Published in final edited form as:

Arch Sex Behav. 2017 August ; 46(6): 1595–1600. doi:10.1007/s10508-017-0997-2.

Human Sexual Orientation: The Importance of Evidentiary Convergence

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The French radio “France Inter” announced in February 2017 that a manual will be distributed to French private schools claiming that “male homosexuality mainly results from a psychological development associated with the excessive or insufficient influence of the father or the mother during childhood; or from perversions of adults that have provoked a sexual attraction for the same sex, or a repulsion for the other sex” (<https://www.franceinter.fr/emissions/la-revue-de-presse-de-frederic-pommier/la-revue-de-presse-de-frederic-pommier-26-fevrier-2017>). News such as this is a constant reminder that it remains important to periodically restate the following: homosexuality is not a choice; rather, it is largely the result of biological factors acting mostly during prenatal life (Bailey et al., 2016; Ernulf, Innala, & Whitam, 1989) potentially interacting with various post-natal influences, both types of influences eventually varying between men and women (Diamond & Rosky, 2016). In this context, there were aspect of the Target Article by Breedlove (2017) that we found perplexing.

Breedlove presents a personal view of how he became convinced that biological factors, essentially sex steroid hormones, play a role in the development of sexual orientation in women, but not men. In doing so, he critically reviews some of the data that have been collected over the years to support this idea, but finds most of the data inconclusive with the exception of the masculinization in 2D:4D digit ratios, otoacoustic emissions, and auditory evoked potentials in women that suggest a hyper-androgenization of lesbians. He also indicates that data do not seem to support a mirror image role for testosterone in the control of male homosexuality (or androphilia) and suggests a possible explanation.

This article makes a number of important points but, for us, puts too much emphasis on the significance of 2D:4D digit ratios (as well as otoacoustic emissions and auditory evoked potentials). The idea of a prenatal biological control or modulation of sexual orientation is supported, in our opinion, for both men and women in light of the convergence of various other data sets. It also seems to us that Breedlove was a little too quick to dismiss various sources of evidence supporting a role for biological factors in the control of sexual orientation.

Explanations Rejected

We agree with Breedlove when he says that the John/Joan case did not conclusively demonstrate by itself a role of prenatal androgen on gender identity and sexual orientation because the penile destruction during circumcision had occurred only at 7 months of age and sex reassignment about a year later leaving room for socialization as a male (Colapinto, 2000; Diamond & Sigmundson, 1997). This case, however, has been an eye-opener for the world and has changed the way we think about gender identity and sexual orientation. Even if this boy underwent a relatively late sex reassignment into a girl, this case remains highly suggestive: it seems unlikely that the gendered socialization during the first year of life could have been more powerful than a later socialization until adulthood (see, however, Bradley, Oliver, Chernick, & Zucker, 1998).

Similarly, girls affected by congenital adrenal hyperplasia (CAH) do not conclusively demonstrate that female homosexuality is influenced by prenatal androgens. Alternative explanations can, and have, been presented for the increased incidence of homosexuality, or more precisely of non-exclusive heterosexuality, in this population (i.e., clitoral hypertrophy and other masculinizing effect on the genitalia, imperfect socialization as females, disturbance of socialization by the extensive interaction with medical doctors, etc.) and it is impossible to conclusively exclude these influences. But the fact that the incidence of homosexuality increases with the severity of the androgen exposure (Meyer-Bahlburg, Dolezal, Baker, & New, 2008) furnishes some support to the hormonal interpretation even if certain confounds remain (more severe masculinization of the genitalia with more extreme forms of CAH).

Finally, the smaller size of the sexually dimorphic nucleus, INAH3 (heterosexual males > heterosexual females), in the hypothalamus in gays as compared to heterosexual men (LeVay, 1991) does not prove in and of itself that the volume of this nucleus is based on prenatal testosterone and determines sexual orientation. We are facing here the classical chicken and egg problem. The brain is known to be plastic and the difference in INAH3 volume could be a consequence of some aspects of the lifestyle of gay men, rather than the cause of their orientation. This interpretation is, however, made unlikely by the facts that: (1) animal models exhibit similar sexually dimorphic nuclei of the preoptic area (Balthazart & Ball, 2007), which develop under the early influence of testosterone and are present before animals express sexual behavior (Roselli, Reddy, & Kaufman, 2011), and (2) morphological brain plasticity in response to environment or behavior is more prominent in the cortex (telencephalon) than in the hypothalamus where it mostly relates to changes in the hormonal milieu (Garcia-Segura, 2009; Pascual-Leone, Amedi, Fregni, & Merabet, 2005).

