little evidence that socialization (e.g., interactions with the parents, societal pressure, learning processes, etc.) plays a substantial role in the development of same-sex attraction. It is perfectly clear, however, that each of the mechanisms identified only explains a part of the variance in sexual orientation. For example, a precise estimation of the impact of the older brother effect indicates that between only 15 and 29 percent of homosexual males owe their orientation to this mechanism (Blanchard & Bogaert, 2004). The importance of testosterone's impact is less precisely defined but, in the best documented case (i.e., girls affected by congenital adrenal hyperplasia [CAH] resulting in exposure to an excess of androgens) only a maximum of 30% of the subjects develop same-sex attraction in adulthood (Hines, 2010, 2011; Meyer-Bahlburg et al., 2008; Money et al., 1984; Zucker et al., 1996). Similarly, the associations of genes with homosexuality, even if they are statistically significant, only explain a small percentage of the phenomenon. For example, Ganna et al. (2019) indicate that all linked genes combined explain a maximum of 25% of the variability with each individual gene explaining only a few percent of the variance.

This begs the very fundamental and rarely addressed question of whether the multiple biological mechanisms that have been identified so far interact in some way to influence sexual orientation. In other words, are the genetic, hormonal, and immune influences acting independently (Fig. 1A) or are they

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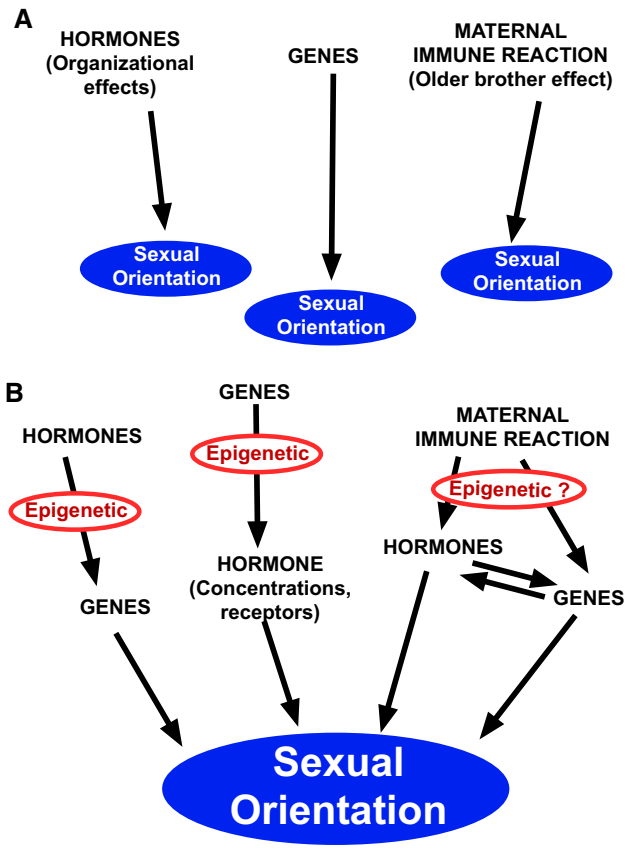

Fig. 1 Schematic representation of two ways through which 3 separate biodevelopmental processes could determine sexual orientation. Either hormonal, genetic or immune factors act independently in different sets of subjects to determine their orientation (**A**) or they interact to determine orientation by additive mechanisms (**B**)

additive (Fig. 1B) and only determine a given type of sexual orientation when acting together? This means that in the first case people displaying same-sex attraction owe their phenotype to different mechanisms (Swift-Gallant et al., 2019). Consequently, it should be possible to distinguish in these populations different sub-groups characterized by other aspects of their sex role or gender expression. In contrast, in the second case the different mechanisms combine their actions to determine the adult phenotype. Their phenotype should therefore be relatively more unitary since groups of subjects owe their orientation to the additive action of the same mechanisms. This question is far from being resolved and there is actually evidence pointing to both possibilities, although most of the recent data described in Vanderlaan et al. (2022) tend to support the first of these two options.

