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Review article

Through a glass, darkly: Human digit ratios reflect prenatal androgens, imperfectly☆

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ABSTRACT

On average, the length of the index finger (digit 2) divided by the length of the ring finger (digit 4) on the right hand, is greater in women than in men. Converging evidence makes it clear that prenatal androgens affect the development of digit ratios in humans and so are likely responsible for this sex difference. Thus, differences in 2D:4D between groups within a sex may be due to average differences between those groups in prenatal androgen exposure. There have been many reports that lesbians, on average, have a smaller (more masculine) digit ratio than straight women, which has been confirmed by metaanalysis. These findings indicate that lesbians were, on average, exposed to greater prenatal androgen than straight women, which further indicates that greater levels of prenatal androgen predispose humans to be attracted to women in adulthood. Nevertheless, these results only apply to group differences between straight women and lesbians; digit ratios cannot be used to classify individual women as gay or straight.

1. Introduction

Hormones and Behavior, founded by one giant of behavioral endocrinology—Frank A. Beach—has been primarily concerned with an idea formalized by another—William C. Young. No concept permeates as many papers published in the journal's first half century as the organizational hypothesis (Phoenix et al., 1959). The authors of that paper were too cautious to float the idea that prenatal exposure to androgens such as testosterone might also organize the human brain, but others have (Ellis and Ames, 1987). We cannot rigorously test the organizational hypothesis in humans because deliberate, randomly assigned manipulation of fetal steroid levels would be unethical. In so-called "experiments of nature," people with a clinical condition that alters early exposure or sensitivity to steroid hormones are compared to control participants, to look for differences in behavior that might be attributable to the differences in early steroid action. Of course, these are not "experiments" precisely because differences in hormone exposure are *not* deliberately applied to subjects chosen at random. Such studies might be more aptly considered "opportunities for endless debate" as we can never fully exclude the possibility that factors covarying with any clinical condition, including social and medical reactions to the condition itself, are actually responsible for any differences in behavior.

We could more directly test the organizational hypothesis in humans by looking for behaviors in adults that correlate with measures of prenatal androgen exposure. If women who report same-sex attraction had, on average, higher fetal levels of androgen than straight women, that result would indicate that androgens organize fetal brains to later display gynephilia (sexual attraction to women). Fetal measurement, however, entails some risk, and therefore is usually limited to a single assay of amniotic fluid (itself a proxy for levels of hormone circulating in the fetal brain) at one particular time of day, during one of the 250 or so days in utero, and so provides only a brief snapshot of total exposure. Therefore, a null result—no correlation of amniotic steroid assays with the behavior of interest—may be because circulating androgens weren't reflected precisely enough, or measured at the right point in development, or in a large enough sample to reach statistical significance, etc. Interestingly, there is an asymmetry of logic in interpreting studies of amniotic levels of hormone and behavior. Findings that measures of amniotic androgen *do* significantly correlate with a behavior, *despite* the many limitations of the amniotic snapshot, cannot be readily dismissed. As a hypothetical example, if lesbians were found to have had higher amniotic levels of androgens than straight women, that would be difficult to explain unless elevated prenatal androgens incline girls to be

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attracted to women when they grow up. Assuming such a finding was replicated, of course.

Thus, any method to estimate the prenatal androgen exposure of human adults from non-clinical populations would offer researchers hope of detecting organizational influences on human behavior. Refining earlier reports (Ecker, 1875; George, 1930), John T. Manning reported that the ratio of the length of the second digit (2D, the index finger), divided by the length of the fourth digit (4D, the ring finger) was, on average, lower in males than females (Manning et al., 1998); in other words, males on average have a longer ring finger, relative to their index finger, than females. The presence of this sex difference in two-year olds, raised the possibility that the 2D:4D of adults might offer a retrospective marker of their prenatal androgen exposure. Does it?

2. Do digit ratios reflect prenatal androgen exposure in humans?

The scientific literature has so far identified only four proximate mechanisms for producing a sex difference in the mammalian body. These are: a) direct effects of sex chromosomes, known to control sexual differentiation of the gonads, b) antimullerian hormone (AMH), secreted by the testes to suppress development of the female genital tract in males, c) androgens such as testosterone and its metabolites, which masculinize the wolffian ducts and external genitalia in males, and d) social influences, such as those that encourage the sexes to dress and conduct themselves differently and which potentially could explain many sex differences in human behavior and outlook. As Phoenix et al. pointed out, most of the sex differences in the body, especially those in the external genitalia, are the direct or indirect result of androgens like testosterone masculinizing structures in males. Thus a reasonable first guess at the origins of any sex difference in the human body is that it may be due to sex differences in androgen exposure. Manning's report that digit ratios differed between the sexes in two-year olds would seem to rule out the possibility that pubertal or post-pubertal androgens are responsible, and subsequent demonstrations of the sex difference in fetal humans (Galis et al., 2009; Malas et al., 2006), confirms that notion and also rules out the possibility that social influences somehow inculcate the sex difference in digit ratios.