All this being said, the relevant data are admittedly associated with a large amount of individual variance. For example, only a fraction of CAH girls express attraction for women. Likewise, there is a substantial overlap in the volumes of INAH3 between homosexual and heterosexual men, even if a statistical difference exists between average values. Hormonal influences are, thus, not the only possible interpretation (for detailed discussion, see Balthazart, 2011).

We agree therefore that none of these studies is fully conclusive by itself. At best, individual experimental data suggest that a given biological factor influenced the sexual orientation of a fraction of individuals or explains a small fraction of the variance associated with sexual orientation. And even those limited conclusions could be denied and alternative explanations be presented. This is the case for every single type of data that has been produced to support the idea of a biological control of sexual orientation. When taken as whole, however, these data and others not reviewed in the target article become convincing for us; they provide convergent evidence which all points in the same direction (Bailey et al., 2016). In our opinion, no single study demonstrates a critical role of any biological factor on sexual orientation. The same is true for 2D:4D digit ratios.

2D:4D Digit Ratios in Lesbians versus Other Sources of Evidence

Keeping these limitations in mind, we have a problem understanding why 2D:4D digit ratios, a marker of prenatal exposure to testosterone, finally convinced Breedlove that prenatal testosterone has a significant influence on sexual orientation (Brown, Finn, Cooke, & Breedlove, 2002). This marker has indeed a few major advantages including the facts that (1) it cannot probably be modified by social influences, (2) the ratio is determined early in life, and (3) it is extremely easy to obtain this measure in a large number of subjects. This marker has also been shown to be reliable in terms of the average differences between men and women and also between homosexual and heterosexual women. Multiple studies, including meta-analyses (Grimbos, Dawood, Burriss, Zucker, & Puts, 2010), have confirmed the statistically significant differences between average values in these two types of populations (for a detailed list of references, see Breedlove, 2017).

But even if we accepted these facts, this measure also has its drawbacks. It is first extremely noisy and correlates only poorly with the sexual orientation of subjects. It only explains a small part of the variance in the relationship and as clearly acknowledged by Breedlove, 2D:4D ratios alone do not provide conclusive evidence for the sexual orientation or even the sex of a given subject. This is clearly demonstrated by a study of androgen insensitive XY subjects as compared to control men and women (Berenbaum, Bryk, Nowak, Quigley, & Moffat, 2009). The study statistically confirmed their average absence of masculinization of the 2D:4D digit ratio, as well as the previously established sex difference in control subjects, but showed that this ratio was unable to predict group membership in about one third of control women and two thirds of control men. It must be noted, however, that 15 out of the 16 subjects affected by complete androgen insensitivity syndrome (CAIS) were classified as women and only one as men based on these data, which provides some support for the idea that 2D:4D digit ratios are generally valid markers of early androgen action (Berenbaum et al., 2009) contrary to what has been claimed by others (Wallen, 2009). In other words, the data suggest that straight females were exposed to very little testosterone, CAIS women were exposed to testosterone that could not act on its targets, whereas men were exposed to high concentrations of testosterone.

Secondly, it must be noted that like all putative markers of prenatal androgenization, the 2D:4D ratios obtained critically depend on the population studied and how well controls are matched to homosexual subjects. Testing an entire class of students at a college or university

(with the risk of false declarations concerning sexual orientation) or sampling individuals during a gay pride event, or in a gay bar, probably does not match the same control populations and possibly affects study outcomes. This presumably explains why some studies failed to replicate either the sex differences or female sexual orientation differences that had been previously reported.

An additional limitation includes the fact that measurement obtained using photocopies provide different digit ratios than direct measurement (Manning, Fink, Neave, & Caswell, 2005), which might reflect differences in soft tissues rather than in bone lengths (Wallen, 2009). A further potential limitation and one that is somewhat surprising, is that differences in 2D:4D digit ratios are often stronger in the right hand than in the left hand, despite the fact that both hands were presumably exposed to the same endocrine milieu.

Although many experts remain extremely critical, it is our opinion that the bulk of evidence derived from the literature on animal, CAH XX women, and CAIS XY women suggests that the 2D:4D ratio is an indirect marker of prenatal androgenization. Therefore, we agree with Breedlove's conclusion that there is a difference in the average digit ratios of lesbians versus straight women, indicating that the former were hyper-androgenized during their early life. But we do not think that this is the only, or even the main, argument supporting the notion that prenatal testosterone determines or influences sexual orientation in women because this factor explain only a small part of the variance in the data. As acknowledged by Breedlove, one cannot "...use digit ratios to make any accurate prediction about the sexual orientation of an individual." As such, 2D:4D digit ratios are just one piece in a much larger puzzle.

Why Are the Results Different for Males?