Arguments Suggesting Independence of Mechanisms

A number of studies have indeed identified heterogeneities within homosexual populations of each sex suggesting that these different subgroups may owe their sexual orientation to different mechanisms. Note, however, that the examples of heterogeneity often concern the indirect evidence, as defined by Vanderlaan et al. (2022) (see above), such as the ratio of the length of the second to the fourth finger (2D:4D) that is presumed to reflect the perinatal exposure to testosterone. It is reasonably well established that this ratio is masculinized in homosexual women, but this effect is observed more reliably in lesbians showing additional masculinized traits (i.e., "butch" lesbians) than in more feminine lesbians (i.e., "femme" lesbians; Brown et al., 2002b; Grimbos et al., 2010). The hypothesis is thus that "butch" lesbians owe their same-sex attraction to an early exposure to concentrations of testosterone that are higher than is typical for females, while the homosexuality of "femme" lesbians is due to another mechanism.

A similar distinction is made in modern Western culture between two types of gay men, one of which is either masculine or hyper-masculine (i.e., "bears") versus the other which displays more feminine traits (i.e., "twinks"; Blankenship, 2013; Hennen, 2005; Moskowitz et al., 2013). Somewhat similar sub-groups of same-sex attracted men exist in Mexico, more specifically among the Zapotec population in the Istmo region of Oaxaca, where more feminine male androphiles are identified as *muxe gunaa*, whereas more masculine male androphiles are labeled as *muxe nguiiu* (Gomez et al., 2017, 2018). With respect to hormonal mechanisms, the situation is, of course, the opposite of what is seen in lesbians. The more feminine androphilic males are assumed to have been exposed to less testosterone than is typical, whereas masculine androphilic males owe their same-sex attraction to another unidentified mechanism or possibly a paradoxical effect of the exposure to an excessive action of testosterone (Swift-Gallant, 2019). The 2D:4D ratio has been relatively widely recognized as being masculinized in butch lesbians, However, results in gay men are quite variable, sometimes showing a feminization, sometimes a hyper-masculinization and sometimes no effect at all (Breedlove, 2010, 2017). Balthazart and Court (2017) speculated previously that this variability might relate to the variable proportion of the two sub-groups of gay men in a sample. To date, no data set directly addresses this question largely because gay communities in North America, where much of this research is carried out, are resistant to the idea that some gay men behave in a feminine fashion (Bailey, 2003; Madon, 1997). Consequently, it has been very difficult to collect this type of data.

There are, however, recent data that relate to this question. Swift-Gallant et al. (2021) analyzed the 2D:4D ratio of gay men who were asked to identify their preferred anal

sex role (ASR) while engaging or fantasizing about sex. The options given were: top (insertive), bottom (receptive), versatile, or decline to answer. Quite interestingly, the 2D:4D ratio of the right hand was significantly different between tops and bottoms with the versatile group being intermediate. Bottoms had a larger, more female-typical 2D:4D ratio than tops suggesting a lower action of testosterone during early life. Obviously, this anal sex role categorization does not exactly overlap with the bear-twink distinction but it is of note that the self-identified tops were more gender conforming (displaying masculine characteristics) than the bottoms. It is therefore tempting to speculate that, like in women, these anal sex role categories reflect a differential early exposure to testosterone action: higher than average in tops/bears and lower than average in bottoms/twinks, even if these subcategories do not precisely overlap.

This suggests that testosterone has biphasic effects of sexual orientation. Although at first this may appear surprising, research in rodents actually supports this possibility (reviewed in Swift-Gallant, 2019). The established theory of sexual differentiation posits that exposure during development to substantial concentrations of androgens, or their estrogenic metabolites, promotes male-typical behaviors and male-typical sexual preference (gynephilia). In contrast, exposure to very low levels promote female-typical behaviors and androphilia (e.g., Bakker et al., 1993, 1996; Dela Cruz & Pereira, 2012; Henley et al., 2010; reviewed in Bailey et al., 2016; Balthazart, 2020; Roselli, 2018). However, several studies in mice have now demonstrated that injections of very large doses of androgens or genetic manipulations leading to the over-expression of androgen receptors alter sexual partner preference such that same-sex attraction is enhanced, while male-typical copulatory behavior is maintained (Swift-Gallant et al., 2016a, b; see Swift-Gallant, 2019 for a general review of this evidence). It would thus not be so surprising that similar nonlinear actions of testosterone are at work in humans (Bogaert & Hershberger, 1999; Skorska & Bogaert, 2017).