Two other candidate mechanisms for producing sex differences, direct sex chromosome effects and AMH, are disproved by reports that the digit ratios of women with androgen insensitivity syndrome (AIS) are feminine (Berenbaum et al., 2009; van Hemmen et al., 2017). These women carry a Y chromosome like males, and produce AMH like males, which is why their Mullerian duct structures do not develop. If either of those factors was responsible for masculinizing 2D:4D, then women with AIS should have masculine ratios, yet they do not. Thus, by elimination, either the sex difference in digit ratios is due to the prenatal influence of androgens or there is a fifth, so far unsuspected mechanism of sexual differentiation at work, and digit ratios are the only structure known to respond to it.

It is logically impossible to disprove the presence of a totally unknown fifth factor, primarily because it's unknown—where would you start? However, there are ample demonstrations that prenatal androgens indeed affect digit ratios in adulthood, supporting the notion that the hormones are also responsible for the sex difference. There are at least four reports that people with congenital adrenal hyperplasia (CAH) have more masculine (i.e., lower) digit ratios on the right hand than same-sex controls (Brown et al., 2002c; Okten et al., 2002; Oswiecimska et al., 2012; Rivas et al., 2014). Interestingly, CAH has little or no effect on the left hand 2D:4D (Brown et al., 2002c; Buck et al., 2003), and the sex difference in digit ratios is either reduced or absent on the left (Honekopp and Watson, 2010), indicating that, for reasons unknown, the right hand is more sensitive to prenatal androgen than the left. There are two reports that digit ratios are larger (more feminine) in men with Klinefelter's syndrome (Chang et al., 2015; Manning et al., 2013), which results in reduced prenatal androgen production. Digit ratios do *not* vary with a polymorphism in the androgen receptor (AR) gene that affects the protein's effectiveness (Honekopp, 2013), perhaps because a less effective AR results in reduced negative feedback, and therefore a compensatory increase in circulating testosterone (Crabbe et al., 2007; Ma et al., 2014; Skjaerpe et al., 2009; Stanworth et al., 2008).

Sex differences in digit ratios have also been reported in other species (Baxter et al., 2019), although they are not always in the same direction as in humans (Baxter et al., 2018). They have been most extensively studied in mice (Brown et al., 2002a), where providing exogenous prenatal androgens decreases 2D:4D, and blocking prenatal androgens either pharmacologically or by disabling the androgen receptor in paws, increases them (Zheng and Cohn, 2011). The latter report also documented that digit ratios in mice were feminized (increased) by estrogen receptor stimulation, another source of variance in addition to genes (Gobrogge et al., 2008).

Given the sex difference in digit ratios, their masculinization in CAH, demasculinization in Klinefelter's, and feminine nature in AIS, it would seem to be obvious that 2D:4D does indeed correlate with fetal androgen action. Especially because each of these reports has been independently replicated at least once. With the addition of findings that eliminate every other known proximate driver of mammalian sexual differentiation (society, sex chromosomes, AMH) to account for the sex difference in digit ratios, one might expect there would be broad consensus that 2D:4D indeed reflects prenatal androgen action. Yet there is no such consensus, as a report in *Science* quoted several researchers expressing doubts about whether digit ratios actually reflect prenatal androgen exposure at all (Leslie, 2019). It is not easy to explain this resistance, as critics of 2D:4D research merely dispute the association with prenatal androgen without coming to grips with the data, or offering any alternative explanation for how the sex difference and effects of CAH, AIS and Klinefelter's on digit ratios could come about if 2D:4D is *not* responsive to prenatal androgen. The only alternative offered in the perspective story was the data-free assertion that men's fourth digit is longer because “as the hands get bigger…the fourth finger lengthens more than the second.” This rather fuzzy notion ignores findings that the sex difference in ratios is present as early as the 14th week of gestation (Galis et al., 2009; Malas et al., 2006), when the entire fetus is less than 4 in. long.