The results for lesbians (or non-heterosexual women) would logically suggest that the opposite relationship should be observed in men: one would expect that gays have less masculinized (larger) 2D:4D digit ratios. However, a large number of studies have failed to identify such a difference (Grimbos et al., 2010). Similarly, there appears to be no significant difference in otoacoustic emissions related to male sexual orientation, despite the existence of such a difference in females (McFadden, 2011).

Breedlove offers a convincing explanation for these findings. Behavioral endocrinology indeed established decades ago that there is an excess of circulating testosterone to activate male sexual behavior in adulthood (Damassa, Smith, Tennent, & Davidson, 1977; Grunt & Young, 1953). The full behavior can be restored in castrated males by treatments that produce plasma concentrations that are only about 10% of what is seen in a sexually mature male (Damassa et al., 1977). There is, therefore, no correlation between individual differences in behavior and in circulating testosterone concentrations. By analogy, the same excess of testosterone might influence male behavioral ontogeny and sexual differentiation and therefore not be a limiting factor. Although, to our knowledge, this was never formally demonstrated, there are suggestions in the animal literature that this could indeed be the case. For example, the founding paper of the hormonal theory of sexual differentiation already demonstrated that the dose of testosterone required to defeminize behavior in

females is much lower than the dose required to masculinize their genitalia (Phoenix, Goy, Gerall, & Young, 1959).

However, this leaves unanswered the question of the origin of male same-sex sexual orientation. Breedlove postulates that the circulating concentration of testosterone cannot be responsible, but possibly sensitivity of the brain to this steroid is key. This conclusion evoked for us some thoughts and hypotheses that are clearly testable.

First, it is fairly well established that 2D:4D digit ratios are more reliably masculinized in butch (more masculine) than in femme (more feminine) lesbians (Brown et al., 2002). We think that additional data should be collected to test whether the absence of difference in the 2D:4D digit ratios between gay and straight men does not result from the failure to distinguish between different forms of male androphilia before “we abandon the idea that gay males are under-masculinized”. Gay men self-label themselves into categories including the more feminine (potentially hypo-masculinized, self-identified as “twinks”) and more masculine or hyper-masculine (hairier and heavier and potentially hyper-masculinized, self-identified as “bears”) individuals (Blankenship, 2013; Hennen, 2005; Moskowitz, Turrubiates, Lozano, & Hajek, 2013). Similar gendered variations are not restricted to Anglo-Saxon culture. For example, in non-Western cultures such as the Istmo Zapotec (found in the Istmo region of Oaxaca, Mexico) highly feminine male androphiles are recognized as *muxe gunaa*, whereas relatively masculine male androphiles are recognized as *muxe nguiiu* (Gomez, Semenyua, Court, & Vasey, 2017).

It is interesting to speculate as to whether a mix between high 2D:4D ratios and low 2D:4D ratios in these more feminine and more masculine populations of homosexual men is responsible for the failure to find any difference associated with male sexual orientation to date. If this explanation is correct, one would expect that 2D:4D ratios in gay men should be associated with more variance than in straight men.

One interesting related observation is that in the published meta-analysis of 2D-4D ratios, it was reported that this ratio is, on average, more masculine (smaller) in gay than in straight men in the European samples, whereas it is more feminine (larger) in North American samples, albeit these differences were generally not significant (Grimbos et al., 2010). This geographic difference was apparently related, in part, to the different ethnic composition of the samples. When compiled together, these data indicated no significant difference between homosexual and heterosexual men. One is left to wonder whether the recruitment of the different types of gay men (e.g., twinkies vs. bears) in these studies was differently biased in the Europe and the North American samples, thus leading to these discordant results. Based on the dichotomy described between butch and femme lesbians, this potential difference should probably be investigated in gay men.

Second, the idea that specific changes in the brain sensitivity to testosterone might be at the origin of male homosexuality could be elaborated upon a bit further.. Breedlove postulates that there may be variation in the promoter regions of genes related to specific aspects of brain development and this would lead to a specific sexual orientation. This is indeed a possibility, but there are currently no data supporting this idea as Breedlove admits: “I can

offer no guidance to those studying genetic influences on sexual orientation". We would like to offer a potential line of research that might be worth pursuing here.