Other arguments reviewed in Vanderlaan et al. (2022) support the existence of sub-groups among homosexual populations. For example, the fraternal birth order effect seems to apply to gay men with a receptive (bottom) anal sex role, but not an insertive (top) one (Swift-Gallant et al., 2018; Wampold, 2018). In addition, the large genome wide association study of Ganna et al. (2019) revealed that genotypes that are associated with having had same-sex sexual behavior are not associated with markers of high prenatal androgen exposure such as the 2D:4D ratio or height. These data suggest that genetic and hormonal mechanisms do not overlap, while any possible overlap between genetics and the fraternal birth order effect have not yet been assessed. Rather, the existing evidence indirectly suggests that different markers of biodevelopmental processes apply to different subgroups of subjects and consequently that multiple mechanisms are acting largely orthogonally/independently to promote same-sex orientation (Fig. 1A).

Handedness, i.e., the propensity to use more or less exclusively the right or left hand is, of course, also controlled by the brain and develops mostly during prenatal life under various hormonal, genetic, and immunological influences (Lalumière et al., 2000). Handedness often differs between homosexual and heterosexual populations within both sexes, but the association with sexual orientation is not very stable so that in some studies a difference is observed while in others it is not. Since aspects of the developmental processes that control handedness remain unclear, it is difficult to use this information to separate sub-populations of same–sex people associated with the action of a given mechanism.

Arguments Suggesting Additivity of Mechanisms

The presence of heterogeneity (sub-groups) among same-sex populations does not exclude that multiple biodevelopmental mechanisms could simultaneously modulate to variable degrees the sexual orientation of specific groups of subjects. Indeed, a few data sets show that, when signs of action for a given developmental mechanism are present in specific homosexual populations, there can also be evidence that another mechanism has been active. This is, for example, the case for the fraternal birth order. This effect only applies to gay men who prefer a receptive role in anal sex (bottoms) but not to tops (Swift-Gallant et al., 2018; VanderLaan et al., 2022; Wampold, 2018) and bottoms have a feminized 2D:4D ratio as compared to tops (Swift-Gallant et al., 2021). This represents a putative additivity between the immunological disruption present in subjects born to mothers who previously had multiple sons and a below average early exposure to testosterone.

In addition, the increased rate of homosexuality in girls affected by CAH (Hines, 2010, 2011; Meyer-Bahlburg et al., 2008; Money et al., 1984; Zucker et al., 1996) represents an obvious interaction between genetic and endocrine mechanisms—a genetic mutation disrupts the synthesis of corticosteroids, which leads to increased androgen exposure, masculinized 2D:4D ratio, and same-sex attraction (Meyer-Bahlburg et al., 2008). Fernandez et al. (2018) constitutes another example of a genetic mechanism (a polymorphism) potentially leading to a change in steroid action resulting in same-sex attraction. More specifically, polymorphisms of the steroid receptors have been identified in transgender people who present in a gender non-conforming manner and who often express same-sex attraction (Fernandez et al., 2014a, b, 2018).

These examples demonstrate that the three types of biodevelopmental mechanisms that are thought to affect sexual orientation can potentially act in an additive manner within the same subjects (Fig. 1B) even if this mode of action is, at present, supported by fewer data than the independent mode of action. There is a substantial body of evidence in both animal models and humans suggesting that sexual differentiation is influenced by an interaction between mechanisms, albeit these interactions have not been tested specifically in the context of sexual orientation (in humans) or sexual partner preference (in animals). This research is reviewed briefly in the following sections.

Modifications of Hormonal Action Mediated by Genetic Mechanisms

Research accumulated over the past 60 + years in both animal models and humans has identified that multiple forms of interaction between genetic, hormonal, and immune processes are conceptually possible (see Fig. 1B). It is first obvious that the hormones that mediate sexual differentiation of brain and behavior (i.e., essentially testosterone and in some cases the estradiol derived by its aromatization in the brain) are produced by the testes. The development of the testes in mammals is determined by the *SRY* gene located on the Y chromosome (Capel, 1998; Goodfellow & Lowell-Badge, 1993). All subjects with an XY genotype will thus have the *SRY* gene that will be transcribed into the tdf protein (testis determining factor) inducing the development of the undifferentiated gonads into testes. During early fetal life, the testes start secreting large amounts of testosterone that masculinizes the brain and contributes to the expression of gynephilia (i.e., sexual attraction to females) in men.