3. Why are digit ratios so maligned?

Several hypotheses come to mind when trying to explain why some researchers adamantly deny that digit ratios reflect prenatal androgen despite converging evidence to the contrary from so many sources. One potential drawback of measuring digit ratios is that it is a very low-tech endeavor: a simple ruler costing about $1 is sufficient to measure them. The ability to rapidly and easily measure digit ratios has surely contributed to the steady increase in the number of biomedical publications examining them since Manning et al.'s (1998) report (Fig. 1). In an era of big science projects like multi-national cyclotrons, big data analytics from technology giants like Facebook and Google, and highly sophisticated neuroscience techniques like optogenetics, measuring a patently obvious structure like a finger with a simple ruler may not meet subjective criteria for a “sciencey” appearance. At the very least, such research is easily criticized and dismissed as long as skeptics ignore the converging evidence reviewed above, and shrug off the burden of providing any alternative explanation for those data. Simply put, it is easier to criticize an endeavor than to think critically about it.

Another source of disquiet about the use of digit ratios is the unfortunate yet undeniable fact that they do not reflect prenatal androgen action *perfectly*. If they did, then every woman would have a larger digit ratio than every man, and in that case the sex difference would have been noticed well before the nineteenth century. In fact, there is considerable overlap between the sexes in the distribution of digit ratios, much more overlap than say, the sex difference in human height. For the sex difference in digit ratios, Cohen's d′ is about 0.5, which Cohen

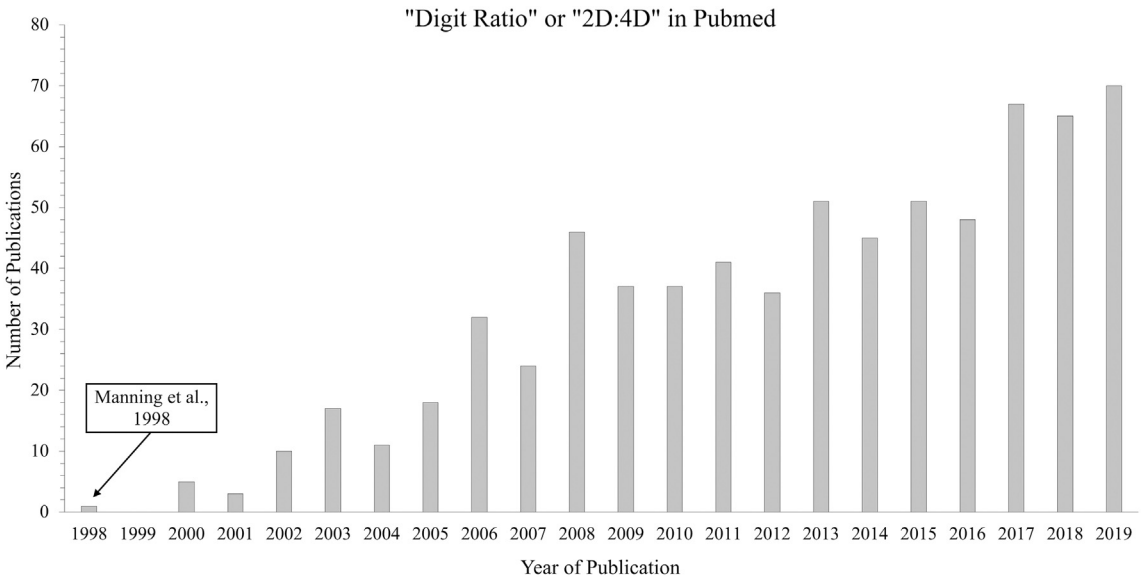

Fig. 1. Rise in publications using digit ratios. These data were gathered from pubmed.gov using the search terms indicated. No studies in the database were indexed by these terms prior to the Manning et al. (1998) report.

likens to the difference in height between 14 year-old girls and 18 year-old girls (Cohen, 1988). Thus denying that there is a sex difference in right-hand digit ratios would be equivalent to denying that 18 year-old girls are taller, as a group, than 14 year-old girls.

Rarely do scientists have access to a perfect measure of *anything*, especially factors at work in humans. We've already noted the limitations of amniotic measures of androgen—is that a reason to never use them? Because our measures of any variable are imperfect, scientists resort to statistics to compare *groups* of people, with the idea that many other uncontrolled sources of variance will be normalized, canceling each other out. Of course, even with the judicious use of statistics, studies using digit ratios, like studies using any other measure, will inevitably produce reports with Type I Error (reporting a difference in samples that is not actually present in populations) and Type II Error (reporting no difference between samples when the populations actually do differ). The time-tested remedy for such errors in reports is independent replication(s) from other laboratories, meta-analyses, and so on. This is as true for studies using digit ratios as for studies using cyclotrons, big datasets, and optogenetics. However, one might expect that findings using digit ratios are much more likely to actually be tested via replication attempts than findings using technically demanding methods like optogenetics. We can all think of highly complex experiments that were so difficult to accomplish that probably no one will ever try to repeat them, and therefore they will never be tested for replication. Would the world ever know if that report contained a Type I or Type II error? Which does more harm to our scientific enterprise: published errors that are corrected by replication failures, or errors that are never tested and so never corrected?