A DNA linkage analysis found that male homosexuality was associated with polymorphism in the subtelomeric region of the X chromosome called Xq28 (Hamer, Hu, Magnuson, Hu, & Pattatucci, 1993) and this conclusion was recently confirmed in a study based on a much larger population of subjects (Sanders et al., 2015). To date, no specific gene located in Xq28 has been related to homosexuality but this region contains a couple of interesting genes, mentioned by Sanders et al. that should be further investigated. These include the arginine-vasopressin (AVP) receptor 2. In light of the prominent role played by AVP in the control of social and affiliative relationships (Balthazart & Young, 2014), it is conceivable that any change in this gene could have an impact on sexual orientation, even though expression of this gene is most prominent in the kidney and more limited in the brain. Another gene located in Xq28 and expressed in the brain is the cyclic nucleotide gated channel alpha 2 (CNGA2) that is critical in mice for the control of odor-evoked sociosexual behaviors (Mandiyar, Coats, & Shah, 2005; Spehr et al., 2006). Although the contribution of olfaction to human sexual behavior seems restricted when compared to rodents, the differential hypothalamic responses of gay and straight men to olfactory compounds with presumed pheromonal activity (Savic, Berglund, & Lindstrom, 2005) suggests that CNGA2 could also relate to the control of sexual orientation.

More interesting, however, are the genes of the melanoma-associated antigen (MAGE) family that are also located in Xq28. MAGE-11 in this family encodes for a protein that has been recognized as a co-activator for the androgen receptor and therefore, increases its transcriptional activity in the prostate (Karpf, Bai, James, Mohler, & Wilson, 2009). Its expression is markedly up-regulated by castration (100–1500 fold) as a result of hypomethylation of a CpG island in the 5' promoter of the gene. This increased expression of an androgen co-regulator provides a mechanism that can potentially account for the increased androgen sensitivity in prostate cancer after androgen deprivation. If this gene is expressed in the relevant brain areas, which seems to be the case (see: <http://biogps.org/#goto=genereport&id=4110>), mutation of this gene located in Xq28, or changes in its expression induced by epigenetic mechanisms affecting its methylation, could then provide a mechanism explaining the changes in brain androgen sensitivity postulated by Breedlove to occur during early development in gay males. However, MAGE-11 does not seem to be present in the rat or mouse genome which might explain the absence of spontaneous (and exclusive) homosexual behavior in these species, whereas early manipulations of androgens action in these species nevertheless creates a reversal of sexual behavior and sexual partner preference (e.g., Bakker, Brand, van Ophemert, & Slob, 1993; Bakker, Van Ophemert, & Slob, 1996; Bodo & Rissman, 2008; Henley, Nunez, & Clemens, 2009). MAGE-11 would additionally provide consilience among all the studies that tend to explain homosexuality by genetic or by hormonal mechanism (Bocklandt & Vilain, 2007; Ngun & Vilain, 2014). This would, however, leave open the question as to why such a mutation would change sensitivity to testosterone in the brain, but not in the body. It would also leave open the question as to why such an epigenetic modification of expression in the androgen receptor co-regulator would be heritable and specifically affect the brain. The anatomical distribution of the

expression of this gene in the brain and its regulation during development would, however, be worth investigating.

Conclusion

In conclusion, we are personally convinced that sexual orientation is largely influenced by biological factors (hormonal, genetic, epigenetic) acting mostly during the early stages of ontogeny and probably interacting with later social interactions (Hines et al., 2016). Like Breedlove, we also believe that human sexual orientation is not a choice and that research pertaining to biological influence on sexual orientation does not have as its core purpose the goal of explaining why some people are gay or lesbian, or even less how to change them, but rather aims to explain why people are straight and never question this heterosexual attraction. The masculinized 2D:4D digit ratios of lesbians certainly supports this notion that biology influences sexual orientation, but this is not in our opinion the decisive line of evidence.

As developed in detail elsewhere (Balthazart, 2010, 2011), there are three types of evidence that converge to suggest the existence of biological influences on sexual orientation: (1) experimental studies on animals demonstrating changes in sexual partner preference after perinatal treatments with sex steroid hormones; (2) analyses of clinical cases demonstrating changes in the incidence of homosexuality in people affected by endocrine disorders that substantially modify their embryonic endocrine environment; and (3) the correlation between sexual orientation and measures of various behavioral, morphological, and physiological traits that are known to differentiate under the embryonic influence of testosterone. Among these traits, the 2D:4D digit ratio is probably the one that has been best studied and has produced the most reliable results. However, due to the limitations described before, these data are not fully conclusive by themselves. It is the convergence of different lines of evidence that supports the biological theory of homosexuality.

As a final note, we would like to correct an error mentioned in the first sentence of the abstract of this article. It is true that sexual differentiation in most, if not all, mammals takes place via the action of testicular testosterone that is masculinizing and defeminizing behavior but this is not true in all non-human vertebrates. In birds, for example, sexual differentiation of reproductive behavior is exclusively the result of a demasculinization of females by their ovarian estrogens (Balthazart, Arnold, & Adkins-Regan, 2017).

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