Genetic mutations are present in XY human subjects that result in expression of an inactive androgen receptor, a condition called Complete Androgen Insensitivity Syndrome (CAIS). The unresponsiveness of the cell to androgenic hormones prevents masculinization of the genitalia and secondary sexual characteristics, so that a female phenotype develops that is associated with androphilia (male sexual attraction; Wisniewski et al., 2000). Conversely, in CAH, other mutations partially or completely impair glucocorticoid synthesis and result in fetal exposure to an excess of androgens in XX females. This condition correlates with an increased incidence of gynephilia in the affected women and masculinization of other behavioral traits such as toy preference and preference for more physical activities (Hines, 2011; Meyer-Bahlburg et al., 2008).

All these examples of genetic control over endocrine activity concern general action on global masculinization (or absence of masculinization) in the affected subjects and do not specifically relate to the control of sexual attraction. More subtle genetic effects might be present that would specifically affect sexual orientation via a change in the organizational action of hormones without affecting (or only partly affecting) other sexually differentiated traits. An early linkage genetic study had shown that male homosexuality is associated with markers located in the terminal region of the X chromosome called Xq28 (Hamer et al., 1993). This linkage was identified again in two other studies (Hu et al., 1995; Sanders & Dawood, 2003; Sanders et al., 2015). However, other studies including some genome wide association studies (GWAS) failed to confirm this link (Ganna et al., 2019; Mustanski et al., 2005; Rice et al., 1999), a failure that could potentially relate to methodological differences between studies (see Balthazart, 2020).

The specific genes in the Xq28 chromosomal region that relate to homosexuality have not been formally identified (see for discussion Sanders et al., 2015), but this chromosomal region contains the CNGA2 gene (cyclic nucleotide gated channel alpha 2) that is involved in mice in the control of odor-evoked sociosexual behaviors including odors related to the Major Histocompatibility Complex (MHC; Mandiyan et al., 2005; Spehr et al., 2006). This gene might be relevant to the control of sexual orientation since there is evidence that brain activation by sexual odors is different in homosexual and heterosexual human subject of both sexes (Berglund et al., 2006; Savic et al., 2005).

Another interesting gene located in this chromosomal region is the arginine-vasopressin receptor 2 (AVPR2). Given that vasopressin is playing a key role in the control of affiliative and sociosexual behavior (Balthazart & Young, 2014), the product of this gene might also influence the development of sexual orientation, although expression of AVPR2 appears to be limited in the brain.

Most importantly for the present topic, genes of the Melanoma-associated antigen (MAGE-A) family are also located in Xq28. MAGE-A11 is part of this family and known as a co-activator for the androgen-receptor. MAGE-A11 is overexpressed in human prostate cancer xenographs and in cell lines after androgen deprivation (up to 1500 fold) due to epigenetic mechanisms involving demethylation of a CpG island in the promoter region. This may explain the androgen hypersensitivity exhibited by individuals with prostate cancer exposed to androgen deprivation (Karpf et al., 2009). MAGE_11 is also expressed in various brain regions (olfactory bulbs, hypothalamus, amygdala, and prefrontal cortex; see: http://biogps.org/#goto=genereporti&d=4110). If a loss-of-function mutation or epigenetic modification were affecting its activity, this would provide a specific mechanism that could mediate changes in sexual orientation via a modulation of testosterone activity. In addition, the MAGE-11 gene is specific to primates (Liu et al., 2011) which might explain why exclusive same-sex preference is rarely observed

(see sheep studies for an exception: Roselli, 2018; Roselli et al., 2002) in species other than humans.

To our knowledge, four studies have also identified differences in the genetic structure of steroid receptors that are related to gender identity. A first study based on a small sample indicated the existence of a longer length of the ERβ repeat polymorphism in male-to-female (MtF) transgender subjects (Henningsson et al., 2005). A second study analyzing variations in the structure of the androgen receptor (AR), the estrogen receptor beta (ERβ) and the CYP19A1 gene or aromatase in a larger sample of MtF transgender subjects failed, however, to find genetic differences associated with gender identity in comparison with cisgender subjects (Fernandez et al., 2014a). Analysis of the same genes in female-to-male (FtM) transgender individuals found that transgender subjects differed from the cisgender controls in the median repeat length polymorphism (number of repeats higher in trans than in cis gender subjects) in the ERβ gene but there was no significant difference related to the other genes (Fernandez et al., 2014b). Negative results in these studies might have been the result of the limited sample size and more prominently heterogeneity in the sampled population with regard to age of gender dysphoria onset and sexual orientation. A more recent study concerned a large number of male and female early-onset transgender subjects that had expressed their gender non-conformity early in life. The FtM transgender subjects were, therefore, as usually observed for early onset, gynephiles, whereas the MtF transgender were androphiles (Fernandez et al., 2018). In both groups, multiple genetic modifications were observed in ERβ, ERα, and AR related with gender identity. In these cases, both gender identity and sexual orientation were atypical and thus it is difficult to determine if these genetic differences relate specifically to sexual orientation. These studies would also require replication before their conclusions can be fully accepted (see Lawrence & Zucker, 2014 for discussion).