There is a somatic marker that reflects prenatal androgen exposure rather well, surely better than digit ratios, and that is anogenital distance (AGD). AGD passes all the tests for a biomarker of prenatal androgen: there is a sex difference, and it is affected in both CAH and AIS. Indeed, in a non-clinical sample of women, digit ratios significantly correlated with AGD in the expected direction (Barrett et al., 2015). Despite its superior reflection of prenatal androgen exposure, AGD is limited by practical considerations. One thing digit ratios have already made clear is that *if* there are organizational influences on human behavior, *they are subtle*, requiring large sample sizes to reach statistical significance. As our culture stands at present, we are unlikely to ever persuade hundreds of people to allow us to measure their AGD. There are no cultural barriers to measuring fingers, and so the use of 2D:4D is a case of "searching where the light is." In the meantime, if you compare groups of people and find no difference in their digit ratios, then, just as with any other null finding, you might consider whether your sample was large enough. At the least, you should conduct a power analysis to determine an appropriate sample size to detect a difference *between* the sexes ($d' = 0.50$). If you can detect the sex difference and if you also see a difference between groups *within* a sex, then the only way to gain confidence that the difference is real is to publish the results and see if others can replicate them.

One might think that publishing findings and awaiting replications reflects the very basis of open-minded empirical science, but Leslie (2019) also reports that this very journal *Hormones and Behavior*, which has been so preoccupied with the organizational hypothesis for a half-century now, will not even send out for review any submissions that use digit ratios as proxy for hormones, even though that is precisely how they must be used to test the organizational hypothesis. It is not clear when and how this policy was implemented, as it appears nowhere in print or on the journal's website, and we are not aware that it was ever considered or approved by the journal's Editorial Board. How many board members are even aware of the policy? How many other covert policies are there for determining which submissions will be considered for publication? How are such policies decided if the board is excluded from the process?

Another test of whether digit ratios reflect prenatal androgen levels would be to propose that the organizational hypothesis may indeed apply to humans, and ask whether any behavioral traits that differ *between* the sexes also correlate with digit ratios *within* a sex. As an example, let's consider what may be the largest behavioral sex difference in our species, which is that the majority of men are sexually attracted to women, while the majority of women are attracted to men.

4. Testing the organizational hypothesis for human sexual orientation

Back in 2000, acting upon the mere possibility that digit ratios might reflect prenatal androgen exposure, our laboratory reported that lesbians, on average, have a lower 2D:4D than straight women (Williams et al., 2000). Apparently this paper, which has been cited over 500 times, would today be rejected without external review by *Hormones and Behavior* (Leslie, 2019). Happily, it did find an outlet in *Nature* and has been replicated many times (Hall and Love, 2003;

Kraemer et al., 2006; McFadden and Shubel, 2002; Putz et al., 2004; Rahman, 2005; Rahman and Wilson, 2003; Tortorice, 2002). A few researchers reported no such difference, but a meta-analysis of 16 datasets, including all that had been published at that time (Grimbos et al., 2010), concluded that 58 consecuetive reports of no difference between lesbians and straight women in right-hand digit ratios would be needed to render the effect size statistically nonsignificant. In the meantime, there have been several more replications, including two reports of monozygotic twins discordant for sexual orientation in which the lesbian twins have, on average, more masculine digit ratios than their sisters: one from Japan (Hiraishi et al., 2012) and another from Europe (Watts et al., 2018), replicating an earlier US report (Hall and Love, 2003).

A year after our first report, we gathered another sample, finding that lesbians who self-identified as “butch” had more masculine digit ratios than those who regarded themselves as “femme” (Brown et al., 2002b). That finding fits nicely with reports that girls who experience gender dysphoria have more masculinized ratios than control girls (Wallien et al., 2008), and that women who regarded themselves as having been “tomboys” have lower 2D:4Ds than controls (Atkinson et al., 2017).

The life sciences are said to be undergoing a “replication crisis,”(Baker, 2016) but there has been no problem replicating our report. That is probably due to the fact, noted above, that it is relatively easy to gather samples of people's 2D:4D. We stand by our 2000 report and would be happy to hear any skeptics' speculations about what factor(s) might be responsible for reduced digit ratios in lesbians if the measures do *not* reflect prenatal androgen exposure. Nail biting? Finger pointing? Industrial accidents?