Effects of Hormones on Gene Expression

Sex steroid hormones are potent modulators of gene expression in the context of sexual differentiation and this type of control could also represent a mechanism mediating the interaction between processes that determine sexual orientation. Many genes contain consensus sites in their promotor region that bind occupied androgen (AR) or estrogen (ER) receptors called the androgen or estrogen response elements (ARE and ERE). AR and ER also bind at other less specific sites on DNA (McEwen, 2001; O'Malley et al., 1969; Tsai & O'Malley, 1994). Binding of these receptors modulates (increases or decreases) the expression of the genes containing these consensus elements in an anatomically- and time-specific manner and can in this way affect brain development or activity. Expression of hundreds if not thousands of genes is regulated in this way during the sexual differentiation of the brain (McCarthy, 2008; Schwarz & McCarthy, 2008). These changes could obviously affect sexual orientation.

The last 20 years of research have identified an additional set of mechanisms that affect gene expression in a more or less permanent manner. Methylation of cytosines in the DNA or various chemical changes in the associated histones lead to a permanent repression or facilitation of the transcription of specific genes. These mechanisms globally grouped under the term of epigenetics play a key role in the process of sexual differentiation (McCarthy et al., 2009).

One study by Nugent et al. (2015) is of critical importance in this context. Experiments in rats and mice indicated that a major effect of testosterone on sexual differentiation in the preoptic area is to decrease the activity of DNA methytransferases. The experimental inhibition of the activity of these enzymes mimics the effects of testosterone in neonatal female rats and induces a masculinization of neuronal markers and sexual behavior. Thus, these data suggest that brain feminization requires ongoing suppression of the expression of "male" genes via their methylation. Testosterone inhibits the methyltransferases and promotes the masculinization of brain and behavior.

We do not know at this point whether sexual partner preference would also be affected by these changes in DNA methylation, but this is extremely likely even if the effect is not specific to sexual orientation. Nevertheless, it is very likely that epigenetic mechanisms play a key role in mediating steroid-induced changes in gene expression during the process of sexual differentiation, which in turn could impact sexual orientation.

Is the Older Brother Effect Interacting with Other Mechanisms?

The older brother effect has by and large been studied in isolation and its possible interaction with the genetic or endocrine mechanisms is essentially unknown. Given that it apparently results from the build-up of an immune reaction against the male offspring the mother is producing (Bogaert et al., 2018), interactions with genetic mechanisms are unlikely but hormonal mechanisms could be implicated. And indeed, as already mentioned, the older brother effect seems to apply only for "bottoms" who have a feminized 2D:4D ratio, suggesting lower action of testosterone during early life (Swift-Gallant et al., 2018, 2021; VanderLaan et al., 2022; Wampold, 2018).

What Is Missing? Future Direction of Work

As is obvious from this presentation and the review of Vanderlaan et al. (2022) many questions remain unanswered in the field. Vanderlaan et al. proposed a number of possible directions for future research and all of these suggestions are most welcome. We would like in addition to point again to the fact that all research in humans is by nature only correlational and can only acquire a causal value through comparison with results of animal studies.

Such studies are not numerous and when present they have been almost exclusively devoted to an investigation of hormonal mechanisms. This results in part from the fact that exclusive or nearly exclusive same-sex partner preference has not been, to this date, identified in any mammalian species, except for a sheep population from the western United States (Resko et al., 1999; Roselli et al., 2002). It has, however, been clearly established that modifications of the early endocrine environment affect the development of sexual partner preferences in male and female mice and rats (Bakker et al., 1996; Henley et al., 2009, 2010; Olvera-Hernandez et al., 2015). These data give credence to the human work showing modifications of sexual orientation in subjects affected by endocrine diseases that alter the early endocrine environment. However, in rodent studies, the partner preference is usually not affected in all subjects (30% in Olvera-Hernandez et al., 2015). Quite interestingly, one study published in abstract form only has also related the occurrence of same-sex sexual partner preference to the reproductive status of rat mothers. There was a marked increase in occurrence of same–sex preference in males that were born to multiparous (four previous pregnancies or more) as compared to nulliparous females (34 versus 4%; Hernandez & Fernandez-Guasti, 2019). These conditions might be used to investigate whether there are other differences between the offspring that show, or do not show, a male preference after early treatment with an aromatase inhibitor or after being born to multiparous females. Could they be differentiated based on aspects of their genotype? In general, investigations of the multiple phenotypes of sexual partner preference and of the underlying mechanisms would certainly be rewarding.

In addition, effects of early aromatase inhibition on sex partner preference have been shown to interact with the social rearing conditions and sexual experience (Olvera-Hernandez et al., 2019). In the same vein, it was shown that the perinatal effects of testosterone on sexual differentiation are mediated at least in part by an activation of the cyclooxygenase-2 (COX-2), the enzyme that catalyzes the synthesis of prostaglandin E2 (PGE2) (Amateau & McCarthy, 2004). In rats, pharmacological inhibition of this enzyme during late pregnancy produces male offspring that will show same-sex preference in adulthood (at 90 days of age), but only if they did not have sexual experience with receptive females prior to testing (Diaz-Estrada et al., 2020).

There are no convincing data to date demonstrating effects of the social rearing conditions on human sexual orientation, but work in M. Hines' laboratory has shown that the prenatal endocrine condition interferes with the effects of gendered information presented during childhood (Hines et al., 2016). Girls with CAH who were exposed to an excess of androgens during fetal development were repeatedly told or shown, via short video clips, that a given object or toy was for girls or for boys. Contrary to control girls, the CAH girls did not use this information later to select nor to state that they prefer a toy or object that had been presented as appropriate for their sex. Thus, prenatal testosterone seems to modify learning processes involved in acquisition of gendered behaviors or may alter the motivational salience of gendered information. Whether this effect extends to sexual orientation or depends on the sex of the individual remains, however, to be evaluated. Rodent studies showing interactions between perinatal endocrine conditions and post-natal social environment could suggest novel experimental paths to investigate why early testosterone action in humans only affects sexual orientation of a small fraction of the population.

Early testosterone action has an enduring effect on the digit length ratio in several animal species (Brown et al., 2002a; Howlett et al., 2015; Romano et al., 2005) and this marker could thus be used to explore interactions with genetics or possibly maternal immune responses. One could investigate whether this marker relates to the behavioral phenotype of the subjects including exclusive or non-exclusive same-sex preference, as well as, an insertive or receptive role preference during same-sex sexual interactions. It would also be very interesting to explore effects on sexual orientation of modulation by testosterone of DNA methylation, as identified in Nugent et al. (2015) study of the sexual differentiation of the preoptic area and sexual behavior in rats. A single study explored the possibility of epigenetic modifications associated with same-sex partner preference in sheep, where it was found that a fairly large number of genes were differentially methylated in male-oriented as compared to female-oriented rams (Bhattacharya et al., 2022). Unfortunately, RNASeq did not confirm differential transcription of any of the differentially methylated genes, but this study had a relatively low power and this question deserves further exploration.

Animal models obviously have their limitations. On the one hand, it is not always clear that the partner preference investigated in a rodent is strictly homologous to the sexual orientation measured in humans. On the other hand, gender identity cannot be ascertained in an animal: we cannot be sure this concept really exists and, if it does, it remains inaccessible due to the lack of verbal communication. Note, however, that in humans, gender identity is associated with the expression of a variety of sexually differentiated behaviors

and these traits could of course be investigated in animal species. Even keeping these limitations in mind, we would argue that, in addition to the future research tracks described in Vanderlaan et al. (2022), more attention should be paid to causal studies of the mechanisms inducing same-sex sexual partner preference in animals.

As a final and lighter comment, we would like to mention that although the expression "carving at its joints" has an interesting history and of course applies to the content of this paper, it is a bit abstruse and may deter some potential readers, especially if English is not their native language.

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