If we accept a cornerstone of the scientific method—that repeatedly observed phenomena reflect reality—then we must conclude that lesbians, on average, have lower digit ratios than straight women. Given the converging evidence that digit ratios are affected by prenatal androgen, and do not appear to be affected by the only other identified causes of sex differences (sex chromosomes, AMH, or social influences), then it seems inescapable to conclude that lesbians, on average, had greater prenatal exposure to androgens than straight women. How can that difference be explained unless higher levels of prenatal androgen predispose girls to be more likely to be attracted to women when they grow up?

This result also implicates the organizational hypothesis in the generation of sexual orientation of men. As slightly higher levels of prenatal androgens in girls seem to predispose them to be gynephilic in adulthood, then maybe the reason a vast majority of men are gynephilic is because they were exposed to even higher levels of prenatal androgen than were lesbians. From there, one might predict that gay men were exposed to less prenatal androgen, but neither digit ratios (Williams et al., 2000) nor another putative marker of prenatal androgens, otoacoustic emissions (McFadden and Pasanen, 1999), indicate any difference between gay and straight men in prenatal androgenization. Likewise, the notion that gay men are under-androgenized is difficult to square with the finding that they have a larger average penis size than straight men (Bogaert and Hershberger, 1999). Apparently, differences between gay and straight men are more likely to be due to differences in the brain's *response* to male-typical testosterone levels. Alternatively, there are surely multiple pathways leading to a gay orientation, including the fraternal birth order effect that acts upon only right-handed males (Blanchard et al., 2006). Perhaps some boys are nudged toward an adult gay orientation by slightly lower-than normal levels of prenatal androgen, while others are nudged in that direction by slightly higher-than normal levels.

5. What constitutes a biomarker?

One issue that has clouded the question of whether digit ratios reflect prenatal androgens is the term “biomarker,” which sometimes appears in the scientific literature, though often lacking any definition. The idea seems to be something you can measure that reflects a biological process, either normal or abnormal, in the subject. Prenatal androgen exposure is certainly a biological process, so given the many demonstrations that this process co-varies with digit ratios, they would seem to be biomarkers. The sticking point is a typically unstated connotation about biomarkers, namely that they should allow one to pick out *individual* people, and accurately predict how extensive the biological process was at work for that *particular person*. Clearly digit ratios do not meet this unstated definition of biomarkers because, as we've noted above, they are not *perfect* reflections of prenatal androgen, only statistical covariates. Given the extensive overlap between any two groups, one cannot, using digit ratios alone, accurately classify individuals by sex, much less classify which men have Klinefelter's or which women have CAH, which have AIS, which are lesbians, or which lesbians are femme, etc. Note, however, that human height, which also reflects prenatal androgens and shows a much bigger sex difference than digit ratios, could not perform this function of perfectly identifying women vs. men, either. AGD would probably allow accurate detection of men versus women, but it would not allow us to detect *individual* women with CAH or AIS. So, should AGD be considered a biomarker for prenatal androgen?

On the other hand, if you assemble a group of 100 randomly selected lesbians, and a group of 100 randomly selected straight women, then we would predict that the former group would have a statistically significantly lower 2D:4D than the latter. It seems to us that such a prediction means digit ratios are indeed biomarkers of *something* that matters about female sexual orientation, either prenatal androgens or the mysterious fifth process driving sexual differentiation. No one has ever claimed that digit ratios are biomarkers for detecting *individual* lesbians, but rather that they are biomarkers for revealing the role of prenatal androgen in the sexual orientation of women.

6. Where do we stand?

We noted earlier the increased appearance of digit ratio research (see Fig. 1), but resistance to such publications seems so deeply ingrained, and so detached from any consideration of reports regarding CAH, AIS, Klinefelter's, etc., that we expect that to persist, as well. Our position is that we should welcome digit ratio reports as the only appropriate way to address any lingering replicability concerns. If there is an alternative explanation for why digit ratios are masculinized in CAH, only further investigations could possibly reveal them. Likewise, if the effects of AIS and Klinefelter's, and the basic sex difference are not due to prenatal androgen, only further research could possibly demonstrate that. If digit ratios respond to some fifth, so far unidentified factor, then only further research could reveal what that factor might be and how it affects sexual orientation in women. In short, science will only progress by the gathering of data to test hypotheses, not the pronouncement of opinions by scientists, editors, or anyone else.

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